Guest Editorial: Controversies in Neurology 2017, Athens, Greece

A.D. Korczyn
Sackler School of Medicine Tel-Aviv University, Ramat-Aviv 69978, Israel

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.comtecmed.com/cony/2017/Default.aspx) .

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
the Farr Institute for Health Informatics Research, University of Manchester, UK
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
First Dept. Propedeutic & Internal Medicine, National & Kapodistrian, University of Athens Medical School, Greece

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-a 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-behcet disease: diagnosis & 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 outome, 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 alpha 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
Mathematical Biology, Harvard University, USA
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
Department of Medicine (Neurology), Baycrest Health Sciences, Canada
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
Department of Medicine (Neurology), Baycrest Health Sciences, Canada
Department of Medicine (Neurology), Mt. Sinai Hospital, Canada
Department of Medicine (Neurology), University of Toronto, Canada
Rotman Research Institute, Baycrest Health Sciences, Canada

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 (Aβ-) 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 Aβ phase ≤2 or 0) cases have a low prevalence of ApoE ε4 and a greater conversion rate to dementia than Aβ-/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 Aβ-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 Aβ-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

A. D. Korczyn
Sackler School of Medicine Tel-Aviv University, Ramat-Aviv 69978, Israel

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 □-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
1st Department of Neurology, Eginition Hospital, National and Kapodistrian University of Athens, Greece

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 unknown 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

L. Spiru[1,2], E. Turcu[1], M. Marzan[1]
[1]*Research & Higher Education Department, Ana Aslan International Foundation, Romania*
[2]*Clinical Univ. Dept. of Geriatrics-Gerontology and Old Age Psychiatry, "Carol Davila" University of Medicine and Pharmacy, Romania*

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 R&D 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 de 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
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

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

I. Zaganas, L Mathioudakis, M Bourbouli, K Michaelidou, C Dimovasili
Neurology Laboratory, University of Crete, Greece

Introduction: Apart from the gene mutations associated with familial early-onset Alzheimer's disease (AD) and the *APOE* ε4 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* ε4 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

S. Zygouris[1,2,3], M. i Tsolaki[1,2,4]
[1]*3rd Department of Neurology, Aristotle University of Thessaloniki, Greece*
[2]*Network Aging Research, University of Heidelberg, Germany*
[3]*Psychology & Design, Cannot Not Design + design research organization, Greece*
[4]*Saint John Day Center, Greek Association of Alzheimer's Disease and Related Disorders, Greece*

Recently information & 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
Neurology, 1. Neurology Clinic of the Aeginiteion Hospital, University of Athens, 2. Hellenic Pasteur Institute, 3. Diagnosis and research laboratory Tzartos NeuroDiagnostics, Greece

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 neuri-tis, 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 or 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 pychoactive 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 sould 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
Institute of Clinical Neuroscience, Sahlgrenska University Hospital, Sweden

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
Institute of Clinical Neuroscience, Sahlgrenska University Hospital, Sweden

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 cannibidiol'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 pharmacoresistant epilepsies are providing promising results with overt benefit and acceptable tolerability. A double-blind placebo controlled randomized trail 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 cannibidiol 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 pharmacoresistant 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 bioquivalence 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 all, 2013).

Epilepsy and pregnancy - which antiepileptic 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 localiztion; 2) to know the need for hypothesis-driven strategy when considering each techniqe; 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 another 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 prolaction, 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 phenemenology 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 prominent 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 etal, 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 (Vurallı et al, 2016, Vurallı 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,
Neurology and Neurosciences, Stanford University School of Medicine, USA

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
Neurology, Laniado Medical Center, Israel

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.

L. Edvinsson
Department of Medicine, Institute of Clinical Science, Lund University, Sweden

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
Department of Neurology, University Clinic Hospital, Catholic University of Valencia, Spain

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 onabotulinumtoxinA 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 interventionsAll 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

M. JA. Lainez
Department of Neurology, University Clinic Hospital, Catholic University of Valencia, Spain

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 patients 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

C. Lampl
Headache Medical Center, Ordensklinikum Linz Barmherzige Schwestern, Austria

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

K. Ravishankar
The Headache and Migraine Clinic, Jaslok and Lilavati Hospitals, India

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

R. Shapiro[1], N. Fitz[2], R. Lipton[3], P. Reiner[2]
[1]*Department of Neurological Sciences, Robert Larner College of Medicine, University of Vermont, USA*
[2]*National Core for Neuroethics, University of British Columbia, Canada*
[3]*Department of Neurology, Albert Einstein College of Medicine, USA*

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

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

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 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 excrutiating painful episodes, accompanied by autonomic symptoms. By definition we expect cluter periods with nocturnal attacks, accuring 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 occurance 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 anallysed. Women that are more independent, more involved in professional carrer and single women seem to suffer more often from clusters. Hormonal changes as lack of ovulation, PCOS, higher testosterone levels were observed.Carefull 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 occuring during day time, after carefull 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 symptomes.
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

