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Invited Speaker Abstracts

1571
WFN15-1877
Headache MT 8.1
Psychiatric comorbidities in migraine

S. Baskin. *Behavioral Medicine, New England Institute for Neurology and Headache, Stamford, USA*

The term comorbidity refers to a more than a coincidental association between two conditions. Comorbidities may complicate differential diagnosis, impact quality of life, affect adherence to treatment regimens, lead to therapeutic opportunities and limitations, and may alter the course of the index condition. Migraine is a prevalent disabling neurological disorder associated with a wide range of medical and psychiatric comorbidities. Population and clinic-based studies show that mood and anxiety disorders are prevalent in migraine sufferers. Sleep disorders, post-traumatic stress disorder and personality disorders are also comorbid with migraine. Psychiatric comorbidities are most common in those individuals that have progressed to chronic migraine. Migraine sufferers with psychiatric disorders may have heightened "affective distress" which may increase impairment, lead to non-adherence to treatment and contribute to headache progression. Comorbid anxiety, in particular, is a predictor of long term migraine persistence. Psychiatric comorbidities will be reviewed, treatment options will be explored and hypothetical shared mechanisms between migraine and affective disorders will be discussed.

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1572
WFN15-1930
Headache MT 8.1
Chronic migraine

J. Olesen. *Neurology, The national hospital Glostrup, Glostrup Copenhagen, Denmark*

Chronic migraine (CM)

This is a new diagnosis introduced in 2004 and revised last time in 2013 as part of the International Classification of Headache Disorders, third edition, beta version. It singles out the most severely affected part of the migraine spectre. These patients have traditionally been excluded from drug trials because of suspected treatment resistance. Central sensitization is suspected to play a role in the chronification but no definite differences in pathophysiology between CM and episodic migraine have been demonstrated. For this reason CM should be treated like any other type of migraine. Botulinum toxin has been registered for the prophylaxis of CM but as a last resort after discontinuation of medication overuse and trials of the usual prophylactic drugs.

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1573
WFN15-1867
Headache MT 8.1
Various aspects of pathoplysiology of migraine such as cortical spreading depression

H. Bolay. *Neurology and Algology Neuropsychiatry Centre, Gazi University, Ankara, Turkey*

Migraine is one of the complex disorders of the brain. Migraine headache attacks are generated by the interaction of environmental triggers and intrinsic factors and accompanied by many other diagnostic symptoms such as nausea and altered sensitivity to sensory stimuli. Recent developments built-up evidences indicating a neuronal dysfunction in the cerebral cortex and particularly cortical spreading depression (CSD) waves, as an upstream to cascade of events leading to a migraine attack. CSD is currently considered as the pathophysiological correlate of migraine aura and extensively used for experimental migraine models to understand the mechanisms, genetics and to develop new therapeutics in migraine. CSD is an intriguing phenomenon of mammalian brain characterized by a massive redistribution of ions causing brief excitability state of the gray matter followed by a long term depression. CSD is implicated in perivascular trigeminal nerve activation in the meninges, releasing CGRP and nitric oxide from trigeminal nerve endings and leading to neurogenic inflammation in the dura mater. These peripheral nociceptive effects are preceded by release of proinflammatory molecules, matrix metalloprotease activation, and blood-brain barrier disruption. CSD is also linked to lateralized headache as peripheral nociception is associated with the activation of central structures such as ipsilateral trigeminal nucleus caudalis activation in the brainstem. Familial hemiplegic migraine models unveiled the critical mechanisms of glutamatergic synapse in CSD. Furthermore CSD is capable of activating thalamic reticular nuclei and other subcortical structures associated with medial pain pathway which is consistent with insights provided by neuroimaging studies during migraine attacks.

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1574
WFN15-1826
Headache MT 8.1
Headaches in children

M. Arruda. *Child Neurology, Glia Institute, Ribeirão Preto, Brazil*

0022-510X/$ – see front matter.

Although migraine is common at all ages, the effects of age on migraine prevalence and clinical features are dramatic. Nonetheless, the influence of age on migraine goes far beyond determining its prevalence by also influencing its clinical presentation, differential diagnosis, and therapeutic outcomes. Indeed, the diagnosis and treatment of migraine in children and adolescents resembles a kaleidoscope with many facets and striking peculiarities with some resemblance of migraine at adulthood. Among the resemblances, we found that migraine is the most common diagnose among children seeking care for headache in the primary care and, as in adults, it imposes a significant burden to the children by impacting their quality of life, school attendance and school performance, and sometimes disrupting the family.

Accordingly, proper diagnose and care of migraine in childhood requires a systematic approach and meticulous follow up which is the scope of this chapter. We intend to provide structured processes for the clinician to comfortably navigate the diagnosis and treatment of migraine in childhood. We start by discussing how to move from symptom to diagnose, by excluding the secondary headache syndromes and assigning a primary headache diagnosis. We follow by discussing the management of migraine in terms of defining patient needs as a prelude for choosing medication in order to address current pain and disability. In closing, we by briefly discussing strategies to prevent migraine progression in order to avoid future pain and disability.

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1575
WFN15-1826
Neurorehabilitation MT 10.1 - From Basic Research to Clinical Applications
Auditory complaints of brain-damaged patients: mechanisms and interventions

S. Clarke. *CHUV, Service de Neuropsychologie et de Neuroréhabilitation, Lausanne, Switzerland*

Patients who sustained traumatic brain injury or stroke often complain of auditory problems: not hearing well in one or both ears, not being able to stay in noisy surroundings, perceiving distorted sounds. These complaints occur even when the ear, the auditory nerve, the auditory centers and pathways in the brain stem, the acoustic radiation as well as Heschl's gyrus are intact and standard audiogram within normal limits. We will discuss three putative mechanisms and the resulting options for intervention. First Heschl's gyrus comprises two tonotopic maps, which are normally modulated by attention (Da Costa et al. 2013) but can be distorted in anatomically intact HG of lesioned brains (Da Costa et al. 2015 in prep). Second, disorders of sound localization occur relatively frequently in cases of brain damage, but can (double) dissociate with sound recognition deficits (Clarke and At 2014). Patients who recognize environmental sounds well but have auditory spatial deficits, often complain of not hearing well, either on one or on both sides. Third, auditory spatial cues contribute implicitly in sound recognition, in addition to the explicit capacity to localize sounds (Clarke and Geiser 2015). Deficits in explicit and implicit use of spatial cues can be dissociated in brain-damaged patients and can lead to surprising clinical situations. Depending on the severity of the disturbance and the the overall objectives for rehabilitation different interventions can be proposed.

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1576
WFN15-1874
Neurorehabilitation MT 10.1 - From Basic Research to Clinical Applications
Translational neurorehabilitation in the third world

A. Conforto[a], S. Anjos[b], A. Sterr[c], K. de Andrade[b], L. Cohen[d]. [a]*Neurology, Hospital das Clinicas/São Paulo U. and Hospital Israelita Albert Einstein, São Paulo, Brazil;* [b]*Neurology, Hospital das Clinicas/São Paulo U., São Paulo, Brazil;* [c]*School of Psychology, University of Surrey, Guildford, United Kingdom;* [d]*Human Cortical Physiology and Stroke Rehabilitation Section, NINDS NIH, Bethesda, USA*

Background: Stroke incidence has increased 100% in the last four decades in low- and middle-income countries, where the majority of strokes occur. Most stroke rehabilitation trials have been performed in high-income Western countries. Barriers to translational research in the third world likely include insufficient funding and trained human resources, but differences between characteristics of patients with stroke in developing and developed areas may also play a role.
Objective: We assessed reasons for non-inclusion or exclusion of patients in a proof-of-principle, double-blinded, randomized clinical trial of stroke Rehabilitation in Brazil.
Patients and methods: The protocol compared effects of active and sham low-frequency repetitive transcranial magnetic stimulation of the unaffected motor cortex as add-on therapies to outpatient rehabilitation in the subacute phase after ischemic stroke. The frequencies of reasons for non-inclusion or exclusion of patients were calculated. Descriptive statistical analysis was performed.
Results: Only 5.6% of 571 screened patients were included. Recurrent stroke was responsible for exclusion of 45.4% of potentially eligible patients.
Conclusion: Recurrent stroke is more common in developing than in developed countries, and represented a crucial barrier to enroll patients in the protocol. Researchers in developing countries should be encouraged to design protocols tailored to characteristics of patients in these areas, in order to facilitate recruitment and also to enhance external validity of translational studies.

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1577
WFN15-1890
Epilepsy MT 1.1 - Seizures, Epilepsy and Infections
Infections as a cause for seizures and epilepsy: an underestimated epidemic

A. Kakooza. *Paediatrics and Child Health, Makerere College of Health Sciences, Kampala, Uganda*

The great majority of people with epilepsy are found in the developing countries where poor sanitation and malnutrition are risk factors for infections. The situation in developing countries is further aggravated by the deficient health care delivery systems with the consequences of late, no diagnosis, and/or no treatment for infective conditions. This implies that the number of cases of seizures and epilepsy as a result of central nervous system (CNS) infections may be grossly underestimated.

Endemic infections such as cerebral malaria, neurocysticercosis and human immune deficiency virus are associated with epilepsy, while viral encephalitis, meningitis and complicated malaria may manifest with acute seizures as their presenting symptom. These infections are probably responsible for the higher incidence of epilepsy in the developing countries turning epilepsy into one of the world's most preventable non-communicable conditions.

Seizures resulting from CNS infections are often focal in nature with the time lag between the insult and the onset of epilepsy ranging from months to years for reasons not clearly understood. For the seizures to occur, the infectious agent damages the cerebral cortex through various mechanisms with the risk heightened by the location, severity and individual predisposition of the patient.

In this paper, an epidemiological overview of common infections of the CNS resulting in seizures and epilepsy are discussed with the possible mechanisms of action. There is need for increased awareness of the role of these infections, insights on their neurobiology as well as the development of strategies for the prevention of epilepsy in CNS infections.

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1578
WFN15-1897
Epilepsy MT 1.1 - Seizures, Epilepsy and Infections
Encephalitis, seizures and epilepsy: diagnostic challenges and clinical management

T. Solomon, B. Michael. *Walton Centre NHS Foundation Trust and Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom*

Encephalitis is an inflammation and swelling of the brain, which is often caused by a viral infection, or an autoimmune response in the brain. Encephalitis is an important cause of acute symptomatic seizures as well as subsequent epilepsy. In this talk the definition, epidemiology, and etiology of encephalitis as a cause of seizures are described. Two infectious causes of encephalitis with seizures are then examined in more detail: herpes simplex encephalitis (the most common sporadic viral cause of encephalitis) and Japanese encephalitis (the most common epidemic viral cause). The evidence for seizures occurring in the context of antibody-associated encephalitis, an increasingly important condition, is also discussed,, before acute and longer-term management of encephalitis-related seizures and their potential pathophysiologic mechanisms are considered.

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1579
WFN15-1852
Headache MT 8.2
The pipeline in headache treatment

A. Rapoport. *Neurology, Ucla, Los Angeles, USA*

Abstract invited lecture – The pipeline in headache treatment
Alan M. Rapoport, M.D.

Migraine is a common and disabling disorder that remains underdiagnosed and poorly treated around the world. Advancements in the understanding of migraine pathogenesis have identified new targets for both acute and preventive treatment of migraine and chronic migraine and have engendered the development of targeted and mechanism-based therapies.

At the present time, the specific treatments for the ***acute care of migraine*** are the NSAIDs, the ergots and the triptans. Most innovations in the pipeline are different ways of giving older drugs. Soon sumatriptan will be available as an iontophoretic transdermal delivery system. It will also be able to be given as a powder by blowing through an apparatus to have it sprayed into one nostril. Diclofenac potassium, although available as a tablet, is recently available in a powder form which is dissolved in a small amount of water for drinking, causing it to have a very short half life and more rapid onset of action. Dihydroergotamine (DHE) may soon be available as an orally inhaled drug. Small molecule CGRP receptor antagonists were proven to be effective as an acute care migraine therapy and may still be developed.

Currently the only FDA-approved treatment for ***prevention of episodic migraine*** are 2 beta blockers (timolol and propranolol) and 2 antiepileptics (valproate and topiramate). There is only one approved treatment for ***prevention of chronic migraine*** and that is onabotulinumtoxinA injections. There are 4 companies testing monoclonal antibodies against CGRP ligand or receptor and early results show that they are all effective preventive treatments for migraine and at least one works well in chronic migraine.

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1580
WFN15-1826
Headache MT 8.2
Stimulation techniques in headache therapy

M.J.A. Lainez. *Neurology, Hospital Clínico Universitario. Universidad Católica de Valencia, Valencia, Spain*

The use of neuromodulation for the treatment of headache is not new; in fact, it uses dates back to Roman times. In the modern time, the use of electrical stimulation in the treatment of refractory headache disorders start with the use of occipital nerve stimulation in the occipital neuralgia and the hypothalamic stimulation (DBS) in cluster patients. Several series have been published evaluating the efficacy of DBS in the management of refractory cluster patients. Today DBS is considered a technique with good short and long-term efficacy results, but as very invasive procedure.

Occipital Nerve stimulation has been used in the treatment of chronic migraine with good results in open studies and no so impressive data in clinical trials. In trigeminal autonomic headaches, the results have been better and it could be one of the first line therapies in refractory cluster patients. One of the problems is that the rate of complications related with the device is not low.

Another target for electrical stimulation has been the sphenopalatine ganglion with a new implantable microstimulator; the results in the first trial in cluster have been good with acute and potentially preventive effect and low rate of device related complications. A trial in migraine is ongoing.

Other non-invasive neuromodulation technique like the transcutaneous vagus nerve stimulation has been tried in several headache syndromes with positive results and very good tolerability.

Electrical stimulation play a role in the treatment of refractory (invasive methods) and could be useful in usual (non-invasive) headache patients.

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1581
WFN15-1631
Headache MT 8.2
Monoclonal antibodies for preventive treatment of episodic and chronic migraine

M. Bigal. *VC Clinical Development, Teva Pharmaceuticals, Frazer, USA*

Calcitonin gene-related peptide (CGRP) is a well-studied neuropeptide of relevance for migraine pathophysiology. Jugular levels of CGRP are increased during migraine attacks, and intravenous CGRP

administration induces migraine-like headache in most individuals with migraine. Several CGRP receptor antagonists (CGRP-RAs) were shown to be effective for the acute treatment of migraine, validating the target for the treatment of migraine. However, for a number of reasons, including issues of liver toxicity with chronic use, the development of CGRP-RAs has yet to produce a viable clinical therapeutic. Development of monoclonal antibodies (mAbs) targeting the CGRP pathway is an alternative approach that carries the potential to avoid many of the issues seen with CGRP-RAs. The exquisite target specificity, prolonged half-lives, and reduced potential for hepatotoxicity and drug–drug interactions make mAbs suitable for the preventive treatment of migraine headaches. Currently, four mAbs are being developed for the preventive treatment of episodic or chronic migraine. This presentation will provide an overview of the role of CGRP in the pathophysiology of migraine, followed by a review of the clinical development of CGRP mAbs for migraine.

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1582
WFN15-1799
Epilepsy MT 1.2 - Diagnostic Challenges in Epilepsy
Focal epilepsies refractory to AEDs: Algorithms to identify treatable causes

W. Theodore. *Clinical Epilepsy, NINDS NIH, Bethesda, USA*

Epilepsy can be due to CNS diseases or lesions, or systemic disorders. Patients with presumed focal epilepsy refractory to antiepileptic drugs need comprehensive revaluation. It is important to establish a patient is truly drug refractory. Current guidelines suggest that using two AEDs either sequentially or, preferably, in combination can establish drug failure, as long as drugs are given in adequate doses for enough time. Video-EEG recording can confirm a patient has focal rather than primary generalized epilepsy, and support focus localization. Family members may give clues to etiology such as a history of complex or prolonged febrile seizures, implying potential mesial temporal sclerosis. Family history may suggest heritable syndromes, such as Autosomal Dominant Partial Epilepsy with Auditory Features. History and physical examination may lead to appropriate studies to detect a systemic disorder. Limbic encephalitis is now recognized as a cause of refractory epilepsy, particularly if patients have subacute onset, and cognitive or psychiatric symptoms.

MRI is increasingly sensitive for detecting drug-refractory focal epilepsy structural etiologies. MRI techniques such as magnetization transfer as well as novel approaches to post-processing may detect lesions such as focal cortical dysplasia not seen on standard scans. FDG-PET can detect focal hypometabolism, and subtraction ictal SPECT increased blood flow, in some patients with normal MRI, suggesting reasonable focal resection prognosis, or guiding intracranial EEG studies. Their value when MRI shows a lesion is less clear. Other PET ligands can image neurotransmitter receptor binding, serotonin precursor uptake or neuroinflammation with valuable research results but limited clinical application.

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1583
WFN15-1889
Pain MT 30.1 - Management of Difficult Neuropathic Pain Conditions
HIV-related neuropathy

P.R. Kamerman. *Brain Function Research Group School of Physiology, University of the Witwatersrand, Johannesburg, South Africa*

HIV-associated sensory neuropathy (HIV-SN) is a common complication of HIV infection, and pain associated with the neuropathy results in significant physical, psychological, social and economic impairment. The introduction of less neurotoxic antiretroviral drugs was meant to usher in a new era of HIV treatment, with reduced burden of new cases of HIV-SN. However, current evidence indicates that while there may have been some reduction in new cases, more than 40% of individual is infected by HIV and never treated with neurotoxic agents have this frequently painful and debilitating distal polyneuropathy. Moreover, using less neurotoxic antiretroviral drugs does not slow the rate of symptom progression compared to older, neurotoxic treatments. In this presentation, the audience will be provided with a brief update on the causes and risk factors for HIV-SN in the modern era, and thereafter the presentation will focus on the latest data concerning the mechanisms, impact, and treatment of the painful features of the neuropathy.

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1584
WFN15-1643
Pain MT 30.1 - Management of Difficult Neuropathic Pain Conditions
Complex regional pain syndromes

P. Schestasky. *Neurology, Hospital Moinhos de Vento, Porto Alegre, Brazil*

Complex regional pain syndrome (CRPS) presents with clinical symptoms that can no longer be explained by the initial trauma, including pain, sensory, motor, and trophic symptoms, and impairment of autonomic control of the limb. These symptoms spread distally and go beyond single nerve innervation territories. Typically, the symptoms change through the course of CRPS as a result of the varying pathophysiology. Diagnosis is made clinically after the rigorous elimination of other possible causes, and 3-phase bone scintigraphy can be a useful tool for confirming CRPS. In acute stages, inflammatory symptoms prevail and should be treated with anti-inflammatory agents (steroids), bisphosphonates, or topical application of dimethyl sulfoxide. In chronic stages, many symptoms are related to so-called central neuroplasticity; these include hyperalgesia, sensory loss, motor symptoms, body perception disturbance, autonomic symptoms, and learned incorrect behavior such as nonuse. At this stage, the only medical treatment that is effective against pain without improving the function is ketamine infusions, but this has side effects. Physical therapy, graded motor imagery, and pain exposure/graded exposure in vivo therapy can help to overcome central reorganization. If a relevant mental comorbidity is present, the patient should be referred for psychotherapeutic treatment. Invasive treatment should be restricted to special cases and only offered after psychosomatic assessment. If these recommendations are followed, CRPS prognosis is not as poor as commonly assumed. Whether the patients can return to their previous life depends on particular individual factors. From: Birklein F, O'Neill D, Schlereth T. Complex regional pain syndrome: An optimistic perspective. Neurology. 2015 Jan 6;84(1):89-96.

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1585
WFN15-1839
Neurorehabilitation MT 10.2 - Disease-specific Neurorehabilitation
Stroke rehabilitation

L.S.W. Li. *Medicine, Tung Wah Hospital & University of Hong Kong, Hong Kong, Hong Kong China*

After acute stroke, rehabilitation process induces recruitment of non-used brain cells to form a new network to restore the lost function. However, pattern of recruitment varies among individuals although brain cells from ipsilateral and contralateral hemisphere and cerebella could be recruited to form the network. Inhibitory effect from contralateral hemisphere on the damaged hemisphere, resulting in imbalance between inhibition and excitation, has been shown. Different modalities of intervention such as mirror therapy and brain stimulation were shown to have effects on reduction of imbalance between hemispheres after stroke. New modalities of intervention to enhance neuroplasticity have been developed in last decade. Although most randomized controlled studies were of small sample size, the effectiveness of these modalities such as robotic gait training, mirror therapy and mental imagery is well summarized by some meta-analysis. The task-specific and repetitive training is basically an important factor for enhancing neuroplasticity. Nevertheless, some training modalities such as mental imagery have been shown to have generalization of training effect even after task-specific training. What would be the optimal training with traditional approach combined with various new training modalities is still not yet fully explored.

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1586
WFN15-1844
Neurorehabilitation MT 10.2 - Disease-specific Neurorehabilitation
Rehabilitation in dementia

J. Verghese. *Neurology & Geriatrics, Albert Einstein College of Medicine, Bronx, USA*

The growing dementia epidemic has brought urgency to developing preventive interventions to slow down progression of cognitive decline or prevent conversion to dementia. Over the past two decades a growing body of work in observational studies have identified several lifestyle factors such as participation in cognitively stimulating activities, physical exercise, diet and social interactions as important risk factors for cognitive decline in aging. More recently, evidence is emerging form clinical trials about the efficacy of several of these risk factors, individually or in combination, in preventing cognitive decline. Furthermore, there is increased recognition of non-cognitive features at every stage of the dementia process, from preclinical stages to severe dementia. These non-cognitive features, especially gait and motoric impairments, are associated with several adverse outcomes such as falls, frailty, disability and death in older individuals. Hence, there is also a need to develop interventions that target not only cognitive decline but also non-cognitive features to improve outcomes for individuals, caregivers and the society.

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1587
WFN15-1847
Epilepsy MT 1.3 - Update on the Medical Treatment of Epilepsy
Treating newly diagnosed epilepsy in adults and children - Staying with the old or going for the new

S. Wiebe. *Clinical Neurosciences, University of Calgary, Calgary, Canada*

Objectives: To review and discuss the evidence on new versus "old" antiepileptic drugs (AEDs) in children and adults, and discuss practical guidance for choice of therapy.
Outline: There is an important unmet need for more effective AEDs in children in adults. While some differences in adverse effects are evident among various AEDs, their comparative effectiveness is overall very similar. Novel agents often carry high expectations for improved seizure control, fewer side effects, and better quality of life, but how often are these expectations fulfilled? Are older therapies dismissed too early or not early enough? What are the consequences of early adoption of new agents and can we be too early to adopt? Are there clear-cut cases to justify shunning older AEDs? What further considerations are needed in choosing new vs older therapies? What is the relevance of costs, need for monitoring, and availability? The presentation will review the evidence for some of these questions as they pertain to the choice of newer versus older AEDs. We will touch on some pharmacological agents under development, new molecular targets, and management challenges in special populations with epilepsy, such as pregnancy, the elderly, and patients with comorbidities. The review will focus on selected aspects of these novel concepts, with relevance for the neurology practitioner.

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1588
WFN15-1657
Epilepsy MT 1.3 - Update on the Medical Treatment of Epilepsy
Does mechanism of action matter when selecting an antiepileptic drug?

E. Perucca. *C. Mondino National Neurological Institute, University of Pavia, Pavia, Italy*

Because of poor understanding of the molecular mechanisms involved in seizure generation, traditionally treatment selection in epilepsy has been made empirically by considering the efficacy and tolerability profiles of available antiepileptic drugs (AEDs); assessing their influence on the probability of maximizing seizure control and minimizing side effects; and selecting the drug whose expected effects provide the best match for the characteristics of the individual. While this approach remains generally valid, increasing evidence is accumulating that knowledge of mechanisms of AED action can provide useful information to guide treatment in certain situations. For example, in a person who failed initial treatment with a specific AED, many physicians are likely to use as alternative therapy a drug acting by a different mechanism. Knowledge of mechanisms of action can be particularly valuable when using combination therapy. Specifically, there is evidence suggesting that simultaneous use of two sodium channel blockers (particularly carbamazepine, oxcarbazepine, phenytoin, lamotrigine, and lacosamide) may result in undesirable potentiation of adverse central nervous system effects, whereas combining drugs with different mechanisms may lead to more favorable effects. Ongoing research aimed at identifying the molecular defects underlying the epilepsy in an individual is likely to increase considerably the routine application of precision medicine, e.g. the rational selection of treatments known to correct the defect identified in the individual person. A typical example of precision medicine is the use of the ketogenic diet to control seizures in patients in whom appropriate testing has led to the diagnosis of GLUT-1 deficiency syndrome.

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1589
WFN15-1786
Pain MT 30.2 - Descending Control of Pain. From Brain to Dorsal Horn
Anatomical-physiological bases

L. Villanueva. *INSERM Paris Descartes University UMR 894, Center of Psychiatry and Neurosciences, Paris, France*

In the field of pain research, Patrick Wall and Peter Nathan were among the first to conceptualize the idea that the Central Nervous System has many ways and strategies for modifying the incoming nociceptive information it receives. At present it is generally accepted that pain sensations are not merely inputs conveyed to the brain by a specialized chain of neurons, or of separated unidirectional ascending pathways which convey the information that inevitably produces the sensory experience of pain. Selection subserved by endogenous modulation networks is the main feature of sensory processing by which the brain is able to modify the features and efficacy of varied inputs arising from the outside world. Some of the particular features of pain perception result not only from the unique anatomo-functional organization of transduction mechanisms and bottom-up ascending pathways but also from the close interactions between bottom-up and top-down central regulation mechanisms. Such interactions create dynamic functional states that change under the influence of processes not necessarily related to pain, including environmental factors and biological rhythms. This may explain the crucial role of comorbidity mechanisms in persistent pain situations, dysfunctional pain and the large variability of pain perceptions and reactions in apparently identical experiments with highly trained subjects and on patients admitted to an emergency clinic. This talk outlines briefly the more relevant features of central regulation mechanisms of nociception, on the basis of animal studies that provide valuable translational models in our understanding of human endogenous pain modulatory systems.

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1590
WFN15-1818
Pain MT 30.2 - Descending Control of Pain. From Brain to Dorsal Horn
Evidence in humans

D. Bouhassira. *Pathophysiology and Clinical Pharmacology of Pain, Inserm U987, Boulogne-Billancourt, France*

The spinal transmission of pain signals is modulated by descending systems which can tonically or phasically, inhibit or facilitate the activity of dorsal horn nociceptive neurons. In humans, both the spinal nociceptive flexion (RIII) reflex and the concomitant painful sensation are inhibited in an intensity dependent manner by heterotopic painful stimuli. On the basis of this methodology, it has been demonstrated that, like in rats, Diffuse Noxious Inhibitory Controls (DNIC) are sustained in humans by an anatomical spino-bulbo-spinal. Over the last twenty years, DNIC-like experimental paradigms, based on the classical "pain inhibits pain phenomenon", have been used in a large number of studies in humans for assessing descending pain modulation. More recently, the broader term Conditioned Pain Modulation (CPM) was coined because protocols used in numerous studies could not be directly compared to the initial DNIC paradigm.

Studies in patients with chronic pain have shown that alterations of descending pain modulation could play a major role in the development and maintenance of pain in various clinical conditions, including fibromyalgia, irritable bowel syndrome, post-surgical pain or neuropathic pain. It has also been shown that alterations of pain modulation could be a predictor of the response to treatment. The main results of these studies will be summarized and discussed in this session.

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1591
WFN15-1841
Stroke MT 3.1- Challenges in Stroke Care Around the World
The global challenge of dementia – targeting the vascular contribution

V. Hachinski. *Clinical Neurological Sciences, Western University, London, Canada*

The global challenge of dementia: Targeting the Vascular contribution

Vladimir Hachinski, MD, DSc, FRCPC
Distinguished University Professor
Department of CNS
University of Western Ontario
London, Canada

Next year, globally, people 65 years of age or older will equal the number of children aged 5 years or younger. This poses a double challenge, prevent or delay dementia in the elderly and assure that children grow up with healthy habits and low risk for dementia and stroke.

The risk factors for stroke and dementia are virtually the same. This represents an opportunity to prevent or delay both.

A potential for modifying risk factors is exemplified by the fact that in the past 20 years stroke incidence has increased by 225% in low and middle income countries while it has declined by 42% in high income countries. The latter are also the countries showing trends in a decreasing incidence of dementia.

In preventing and delaying stroke and dementia we need to coordinate, integrate and focus our efforts into a three stage approach:

1. Information
2. Motivation
3. Enablement

The fact that stroke declined by almost one half in the high income countries, and more than doubled in middle and low income countries in two decades suggests that the big differences are not due to changes in the genetic makeup, but improvements in risk factor control.

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1592
WFN15-1937
Neuroimaging MT 9.1 - Demyelinating Diseases
Radiologically isolated syndrome

F. Fazekas[a], N. De Stefano[b], M. Filippi[c], F. Barkhof[d], A. Rovira[e]. *[a]Department of Neurology, Medical University of Graz, Graz, Austria; [b]Department of Neurological and Behavioural Sciences, University of Siena, Siena, Italy; [c]Division of Neuroscience, Vita-Salute San Raffaele University, Milano, Italy; [d]Department of Radiology & Nuclear Medicine and Neurology, VU University Medical Center, Amsterdam, Netherlands; [e]Magnetic Resonance Unit Hospital Vall d`Hebron, Autonomous University of Barcelona, Barcelona, Spain*

MRI allows to advance the diagnosis of MS already at the time of a first clinical episode producing signs and symptoms suggestive of an inflammatory demyelinating disorder in that it serves to demonstrate dissemination in space and dissemination in time of lesions within the central nervous system (1). This comes from a high sensitivity of MRI for demyelinating lesions - at least in white matter- and lesion distribution characteristic for MS. A situation where MS typical MRI findings are detected incidentally, i.e. without suggestive or even any clinical symptoms has been termed radiologically isolated syndrome (RIS). In general the existence of such a situation does not come as a

surprise as MS lesions are supposed to accumulate over time and only every 5th to 10th lesion is likely to be symptomatic. A challenge and discussion, however, is how to manage such patients. First, it is certainly important to consider and exclude alternative diagnoses that can mimic MS radiologically like age related white matter lesions or some other inflammatory processes. Second, lesion number, location such as in the spinal cord, and contrast enhancement are likely indicators of the probability of also developing clinical symptoms. While treatment is not recommended at this stage this information has to be conveyed to the patient and should be considered when planning clinical and MRI follow-up intervals.

(1) Rovira A. et al., Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. Nat Rev Neurol 2015;11:471-482.

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1593
WFN15-1927
Neuroimaging MT 9.1 - Demyelinating Diseases
Pediatric immune-mediated central nervous system demyelinating disorders

S. Tenembaum. *Neurology, National Pediatric Hospital Dr. J. P. Garrahan, Buenos Aires, Argentina*

Neuroimaging MT 9.1- Demyelinating diseases
“Pediatric immune-mediated central nervous system demyelinating disorders”
Silvia Tenembaum

Acquired immune-mediated demyelinating syndromes of the central nervous system (CNS) have a variety of presentations in children and adolescents. ADEM is a polysymptomatic disorder associated with encephalopathy. Conversely, other demyelinating conditions affect only a discrete region within the CNS, such as clinically isolated syndromes involving the brainstem, spinal cord or optic nerves. While these syndromes are typically monophasic in childhood, recurrences can occur raising the possibility of a chronic disorder such as multiple sclerosis (MS) or neuromyelitis optica (NMO). But similar clinical presentations can occur in children suffering from an infectious, neoplastic, metabolic or vascular disease.

Although the diagnosis of MS classically relies on the demonstration of dissemination in space and time, the exclusion of other neurological disorders is essential, particularly in children. Brain MRI abnormalities are also common in patients with NMO and some may be relatively unique by virtue of localization and configuration. Thus, characteristics of brain abnormalities in children with a relapsing disorder have an important role in the differential diagnosis of MS, NMO and its spectrum disorder (NMOSD). Differentiating these conditions has therapeutic implications as well.

This presentation will review the main neuroimaging features and diagnostic criteria of MS and NMO/NMOSD starting in children and adolescents, highlighting those atypical features or red flags that may serve to distinguish alternative diagnoses.

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1594
WFN15-1914
Neurological Infections MT 12.1 - Viral and Related Infections
HIV

A. Penalva de Oliveira. *Neurology, Instituto Emílio Ribas, São Paulo, Brazil*

The introduction of HAART reduced the incidence of most neurologic opportunistic infections in HIV-infected patients. However, HIV-associated neurocognitive disorders (HAND) currently persist in highly prevalence and constitute a true "hidden epidemic". Otherwise, this is not a world-wide reality, places where HAART access is not full or HIV diagnostic too late, opportunistic infections of the CNS are still prevalent. The classification of HAND categories basically depends on two variables: neuropsychological assessment and evaluation of the disease impact on daily living activities: ANI - asymptomatic neurocognitive impairment; MND - mild neurocognitive disorder; HAD - HIV-associated dementia. The profile of neurocognitive manifestations changed dramatically, characterized by a reduced incidence of HAD and increased MND and ANI. The immune scenario has also become more complex, since all categories of HAND can be observed with moderate or even very discrete levels of immunosuppression. Even, it is known that systemic treatment success, do not guarantee to avoid cognitive decline. The main risk factors associated with HAND are: Low CD4+; Age > 50 years; Hepatitis C virus co-infection; Diabetes or insulin resistance; Cardio-vascular disease; and Lower education level. The central strategy of treating HAND is based on the concept of the CNS penetration effectiveness (CPE) score of the antiretroviral drugs, which estimates the effectiveness of antiretroviral treatment in the CNS. CPE score has demonstrated correlation with the decrease of the viral load of HIV and cognitive improvement in most studies, but not all. However, considering the information currently available, it is suggested to structure schemes with high CPE.

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1595
WFN15-1896
Neurological Infections MT 12.1 - Viral and Related Infections
Japanese encephalitis

T. Solomon. *Walton Centre NHS Foundation Trust and Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom*

Japanese encephalitis is one of the most important causes of encephalitis globally, with an estimated 70,000 cases every year. The disease is caused by the mosquito-borne Japanese encephalitis virus, a zoonotic infection transmitted naturally among birds and pigs. Although principally a disease of Asia, the virus is spreading, and is closely related to similar viruses including West Nile virus, and Rocio virus in South America. In this talk we will consider the viruses evolution and spread, and possible impact of climate change; our understanding of the clinical features and how this might lead to improved management; hopes for developing new treatments; and the impact of the enormous efforts of the WHO, regional Governments, and academic partners to bring the disease under control across Asia, through better surveillance, improved diagnosis, and more comprehensive vaccine roll out.

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1596
WFN15-1936
Stroke MT 3.2 - New Opportunities for Management of Acute Stroke
Neuroimaging in stroke: therapeutic implications

G.A. Donnan. *N/A, The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia*

Neuroimaging has revolutionised our approach to stroke therapy. For ischaemic stroke MRI has been the mainstay over recent decades because of the extraordinary amount of information which can be generated ranging from mismatch, vessel status through to metabolic parameters. After initial problems with threshold values (or lack thereof) MR mismatch as a signature of viable tissue and a target for therapy has become established in recent trials. However, CT perfusion (CTP) has now superseded MR because of the automatic co-registration of viable versus non-viable tissue, the generation of angiographic data and including the status of vessel co-laterals. Importantly, CTP is more widely available, can be performed within a shorter timeframe and is not plagued by MR limitations of claustrophobia and other contra indications to use. There is a reasonable argument that CTP should be standard initial imaging modality because of its features outlined above and its usefulness in acute intra cerebral haemorrhage to identify patients at risk of haematoma expansion with the spot sign and exclusion of underling AVMs. The recent finding that contrast induced nephropathy is inconsequential when sensible pre-scan clinical screening is undertaken is reassuring. Automated software such as RAPID also makes CTP an appealing and pragmatic stroke imaging tool within the therapeutic decision making framework.

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1597
WFN15-1843
Stroke MT 3.2 - New opportunities for Management of Acute Stroke
Reperfusion strategies, proven, disproven and uncertain

P. Ringleb. *Neurology, University hospital Heidelberg, Heidelberg, Germany*

Reperfusion strategies, proven, disproven and uncertain
Peter A. Ringleb

Reperfusion of occluded vessel is a major topic of acute stroke treatment for decades. First experiences were done in the 1980 with intra-arterial medical thrombolysis. This was followed by intravenous rtPA treatment in the 1990s, because it is much easier to deliver to a relevant cohort of patients. However recanalization rate of especially large vessels like Carotid-T, proximal MCA or Basilar artery with iv-rtPA is limited. Hence, several mechanical devices for recanalization of intracranial vessel occlusions have been developed for more than a decade and were approved for clinical use on the basis of uncontrolled case series. First randomized clinical trials comparing the new devices with standard treatment, including thrombolytic therapy, failed. After these negative results several new trials with changes in design (e.g. shorter time window and only proximal vessel occlusions) and the use of modern devices like stent-retrievers have been launched. In October 2014 the first of these new trials was presented and showed a clear superiority of thrombectomy. Based on this result interim analyses of five other studies were performed and most were prematurely terminated because of overwhelming efficacy. Currently five studies have already been published and two more studies have been presented at scientific conferences. This talk will give an overview about the recanalization trials and will especially provide a discussion for which clinical situation evidence for superiority of mechanical thrombectomy still is lacking.

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1598
WFN15-1858
Stroke MT 3.2 - New Opportunities for Management of Acute Stroke
Management of acute intracerebral hemorrhage – when to start and how to treat

C. Anderson. *Neurological and Mental Health Division, The George Institute for Global Health, Camperdown, Australia*

Hypertension is common in all types of acute stroke, but whether prompt lowering of BP provides benefits without excessive risk has been a matter of longstanding controversy … until recently.

The Intensive Blood Pressure Reduction in Acute Intracerebral Haemorrhage (ICH) Trial (INTERACT2) provides important new evidence of the efficacy and safety of early intensive BP lowering in ICH, where management of this condition has been largely supportive, and often nihilistic, in the absence of a proven treatment. The INTERACT2 results, together with other trial and observational data, has pushed guideline recommendations and clinical practice around the world towards more aggressive management of BP (towards a systolic target of <140 mmHg) rather than the conventional level of control (<180 mmHg). Further trial data also highlights the importance of early and smooth control of systolic BP, not just in the first 24 hours but over the subsequent several days after ICH.

The effectiveness of early intensive BP lowering in routine clinical practice will depend on better understanding the barriers and facilitators of changing systems for delivering such care using streamlined protocols and quality improvement strategies. Planned extensions of INTERACT2 include studies of very early pre-hospital paramedical initiation of BP lowering therapy and multifaceted Health Systems Intervention strategies designed to reconfigure systems of care to enhance delivery of early BP lowering treatment across a range of health care settings. Effective implementation of complex interventions requires system changes in clinical practice.

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1599
WFN15-1856
Neuroimaging MT 9.2 - Cerebrovascular Imaging
Brain imaging in patients with transient ischemic attack

F. Purroy. *Stroke Unit. Clinical Neurosciences Group, Hospital Universitari Arnau de Vilanova. IRBLleida, Lleida, Spain*

Since the new tissue definition of transient ischemic attack (TIA), diffusion weighted imaging (DWI) has become essential for the management of patients with transient neurological symptoms. Despite transient of symptoms up to one out of three patients had acute ischemic lesions. But, what is more important, classically defined TIA patients (duration of symptoms less than 24 hours) who have abnormalities on DWI have a higher risk of early recurrent ischemic events than those without such abnormalities. It has been demonstrated how the incorporation of neuroimaging data in the clinical prognostic scores, like ABCD2 score, improves its predictive power. Furthermore, not only the presence of acute ischemic lesions but also the pattern of distribution matters. Patients with scattered lesions due to large artery atherosclerosis have the highest risk of stroke recurrence. Moreover, perfusion imaging with perfusion MRI or CT perfusion may improve the detection of ischemic lesions. The combination of DWI and perfusion MRI can document the presence of a cerebral ischemic lesion in approximately half of all patients. Finally, other neuroimaging parameters different from DWI, such us

the presence cerebral microbleeds, have emerged as novel predictors of stroke recurrence.