A. Chaudhuri
Neurology, Queen's Hospital, UK

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

A. Chaudhuri[1], P. Behan[2]
[1]*Neurology, Queen's Hospital, UK*
[2]*Neurology, University of Glasgow, UK*

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 enviormental 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 sclertosis 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
University of Medicine, Tirana UHC Mother Teresa, Tirana, Albania

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
Department of Clinical Neuroimmunology, University School of Medicine, Poland

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 mater. Multiple molecular and cellular components mediate neuroinflammation in MS. They unclude 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 af 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

J. Losy
Department of Clinical Neuroimmunology, University School of Medical Sciences, Chair of Neurology, Poland

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

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

F. Paul
NeuroCure Clinical Research Center, Charité Universitätsmedizin Berlin, Germany

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.

U. Rot
Department of Neurology, University Medical Centre Ljubljana, Slovenia

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 integritiy 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 CFS 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 biomarkes could also serve as predictors of possible, severe side effects. In natalizumab treated patients CSF OB sometimes dissappear 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 acitivity 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?

O. Stuve[1,2,3]
[1]Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[2]Department of Neurology, Klinikum rechts der Isar, Technische Universität München, Germany
[3]Neurology Section, VA North Texas Health Care System, Medical Service, Dallas, TX, U.S.A.

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 no 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

B. Van Wijmeersch
Biomedical Institute, University Hasselt and Rehabilitation & MS-Centre Overpelt, Belgium

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
Institute of Neuropathology, University Medical Center Göttingen, Germany

Multiple sclerosis (MS) is an inflammtory 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 intial 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 used and therapy might be de-escalated when inflammtion within the lesions is decreased.

Brain atrophy measurements should be used to guide therapy in ms - yes

R. Zivadinov
Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, USA
MR Imaging Clinical Translational Research Center, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, USA

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
Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, USA
MR Imaging Clinical Translational Research Center,, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, USA

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 irritble bowel syndrome

M. Rogha[1], H. Imani[1], **H. Ebrahimi**[1], B. Amra[2]
[1]*Neurology department, Islamic Azad university of Najaf abad,school of medicine, Iran*
[2]*Respiratory department, Isfahan University of medical science, Iran*

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, version20, independent t-test, Chi-square test and regression test. Results: One hundred IBS patients included [74women; age38.06±11.09Years].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?

A. Papassotiropoulos
Molecular Neurosciences, University of Basel, Switzerland

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

E. Bayram[1], Ö. E. Yalap[2], Ö. Aydin[3], H. I. Ergenc[1,3], **M. C. Akbostanci**[1,2]
[1]*Department of Interdisciplinary Neuroscience, Institute of Health Sciences, Ankara University, Turkey*
[2]*Department of Neurology, Faculty of Medicine, Ankara University, Turkey*
[3]*Department of Linguistics, Faculty of Language, History and Geography, Ankara University, Turkey*

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

M. Cenk Akbostancı
School of Medicine, Department of Neurology, University of Ankara, Turkey

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?

H. Ebrahimi[1], Ahmad Sobhani[1], Ali Ebrahimi[2], Mohammad Saadatnia[3]
[1]*Neurology department, Islamic Azad university of Najaf abad,school of medicine, Iran*
[2]*Advanced science technology, Islamic Azad university of Najaf abad,school of biomedical engineering, Iran*
[3]*Neurology department, Isfahan University of medical science, Iran*

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 deiminitation 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/mlvs30/43±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 as40/14ng/ml.at this cut–off point,the sensitivity and specificity were73%, 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

B.O. Popescu
Department of Neurology, Colentina Clinical Hospital, 'Carol Davila' University of Medicine and Pharmacy Bucharest, Romania
Laboratory of Molecular Medicine, 'Victor Babeș' National Institute of Pathology, Romania

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

B. Ovidiu Popescu
Department of Neurology, Colentina Clinical Hospital, 'Carol Davila' University of Medicine and Pharmacy Bucharest, Romania
Laboratory of Molecular Medicine, 'Victor Babeș' National Institute of Pathology, Romania

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?