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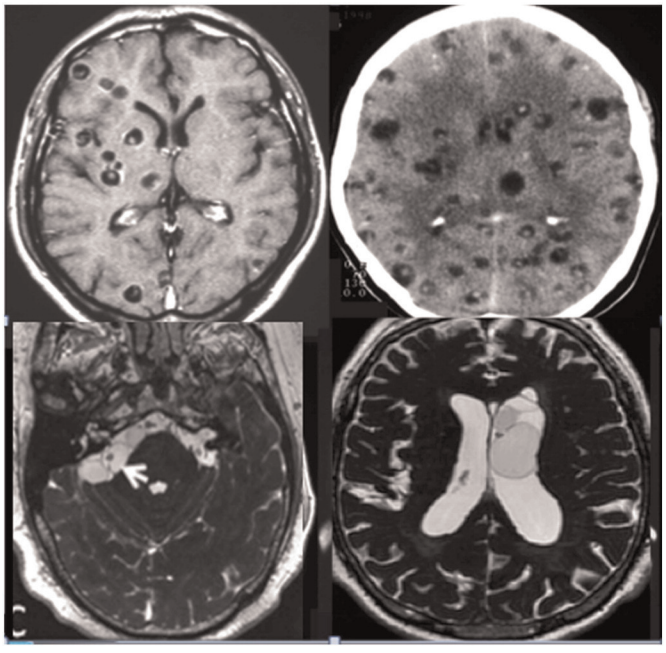
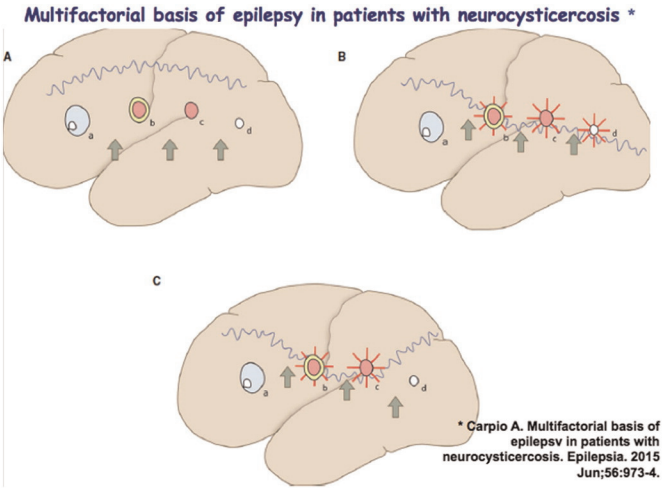
1600
WFN15-1794
Neurological Infections MT 12.2 - Parasitic and Fungal Disorders
Neurocysticercosis

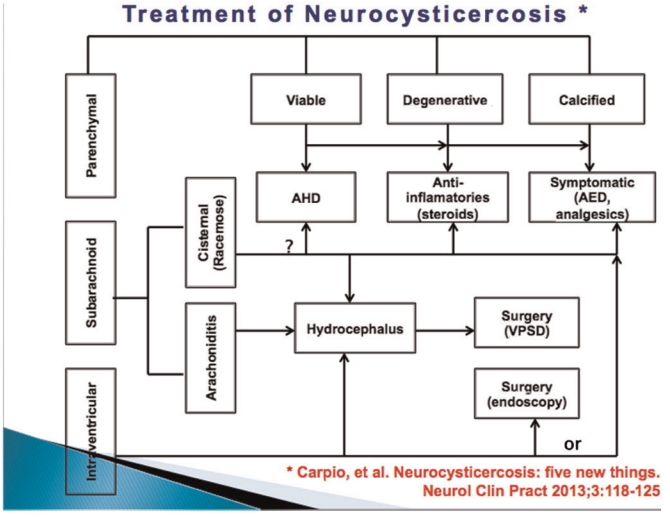
A. Carpio. *School of Medicine, University of Cuenca, Cuenca, Ecuador*

Neurocysticercosis (NC), the most common parasitic brain disease worldwide, is still a cause of unacceptable morbidity and mortality in endemic areas and is an emerging public health problem in high-income countries. Its clinical heterogeneity is related to localization, number and stage of evolution of the parasites, gender, age and intensity of the host brain inflammatory reaction.. In Inflammation is the main phenomenon responsible of symptomatology. Control of the inflammatory reaction in NCC is under debate today: it can surely reduce frequency of some complications, but it can also contribute to the poor clinical evolution of some patients. Acute symptomatic seizures are the most common symptom in patients with parenchymal parasites, but most do not evolve into epilepsy. Co-existence of cysticercus antibodies does not necessarily imply causation of epilepsy. Because of the high prevalence of each condition in developing countries, a causal as well as fortuitous relationship between the two pathologies might exist.

NC diagnosis is based mainly on neuroimaging. New imaging techniques have improved detection of the scolex and visualization of cysts in the CNS. Immunological testing could be useful, particularly when imaging is equivocal. A study to assess the reliability, sensitivity and specificity of new set of diagnostic criteria is currently under way, which might allow early detection of, and differentiation between, parasites located in the parenchyma or in the extraparenchymal compartments. Based on disappearance of parasites, antihelminthic drugs as currently used are effective in approximately one third of patients with parenchymal viable cysts.







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1601
WFN15-1873
Neurological Infections MT 12.2 - Parasitic and Fungal Disorders
Trypanosomiasis

M. Bentivoglio. *Dept Neurological and Movement Sciences, University of Verona, Verona, Italy*

Nervous system infections caused by the flagellate protozoan trypanosomes include American trypanosomiasis or Chagas disease, caused by the intracellular *Trypanosoma cruzi*, transmitted by many species of triatomine bugs, and human African trypanosomiasis (HAT), also called sleeping sickness, caused by the extracellular *Trypasonoma brucei*, inoculated through bites of tsetse flies (genus *Glossina*). During its chronic phase *T. cruzi* infection attacks mainly the autonomic nervous system, with heart and gastrointestinal tract denervation. Chagas disease, which is highly invalidating, remains a public health issue in Latin America despite recent progress in vector control. In HAT, the first, haemolymphatic stage evolves into the second, meningoencephalitic stage, targeting the central nervous system when parasites cross the blood-brain barrier. HAT, which has two forms caused by *T. brucei gambiense* and *rhodesiense*, respectively, has a focal distribution in sub-Saharan Africa, mostly in resource-poor and politically unstable settings. Both forms of HAT

are fatal if left untreated and drugs currently available to cure the second stage are very toxic. Despite the recent decline in the number of reported new HAT cases, diagnostic progress in HAT staging and therapy are urgently needed. Both Chagas disease and HAT are included in the group of "neglected tropical diseases" which have long been absent from the public health agenda in wealthy countries. Both these diseases pose intriguing problems on mechanisms by which parasite-derived molecules and host immune response interact with nervous system cells. It is time for clinical and basic neuroscience to be at the forefront in the fight against these diseases.

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1602
WFN15-1900
Stroke MT 3.3 - The Long-term Perspective
Secondary prevention after stroke – proven strategies and controversial issues

G.A. Donnan. *N/A, The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia*

There have been remarkable advances in secondary stroke prevention over the last 30 years. We now have evidence that early risk of recurrent stroke after an index event is much higher than previously realised with about 10% risk at 14 days. The overall risk at one year is about 11%, 26% at five years and 40% at 10 years. The categories of intervention of proven benefit now include management in acute specialty units, use of a variety of antiplatelet agents, anticoagulation and carotid revascularisation. The benefit of these interventions vary from a relative risk reduction for recurrent stroke of around 80% for management in acute specialty units versus standard outpatient clinics to around 12% for aspirin versus placebo.

The introduction of these secondary prevention interventions has significant implications for public health worldwide given that recurrent strokes account for 25-30% of all strokes. If the interventions were uniformly applied the potential to reduce the burden of stroke by around 25% overall exists. Given that, recurrent stroke still occurs in spite of these interventions, there is obviously room for further improvement.

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1603
WFN15-1933
Stroke MT 3.3 - The Long-term Perspective
Brain recovery – what is the future?

N. Ward. *Sobell Department of Motor Neuroscience, UCL Institute of Neurology, London, United Kingdom*

Stroke is the commonest cause of severe physical disability in the world. Inability to use the arm and hand is a major contributor to this problem. Currently, recovery of arm/hand movement is unpredictable and it is not clear why some stroke survivors recover whilst others do not. After stroke, there is little restoration of neural tissue, and so reorganization of surviving neural networks appears to be important for recovery of function. Optimal recovery of movement therefore depends on at least two things. Firstly, preservation of neural pathways that convey sensory signals into the brain and instructions to move out of it. Secondly, a post-stroke increase in the potential for neuroplasticity that allows surviving brain regions to reorganise into effective networks capable of supporting arm and hand function. Failure of either will lead to failure of recovery. Advances in brain imaging will soon allow us to examine changes in organization of the human brain after stroke at multiple levels, ranging from large scale networks to alterations in synaptic physiology. These techniques will provide the appropriate intermediate level of description with which to bridge the gap between what we know about recovery after stroke from animal models compared to what we know from studies of behaviour in humans. A more detailed knowledge of how these processes are related to impairment and recovery following stroke will provide a mechanistic framework for understanding how to treat our patients more effectively.

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1604
WFN15-1635
Neuroimaging MT 9.3 - Dementia
Parkinson disease imaging

D.J. Brooks. *Nuclear Medicine, Aarhus University, Aarhus, Denmark*

80% of Parkinson's disease patients develop dementia if they survive more than 20 years with the disorder. Mechanisms include cortical Lewy body disease, loss of frontal dopamine and cortical acetylcholine, amyloid and tau deposition. In cognitively intact PD MRI shows cortical thinning and changes in white matter diffusivity. Functional MRI shows loss of resting state basal ganglia and default mode network connectivity which progresses as cognitive problems develop. Levels of thinning correlate with memory and executuve difficulties.

F-dopa PET shows loss of frontal dopamine in PD with dementia (PDD). Acetylcholine esterase PET markers show posterior cortical loss of cholinergic function in early PD which spreads to become global in PDD. Amyloid deposition can be detected in a minority of non-demented PD cases and its presence is associated with a more rapid progression to PD-MCI and PDD. It is now possible to detect tau tangles in PD and work is on-going to determine their contribution to the cognitive problems of these patients.

Finally PD is associated with inflammation in the form of microglial activation. Cortical inflammation is present even in early PD and levels correlate with performance on verbal fluency and exeutive tasks. PDD cases show more widespread inflammation suggesting microglial activation may drive the dementing process.

In summary, dementia in PD is multifactorial but imaging can be used to characterise its nature in each individuals and help rationalise a personalised therapeutic approach.

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1605
WFN15-1792
Neuroimaging MT 9.3 - Dementia
Imaging in Alzheimer disease prevention

J. Masdeu. *Neurology, Weill Cornell Medical College, Houston, USA*

Neuroimaging comprises a powerful set of instrumentsto diagnose the different causes of dementia, clarify their neurobiology and monitor their treatment. Magnetic resonance imaging (MRI) depicts volume changes with neurodegeneration and inflammation, as well as abnormalities in functional and structural connectivity. MRI arterial spin labeling allows for the quantification of regional cerebral blood flow, characteristically altered in Alzheimer's disease, diffuse Lewy-body disease and the frontotemporal dementias. Positron emission tomography allows for the determination of regional metabolism, with similar abnormalities as flow, and for the measurement of β-amyloid and abnormal tau deposition in the brain, as well as

regional inflammation. These instruments allow for the quantification *in vivo* of most of the pathological features observed in disorders causing dementia. Importantly, they allow for the longitudinal study of these abnormalities, having revealed, for instance,that the deposition of β-amyloid in the brain can antecede by decades the onsetof dementia. Thus, a therapeutic window has been opened and the efficacy of immunotherapies directed at removing β-amyloid from the brain of asymptomatic individuals is currently being tested. Tau and inflammation imaging, still in their infancy, combined with genomics, should provide powerful insights into these disorders and facilitate their treatment.

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1606
WFN15-1939
Neuroimaging MT 9.3 - Dementia
Imaging of network disruption in dementia

F. Agosta[a], M. Filippi[b]. [a]*Neuroimaging Research Unit, Scientific Institute San Raffaele, Milan, Italy;* [b]*Neuroimaging Research Unit, Scientific Institute San Raffaele Vita-Salute San Raffaele University, Milan, Italy*

The clinical use of magnetic resonance imaging (MRI) findings has dramatically changed our ability to diagnose accurately dementia. Despite variation and overlap of atrophy patterns, the assessment of regional atrophy on structural MRI may aid in discriminating different clinical phenotypes. Preliminary studies in pathologically proven cases suggested that distinct patterns of tissue loss could assist in predicting *in vivo* the pathological subtype. In addition, although the cellular mechanisms underlying the stereotypical progression of pathology in neurodegenerative dementia are incompletely understood, increasing evidence indicates that misfolded protein aggregates can spread by a self-perpetuating neuron to neuron transmission. Novel neuroimaging techniques can help elucidating how these disorders spread across brain networks. Recent knowledge from structural and functional connectivity studies suggests that the relation between neurodegenerative diseases and distinct brain networks is likely to be a strict consequence of diffuse network dynamics. Diffusion tensor MRI also showed that measurement of white matter tract involvement can be a valid surrogate to assess the *in vivo* spreading of pathological proteins in these conditions. Characterizing network breakdown in neurodegenerative diseases will help anticipate and perhaps prevent the devastating impact of these conditions.

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1607
WFN15-1638
Neurological Infections MT 12.3 - Neuroinfection Update
Post infectious and vaccine related neurological conditions

J. Chopra, M. Goyal, V. Lal. *Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh, India*

Posinfectious and vaccine related neurological disorders constitute a clinically and radiologically heterogeneous group of immune mediated inflammatory disorders, characterized pathologically by a widespread demyelinating process involving the white matter of brain and spinal cord. These disorders, also known as acute disseminated encephalomyelitis (ADEM), though characteristically monophasic can rarely have a recurrent or multiphasic course as well. The commonest viral infections which are associated with ADEM are measles (1/1000), varicella (1/10000) and rubella (1/20000). Vaccination related ADEM is seen commonly following Pasteur vaccine (1/1000), smallpox vaccine (5/ million) and Japanese Encephalitis vaccine (0.2-2/ 100000). The main mechanism invoked for pathogenesis of these disorders is believed to be molecular mimicry, though several other mechanisms are also thought to contribute to pathogenesis, at least in parts. The common presentation includes an acute encephalopathy with multifocal neurological signs, often 1-2 weeks after a nonspecific viral infection or vaccination. Though characteristically both brain as well as spinal cord are involved simultaneously, variants which may affect only a part of neuraxis are well described. The true incidence of ADEM remains undetermined, but is supposed to be higher in developing than developed countries due to high prevalence of infections. Diagnosis relies on a combination of clinical and radiological findings in absence of specific biomarkers. The mainstay of treatment is immunosuppressive therapy in form of steroids, intravenous immunoglobulin and plasmapheresis in varying combinations. Prognosis is usually good with complete recovery in a significant number of cases.

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1608
WFN15-1836
Neurological Infections MT 12.3 - Neuroinfection Update
Prion encephalopathies

H. Mizusawa. *Neurology, National CenterHospital National Center of Neurology and Psychiatry, Tokyo, Japan*

Prion disease is a group of diseases which are caused by abnormal Prion protein (PrP^{Sc}) transformed from normal Prion protein (PrP^{C}) in the brain. PrP^{Sc} is transmissible to other humans and animals. It is a very rare and fatal disease characterized by rapidly progressive dementia and other neurological manifestations. The neuropathology includes neuronal loss, astrogliosis and spongiform change. Therefor Prion disease is also called as transmissible spongiform encephalopathy (TSE). It is classified into 3 categories according to origins of PrP^{Sc}, sporadic Creutzfeldt-Jakob disease (CJD) by obscure origin, genetic Prion disease by PrP gene mutation and environmentally acquired Prion disease by known origin. After discoveries of transmissibility and Prion hypothesis, many studies have been performed but there remain important questions, how does PrP^{C} change into PrP^{Sc}, what is the main function of PrP^{C}, how does PrP^{Sc} disturb neurons, and how does Bovine Spongiform Encephalopathy (BES)-Prion gain oral transmissibility to human. We have developed a nation-wide surveillance system and Research Committees on Prion disease in Japan. Many important discoveries related to such activities include RT-QUIC method, plaque type of dura-associated CJD, V180I-genetic CJD and so on. Recently, causative proteins of Alzheimer's disease, Parkinson's disease and other neurodegenerative diseases were reported to be transmissible and self-propagating. They appear very similar to TSE-prion in animal brains. It is the time now for us to internationally cooperate to elucidate the questions and overcome Prion disease.

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1609
WFN15-1647
Neurological Infections MT 12.3 - Neuroinfection Update
Tuberculosis

J. Luis Soto-Hernandez. *Infectious Diseases, National Institute of Neurology and Neurosurgery, Mexico City, Mexico*

Neuroinfection Update Tuberculosis

On March 24, 1882 Robert Koch announced the discovery of the cause of tuberculosis (TB), that day is named the World TB day and

its main 2015 year message is that globally every year 9 million people get sick with TB and 3 million people don't get the care they need. TB is second to HIV/AIDS as the greatest killer worldwide by an infectious agent, and causes one fourth of all HIV-related deaths. In 2013 an estimated 480 000 people developed multidrug resistant TB (MDRTB). A study of 14 years period of all TB cases diagnosed in California found that 9% of patients died during antituberculous therapy and one half of deaths occurred before 60 days of treatment in advanced, meningeal and disseminated forms of TB. Patients treated by private care providers had 3 times increase in risk of death, pointing that public health departments need a strong partnership with private care providers for early detection, adequate treatment and follow up of TB patients. Most cases of MDRTB result from inappropriate drug choice, poor adherence or treatment interruptions. MDRTB is a major challenge for TB eradication and the cost of each new case of MDRTB is 10 to 15 times higher than the cost of treatment of a drug sensitive TB case. All new TB patients need an HIV test and all HIV + patients need screening for TB. When possible, susceptibility to first-line drugs should be performed in all initial isolates of new TB patients.

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1610
WFN15-1845
Neurocritical Care MT 4.1 - Essential Concepts in Neurocritical Care
Introduction to emergency neurological life support (ENLS)

J. Hemphill. *Neurology, University of California San Francisco, San Francisco, USA*

Emergency Neurological Life Support (ENLS) represents a new paradigm in education regarding the management of patients with neurological emergencies during the initial "golden hour" after occurence. Extensive training exists for the management of acute cardiac and other resuscitation emergencies with programs such as ACLS (Advanced Cardiac Life Support) and ATLS (Advanced Trauma Life Support) gaining wide acceptance. However, neurological education has lagged behind these efforts. The goal of ENLS is to create a set of standard protocols that can be used by early care providers in the pre-hospital, emergency department, and intensive care unit settings, with emphasis on evidenced-based practices and guidance on best practices when high quality evidence is lacking. ENLS consists of a set of 13 modules that cover a range of neurological emergencies including stroke, status epilepticus, central nervous system infections, and neurotrauma. Importantly, ENLS also includes modules on aspects of care that cross disease categories, such as airway management and evaluation of the comatose patient. ENLS was developed by the Neurocritical Care Society and consists primarily of an online training program that includes video presentations, slide sets, standardized protocols, and a test after completion of each module. Each module was developed by a team that is led by both a neurointensivist and an emergency medicine physician. In-person didactic training may be used to augment the online program. After successful completion of all module tests, one becomes "ENLS certified."Additionally, training and certification is also available to those who wish to host an ENLS in-person course ("train-the-trainer" program). All ENLS protocols are available online worldwide for no charge at http://enlsprotocols.org/.

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1611
WFN15-1904
Neurocritical Care MT 4.1 - Essential Concepts in Neurocritical Care
Diagnosis and evaluation of coma in the emergency department and ICU

T. Bleck. *Neurological Sciences, Rush Medical College, Chicago, USA*

The diagnosis and evaluation of coma in the emergency department and ICU depends primarily on the physical examination. The four major components of the exam include pupillary reflexes, eye movements, the respiratory pattern, and the response to stimulation. Using these findings, one can determine whether the brainstem or the cortex is most likely responsible for the patient's coma. Signs of brainstem dysfunction merit emergent imaging, usually with CT, to help detect mass lesions or consideration of thrombolysis in basilar artery occlusion. Preserved brainstem function leads to a workup for diffuse or bilateral hemisphere conditions. In the latter circumstance, biochemical and electrophysiologic studies are usually more revealing. Examples from various causes of coma will be demonstrated.

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1612
WFN15-1816
Neurocritical Care MT 4.1 - Essential Concepts in Neurocritical Care
Management of refractory increased intracranial pressure

T. Steiner. *Department of Neurology, Klinikum Frankfurt Höchst, Frankfurt, Germany*

Before the treatment comes the monitoring of intracranial pressure (ICP) and the discussion on thresholds that induce therapy which may differ in different diseases. There are several ways of monitoring ICP. The only randomized controlled trial (RCT) was performed for patients with traumatic brain injury (TBI) and that study measured ICP within the parenchym and used an ICP of 20 mmHg as treatment threshold. But ICP may develop differently and may be monitored and treated differently according to different indications (e.g. in patients with encephalitis, focal space occupying lesions like tumors, ischemic stroke or hemorrhagic stroke) is not clear. For patients with intracranial haemorrhage (ICH), a small sub-study that looked at ICP-recordings through external ventricular drainages (EVD) found 90% of ICP readings below 20 mmHg, and about 2% above 30 mmHg. The percentage of readings above 30 mmHg was independently associated with an increased mortality ($p < 0.001$) and poor modified Rankin Scale score at 30 days ($p = 0.01$). The presentation will demonstrate different ways of ICP-monitoring and ways to treat elevated ICP according to different types of pathology.

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1613
WFN15-1819
Neuromuscular Disorders MT 7.1 - Advances in the Diagnosis of Neuropathies
Antibody testing in inflammatory neuropathies: what and when to test

E. Nobile-Orazio. *Medical Biotechnology and Translational Medicine 2nd Neurology, Milan University Humanitas Clinical and Research Institute, Rozzano Milan, Italy*

Chronic immune-mediated neuropathies are deemed to be caused by an immune response against nerve. They include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN), neuropathies associated with monoclonal gammopathy and paraneoplastic neuropathies. A number of antibodies have been associated with these neuropathies even if their pathogenetic and diagnostic relevance is not always defined. Antibodies to different myelin antigens have been reported in CIDP even if they were not consistently associated with this diagnosis. Attention has been recently devoted to antibodies against myelin or axonal proteins at the node of Ranvier including contactin-1 (CNTN1) [20] and neurofascin-155(NF155). Even if they are only found in 5% of the patients, they are associated with some distinctive clinical features and response to therapy supporting the hypothesis that different antibodies may underlie different forms of CIDP and response to therapy. IgM antibodies to the ganglioside GM1 have been reported in 40-50% of patients with CIDP. These antibodies are not specific for MMN as they can be found in 5-10% of MND patients. Testing for the combination of GM1 with galactocerebroside increases the sensitivity of anti-GM1 testing to approximately 75% in MMN patients with a marginal reduction of their specificity. Almost 50% of patients with neuropathy associated with IgM monoclonal gammopathy have antibodies to the myelin-associated glycoprotein (MAG). These antibodies are almost invariably associated with a demyelinating neuropathy and are usually associated with a benign prognosis. Other anti-neural antibodies have been reported in this neuropathy even if only those to GQ1b were associated with a typical form and response to immune therapy.

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1614
WFN15-1902
Neuromuscular Disorders MT 7.1 - Advances in the Diagnosis of Neuropathies
Genetic testing in inherited neuropathies: what and when to test

M.M. Reilly. *MRC Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery and ION < University College London, London, United Kingdom*

Genetic testing in inherited neuropathies: What and when to test
Professor Mary M Reilly, MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, Queen Square, London UK

There are now more than 80 identified causative genes for the inherited neuropathies. This makes it challenging for clinicians to decide which genes to test and in what order for an individual patient.

Despite the advent of next generation sequencing, careful phenotyping is still the first step in acheiving an accurate genetic diagnosis. Most diagnostic laboratories are using next generation sequencing techniques (NGS) and have developed disease-specific, or mulit-gene, testing panels which employ NGS to regions of the exome that contain known inherited neuropathy genes. These disease-specific panels are currently the best method for simultaneously screening a large number of CMT genes and, until the coverage of WES (whole exome sequencing) and WGS (whole genome sequencing) improves, they are likely to remain a comprehensive tool in genetic diagnosis of patients with CMT.

In the case of a patient with sporadic or autosomal dominant CMT1 and with the typical homogenous motor conduction slowing, we still recommend testing for the 17p duplication with conventional methods as a first step. Otherwise we use a targeted CMT panel approach depending on the phenotype. We use WES for those patients who still do not have a genetic diagnosis but this currently is still done in the research side of our service. Careful in depth phenotyping remains crucial not only in choosing what tests to do but in helping to determine if variants identified by genetic testing are pathogenic which is currently the major diagnostic challenge.

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1615
WFN15-1828
Multiple Sclerosis and other Demyelinating Diseases MT 6.1
Monitoring drug safety in clinical practice

P. Vermersch. *Service de Neurologie Générale et Pathologie Neuro-Inflammatoire, University of Lille Nord de France, Lille, France*

In individual MS patients, the uncertainty of the benefit risk ratio makes the treatment decicions complex. To optimally monitor the treatments, risk managment plans or minimization strategies are highly recommended. Some new drugs are considered more effective but associated with some safety issues. Mitoxantrone was one the first example of the need to monitor with regular blood testing because of the risk of leukemia and a routine assessement for any cardiac event not only prior to each dose but also several years after. Fingolimod also appears to be associated to a small risk of cardiac event detected potentially after the first dose. Blood testing including liver enzymes are also recommended with fingolimod and with the new oral drugs. With natalizumab, the main concern is the risk of PML. Recent data have made it possible to stratify this risk on the basis of anti-JC antibody virus testing, duration of drug exposure, and former use of immunosuppressants. Many MS experts recommend to discontinue natalizumab in patients with a high JCV index after 18 months or 2 years. A systematic MRI assessment may contribute to early diagnosis. The principal adverse effect of alemtuzumab is secondary autoimmunity affecting the thyroid gland in 30% of patients but less commonly causing immune thrombocytopenic purpura. Blood test monitoring is mandatory each month during the treatment period but also many years later. In many centres, MS specialist nurses play a key role in supporting patients about treatment options as well as monitoring patients.

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1616
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Multiple Sclerosis and other Demyelinating Diseases MT 6.1
Risk stratification of second –line therapies

O. Fernandez. *Neurosciences, Institute of Neurosciences, Service of Neurology, Hospital Universitario Regional de Málaga, Instituto de Invetigación Biomédica de Málaga (IBIMA), Málaga, Spain*

Risk stratification of second –line therapies
Oscar Fernández
Instituto de Neurociencias Clínicas
Hospital Universitario Regional de Málaga
Instituto de Investigación Biomédica de Málaga (IBIMA)
oscar.fernandez.sspa@gmail.com
Oral presentation

The treatment of multiple sclerosis is becoming more complex as many new therapies are becoming available. By now we have at least 12 different therapies, making the clinical decision of which drug or therapy have to be used in a given patient more and more difficult, as clinicians do not have evidence based measures to take that decision. The direct comparison, head to head, is very scant between the

different therapies and indirect comparisons are really not of value, due to the fact of the differences between the populations included in the different studies.

One way to reduce uncertainty has been the building of a construct called lines of therapy, starting with drugs/therapies considered to have maybe less efficacious but being otherwise less toxic. Therefore we have first line or platform therapies (interferon beta, glatiramer acetate, dimethylfumarate, teriflunomide), second line (natalizumab, fingolimod, alemtuzumab, mitoxantrone), third line (experimental therapies as rituximab, ocrelizumab, ofatumumab, etc.) and even a fourth line could be considered (autologous hematopoietic stem cell transplantation).

In this lecture the risk associated with those therapies considered of second line or higher will be addressed and some clues given to practicing physicians to try to reduce, as much as possible, the incidence of the severe adverse effects that could be associated with their usage.

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1617
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Neurocritical Care MT 4.2 - Topics in Neurocritical Care I
Super-refractory status epilepticus

T. Bleck. *Neurological Sciences, Rush Medical College, Chicago, USA*

Shorvon defined the progressive phases of drug resistance in status epilepticus as (1) established status epilepticus (ESE: e.g., failure of a benzodiazepine), refractory status epilepticus (RSE: e.g., failure of another conventional antiseizure drug), and super-refractory status epilepticus (SRSE; e.g., failure of subsequent therapies, often requiring prolonged infusions of general anesthetic agents). In the SRSE patient, three simultaneous aims must be pursued: termination of ongoing seizure activity, prevention of its recurrence, and management of associated conditions and complications. When attempts to wean general anesthetics fail, the addition of conventional antiseizure drugs, often including phenobarbital, may be useful. Less frequently employed drugs such as ketamine are sometimes useful. A phase 3 trial of allopregnenolone should begin soon. Conventional antiseizure drugs are also typically to prevent recurrence, even if they were unsuccessful in terminating RSE. Nonpharmacologic treatments such as hypothermia and electroconvulsive therapy are sometimes useful. Attention to the etiology of SRSE ('source control') is also necessary. Autoimmune encephalitides are increasingly recognized in these patients and mandate immunotherapy. The role of anti-inflammatory therapy in other SRSE patients remains to be determined. Complications such as rhabdomyolysis and hyperthermia require management. Despite the severity of this condition, and its often exceptionally long duration (counted in months), good outcome have been reported in over ⅓ of published cases.

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1618
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Neurocritical Care MT 4.2 - Topics in Neurocritical Care I
Acute neuromuscular respiratory failure

A. Rabinstein. *Neurology, Mayo Clinic, Rochester MN, USA*

Acute neuromuscular respiratory failure can be divided into primary and secondary forms. Patients with primary neuromuscular respiratory failure are most often admitted for the neuromuscular disease, and it is not uncommon for that disease to be previously known (such as myasthenia gravis or motor neuron disease). Secondary neuromuscular respiratory failure develops in the hospital and affects critically ill patients, most often after septic shock with multiorgan failure. Recognizing the cause of the neuromuscular respiratory failure is crucial because patients with unknown cause have poor prognosis. In terms of management, the initial assessment of the patient should include a focused physical examination with special attention to the diaphragmatic function (diaphragmatic insufficiency best manifested by paradoxical breathing pattern), a chest film, arterial blood gases and bedside respiratory function tests. Decisions on triaging and ventilation will be influenced by the cause of the weakness. Patients with Guillain-Barre syndrome should be intubated electively when they have experienced a rapid course or have signs of dysautonomia. In contrast, patients with myasthenic crisis are best managed with non-invasive ventilation (BiPAP mask), which can avert intubation and invasive mechanical ventilation if initiated promptly and, when successful, can drastically reduce the length of ICU stay.

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1619
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Neurocritical Care MT 4.2 - Topics in Neurocritical Care I
Fulminant bacterial meningitis

A. Rabinstein. *Neurology, Mayo Clinic, Rochester MN, USA*

Fulminant meningitis is characterized by its rapid course with compromise of the level consciousness. It represents the most severe form of acute bacterial meningitis. These cases should be managed with immediate initiation of broad antibiotic coverage (third generation cephalosporin, vancomycin and, in select cases, ampicillin) and dexamethasone should be started concurrently with the first dose of the antibiotics. Older and immunosuppressed patients, those with sepsis syndrome and multiorgan failure, and low cellular reaction on the cerebrospinal fluid (leukocytes < 500 per mm3) have increased risk of developing a fulminant course. Complications can include global brain edema, hydrocephalus and cerebral ischemia or hemorrhage from vasculitis. In-hospital mortality from fulminant meningitis is high, but survivors have good chances of returning to their previous level of function. Therefore, aggressive management in the ICU is strongly advised.

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1620
WFN15-1785
Neuromuscular Disorders MT 7.2 - Novel issues in neuropathies
Advances in the diagnosis and treatment of
Guillain-Barre Syndrome

R. Hughes. *Cochrane Neuromuscular Disease Group, Institute of Neurology, London, United Kingdom*

The diagnosis of Guillain-Barré syndrome (GBS) remains clinical, involving exclusion of many other causes of acute flaccid paralysis, with no diagnostic blood tests. Cerebrospinal fluid is commonly and neurophysiological tests sometimes normal in the first week. MRI scanning usually shows post-gadolinium nerve root enhancement, useful but not specific in difficult diagnostic situations, especially in children. The Brighton international consensus guidelines codify diagnostic probability for epidemiological purposes. Distinguishing GBS from the acute onset of a more chronic neuropathy remains difficult. Recognition of subtypes requires neurophysiological studies.

Early motor nerve conduction block occurs in both acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) making repeat studies necessary. New methods seek to make the distinction earlier. Antibodies to gangliosides GM1, GD1a and GalNacGD1a are especially common in AMAN and to GQ1b in Fisher syndrome. Glycoarrays detect antibodies to ganglioside-glycolipid complexes also in AIDP. New studies explore the role of antibodies to nodal and paranodal proteins. Prognostic algorithms now allow identification of poor prognosis at an early stage, enabling selection of high risk cases for clinical trials. New Rasch ordered disability and impairment scales provide improved outcome measures for clinical trials and clinical practice. Trials of a second intravenous immunoglobulin course and of the complement inhibitor eculizumab use both. Cochrane reviews recognise the importance of pain and need for rehabilitation during and after the acute stage. The dearth of research on both is a challenge. The International Guillain-Barré syndrome outcome study (IGOS) www.gbsstudies.org and new trials should provide the answers.

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1621
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Neuromuscular Disorders MT 7.2 - Novel issues in neuropathies
Neuropathy in leprosy: an unknown disease in several countries

O. Nascimento. *Neurology, Universidade Federal Fluminense, Rio de Janeiro, Brazil*

Leprosy is essentially a chronic infectious neurological disease. It is one of the most common treatable peripheral neuropathies. *Mycobacterium leprae* is the infectious agent and the different clinical presentations are determined by the quality of the host immune response. Early detection of leprosy neuropathy and treatment are the most important steps in preventing deformity and disability. Seventeen countries reported more than 1000 new cases, representing 94% of the new globally detected cases (WHO, 2009). Some sporadic cases can be seen in countries receiving immigrants from underdeveloped countries. In a North and South America Peripheral Neuropathy Project we have observed a relative higher percentage of leprosy in the group of infectious neuropathy, respectively 26/53 (49%), and 39/141(28%), when comparing both USA and our patients in Brazil. European countries are also not free of these sporadic cases. The early recognition of the clinical leprosy presentation is essential. Mononeuritis and mononeuritis multiplex are the most common. The frequent anesthetic skin lesions are absent in the pure neuritic form. There are clinical presentations with severe neuropathic pain. Leprous late-onset neuropathy (LLON) clinical presentation should be considered facing a patient who develops an inflammatory neuropathy many years after a previous skin leprosy treatment. A predominant demyelinating lesion is seen in the early stages, so we should take into account that leprosy can mimic other chronic inflammatory neuropathies. In conclusion, leprosy neuropathy is an overlooked diagnosis that may occur even in developed countries and can mimic or be in association with several acquired and hereditary neuropathies.

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1622
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Neuromuscular Disorders MT 7.2 - Novel issues in neuropathies
New therapeutic options in chronic inflammatory neuropathies

J. Leger. *National Referral Center for rare Neuromuscular Diseases, University Hospital Pitié-Salpêtrière and University Pierre et Marie Curie, Paris, France*

The spectrum of inflammatory neuropathies comprises an acute form, Guillain-Barré syndrome (GBS) and chronic forms, mainly chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy with persistent conduction block (MMN), and polyneuropathy associated with IgM monoclonal gammopathy binding to myelin-associated-glycoprotein (IgM anti-MAG neuropathy). These neuropathies have common features, which are clinical and electrophysiological signs indicative of a demyelinating process, raised protein in CSF, the presence in some of them of serum auto-antibodies binding to recognized antigens of the peripheral nerve myelin, and signs of demyelination/remyelination in nerve biopsies. Chronic inflammatory neuropathies need to be distinguished on defined criteria, because the response to treatment may differ according to the type of the neuropathy. For example, MMN and IgM anti-MAG neuropathy do not respond to corticosteroids, while CIDP may respond either to corticosteroids, plasma exchange or high-dose intravenous immunoglobulin (IVIg) /subcutaneous immunoglobulin (SCIg). Guidelines have been edited in 2006, then revised in 2010, by a joint task force of the European Federation of Neurological Societies and of the Peripheral Nerve Society, on management of respectively CIDP, MMN and paraproteinemic demyelinating neuropathies. This review will give an update on the therapy of these immune-mediated neuropathies, mainly giving an overview of the various treatment options, and precising the best regimen for immunomodulators to be given for first-line and long-term therapy.

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1623
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Neuromuscular Disorders MT 7.2 - Novel issues in neuropathies
Pure motor neuropathy or lower motor neuron disease: clues to the distinction

R. Guiloff. *Neurology, Imperial College NHS Trust, London, United Kingdom*

The differential diagnosis between pure motor neuropathies and diseases affecting lower motor neurons remains a matter of clinical judgement. It requires a careful analysis of clues from clinical phenotypes and from a number of investigations.

Multifocal motor neuropathy, variants of chronic inflammatory demyelinating polyradiculoneuropathy, radiculopathies and other acquired and inherited motor neuropathies will be contrasted with conditions affecting lower motor neurons including motor neuron disease, forms of spinal muscular atrophy and other diseases affecting anterior horn cells.

The diagnostic contribution of electrophysiology, cerebrospinal fluid examination, imaging, neuropathology, antibody studies, other ancillary investigations and response to therapy will be discussed.

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1624
WFN15-1929
Multiple Sclerosis and other Demyelinating Diseases MT 6.2
Treatment of progressive MS – are we any closer?

A. Thompson. *Faculty of Brain Sciences, Institute of Neurology Department of Brain Repair and Rehabilitation, London, United Kingdom*

Over the last twenty years, Multiple Sclerosis (MS) has moved from being an untreatable condition, with few therapeutic options to a position of active management underpinned by a range of oral and injectable treatments. These advances however are restricted to

patients with the relapsing/remitting form of MS (RRMS), while for those with the progressive forms of the condition there are virtually no treatments available. These patients constitute over 50% of the 2.3 million people with MS worldwide and addressing their needs is all the more important as progression is the main determinant of disability in MS and carries the greatest economic burden.

The reasons behind this therapeutic vacuum include (1) poor understanding of the mechanisms underlying neurodegeneration and the identification of potential treatment targets (2) lack of clarity in defining the progressive phenotype (3) developing appropriate trial design with effective biomarkers and clinical outcomes (4) the need for improved symptom management and rehabilitation.

A number of initiatives have emerged including the International Progressive MS Alliance (PMSA), which has united MS Societies and clinical academics worldwide. We are now seeing important insights into pathological mechanisms, greater clarity over clinical phenotypes and innovative trial designs. Results from clinical trials have been mixed, with some cause for optimism. However, the imminent outcome from several major studies has the potential to change the direction of travel irrevocably.

If we are to have the same impact on progressive MS as seen in RRMS, we will need a focused, global and consistent approach going forward.

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1625
WFN15-1884
Multiple Sclerosis and other Demyelinating Diseases MT 6.2
The role of hormones and gender in MS

D. Sadovnick[a], R. Bove[b], T. Chitnis[b]. [a]*Medical Genetics and Neurology, University of BC, Vancouver, Canada;* [b]*Neurology, Harvard University, Boston, USA*

The etiology of multiple sclerosis(MS) remains unclear but genes, environment and interactions thereof are knownto have roles. Initially, it wasbelieved that MS either had a male preponderance or that both sexes wereequally affected. It was only in themid-1950's that the female preponderance was been recognized and for a longtime said to be about a 1.5-1.8:1 sex ratio. More recently, the sex ratio hasincreased to over 3:1 in most regions with the increase being attributed onlyto a rise in the number of affected females.

There also appears to be a maternalfactor in the risk to develop MS, as shown by studies in ½ siblings and twinsas well as HLA transmission, even when the mother is unaffected.

Of particular interest is MS duringgestation and after delivery. Compared to pre-pregnancy relapse rates, pregnantwomen with relapsing/remitting MS tend to have reduced MS relapses duringgestation, particularly in the third trimester with an increased relapse rateafter delivery. It remains unclear whythis occurs but a role for hormones has been indicated. For example, there is asharp decrease in estrogen levels at delivery and the loss of the immunosuppressivestate of pregnancy is probably important.

This talk will focus on the gender andhormonal issues as related to MS susceptibility disease course; thuspotentially impacting MS pathophysiology, prevention and treatment.

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1626
WFN15-1916
Multiple Sclerosis and other Demyelinating Diseases MT 6.2
Our current understanding of neuromyelitis optica and its spectrum

K. Fujihara. *Department of Multiple Sclerosis Therapeutics, Tohoku University, Sendai, Japan*

More than a century has passed since the first report of neuromyelitis optica (NMO) or Devic's disease. The discovery of NMO-specific aquaporin-4 (AQP4)-IgG has truly accelerated clinical and experimental research of NMO and contributed to establishing "NMO spectrum disorders (NMOSD)", a wider clinical spectrum than a typical severe opticomyelitis in the original description. The prevalence of NMOSD is estimated to be 0.5 ~ 5/100,000 in most parts of the world.

The international consensus diagnostic criteria of NMOSD were recently published (Wingerchuk DM et al, Neurology 2015). The new criteria are based on AQP4-IgG serostatus (1. NMOSD with AQP4-IgG, and 2. NMOSD without AQP4-IgG or with unknown serostatus). The diagnostic criteria are expected to facilitate early diagnosis and treatment to improve the long-term prognosis. A fraction of patients with AQP4-IgG-seronegative NMOSD are myelin oligodendrocyte glycoprotein (MOG)-IgG-seropositive, and they have some unique features.