D. Pokhabov[1,2], Vladislav Abramov[1,2], Denis Pokhabov[2]
[1]*Center of innovation neurology, movement disorders and botulinum therapy, Federal State Budgetary Institution "Federal Siberian Scientific Clinical Center of Federal Medical-Biological Agency", Russia*
[2]*neurologic disease, Federal State Budgetary Educational Institution of Higher Education "Krasnoyarsk State Medical University named after Professor V.F. Voyno-Yasenetskogo of Ministry of Healthcare of Russia, Russia*

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-analysises. Authors of abstract used self-development method of thempo-rhytmic 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

*-p0.05 (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 (p0.05) 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

I. Rektorova, I. Rektorova
Department of Neurology, CEITEC Masaryk University, School of Medicine, St. Anne's Hospital, Czech Republic

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 amnestic (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

H. Reichmann
Department of Neurology, University Hospital Dresden, Germany

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 pimavanserine 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

H. Reichmann
Department of Neurology, University Hospital Dresden, Germany

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 manganes 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' disease (PD) patients. The most frequently used medications have been clozapine and quetiapine. Recently a selective 5-HT2A 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 imporvement 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 (KYNAC) 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

G. Xiromerisiou
Department of Neurology, Papageorgiou Hospital, Greece

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

M. Chopp,
Neurology, Henry Ford Hospital, USA

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 microvascularl occlusion, and, importantly, they can be designed to amplify targeted therapeutic benefit.

Cpap is the one and only reliable treatment for osas?

N. T. Economou
Psychiatry - Sleep Study Unit, University of Athens – Eginition Hospital, Greece

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)

A. Kotroni
Physical Rehabilitation Medicine, Kat Hospital, Greece

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

P. Manthos
Rehabilitation day clinic "Iatriki Askisi", MD, Greece

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. Owning 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?

E. Stelmasiak
Wellness Coaching, The Wellness Institute, Poland
Wellness Clinic, Medicover Hospital, Poland

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

A. Tsivgoulis
University Hospital of Larisa, Instructor of Neurology, Greece

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 heterogenity 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

H. Ebrahimi, M. R. Torknejad, N. Taeed
Neurology department, Islamic Azad university of Najaf abad,school of medicine, Iran

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

M. Edip Gurol
Neurology, Massachusetts General Hospital, USA

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
Rehabilitation Department, Animus Rehabilitation Centre, Greece

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

W.D. Heiss
Neurology, Max Planck Institute for Metabolism Research, Germany

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 poststroke 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
Stroke Unit, Metropolitan Hospital, Greece

Current guidelines for acute ischemic strong 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

M. Köhrmann
Dept. of Neurology, Universitätsklinikum Essen, Germany

The optimal treatment regimen for patients with kryptogenic 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 kryptogenic 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-execute 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

V. A. Lioutas
Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, USA

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
Second Department of Neurology, National & Kapodistrian University of Athens, Greece

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
UCL Institute of Neurology, Stroke Research Centre, UK

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 ε4/ ε4* or *ApoE ε2/ ε4* genotypes has been described, while other studies report higher clinical impact of statins in those with lobar haemorrhages. Statins are also associated with lobar microbleeeds, 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

A. Athanassiadou
General Biology, University of Patras Medical School, Greece

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-sunuclein 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

J. Holton
UCL Institute of Neurology, Queen Square Brain Bank, UK

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

R. Matsas
Cellular and Molecular Neurobiology, Hellenic Pasteur Institute, Greece

α-Synuclein (αSyn) is the major gene linked to sporadic Parkinson's disease (PD) while the G209A (p.A53T) αSyn 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 αSyn and Tau. The identified neuropathological features closely resembled those in brains of p. A53T-patients. Small molecules targeting αSyn, 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?

C. Proukakis
Clinical Neuroscience, University College London Institute of Neurology, UK

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

L. Stefanis
Second Dept of Neurology, National and Kapodistrian University of Athens Medical School, Greece

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

A. Bazou
Faculty of Philology, Department of Classics, National and Kapodistrian University of Athens, Greece

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 in 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

K. Dimitrios
Multiple Sclerosis Center, Hadassah Hospital, Israel

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 nowdays.

The point of unity in Mesopotamia

H. Ebrahimi
Neurology department, Islamic Azad university of Najaf abad,school of medicine, Iran

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

A. Papanicolaou
Pediatrics, Neurobiology and Anatomy, The University of Tennessee, College of Medicine, USA

A prerequisit 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

N. Papavramidou
History of Medicine, School of Medicine, Aristotle University of Thessaloniki, Greece

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

C. Yapijakis
School of Medicine, National and Kapodistrian University of Athens, Greece

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' (Παραγγελίαι), 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 philanthrophy (friendship for humans), there is also friendship of the art (of medicine)".

From hippocrates to the 21th century; the role of physicians in society

P.N. Zirogiannis[1], S. Provatopoulou[2]
[1]*former Director, Nephrology Department, General Hospital of Athens "Georgios Gennimatas", Greece*
[2]*Nephrologist, Nephrology Department, Lamia General Hospital, Greece*

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

A. Revonsuo
Centre for Cognitive Neuroscience, Department of Psychology, University of Turku, Finland
Dept. Cognitive Neuroscience and Philosophy, School of Bioscience, University of Skövde, Sweden

The conscious mind is our life as we experience it: we see the world, feel our emotions and think our thoughts, thanks to consciusness.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?