NMO has long been discussed in the category of inflammatory demyelinating diseases, but accumulated evidence strongly suggests that AQP4-IgG-associated NMOSD is an autoimmune astrocytopathic disease. Meanwhile, MOG-IgG-seropositive NMOSD appears to be an inflammatory demyelinating disease.

A variety of immunesuppressants and monoclonal antibodies are being administered to patients with NMOSD in clinical practice or evaluated in clinical trials. Of particular note is that some disease modifying drugs for multiple sclerosis (MS) can aggravate AQP4-IgG-positive NMOSD, suggesting the importance of early diagnostic distinction between NMOSD and MS. Management of AQP4-IgG-seronegative NMOSD has not been established.

Recent progress of research on NMOSD and the future challenges will be reviewed in the presentation.

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1627
WFN15-1909
Neurocritical Care MT 4.3 - Topics in Neurocritical Care II
Aneurysmal subarachnoid hemorrhage: state of the art

A. Rabinstein. *Neurology, Mayo Clinic, Rochester MN, USA*

Subarachnoidhemorrhage from a rupture aneurysm is a very complex disease. The brain can beinjured from the immediate effects of the acute bleeding, but can also bethreatened by secondary insults hours and days later. Early and delayedsystemic complications are common and can be very serious. The time course of the disease can be divided intoa first phase (from aneurysm rupture to aneurysm treatment) of resuscitationand stabilization and a second phase (from aneurysm treatment to the end of theacute hospitalization) of prevention and treatment of secondary insults. In the first phase, the main complications are hydrocephalus and aneurysm rebleeding. In the second, the priority is to recognize and treat delayed cerebral ischemia, mostly caused by delayed vasospasm. In addition, multiple medical complications can occur, including heart failure from stress cardiomyopathy, infections, hyponatremia, volume contraction from polyuria, and venous thromboembolism. Despite its critical nature, subarachnoid hemorrhage can have a very good prognosis in all but the most severe cases. Achieving a good outcome is highly dependent on the administration of specialized neurocritcal care.

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1628
WFN15-1632
Neurocritical Care MT 4.3 - Topics in Neurocritical Care II
Value of hypothermia after cardiac arrest

L. Castillo. *Intensive Care, Universidad San Sebastian, Santiago, Chile*

The Hypothermia is a thecnics that reduce the body temperature and control to CMRo2 and ameliorate the ICH.

In cardiac arrest the control of temperature and your reduction show in many papers publish in differents journal increase the patients number without severe neurological damage and increase the pátients with minimun neurological failure after cardiac arrest specificly to tachicardia and Ventricular fibrilation.

In the lasts five years also show two very interesting papers that the use of 33 °C or 35 °C degree is the same for the aim the objective, the brain protection after cardiac arrest,however the guidelines are not change yet in the emergency and cardiac field.

I show you this information.

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1629
WFN15-1821
Neurocritical Care MT 4.3 - Topics in Neurocritical Care II
Prognosis of neurological outcome after cardiac arrest

S. Hocker, E. Wijdicks. *Neurology, Mayo Clinic, Rochester, USA*

Despite improving resuscitation practices, neurologicimpairment caused by anoxic-ischemic brain injury during circulatory arrest remainscommon. Important principles in the prognostication of outcome after cardiacarrest include assessing the severity of brain injury, allowing appropriatetime for assessment and excluding confounders. Hypothermia protocols have been increasingly used totreat comatose patients after resuscitation and experience with prognosticationin the setting of therapeutic hypothermia has led to an improved understandingof the impact of sedation, organ injuries and hypothermia itself on brainfunction. Early identification of patients with limited chance for meaningfulneurologic recovery can assist relatives in decision making and avoidinappropriately aggressive treatments, and alternatively identification ofpatients with inconclusive initial assessments provides justification forprolonged observation with repeated assessments. Evidence for predictors ofpoor outcome in adult comatose survivors of cardiac arrest are discussedincluding those treated or not treated with temperature modulation. Knowledgegaps are identified and an evidence based prognostication approach is reviewed.

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1630
WFN15-1809
Neuromuscular Disorders MT 7.3
Genetic strategies to treat inherited muscle disease

K. Davies. *Physiology Anatomy and Genetics, Univesrity of Oxford, Oxford, United Kingdom*

Genetic approaches for thetreatment of inherited muscle diseases have advanced rapidly in recent years.Most of the advances have occurred in the treatment of Duchenne MuscularDystrophy (DMD), a muscle wasting disease where patients present withdifficulties walking upstairs around the age of 3-5 years and are typicallywheelchair bound by age 12 years. Theygenerally die from respiratory failure or cardiomyopathy in theirtwenties. DMD is caused by mutations inthe dystrophin gene encoding the large cytoskeletal protein which associateswith other proteins at the sarcolemma to form the dystrophin-associated proteincomplex (DAPC). In the absence ofdystrophin, the DAPC is lost at the sarcolemma which subsequently becomes moresusceptible to contraction-induced injury. Currently the only treatmentapproved is in the form of corticosteroids, which have very limit benefits andare plagued by a number of side effects.

Genetic approachesto treat DMD being pursued include exon-skipping, read-through of stop codons, deliveryof dystrophin mini-genes and the modulation of expression of the dystrophinrelated protein, utrophin. Despite significant progress,the problem of targeting all muscles (40% of the total body mass) including diaphragmand heart, at sufficiently high levels remains a challenge. Any therapy alsoneeds to take account of the immune system and some of these treatments aremutation specific. The current status ofdevelopment of therapies will be presented.

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1631
WFN15-1851
Neuromuscular Disorders MT 7.3
The use of steroids in the management of Duchenne muscular dystrophy

A. Dubrovsky, L. Mesa. *Neurology, Fundacion Favaloro - Institute of Neuroscience - Neuromuscular Unit, Buenos Aires, Argentina*

At the moment, corticosteroid are widely accepted as standard treatment in DMD, efficacy having been proved in several clinical trials. The most frequently used corticosteroids are Deflazacort and Prednisone, Deflazacort is preferred because of milder side effects. Recent large natural history studies have demonstrated benefits of corticosteroid treatment in DMD patients, among them prolonged ambulation, improved pulmonary function, prevention of scoliosis and cardiac complications. Cushing features, weight gain, delayed growth, cataracts and osteoporosis are among the worrysome side effects due to long term use of the medication.

Even though treatment with steroids is intended to continue for many years in DMD, the optimum maintenance dose has not been established. Dose management after several years of administration is completely empirical and subjective, it varies depending on the patient and the physician.

The mechanism of action of steroids is uncertain and is probably related to its anti-inflammatory action, protein synthesis and expression, and calcium metabolism.

A low percentage of DMD patients appear not to respond so well to steroid treatment. The “non responder” condition may be partly related to genetic modifiers such as nucleotide polymorphisms in SPP1 and LTBP4 genes.

Nevertheless, it is important to keep in mind that appropriate care of DMD patients relies not only on CS treatment but also on a multidisciplinary medical, and rehabilitative approach including respiratory support as well as adequate cardiac managment.

While major advances in molecular therapies are expected, proper management of DMD has profound implications for the future of patients and families.

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1632
WFN15-1783
Neuromuscular Disorders MT 7.3
Cardiorespiratory management in neuromuscular disease

K. Bushby, K.A.T.E. Bushby. *MRC Centre for Neuromuscular Diseases, Institute of Genetic Medicine, Newcastle Upon Tyne, United Kingdom*

Cardiorespiratory management in neuromuscular diseases

Neuromuscular diseases (NMD) are often multisystem conditions, with implications for management beyond the weakness of skeletal

muscle which limits ambulation and other activities of daily living. The co-ordinated care of patients with inherited NMD should be based on a specific understanding of these additional complications: so that management must start with clear diagnosis, based on the underlying genetic defect. These diagnoses then inform the particular risks of cardiovascular and/ or respiratory impairment.

Some of the most common forms of inherited NMD carry significant complications in these areas, such as myotonic dystrophy and Duchenne and Becker muscular dystrophy. Other rare forms of NMD, such as laminopathy, may prove very difficult to manage from the perspective of cardiorespiratory care and require particular attention to these frequently life threatening complications. As we begin to achieve more diagnoses in previously uncharacterized NMD, the spectrum of cardiorespiratory complications is broadening. Meantime for any patient with an undiagnosed NMD, the need for surveillance in these areas is paramount until the risk can be quantified as intervention can be life saving.

Within the toolkit of investigations which should be available as part of the proper care of patients with NMD should be a full suite of cardiac and respiratory investigations, with targeted treatments including management of arrhythmia and cardiomyopathy as appropriate, as well as staged interventions for the sequelae of respiratory muscle weakness. These interventions already provide life changing therapies for many patients with NMD and are proven to improve quality of life and longevity.

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1633
WFN15-1928
Multiple Sclerosis and other Demyelinating Diseases MT 6.3
Special issues in pediatric multiple sclerosis

S. Tenembaum. *Neurology, National Pediatric Hospital Dr. J. P. Garrahan, Buenos Aires, Argentina*

Multiple Sclerosis and other Demyelianting Diseases. MT 6.3
"Special issues in pediatric multiple sclerosis"
Silvia Tenembaum

The recently published revised diagnostic criteria enable the differentiation of MS, acute disseminated encephalomyelitis (ADEM), neuromyelitis optica (NMO), and other immune mediated inflammatory disorders of the CNS. Nevertheless, MS diagnosis in childhood is still challenging, even using rigorous inclusion criteria and standardized definitions. In addition, advances in diagnostic biomarkers may prove to be useful in the future.

Environmental factors associated with pediatric MS risk and possibly outcomes include vitamin D deficiency, extreme obesity, second hand smoking, and EBV infection.

Regarding MS outcomes, our understanding of the cognitive consequences of early onset MS has grown. However, further work is needed to redefine the course of cognitive function and to develop strategies for effective cognitive rehabilitation specifically tailored to children and adolescents.

Finally, treatment strategies for pediatric patients with MS need to be discussed. There is only limited approval for beta-interferons and glatiramer acetate use in pediatric patients over the age of 11 by the EMA, although safety data for beta-IFN-1a tiw for children older than 2 years of age is included in the European label. Considering that there have been significant advances in MS therapeutics for adult patients, clinical trials of newer MS agents in children are required to bring information regarding the efficacy and safety of newer drugs.

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1634
WFN15-1778
Multiple Sclerosis and other Demyelinating Diseases MT 6.3
Providing information for newly diagnosed people with multiple sclerosis

A. Solari. *Unit of Neuroepidemiology, Fondazione Istituto Neurologico C. Besta, Milan, Italy*

Over the last 20 years, advances in neuroimaging and related modification of diagnostic criteria have brought the multiple sclerosis (MS) diagnosis forward. This, together with the introduction of disease-modifying drugs, has produced a change in the care of newly diagnosed people with MS: Diagnosis disclosure and long-term treatment decisions have moved closer together, and often coincide. Providing adequate information at this critical moment is a common claim of MS patients, even in the most recent surveys. This can be taxing in the stressful circumstance of diagnosis communication, as studies found that the emotional burden on MS patients at diagnosis is high. In addition, MS diagnosis is a process rather that a single event. Proper disclosure and effective communication require thoughtfulness, sensitivity, respect, and responsiveness to the specific needs of that patient. Information and decision aids provide reliable information in an understandable format to support the patient-clinician exchange and inform decision making. We will discuss the available evidence on the effect of these tools on patients' knowledge of MS, the achievement of 'informed choice', care satisfaction, and other relevant outcomes. The development of information and decision aids tools that satisfy quality standards, as well as their necessary periodic updating, is resource demanding. International, web based resources that are produced and updated with direct involvement of key stakeholders may be the most effective way forward.

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1635
WFN15-1899
Multiple Sclerosis and other Demyelinating Diseases MT 6.3
Perceptions of multiple sclerosis patients regarding their clinical care

J. Nogales-Gaete. *Neurology, Hospital Barros Luco - U. de Chile, Santiago, Chile*

The knowledge regarding the health care team concerning to the perceptions of patients with multiple sclerosis (MS) in relation to their attention and illness is not only an ethical imperative but also a clinical one.

The perceptions have a considerable dynamism and diversity depending on the patient, the illness and the professionals in charge of the patients. Respect to the patients, it is important to consider their biographical and psychosocial characteristics as well as the support net. In relation to the illness, it is important the impact of the disease on the patient's life quality. Also the changing symptomatology and, at times, absent result in a permanent uncertainty for the patient, making difficult the adaptation to an ever-changing disease. Regarding the health care, a transcendental element is the diagnosis process and the communication with the patient. The difficulty and mistakes to achieve a medical definite diagnosis usually determine permanent doubts and mistrust. In relation to the team, patients value the updated knowledge and the direct experience with patients with MS. They appreciate when the information is proposed in a schematic and comprehensive way, making emphasis in the kind of information useful for the everyday life over the quantity or "the clinical relevance" of the information.

The perceptions of those who have to live with MS, influence on the safety and trust at the moment of taking treatments decisions in good or bad settings, so they are clinically relevant.

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1636
WFN15-1846
Neurocritical Care MT 4.4 - Advances in the Management of Intracerebral Hemorrhage
Hematoma evacuation: only minimally-invasive

J. Hemphill. *Neurology, University of California San Francisco, San Francisco, USA*

Intracerebral hemorrhage (ICH) remains a disease with high risk of morbidity and mortality. Although recent studies of acute blood pressure control and supratentorial hematoma evacuation have suggested the possibility of modest benefit to functional outcome in some patients, evidence-based treatment options remain limited. An enticing potential treatment strategy involves minimally invasive hematoma evacuation. Preliminary data has been promising and a current randomized clinical trial (MISTIE III) is funded by the US National Institutes of Health and is currently enrolling patients. This talk will highlight some of the challenges in clinical trial design in intracerebral hemorrhage, specifically as they relate to hematoma evacuation surgery, discuss the current American Heart Association and European Stroke Organization guidelines for ICH management,and detail the status of new and novel investigations into minimally-invasive hematoma evacuation for ICH.

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1637
WFN15-1911
Neurocritical Care MT 4.4 - Advances in the Management of Intracerebral Hemorrhage
Edema development after intracerebral hemorrhage: clinical relevance and treatment options

A. Rabinstein. *Neurology, Mayo Clinic, Rochester MN, USA*

Perihematoma edema is a ubiquitous complication of intracerebral hemorrhage. The extent of edema is highly dependent on the volume of the hematoma: larger hematomas have more absolute amount of edema but smaller hematomas have more relative edema (i.e. more edema in relation to the hematoma volume). The formation of edema starts within the first hours and increases rapidly for the first 2-3 days. Subsequently, edema continues to form at a much slower pace until peaking towards the end of the second week, after which reabsorption mechanisms predominate. In the first hours, the driving mechanism for edema formation is the generation of hydraulic forces by the extrusion of proteins that occurs as a consequence of clot retraction. During this phase, there is also cytotoxic edema that increases the transendothelial sodium gradient. Then, over the next 2-3 days, vasogenic edema forms due to the activation of inflammatory cascades by various triggers, including thrombin. After this period, vasogenic edema continues to form principally by the pro-inflammatory effects of iron (that accumulates in the perihematoma region because of hemolysis of red blood cells). Perihematoma edema can serve as a surrogate marker of secondary injury and has been used in several phase II trials of neuroprotective interventions for intracerebral hemorrhage. When severe, the edema itself needs to be treated because it can provoked additional mass effect and neurological deterioration. The usual measures employed to treat brain edema in other acute brain diseases apply to these cases.

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1638
WFN15-1944
Neurocritical Care MT 4.4 - Advances in the Management of Intracerebral Hemorrhage
New monitoring tools: beyond ICP and partial tissue oxygenation (ptiO2)

J.I. Suarez. *Vascular Neurology and Neurocritical Care, Baylor College of Medicine, Houston, USA*

Spontaneous intracerebral hemorrhage (ICH) is a common neurological emergency which carries high morbidity and mortality. There are currently no proven pharmacological treatments for ICH, and the role of surgical intervention remains controversial. Management of ICH patients in the neurocritical care unit (NCCU) is largely based on maintenance of adequate cerebral perfusion pressure (CPP) and substrate delivery, by manipulating systemic blood pressure and intracranial pressure (ICP) using targets derived mainly from traumatic brain injury literature and guidelines. The advent of new neuroimaging and neuromonitoring techniques in the past few years has allowed for better understanding of the underlying pathophysiological mechanisms of ICH and the consequences of associated neuronal dysfunction. These techniques have elucidated the role of the perihematomal penumbra and mitochondrial dysfunction in ICH. Several methods have been used to monitor ICH patients including the traditional ICP and CPP measurements, electroencephalogram (EEG), and $ptiO_2$. Other promising technologies that need to be considered include quantitative continuous EEG (cEEG), regional and global cerebral blood flow (CBF) measurements, cerebral microdyalisis, and volumetric integral shift spectroscopy (VIPS). This lecture will review the developments in neuromonitoring and their application to ICH, highlighting the importance of multimodality neuromonitoring (MMNM). More recent literature suggests that MMNM will likely consist in the near future of noninvasive monitors that deliver continuous measurement of cerebral hemodynamics, oxygenation, and metabolism over multiple regions of interest simultaneously. The most challenging aspect of MMNM in ICH will be to demonstrate that it can result in improved clinical outcomes while decreasing resource utilization.

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1639
WFN15-1626
Neuromuscular Disorders MT 7.4
Next generation sequencing and muscle diseases

V. Straub. *John Walton Muscular Dystrophy Research Centre, Newcastle University, Newcastle upon Tyne, United Kingdom*

Genetic muscle diseases form a large group of diseases each of which is individually rare. They are present in all populations and affect both sexes and children and adults. Most result in chronic long term disability posing a significant health care burden for society. Over the past 25 years diagnostic methods have allowed us to identify disease genes in most of the larger families with muscle diseases and for the more frequently occurring muscle diseases. As a precise genetic diagnosis is a prerequisite for the monitoring of disease complications, the counselling of families and therefore the overall quality of life of a patient, it is a major challenge to identify

the genetic cause for all patients with muscle diseases. The use of next generation sequencing technologies (NGS), namely exome and genome sequencing, has turned out to be an enormously powerful tool to identify causative mutations in single families, cohorts of well characterized independent patients, or even single sporadic cases. In addition to the identification of disease genes, NGS will also contribute to an improved understanding of disease pathomechanismsm, disease modifiers and the development of biomarkers. These additional benefits of NGS will rely on strong bioinformatics expertise, data sharing policies and willingness for networking. Results from two such networking projects applying NGS, Neuromics and MYO-SEQ, will be presented. The projects are already showing that the identification of novel muscle genes can facilitate personalized medicine, improve standards of care and accelerate the development of target–driven therapies.

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1640
WFN15-1883
Neuromuscular Disorders MT 7.4
Management of myasthenia gravis

I. Illa. *Neurology, Hospital Sant Pau. Universitat Autònoma Barcelona, Barcelona, Spain*

Myasthenia gravis (MG) is an autoimmune disease characterized by fluctuating muscle weakness and fatigability. The key to management is to understand that MG is a heterogeneous disease with several pathogenic subgroups. Clinically, patients may present with an ocular or generalized form of the disorder. Weakness varies from mild, to severe, and can be life-threatening. MG affects patients of all ages but the incidence is highest in those over 70–80 years. Thymic involvement is also variable, ranging from normal to hyperplasia or thymoma. Immunologically, 80% of patients have antibodies to acetylcholine receptor (AChR) and 10-15% have antibodies to muscle-specific kinase (MuSK). Antibodies to LDL receptor-related protein 4 (LRP4)], low-affinity anti-AChR antibodies or cortactin have also been described.

Accordingly, treatment varies, from AChE inhibitors for symptomatic therapy to thymectomy and, mainly, immunotherapy. Most patients respond to steroids or other immunosuppressants, but some are refractory to standard therapy. Current immunotherapies undoubtedly provide benefit and have greatly improved the quality of life of MG patients but are associated with side-effects. Increasing knowledge about the immunopathogenesis of MG is providing a rationale for treatment with new agents. In this session I will provide an update on the management of MG according to a recently designed guideline.

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1641
WFN15-1830
Neuromuscular Disorders MT 7.4
Statins and myopathies

D. Hilton-Jones. *Neurology, John Radcliffe Hospital, Oxford, United Kingdom*

Statins are now one of the most widely prescribed group of drugs worldwide, and in some countries can be bought without prescription, or medical advice, "over the counter". They have come into widespread use because they are so effective in lowering serum cholesterol, which in turn is associated with a substantial reduction in cardiovascular and cerebrovascular morbidity and mortality. They act by inhibiting 3-hydroxy-3-methyglutaryl coenzyme A reductase (HMGCR), a rate limiting enzyme in the synthesis of cholesterol. Thousands of papers have been published describing issues concerning skeletal muscle, but despite the many millions of patients studied, in often enormous clinical trials, mostly cardiologically-led, considerable confusion and uncertainty remains as to associated muscle syndromes precipitated by them, and the question of whether or not they are safe to be given to patients with an established myopathy. This presentation will review the available data and discuss clinical features.

In brief summary, there are four main skeletal muscle "syndromes" associated with statin use:

1) Asymptomatic elevation of serum creatine kinase (CK) (probably common)
2) Myalgia, often associated with a raised CK (common)
3) Rhabdomyolysis (rare but potentially fatal)
4) An immune-mediated necrotising myopathy that persists despite statin withdrawal, and responds to immunosuppressant drug treatment (probably very rare). It may be associated with antibodies against HMGCR

In the majority of patients with a pre-existing myopathy, statins are probably safe, but certain precautions are required.

Statins are often wrongly blamed, by patients and physicians, for neuromuscular symptoms, potentially depriving patients of an effective therapy.

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1642
WFN15-1853
Movement Disorders MT 2.1 - Movement Disorders revisited
Parkinsonism and Parkinson's disease

K. Kompoliti. *Neurological Sciences, Rush University Medical Center, Chicago, USA*

Parkinsonism is a clinical syndrome characterized by bradykinesia and at least one of: rest tremor, muscular rigidity and postural reflex abnormalities. Bradykinesia is the defining feature of parkinsonism and is characterized by decrement (fatigability) and breaking down of the movement. Parkinson's disease is the most common neurodegenerative cause of parkinsonism, accounting for approximately 80% of cases of parkinsonism. Other neurodegenerative conditions presenting with parkinsonism include Multiple System Atrophy, Progressive Supranuclear Palsy and Corticobasal Degeneration. These conditions tend not to respond as well to dopaminergic treatments and have a worse prognosis compared to typical Parkinson's disease. Parkinsonism can also be symptomatic, resulting from drugs, toxins, infections, vascular disease and rarely structural lesions. Parkinsonism remains a clinical diagnosis and laboratory and imaging tools are mostly ancillary to making the diagnosis.

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1643
WFN15-1850
Movement Disorders MT 2.1 - Movement Disorders revisited
Dystonia

F. Cardoso. *Internal Medicine, Neurology Service, Belo Horizonte, Brazil*

Dystonia Revisited
Francisco Cardoso MD PhD FAAN
Neurology Service, Internal Medicine Department, UFMG, Belo Horizonte, MG, Brazil

The aim of this talk is to provide a review of new developments in the field of dystonia in the past few years. The first issue is the appearance of a new proposal of definition and classification of dystonia (Albanese et al. 2013). Although not much has changed in comparison to previous data, there have been a few novelties: the authors have placed emphasis on the possibility of tremor being the main feature of dystonia; and the notion of idiopathic dystonia is reinstated. Similarly to other areas of neurology, there has been a great impact of genetic findings. As of the writing of this abstract, 25 loci have been identified in association with diseases where dystonia is the main feature. Moreover, there has been the recognition of additional new genetic diseases where dystonia is part of the clinical picture. Although in general the identification of these conditions does not have a practical implication, they have allowed a better understanding of the pathogenesis of dystonia. There is also growing evidence that the cerebellum plays a key role in the generation of dystonic movements. From a therapeutic point of view, there is still a need for more effective oral therapies for dystonia. However, there has been a growth in the use of deep brain stimulation both for generalized and more localized forms of dystonia.

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1644
WFN15-1912
Dementia MT 5.1 - Dementia and Cognitive Reserve: A Global Perspective
Low cognitive reserve and higher prevalence of dementia in developing countries

R. Nitrini. *Neurology, University of São Paulo Medical School, São Paulo, Brazil*

Cognitive Reserve (CR) is a hypothetical construct believed to explain individual differences in the relationship between neuropathology and cognitive performance. Proposed markers of CR include: education attainment, occupational achievement, mental activities and premorbid IQ. Rather than postulating that brains of individual with high CR are grossly anatomically different from those with less CR, the CR hypothesis posits that high CR individuals process tasks in a manner that allows them to cope better with the brain damage. Brain reserve, understood as the higher brain efficiency due to anatomical differences, is encompassed by the more general expression CR, although they may represent two closely interacting but different resources. High CR has been proposed to explain the lower incidence of dementia in individuals with higher levels of education. Low CR may be responsible for the higher prevalence of dementia in relatively younger individuals in studies from Latin America and in minorities in developed countries. Even very low levels of educational attainment, is probably able to increase CR. Otherwise, the role of brain reserve has been shown by studies relating higher rates of dementia prevalence in old age with low performance in neuropsychological tests at age of 11(Lothian Studies) and with low school grades at the age of 10 (Uppsalla Study). Bad nutritional conditions during prenatal period or early childhood may probably predispose to dementia in old age. Both CR and brain reserve may be responsible for higher prevalence of dementia in developing countries.

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1645
WFN15-1835
Dementia MT 5.1 - Dementia and Cognitive Reserve: A Global Perspective
The role of different languages and cultures in dementia

S. Alladi. *Neurology, Nizam's Institute of Medical Sciences, Hyderabad, India*

With the rising numbers of persons with dementia globally, the focus of research has shifted towards understanding potentially protective factors that may reduce its risk or delay its onset. Several lifetime experiences such as education, occupational complexity, social engagement and other cognitively stimulating activities are considered to improve cognitive reserve and enhance ability to withstand effects of disease pathologies. These factors are however known to vary widely between different countries and cultures. Recent evidence also suggests that the ability to speak more than one language (bilingualism) has a significant role to play in facilitating cognitive reserve. While several studies reported a delay in the onset of dementia in bilinguals, others found no effect or an effect confined to parts of the examined population, making this a topic of recent debate. In this talk, the role of different cultural and lifetime experiences such as bilingualism, education and occupation with respect to their potentially protective effects on dementia will be discussed, with particular reference to the context of India, a developing country. The mechanisms underlying this association will be discussed in a range of cognitive disorders, including Alzheimer's disease, Frontotemporal dementia, stroke and mild cognitive impairment. In the background of a wide degree of sociocultural, educational and lingusitic mileau that exists globally, the role of these factors in clinical expression of dementia is likely to be significant.

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1646
WFN15-1620
Movement Disorders MT 2.2 - Environmental factors and metals in Movement Disorders
Environmental factors and movement disorders

M. Youdim, O. Weinreb, M. Fridkin, H. Zheng. *Eve Topf Center of Excellence, Technion-Faculty of Medicine, Haifa, Israel*

Designed multi target iron chelstors possessing neuroprotective, neurorestorative and mitochondrial biogenesis activities for Parkinson's disease

Moussa B.H. Youdim
Technion. Rappaport Faculty of Medicine
Eve Topf Center of Excellence
Haifa, Israel

One major pathology of Parkinson's disease (PD) is accumulation of iron in substantia nigra pars compacta and increase in monoamine oxidase (MAO).The iron and glutaminergic excitotoxicity contributes to the onset of oxidative stress and via in hydrogen peroxide generated by the reaction of MAO. Our multi target non-toxic, brain permeable iron chelator drugs, M-30 and HLA-20, possess propargyl MAO inhibitory moiety, with neuroprotective and neurorestorative activities. These drugs possess antiapoptotic, pro-survival neurorescue effects, induction of neuronal differentiation They possess neurorestorative activity in animal models of Parkinson's disease. They induce the outgrowth of neuritis in neuronal cell cultures, trigger cell cycle arrest in G0/G1 phase and enhance the expression of growth associated protein-43, HIF (Hypoxia Inducing Factor) and increase brain levels BDNF,GDNF, VGEF and erythropoietin. This is associated with the inhibition of iron dependent prolyl-4-hydroxylase, that regulates HIF. The dual control of mitochondrial biogenesis and energy metabolism is regulated by silent information regulator-1 and -3 (SIRT1 and SIRT3). The peroxisome proliferator activated receptor γ co-activator 1α (PGC-1α) is a transcriptional co-activator that is a central inducer of mitochondrial biogenesis in cells. SIRT1 is necessary for HIF-1α protein accumulation and activation of

HIF-1 target genes and activates PGC-1α-mediated transcription of nuclear factor (Tfam) and mitochondrial genes encoding for proteins promoting mitochondria proliferation. M30 and HLA-20 activate SIRT1, PGC-1α, and Tfam in cell cultures and consider them as a novel therapeutic approach for neurodegenerative disorders.

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1647
WFN15-1855
Movement Disorders MT 2.2 - Environmental factors and metals in Movement Disorders
Copper

K. Kompoliti. *Neurological Sciences, Rush University Medical Center, Chicago, USA*

Movement disorders associated with copper metabolism are mostly related to Wilson disease. Wilson disease is an inherited disorder, in which excessive amounts of copper accumulate in the body, particularly in the liver, brain, and eyes. The manifestations of this condition include a combination of liver disease and neurological and psychiatric problems. Liver disease usually happens early, in childhood and adolescence, while neurological or psychiatric manifestations are usually the presenting features in adults diagnosed with the disease. Neurological and psychiatric manifestations include dystonia, tremors, parkinsonism, chorea, gait impairment, speech problems, cognitive impairment, depression, anxiety, and mood swings. In most individuals with Wilson disease, copper deposits in the cornea form a green-brownish ring, called the Kayser-Fleischer ring, which is present in the majority of patients with neurological involvement. Abnormalities in eye movements, such as a restricted ability to gaze upwards, may also occur. The diagnosis of Wilson disease is of paramount importance because of the specific chelation treatments available.

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1648
WFN15-1811
Dementia MT 5.2 - Clinical presentations of dementia - beyond memory: language, motor functions and behavior
language in dementia

M. Elalouoi Faris. *Hôpital des Spécialités, Mohamed-V University, Rabat, Morocco*

Memory disorders are the clinical core of dementia syndrome and their presence is necessary for the diagnosis of dementia according to the DSM-IV and the ICD-10. Historically, language disorders in dementia have been reported by Aloïs Alzheimer in 1907 since the description of his first patient “Auguste D. For several years, various studies have emphasized the importance of language disorders in the diagnosis of dementia. Lexical disorders in Alzheimer's disease are prominent while phonology, morphology and syntax are generally respected. The lexical-semantic disorders can be recognized early in the disease even in its prodromal phase. Recently, cognitive neuropsychological studies have analyzed the nature of the written language disorders in Alzheimer's disease and have shown the presence of central and peripheral agraphia from the early stage of the disease. The overall deterioration of semantic knowledge are the main disorders in “Semantic Dementia” with which the expressive and receptive language are severely impaired. In primary progressive aphasia (logopenic and non-fluent aphasias) language impairment dominate for years the clinical picture of the diseases before the appearance of dementia.

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1649
WFN15-1926
Dementia MT 5.2 - Clinical presentations of dementia - beyond memory: language, motor functions and behavior
behavior in dementia

F. Manes. *Neurosciences, INECO/Favaloro University, Buenos Aires, Argentina*

The Interface Between Psychiatric Conditions and behavioral variant Frontotemporal Dementia (bvFTD)

Facundo Manes
Institute of Cognitive Neurology (INECO), and Institute of Neuroscience, Favaloro University, Buenos Aires Argentina

Diagnosis of early bvFTD can prove very difficult. Several factors make diagnosis of this neurodegenerative disease especially challenging. First, patients may develop behavioral symptoms while presenting normal neuroimaging. In patients that develop atrophy at the early stages, radiologists usually call atrophy pattern unremarkable and it may conduce to misdiagnosis. Secondly, changes in social cognition may be disregarded for a long time before they become impairing enough to concern the caregivers and overall cognitive functioning is frequently within normal ranges delaying early diagnosis. Third, subtle neuropsychiatric symptoms can be ignored or thought as part of a primary psychiatric condition. bvFTD patients show an array of behavioral changes which overlap with those found in psychiatric disorders. These symptoms can be summarized as personality changes, but more specifically, they involve a shift towards impulsive and socially inappropriate behavior. In this presentation I will review some psychiatric conditions that can mimic early bvFTD such us personality disorders and age-related personality change, atipical depression, bipolar disorders, late onset atypical psychosis, alcohol abuse, obsessive-compulsive disorder and ageing adult attention deficit hyperactivity disorder.

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1650
WFN15-1875
Sleep Disorders MT 11.1 – REM-Sleep, Cognition and Neurodegeneration
Diagnosis and phenomenology of REM-sleep behaviour disorder (RBD)

C. Schenck. *Psychiatry and Sleep Medicine, University of Minnesota Medical School, Minneapolis, USA*

RBD is a parasomnia of abnormal behavioral release during REM sleep, with loss of the customary skeletal muscle atonia of REM sleep and the acting-out of dreams that are confrontational, aggressive and violent, and which commonly result in injuries, thus triggering referral for evaluation. Video-polysomnography is required to confirm the diagnosis.The most common RBD behaviors include talking, shouting (including profanities), kicking, throwing punches, sitting up, and jumping from bed. Life-threatening injuries can occur with RBD, thus encouraging prompt diagnosis and therapy, which is highly effective in >80% of reported cases with bedtime clonazepam and/or melatonin. RBD predominantly affects middle-aged and

older men. Longitudinal studies of patients with idiopathic RBD have revealed that >80% will develop synucleinopathy neurodegeneration (Parkinson's disease; dementia with Lewy bodies; multiple system atrophy), with the mean interval from RBD onset to overt neurodegeneration being 12-14 years (data from 3 centers). Thus, RBD is now considered to be an early biomarker of neurodegeneration, which has accelerated the search for promising neuroprotective therapies. RBD also affects up to 50% of patients with narcolepsy-cataplexy. RBD has been found in virtually all categories of CNS disorders. The phenotype of RBD in patients <50 years of age has recently been found to differ from the classic RBD phenotype described above. Younger RBD patients have greater gender parity, less severe RBD, greater association with narcolepsy, greater association with psychiatric disorders and with antidepressant use. Most antidepressants (esp. SSRIs, venlafaxine, TCAs) can trigger RBD.

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1651
WFN15-1915
Sleep Disorders MT 11.1 – REM-Sleep, Cognition and Neurodegeneration
RBD in Parkinson's disease: burden, diagnosis and measures

M. Behari. *Neurology Department, All India Institute of Medical Sciences, New Delhi, India*

REM sleep behavior disorder or RBD is a sleep disorder is characterized by absence of muscle hypotonia during the rapid eye movement (REM) sleep resulting in the person acting out his or her dreams, sometimes in dramatic or violent and extremely agitated, ways moving their limbs, getting up and engaging in actions associated with walking. Some may even talk, shout, scream, hit, and punch, during their rapid eye movement (REM) sleep. It is common in males (90%), the average age is 60 years.

REM sleep Behavior Disorder (RBD) is considered as a biomarker of Parkinson's disease (PD). However, it is reported in only 80-90% of patients with PD. On the other hand, conversion rate of isolated idiopathic RBD (iRBD), is >90%. Going by these observations, RBD forms an integral part of morbidity in PD. Though per se, RBD causes major problem to the bed partner of the affected person, whereas the patient remains blissfully unaware of it, unless it causes injury due to falls during dream enactment or marital discord. Diagnosis can be made by careful history and confirmed by polysomnography.

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1652
WFN15-1924
Movement Disorders MT 2.3 - Translation and Intervention in Movement Disorders
Invasive therapies for movement disorders

A. Antonini. *Neurology, IRCCS San Camillo Hospital - 1st Neurology Clinic, Padua, Italy*

The management of Parkinson's disease (PD) becomes challenging when motor fluctuations (wearing off, delayed on and sudden off periods) and dyskinesia develop. At this stage patients cannot be adequately controlled by adjustments of oral medication. Gradual worsening of these disabling phenomena has important negative consequences for quality of life of patients and caregivers. When patients are at this stage we can consider, three invasive therapies:1) apomorphine, administered subcutaneously via daytime intermittent bolus injection or continuous pump infusion; (2) continuous duodenal/jejunal levodopa/carbidopa pump infusion (DLI), administered via gastrojejunostomy; (3) deep brain stimulation (DBS)bilateral stimulation of the subthalamic nucleus (STN) or globus pallidus (GPi). No specific guidelines exist concerning the decision making regarding which therapy should be chosen for individual patients. Each of these therapies can improve off motor symptoms and reduce dyskinesia, although the level of evidence is currently highest for DBS followed by levodopa/carbidopa intestinal gel. In day-to-day clinical practice, therapeutic decisions often need to be made in patients who would not fit the strict inclusion/exclusion criteria of clinical trials; other factors such as the severity of cognitive, psychiatric, speech, balance and general medical conditions also require consideration. A multidisciplinary approach towards evaluating the contribution of these factors on impaired QoL is highly recommended. Determination of absolute and relative contraindications should follow, as some patients may be suitable for a single therapy while others may have greater choice. An individual risk–benefit assessment should consider patients' preferences and define which therapy is most likely to restore daily functions and QoL.

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1653
WFN15-1789
Movement Disorders MT 2.3 - Translation and Intervention in Movement Disorders
Neuroplasticity and exercise therapies for movement disorders

E. Wolters. *Dept of Neurology, Universities of Zurich, Switzerland; Maastricht, Netherlands; Amsterdam, Netherlands*

In neurodegenerative disorders, including PD, cell necrosis and/or apoptosis is the result of a cascade of inter-related events (oxidative stress, mitochondrial dysfunction, protein aggregation and misfolding, neuroinflammation, excitotoxicity). These events offer potential targets for neuroprotective therapy. As of now, though, no drugs have surfaced to date, that unequivocally have that property.

Neuroprotection might also be promoted by neurotrophic factors, stimulating neuroplasticity (neuroprevention and neurorestoration), even if deficiency of neurotrophic factors is not the primary cause of this disorder. Neuroplasticity is the life-long brain's ability to act and react, both in neural development and repair.

The identification of NGF, BDNF, GDNF, Insulin like growth factor-1 (IGF-1), and more recently cerebral dopamine neurotrophic factor (CDNF) and mesencephalic-astrocyte–derived neurotrophic factor (MANF), stimulating DA neuronal growth and branching, provided new hope for therapeutic strategies based on neurotrophic factors or downstream components of their signalling pathways. So far, however, clinical trials were not very successful.

To a certain extent, forced physical exercise (FPE) is found to prevent (there is an inverse relationship between the amount of exercise undertaken and the risk of developing PD) and slow down the progression of PD. Research showed that forced exercising not only does lower free radical production by increasing the production of superoxide dismutase and nitric oxide synthase, but also increased the production of BDNF, NGF, IGF-1 and vascular endothelial growth factor. The clinical effects of FPE, thus, might be related to its activation of the release of neurotrophic factors, facilitating neurogenesis and synaptogenesis.

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1654
WFN15-1854
Movement Disorders MT 2.3 - Translation and Intervention in Movement Disorders
Cognitive therapies for psychogenic movement disorders

K. Kompoliti. *Neurological Sciences, Rush University Medical Center, Chicago, USA*

Psychogenic Movement Disorders (PMDs) represent a clinical territory that overlaps both neurology and psychiatry. The term PMD has been used to describe disorders that cannot be attributed to any known structural or neurochemical disease, but result from an underlying psychiatric illness or malingering. When approaching treatment of PMDs, clinicians must rely primarily on expert opinion rather than evidence-based data. Outside of movement disorders, there have been over 30 randomized controlled trials with two thirds of the studies involving somatization disorder. In contrast, only few randomized controlled trials focused on conversion disorder, using hypnosis and paradoxical intention, with inconclusive results. In regards to the treatment of PMDs, the literature is particularly sparse with only few, mostly open label studies, published utilizing psychodynamic psychotherapy or cognitive behavioral therapy. Most recently, treatment strategies involving both physical rehabilitation (physical, occupational and speech therapy) in combination with psychotherapy are becoming more prominent.

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1655
WFN15-1840
Dementia MT 5.3 - Vascular, Neurodegenerative and Immune Mechanisms in Dementia
Vascular mechanisms of dementia

V. Hachinski. *Clinical Neurological Sciences, Western University, London, Canada*

Vascular mechanisms of dementia
Vladimir Hachinski, MD, DSc, FRCPC
Distinguished University Professor Department of CNS University of Western Ontario London, Canada

As a cause

Any type of ischemic or hemorrhagic stroke results in direct brain damage and depending on its location and extent, may have cognitive consequences.

As a contributor or trigger of neurodegeneration

Interestingly, after a stroke the slope of cognitive decline becomes accelerated in patients who have had a stroke, especially in executive function and processing speed. This suggests that the vascular component either triggers or interacts with underlying neurodegenerative pathology. Hypertension accelerates amyloid deposition and high homocysteine levels enhance tau protein deposition in the brain. Cerebral infarcts in the presence of amyloid are larger and grow and inflammation is greater and it festers compared to control animals. Some of these changes can be blocked by the use of anti-inflammatory agents. After a cerebral infarct white matter inflammation correlates better with cognitive status at 6 months than the initial cognitive status, suggesting that treating the inflammation may present some cognitive deterioration.

As consequence

Alzheimer pathology is associated with increased deposition of amyloid in cerebral blood vessels often resulting in amyloid angiopathy. This can lead to cerebral infarcts and also cerebral hemorrhages.

Clearly, the best strategy is to prevent, block or modify the vascular mechanisms as means of preventing not only stroke, but dementia.

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1656
WFN15-1940
Dementia MT 5.3 - Vascular, Neurodegenerative and Immune Mechanisms in Dementia
Cognitive impairment and dementia after meningoencephalitis

R. Kalaria. *Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom*

The global burden of all-cause communicablediseases is more than 4-fold greater in the developing compared to thedeveloped world. Current trends reveal thatcertain form of cognitive impairment is present in the chronic stages of allinfectious diseases. The overall rates are ~30-40% worldwide but many exhibit frank dementia. Different agents are responsible including viral, bacterial, fungal, and parasitic organisms. Viralencephalitides is often insidious whereas bacterial agents alter level of consciousness. Cognitive/behavioral symptoms andneuropsychological profile need to be compatible with presence of fever, peripheral leukocytosis or CSFpleocytosis caused by the infectious agent. The most common cause of cognitive impairment in infectious diseases is HIVin which ~70% of the patients may develop focal or generalised neurologicalcomplications including headache and seizure activity. The Frascati criteria have been usedto determine HIV associated neurocognitive disorders (HAND) staging (normal,asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder(MND) and HIV-associated dementia (HAD). Symptoms entail disabling cognitive, behavioral and motordysfunction with memory loss, impaired manipulation of acquired knowledge,personality changes and general slowing of thought processes. Many features are akin to dementia associatedwith small vessel diseases of the brain. The neuropathology of HAND is described thepresence of diffuse infiltration by macrophages and multinucleated giant cells. Perivascular macrophages andinflammatory cells are prominent around blood vessels in addition to abnormalitiesin the deep white matter. However, the precise neurophathological substratesof HAD are elusive. Cognitive testing associated with meningoencephalitis may helppredict those at risk of dementia.

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1657
WFN15-1934
Sleep Disorders MT 11.2 - Treatment of Sleep Disorders
Behavioral and pharmacological therapy of insomnia

C. Morin. *Psychology, Laval University, Quebec City, Canada*

Behavioral and Pharmacological Therapies of Insomnia
Charles M. Morin, Ph.D
Université Laval, Québec Canad

Insomnia is a prevalent sleep complaint that can present as a disorder on its own or as a comorbid condition with other medical and psychiatric disorders. Despite its high prevalence and significant burden, insomnia often remains unrecognized and, when treatment is initiated, it is often limited to drug therapy. This presentation will summarize the most recent research-based evidence documenting the benefits and limitations of behavioral and pharmacological approaches in the management of insomnia. Findings from clinical

trials evaluating the separate and combined effects of behavioral therapy and medication will be summarized, with a special emphasis on initial treatment response and long-term outcome. Despite recent advances in the management of insomnia, no single treatment modality is effective for all patients and, even among treatment responders, few patients actually become good sleepers. The role of maintenance therapy and new models for integrating behavioral and medication therapies will be outlined in order to inform clinical decision-making and optimize the management of insomnia.

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1658
WFN15-1803
Sleep Disorders MT 11.2 - Treatment of Sleep Disorders
Dopaminergic and non-dopaminergic treatment in restless legs syndrome

C. Trenkwalder[a], J. Winkelmann[b], W. Paulus[c]. [a]*Elena Klinik Kassel, University medical Center Goettingen, Goettingen, Germany;* [b]*Dept. Neurology, Technical University Munich, Munich, Germany;* [c]*Dept. Clinical Neurophysiology, University medical Center Goettingen, Goettingen, Germany*

Restless legs syndrome (RLS) can severely affect quality of life both at daytime and at night due to severe sleep disturbances. Pharmacological treatment may become non-avoidable, especially for elderly patients. Treatment guidelines are available from the International RLS Study Group and from several countries. Before any pharmacological treatment is started, co-morbidities, and medications known to induce or worsen RLS should be checked. When ferritin is low or anemia is present, iron formulations can be effective but are not yet approved for RLS therapy. In general, initiation of therapy is recommended with dopamine agonists (pramipexole, ropinirole or rotigotine transdermal patch), in the US and Japan also with the approved gabapentin enacarbil. Other α-2-δ ligands studied to be effective in RLS are gabapentin or pregabaline. For second line therapy, if other medication failed or are no longer effective, opioids (prolonged release oxycodone–naloxone, approved in Europe) are also recommended for severe RLS. Medications like benzodiazepines and other anticonvulsants are no longer recommended. Major complications of dopaminergic therapy consist of augmentation; a worsening of RLS severity and occurrence of symptoms earlier during the day after successful dopaminergic medication has started. Pulsatile dopaminergic agents and high dosages over time are possible risk factors of augmentation. Management of augmentation is not sufficiently studied but may include reducing dopaminergic dosage, switching to a less pulsatile acting dopamine agonist or to an opioid, or both. For the treatment of RLS associated with other comorbidities the same agents may be used as in RLS without comorbidities, despite trials are mostly lacking.

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1659
WFN15-1869
Sleep Disorders MT 11.2 - Treatment of Sleep Disorders
Treatment of sleep disorders in children

M. Grigg-Damberger. *Neurology Sleep Medicine Epilepsy and Clinical Neurophysiology, University of New Mexico School of Medicine, Albuquerque NM, USA*

Identifying and Treating Sleep Disturbances in Children with Neurological Disorders Important Because Children Sleep for Brain

Sleep problems are often more common, severe, and persistent in children with neurological disorders than the general pediatric population. Fragmented or insufficient sleep in them impairs attention, behavior, appetite control, and learning. Severe insomnia in certain neurodevelopmental disorders is so common and striking as to be phenotypic. Using illustrative cases, treatment strategies will be presented for some of the most common clinical challenges: 1) symptomatic obstructive sleep apnea in a child with Trisomy 21 syndrome following adenotonsillectomy; 2) fulminant-onset childhood onset narcolepsy with cataplexy after an infection; 3) severe central and obstructive sleep apnea in Chiari 1 malformation due to posterior fossa compression and tonsillar hypertrophy; and 4) central hypersomnia and alveolar hypoventilation in a child with myotonic dystrophy. Treatment options for obstructive sleep apnea such as positive airway pressure, tongue base reduction, lingual tonsillectomy, oral appliances, rapid maxillary expansion, and weight management will be reviewed. Narcolepsy type 1 in children and adolescents often requires triple therapies, many of which are off-label in this age group. Untreated sleep disordered breathing in Chiari malformation and achondroplasia can lead to sudden death. Children with myotonic dystrophies, Prader-Willi syndrome and other neurological disorders can have central hypersomnias which require treatment with drugs such as modafinil. Lastly, melatonin in small doses combined with cognitive behavioral insomnia therapy for child (and family) can be effective for complex behavioral insomnia in children with particular neurodevelopmental and autistic spectrum disorders.

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1660
WFN15-1860
Sleep Disorders MT 11.2 - Treatment of Sleep Disorders
Treatment of respiratory sleep disorders

P.E. Brockmann. *Sleep Center, Pontificia Universidad Catolica de Chile, Santiago, Chile*

Treatment of respiratory sleep disorders
Pablo E. Brockmann, MD

Obstructive sleep apnea (OSA) is a form of respiratory sleep disorders that occurs in children of all ages. Its characteristics include prolonged episodes with increased upper airway resistance and respiratory effort with partial or complete upper airway obstruction and various combinations of snoring, intermittent hypoxemia, hypercarbia, restless sleep and an increased number of awakenings.

Estimations concerning the prevalence of OSA range from 0.7% to 10.3%, with a peak prevalence between 2 and 8 years of age. Considering the increasing prevalence of OSA and its serious neurocognitive and cardiovascular consequences an early diagnosis and treatment seem to be urgently necessary.

Among the treatment options, adenotonsilectomy has been suggested as the first line treatment for OSA in children. However, adenotonsilectomy has pro´s and con´s. Children with obesity and Down syndrome for example, seem not to improve that much their OSA in comparison with non obese otherwise healthy children. Oral appliances and maxillary expansion have also been tested in a subgroup of children with promising results.

In addition, anti-inflammatory therary has emerged as a possible non-invasive treatment options for milder cases of OSA in children. Several studies have compared the usefulness of nasal corticosteroids and montelukast for treating OSA and reducing its symptoms. In more severe cases, CPAP and BiPAP therapy is necessary.

In this lecture we will analyze different treatment options for respiratory sleep disorders in children and the evidence that supports each one of them.

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1661
WFN15-1849
Dementia MT 5.4 - Diagnosis, Treatment and Prevention of Dementia
Memory binding in the early diagnosis of memory impairment

M. Parra Rodriguez. *Psychology, University Heriot Watt, Edinburgh, United Kingdom*

Memory binding refers to the cognitive function responsible for holding together the features of objects previously experienced such as color, shape, location, etc. Memory binding declines both in normal aging and in elderly people with cognitive impairment though to a greater extent. A newly developed memory binding task, namely the Short-Term Memory Binding Test (STMBT), separates the trajectories of normal and abnormal aging. By asking people to judge whether two consecutive arrays of colored shapes show the same or different items, the task has revealed a binding function which remains preserved across the lifespan but declines in the preclinical stages of Alzheimer's disease (AD), the most common cause of dementia in elderly people. Recent studies have reported that the STMBT detects a pattern of memory impairment in asymptomatic individuals who will inevitably develop early-onset AD due to a PS1 mutation which is similar to that found in older adults with Subjective Cognitive Deficits (SCD). Such STMB deficits become more pronounced as carriers of the mutation approach the age of onset of dementia or SCD progresses to Mild Cognitive Impairment and to AD. STMB deficits in the very early stages of AD contrast with completely normal neuropsychological functions, including those suggested by consensus papers. Recent neuroimaging studies reveal that STMB is independent of the hippocampal function but dependent of areas along the ventral visual stream. This evidence fits recent hypotheses about the impact of AD on extra-hippocampal regions and the usefulness of tasks tapping into such regions for its early diagnosis.

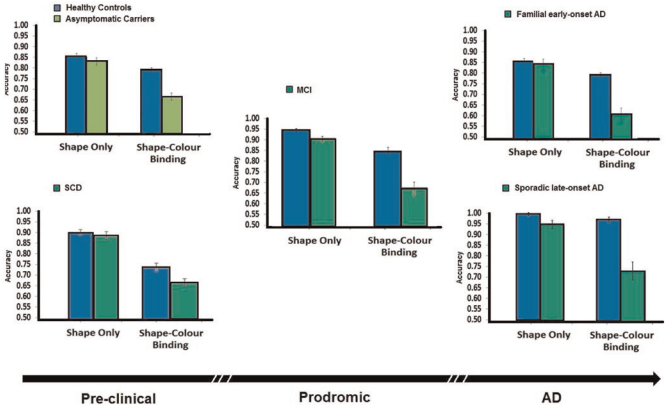

Fig. 1. Mean STMB data from patients at different stages of the disease process ranging from preclinical stages (asymptomatic mutation carriers and SCD) through the clinical stages of AD in its familial and sporadic variants.

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1662
WFN15-1810
Dementia MT 5.4 - Diagnosis, Treatment and Prevention of Dementia
What have we learned from recent clinical trials in AD?

R. Rosenberg. *Neurology, UT Southwestern Medical Center, Dallas, TX, USA*

DNA Aβ42 vaccination in which DNA encoding the Aβ42 peptide is injected is presented as potential therapy to delay or prevent Alzheimer's disease. The injected DNA is translated in the immunized individual to produce Aβ peptide which then triggers immune responses against the Aβ42 peptide. We are the first to show that DNA Abeta42 vaccination administered with the gene gun is highly effective to reduce Aβ42 levels in brain by 41% and the Aβ42-containing plaques by 50% in Alzheimer transgenic mouse models (Qu et al., 2004; 2006, 2007) which was confirmed later in studies by others. The immune response is Th2 (IgG1) in the Alzheimer transgenic mouse and IgG and IgA in New Zealand white rabbits. DNA Aβ42 vaccination is non-inflammatory, as it induces a Th2 immune response (IgG1) and does not produce the pro-inflammatory factors: γ interferon and Il-17 and does not induce proliferation of cytotoxic CD8 cells, all of which are induced in Aβ42 peptide vaccination, resulting in the stopping of a clinical trial. Our research describes the effectiveness, safety and potential therapeutic value of DNA Aβ42 vaccination in persons at risk for Alzheimer's disease (Rosenberg and Lambracht-Washington, 2015).

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1663
WFN15-1636
Dementia MT 5.4 - Diagnosis, Treatment and Prevention of Dementia
Parkinsonism associated with dementia

M. Emre, N.O.N.E. None. *Department of Neurology, Istanbul Faculty of Medicine, Istanbul, Turkey*

Parkinsonism associated with dementia can occur in primary degenerative dementias as well as in secondary forms of dementia. Primary degenerative dementias presenting with this condition mainly include tauopathies and synucleinopathies. Alpha-synuclein or Lewy-body related dementias are more common constituting the second most frequent cause of dementia following Alzheimer disease. The two typical forms of Lewy Body related dementias are Dementia with Lewy Bodies (DLB) and Demantia associated with Parkinson's disease (PD-D). Clinically Lewy-body related dementias are characterized by a predominance of executive and attentional dysfunction, early and disproportinate impairment in visual-spatial functions, less severe amnesia, less severe impairment in language functions and prominent behavioral symptoms such as hallucinations, delusions and apathy. The clinical profile of cognitive symptoms may be determined by the amount of concomitant Alzheimer-type pathology, which often is co-existent in varying degrees, particularly in patients with DLB. Biochemically the most prominent abnormalitiy in PD-D and DLB are cholinergic deficits, although impairment in other neurotransmitter systems can contribute to certain symptoms. Cholinesterase inhibitors have been shown to provide some benefits in both conditions.

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1664
WFN15-1864
Sleep Disorders MT 11.3 - Mechanisms of Sleep Disorders and Sleep in Neurological Disorders
Sleep and refractory epilepsy: mechanisms impacting treatment outcomes

G. Shukla. *Neurology, All India Institute of Medical Sciences, New Delhi, India*

The interrelationship between sleep and epilepsy has always fascinated neurologists and physicians who care for people with epilepsy.

While much research has addressed some major issues – one of the circadian predilection of focal versus generalized seizures, and the activating effect of sleep deprivation on occurrence of breakthrough seizures and on yield of EEG, there is paucity of literature on sleep among pateints with 'difficult to control' epilepsy.

Over the last few years, our group has studied sleep quality and architecture differences among people with refractory epilepsy and the impact thereof on quality of life among these patients. Evidence for poor sleep quality among patients with refractory epilepsy, excessive daytime sleepiness (EDS) among patients with refractory epilepsy, the impact of sleep quality on cognition among patients with epilepsy, and the positive impact on sleep quality through epilepsy surgery, are discussed.

The main observations that we have made and which will be discussed, are the high prevalence of self reported EDS and multiple daytime naps as well as polysomnographically demonstrated reduced total sleep time and sleep efficiency; among patients with refractory epilepsy. The differences in REM sleep versus non-REM sleep among patients with refractory epilepsy, especially non-REM sleep stability will also be discussed.

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1665
WFN15-1870
Sleep Disorders MT 11.3 - Mechanisms of Sleep Disorders and Sleep in Neurological Disorders
Primary or secondary stroke prevention

R. Sacco. *Neurology, Miller School of Medicine University of Miami, Miami FL, USA*

Stroke remains a major public health threat across the globe. Evidence-based recommendations have been published regarding the primary and secondary stroke prevention. Improved management of lifestyle factors, such as smoking, physical activity, obesity, and diet, and treatment of elevations of blood pressure, blood glucose and cholesterol, are critical for improving ideal cardiovascular health and reducing first and recurrent stroke risk. Sleep disorders are emerging stroke risk factors. Data from the Northern Manhattan Study have demonstrated the association between daytime sleepiness, the Epworth scale, and sleep duration and stroke and silent brain infarction. AHA/ASA secondary stroke recommendations for sleep apnea now include: (1) a sleep study might be considered for patients with an ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea and the evidence that the treatment of sleep apnea improves outcomes in the general population; and (2) Treatment with continuous positive airway pressure might be considered for patients with ischemic stroke or TIA and sleep apnea given the emerging evidence in support of improved outcomes. For primary stroke prevention, there are more evidence gaps and the current recommendations for sleep-disordered breathing include: (1) Because of its association with stroke risk, screening for sleep apnea through a detailed history, including structured questionnaires such as the Epworth Sleepiness Scale and Berlin Questionnaire, physical examination, and, if indicated, polysomnography may be considered; and (2) Treatment of sleep apnea to reduce the risk of stroke may be reasonable, although its effectiveness for primary prevention of stroke is unknown.

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1666
WFN15-1822
Hospital Neurology MT 13.1
Neurological complications of medical and surgical therapies

S. Hocker, E. Wijdicks. *Neurology, Mayo Clinic, Rochester, USA*

Neurologists must be prepared to address a wide array ofneurologic problems in clinical practice, many of which are attributable toeither medical therapies or surgical procedures. These complications may resultin significant morbidity or mortality and should be recognized early in orderto interrupt those processes which are potentially modifiable. While some of these neurologic complicationshave been observed and carefully documented over many years, others have only beenrecently described and new therapies are always accompanied by their own set ofcomplications. In this review we will discuss neurologic complications of cardiacsurgeries and procedures and of medical therapies including antimicrobials,cytotoxic drugs, and critical care in general.

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1667
WFN15-1882
Hospital Neurology MT 13.1
Neurological complications of cardiac surgery and interventional cardiology

J. Biller. *Neurology, Loyola University Chicago Stritch School of Medicine, Maywood, USA*

Neurological complications of cardiac surgery and interventional cardiology
José Biller, MD, FACP, FAAN, FANA, FAHA

Neurologic complications of cardiac surgery and interventional cardiac procedures may affect the central nervous system (CNS) or the peripheral nervous system (PNS). The most common CNS complications are strokes and seizures. This presentation provides a succinct neuro-anatomic and pathophysiologic approach to a wide array of CNS and PNS complications associated with selective cardiac procedures including coronary artery bypass graft (CABG), heart valve replacement, cardiac transplantation, cardiac catheterization, percutaneous coronary interventions, electrophysiological studies, surgery for congenital heart disease, and aortic surgery.

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1668
WFN15-1922
Hospital Neurology MT 13.1
Neurological complications after solid organ transplantation

A. Pruitt. *Department of Neurology, University of Pennsylvania, Philadelphia, USA*

Solid organ transplantation (SOT) is the preferred treatment for an expanding range of conditions whose successful therapy has produced a growing population of chronically immunosuppressed patients with potential neurological problems. While the spectrum of neurological complications varies with the type of organ transplanted, the indication for the procedure, and the intensity of long-term required immunosuppression, major neurological complications occur with all SOT types. This presentation reviews central and peripheral nervous system problems associated with SOT with clinical and neuroimaging examples from the author's institutional experience. Particular emphasis is given to conditions acquired from the donated organ or tissue, problems specific to types of organs transplanted and drug therapy-related complications likely to be encountered by hospitalists. Neurologically important syndromes such as immune reconstitution inflammatory syndrome (IRIS), posterior reversible encephalopathy syndrome (PRES), and posttransplantation lymphoproliferative disorder (PTLD) are addressed. Opportunistic infections, including progressive multifocal leukoencephalopathy, varicella zoster virus, and fungal meningitis, and infections associated with the transplanted organ.are also covered.

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1669
WFN15-1788
Neuro-Oncology MT 14.1 - GLIOMAS
Defining the role of radiotherapy and alkylating agent chemotherapy

S. Chang. *Neurological Surgery, UCSF, SF, USA*

Because of the infiltrative nature of glioma, adjunctive therapies, even in the setting of a gross total resection, are warranted for tumor control and to improve survival. Radiation therapy has been the mainstay of treatment for glioma for decades. Technological advances have been incorporated into radiation treatment paradigms with the goal of maximizing tumor control, while minimizing the adverse effects on normal brain thereby maintaining neuro-cognitive function and quality of life. The role of alkylating therapy has recently been defined for glioblastoma, anaplastic oligodendroglioma with codeletion of 1p19q and low grade glioma. The goal of this presentation is to review the role of radiotherapy and alkylating chemotherapy in the management of glioma.

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1670
WFN15-1941
Neuro-Oncology MT 14.1 - GLIOMAS
Angiogenesis inhibition: quo vadis

T. Batchelor. *Neuro-Oncology, MA General Hospital, Boston, USA*

Angiogenesis Inhibitors: *Quo Vadis*
Tracy Batchelor, M.D., Massachusetts General Hospital, Harvard Medical School

The United States Food and Drug Administration has approved 10 anti-angiogenic drugs for over 12 types of cancer since 2001. Bevacizumab, a monoclonal antibody that binds the vascular endothelial growth factor (VEGF)-A ligand, received accelerated approval in the United States as monotherapy for recurrent glioblastoma in 2009. This approval was based on radiographic response rates in two prospective studies. However, bevacizumab did not improve overall survival in two subsequent, randomized phase III trials in patients with newly diagnosed glioblastoma. To date, no survival benefit for newly diagnosed or recurrent glioblastoma patients has been demonstrated in randomized phase III trials of 3 different anti-angiogenic agents (bevacizumab, cediranib, cilengitide). Controversy remains regarding the mechanism of action of this class of agents in glioblastoma and whether survival will ultimately be extended by these expensive and potentially toxic biologics/drugs. Combinations of anti-angiogenic drugs with other drugs may be required to improve survival, similar to other solid cancers. These trials are ongoing. A challenging aspect of anti-angiogenic drug development in glioblastoma is the lack of validated biomarkers of tumor response and tumor resistance. Moreover, defining tumor response and tumor progression in the setting of anti-VEGF therapy has highlighted the limitations of conventional imaging endpoints in this disease. Revised response criteria for anti-angiogenic agents have been developed and incorporated into prospective clinical trials. Magnetic resonance imaging (MRI) and positron emission tomography (PET) techniques that may accurately predict response and progression are under development.

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1671
WFN15-1787
Neuro-Oncology MT 14.1-GLIOMAS
Immunotherapy: new hype or hope?

M. Weller. *Department of Neurology, University Hospital Zurich, Zurich, Switzerland*

The current standard of care for glioblastoma of resection followed by involved-field radiotherapy and concomitant and maintenance temozolomide chemotherapy (TMZ/RT → TMZ) prolongs survival to a median of 16 months in clinical trial populations, but survival with glioblastoma is still below 12 months on a population level. Immune inhibition is one of the biological hallmarks of glioblastoma, prompting the clinical development of various immunotherapeutic strategies that are at present explored in phase I-III clinical trials. Efforts focusing on the antagonism of glioma-associated immunosuppression alone, e.g., blocking the transforming growth factor (TGF)-β pathway, have not been successful. However, abrogating inhibitory signalling to T cells via cytotoxic T lymphocyte-associated protein (CTLA)-4 or programmed death (PD)-1 using various neutralizing antibodies has generated new hope not only for several solid cancers outside the brain, but also for glioblastoma. Various vaccination approaches are also being tested, including dendritic cell-based vaccines, using either crude tumor lysates (DCVax) or tailored mRNA or peptide stimulation (ICT-107). The most advanced approach explored in phase III (ACT IV) is based on the vaccination against a mutant variant of the epidermal growth factor receptor (EGFR), EGFRvIII, which is expressed in approximately 20-30% of all primary glioblastomas. This mutation results in inability to bind ligand and constitutive signalling activity. Moreover, EGFRvIII represents a unique tumor antigen exhibiting a novel peptide sequence and may thus represent one of the most specific tumor antigens in glioblastoma. Phase II trials in glioblastoma patients with EGFRvIII-positive tumors without progression after radiotherapy and concomitant temozolomide chemotherapy treated with the vaccine rindopepimut showed encouraging progression-free and overall survival compared with historical controls, providing the basis for the ongoing randomized, double-blind phase III trial (ACT IV). Meanwhile, the ReACT trial also provides evidence for efficacy of this vaccine at recurrence. High-throughput analyses involving genome, transcriptome, and proteome are likely to result in

the delineation of novel glioma-specific targets for novel immunotherapy approaches in the near future.

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1672
WFN15-1885
Hospital Neurology MT 13.2
An update on 'Paraneuroplastic syndromes of the central and peripheral nervous systems

E. Dropcho. *Neurology, IN University, Indianapolis, USA*

Neurological paraneoplastic disorders are relatively uncommon but clinically important complications of a variety of systemic neoplasms. Paraneoplastic neurological syndromes may present as any of a wide variety of clinical syndromes affecting the peripheral and/or central nervous system and are often a diagnostic challenge. The neurological syndrome is often the presenting feature of the associated neoplasm, so neurologists must be able to recognize and diagnose the syndrome promptly. There is no neurological syndrome which is invariably associated with a tumor, as each can occur with varying frequency in a “non-paraneoplastic” setting. Most paraneoplastic disorders are caused by an autoimmune reaction against shared "onconeural" antigens expressed by the tumor and in the nervous system. Many affected patients have one or more circulating antineuronal or onconeural autoantibodies. There are good but not perfect associations among particular clinical syndromes, autoantibodies, and tumor types. If present in a patient with neurologic impairment, these antibodies raise the suspicion for a paraneoplastic etiology and often guide the search for the underlying neoplasm. Some autoantibodies, particularly those reacting with cell-surface or synaptic protein antigens, directly mediate neuronal dysfunction. For other antibodies and syndromes the immunopathogenesis is less well understood and probably involves cell-mediated neuronal injury. The neurologic outcome of affected patients lies along a spectrum: for some syndromes prompt diagnosis and treatment of the underlying tumor and immunotherapy increase the likelihood of a favorable neurologic outcome, while other patients suffer severe and permanent neurologic disability despite treatment.

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1673
WFN15-1876
Hospital Neurology MT 13.2
B12 and the nervous system

N. Kumar. *Neurology, Mayo Clinic, Rochester, USA*

Optimalfunctioning of the nervous system is dependent on a supply of appropriatenutrients. Particularly important for functioning of the nervous system iscobalamin (vitamin B_{12}; B_{12}). Vitamin B_{12} deficiencyis common in the elderly and after gastric surgery. Many patients withclinically expressed B_{12} deficiency have intrinsic factor-relatedmalabsorption such as that seen in pernicious anemia. Thecommonly recognized neurological manifestations of B_{12} deficiency includea myelopathy with or without an associated neuropathy. MRI abnormalities in B_{12}deficiency include a signal change in the posterior and lateral columns andless commonly subcortical white matter. The clinical presentation is similar tothe myeloneuropathy seen with copper deficiency. Clues to possible B_{12} deficiencyin a patient with polyneuropathy include a relatively sudden onset of symptoms,findings suggestive of an associated myelopathy, onset of symptoms in thehands, concomitant involvement of upper and lower limbs, macrocytic red bloodcells, and the presence of a risk factor for B_{12} deficiency. SerumB_{12} can be normal in some patients with B_{12} deficiencyand serum methylmalonic acid and total homocysteine levels are useful indiagnosing patients with B_{12} deficiency. The presence of a low B_{12}in association with neurological manifestations does not imply cause and effect.The incidence of cryptogenic polyneuropathy, cognitive impairment, and cobalamindeficiency increase with age and the latter may be a chance occurrence ratherthan causative. Thegoals of treatment are to reverse the signs and symptoms of deficiency, repletestores, ascertain the cause of deficiency, and monitor response to therapy.

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1674
WFN15-1859
Neuro-Oncology MT 14.2 - Cell Signaling and Targeted Therapy in Neuro-Oncology
Genomics and targeted therapy for meningiomas

R. Soffietti. *Neuro-Oncology, University Hospital of Turin, Torino, Italy*

Meningiomas are the most frequent intracranial tumors. Most meningiomas are curable by surgical resection. However, tumors that are not completely resectable and tumors with histological signs of increased malignancy (WHO grade II and III meningiomas) tend to progress/recur. Salvage treatment for such cases usually comprises re-resection, radiotherapy and systemic drug therapy. A variety of drugs has been studied in meningiomas, including hydroxyurea, temozolomide, irinotecan, interferon-alpha, mifepristone, octreotide analogues, megestrol acetate with no or very limited activity. Based on a recent comprehensive literature review antiangiogenic agents (bevacizumab, sunitinib, vatalanib) seem to provide rational treatment opportunities against meningioma, as upregulation of angiogenic pathways has repeatedly been described in these tumors. Clinical trials evaluating specific inhibitors in meningiomas bearing SMO or AKT mutations are being launched.

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1675
WFN15-1796
Neuro-Oncology MT 14.2 - Cell Signaling and Targeted Therapy in Neuro-Oncology
The challenge of targeted therapies for glioblastoma

C. Fadul. *Medicine, Dartmouth-Hitchccock Medical Center, Lebanon, USA*

Surgery, radiation and cytotoxic chemotherapy have marginally improved the survival of patients with glioblastoma; 5 year survival is less than 10%. Genomic sequencing of glioblastoma identified that the typical tumor has in average 60 genetic alterations in three major pathways:receptor tyrosine kinase cell signaling, p53 tumor suppression, and retinoblastoma tumor suppression pathways. An increasing number of potential therapeutic agents that can target these genomic alterations have become available. Their benefit in other types of cancer prompted clinical trials in glioblastoma with limited efficacy. Potential reasons include the blood-tumor barrier, tumor genomic heterogeneity, and cellular mechanisms of resistance. There are examples of response to targeted therapy in other gliomas, like in subependymal giant cell astrocytomas treated with mTOR inhibition and in a small number of glioblastomas with the BRAF V600E mutation treated with BRAF/MEK inhibitors. The clinical trials using targeted therapies will have to select patients according

to the genomic alterations from tissue obtained from several tumor regions, use biomarkers that will help identify patients who will benefit the most, and measure concentrations of the agent in tumor and surrounding brain. An effective approach will likely require of multiple agents to overcome resistance, and therefore the safety and pharmacokinetics of combinations will have to be assessed in these studies. Incorporation of tumor genetic profiling into clinical practice involve an interdisciplinary Tumor Board that can take these principles into account. The goal is to eradicate glioblastoma by personalizing targeted therapy according to tumor genetic alterations and individual pharmacogenomic characteristics.

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1676
WFN15-1942
Plenary Lecture 3 – Stroke
Cerebral microhemorrhage: update for the practicing neurologist

C. Cordonnier. *Neurology & stroke unit, Univ Lille, Lille, France*

Cerebral microhaemorrhages (CMHs) are small dot like lesions appearing as hyposignal on gradient echo T2* MR sequences. The development of specific MR sequences raised the interest in this radiological construct that is meant to represent a specific underlying microscopic pathology: perivascular collections of hemosiderin deposits. Those lesions, which were considered as rare and silent before, are becoming frequent and clinically meaningful.

Cerebral microhaemorrhages are interesting biomarkers both from diagnostic and prognostic perspectives. Indeed, deep CMHs may suggest deep perforating vasculopathy while the presence of lobar CMHs is suggestive of cerebral amyloid angiopathy. These radiological biomarkers are becoming surrogate markers for clinical trials and they may eventually help tailoring therapeutic strategies to prevent ICH recurrences and functional decline.

In the setting of ischaemic strokes, CMHs might influence the benefit-risk ratio of long term anticoagulation. In the acute phase, when the administration of iv rtpa is discussed, CMHs might trigger anxiety for the neurologist on duty…

In Alzheimer's disease, CMHs are of special interest as they may have a crucial role in the pathophysiology of AD. Moreover, they may affect clinical course of the disease and may have therapeutic implications. Moreover, the predictive power of BMBs for future cognitive impairment is currently explored both in stroke but also in population-based settings (in so called "healthy" cohorts).

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1677
WFN15-1917
Plenary Lecture 4 - Yahr Award Lecture
New concepts in headache

J. Olesen. *Danish Headache Centre Department of Neurology, Glostrup Hospital University of Copenhagen, Glostrup, Denmark*

Headache is, compared to its prevalence and socio-economic costs, the least funded of all neurological subjects. Nevertheless, impressive advances have been made over the last decade. The diagnosis has been improved by the advent of the second and the third edition of the International Classification of Headache Disorders. Diagnoses are now uniformly made throughout the world. The genetics of headache disorders is an advancing field. So far three genes have been identified in which mutations cause the rare monogenic familial hemiplegic migraine and in a huge meta-analysis using GWAS 38 independent loci have been associated with migraine without aura and migraine with typical aura. Environmental factors have been more difficult to document but low education, low socioeconomic status and hard physical exercise have been identified. The pathophysiology involves important messenger molecules such as nitric oxide, calcitonin gene-related peptide, pituitary adenylate cyclase activating peptide and, interestingly, hypoxia as encountered in high altitude. All provoke migraine. New therapies have changed the field. Candesartan has appeared as a drug of choice for migraine prophylaxis and phase 2 studies have proven efficacy of antibodies against calcitonin gene-related peptide in migraine prophylaxis. Small molecule CGRP receptor antagonists have proven efficacious in acute attack treatment but none is currently in clinical development, possibly due to lever toxicity. Botulinum Toxin A has been registered as a prophylactic agent in chronic migraine.Finally, an international definition of tertiary academic headache referral centers has been developed and such centers have proven their value in even the most difficult chronic headache patients.

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1678
WFN15-1662
WFN Medals Presentation and Presidential Symposium
Neurexins and Company: towards a molecular logic of neural circuits

T. Südhof. *HHMI & Dept. of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, USA*

Neurexins are presynaptic cell-adhesion molecules that bind to postsynaptic ligands to form trans-synaptic cell-adhesion complexes. Neurexins bind to multiple ligands, including neuroligins, LRRTMs, and the complex of cerebellins with GluRd2. The interactions of presynaptic neurexins with their postsynaptic ligands primarily function as signaling complexes that are essential for synapse function, and that shape the properties of synapses such as short- and long-term plasticity. Neurexins are encoded by three extraordinarily large genes, each of which generates longer a- and shorter b-isoforms that are in turn diversified into thousands of alternatively spliced transcripts. The various splice variants of neurexins and the various isoforms of their ligands exhibit strikingly different functional activities and binding affinities; their interactions are likely competitive, and contribute to determining the properties and nature of synapses. Although accumulating evidence demonstrates that neurexins and their ligands perform central functions in the assembly and function of neural circuits, but their precise roles and mechanisms of action are only now beginning to emerge. Moreover, although many mutations in neurexin and their ligands have been associated with autism, schizophrenia and other neuropsychiatric disorders, the mechanisms by which such mutations predispose to these devastating disorders are not understood. In my talk, I will describe our recent studies on how neurexins and their ligands shape synapse properties, and how dysfunction of neurexins and their ligands might predispose to neuropsychiatric disorders such as schizophrenia.

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1679
WFN15-1634
WFN Medals Presentation and Presidential Symposium
DNA Aβ 42 vaccination as therapy to prevent alzheimer's disease

R. Rosenberg, D. Lambracht-Washington. *Neurology & Neurotherapeutics Physiology, University of Texas Southwestern Medical Center, Dallas TX, USA*

DNA Aβ42 vaccination in which DNA encoding the Aβ42 peptide is injected is presented as potential therapy to delay or prevent Alzheimer's disease. The injected DNA is translated in the immunized individual to produce Aβ peptide which then triggers immune responses against the Aβ42 peptide.

We are the first to show that DNA Abeta42 vaccination administered with the gene gun is highly effective to reduce Aβ42 levels in brain by 41% and the Aβ42-containing plaques by 50% in Alzheimer transgenic

mouse models (Qu et al., 2004; 2006, 2007) which was confirmed later in studies by others. The immune response is Th2 (IgG1) in the Alzheimer transgenic mouse and IgG and IgA in New Zealand white rabbits. DNA Aβ42 vaccination is non-inflammatory, as it induces a Th2 immune response (IgG1) and does not produce the pro-inflammatory factors: γ interferon and Il-17 and does not induce proliferation of cytotoxic CD8 cells, all of which are induced in Aβ42 peptide vaccination, resulting in the stopping of a clinical trial. Our research describes the effectiveness, safety and potential therapeutic value of DNA Aβ42 vaccination in persons at risk for Alzheimer's disease.

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1680
WFN15-1920
WFN Medals Presentation and Presidential Symposium
The WFN - the way Ahead

R. Shakir. *President, World Federation of Neurology, London, United Kingdom*

There has been a massive change in Neurology over the past ten years of so. Our depth and spectrum has vastly moved on. We are more aggressive in our approach to disease management and our abilities have vastly improved in neuroimaging, genetics and perhaps as importantly if not more in therapeutics.

Our ability to meaningfully intervene early on, in major brain disorders has put us in the driving seat of acute emergency management. This is now recognised by our fellow physicians in all aspects of care. Neurologists are no longer those who have a vast knowledge of neuroanatomy, physiology, pathology and precise localization in the nervous system, but to trained individuals who in addition provide interventions which are proven to be of material value in their patients physical well being.

This material change is now being translated to the recognition by health care providers of the importance of prevention and management of neurological disorders. The WFN is working closely with the WHO in tackling various disorders such as Dementia, Stroke and epilepsy among many others. The time has come for Neurology to flourish and get the recognition it thoroughly deserves from the public and health care providers.

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1681
WFN15-1807
Plenary Lecture 7
Functional disorders

J. Stone. *Centre Clinical Brain Sciences, University of Edinburgh UK, Edinburgh, United Kingdom*

Functional disorders in neurology: Changing a negative to a positive

Functional symptoms and disorders (also called psychogenic, non-organic and conversion disorders) are a common cause of distress and disability and account for around 1 in 6 new referrals to the neurology clinic. In the last 10-15 advances in understanding, diagnosis and treatment of patients with functional disorders have changed the clinical landscape[1]. These are turning traditionally negative views in to a more positive approach which brings these disorders back within standard neurological practice.

In this lecture I will discuss: 1) The importance of making the diagnosis, not on psychosocial grounds or as a diagnosis of exclusion, but using positive diagnostic clinical signs, such as Hoover's sign of functional leg weakness or the entrainment test of functional tremor; 2) The central role of the neurologist in providing explanation, information (for example www.neurosymptoms.org), and triage of treatment (with some practical examples); 3) Increasing recognition of the evidence base for physiotherapy[2] as well as psychological therapy[3]; 4) Changes in the model that we use to think about the mechanism and aetiology of these problems which now incorporate biological as well as psychological factors[4].

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1682
WFN15-1670
Plenary Lecture 8 - Victor & Clara Soriano Award Lecture
The Physiology of Will

M. Hallett. *Human Motor Control Section, NINDS, Bethesda, USA*

Free will is the perception that people have that they choose to make (most of) their movements. This perception includes both a sense of willing the movement and self-agency that their act of willing was responsible for the movement that was made. The physiology of free will is of interest to neurologists not only for its own sake but also because of the abnormalities of will often encountered in clinical practice. For example, the movements in functional movement disorders look voluntary, but the patients experience them as involuntary. Experiments show that even normal voluntary movements arise subconsciously and the perceptions of willing and agency arise after the fact. There remains some controversy as to whether the sense of willing itself is a driving force for movement, but there do not need be any paradoxes if it is properly understood that the mind is a product of the brain.

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1683
WFN15-1838
Plenary Lecture 9 - Fulton Society Symposium-Soriano Award Lecture
The mirror mechanism and its clinical relevance

G. Rizzolati. *Neurscience, University of Parma, Parma, Italy*

The mirror mechanism and its clinical relevance
Giacomo Rizzolatti, Dipartimento di Neuroscienze, University of Parma, Italy

Mirror neurons are a distinct set of motor neurons that discharge both when the monkey *executes* a specific motor act and when it *observes* another individual doing a similar act. In the first part of my talk, I will review the basic functional properties of monkey mirror neurons. I will show then that mirror neurons encode the goal of motor acts. I will review then their visual properties showing that mirror neurons represent a mechanism that allows a *direct understanding* of what the agent is doing.

Mirror mechanism also exists in humans. I will present fMRI and EEG data proving it and will show that, although there are other mechanisms through which one can understand the behaviour of others, the mirror mechanism is the only one that allows understanding others from the inside providing the observer with a *"first-person"* person grasp of others' motor goals, intentions and emotions.

I will address then some clinical problems and namely the relationship between the mirror mechanism and autism with particular emphasis on Stern's vitality forms, and the neural basis of "action observation" treatment in motor rehabilitation after stroke and other motor disturbances.

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1684
WFN15-1700
Plenary Lecture 10 - Bharucha Award Lecture
Guillain-Barré Syndrome and CIDP: one disease or many?

R. Hughes. *Cochrane Neuromuscular Disease Group, Institute of Neurology, London, United Kingdom*

Guillain-Barré Syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) form a fascinating spectrum of diseases of varying severity, time course, anatomical distribution, pathology and system involvement. The most acute forms of GBS merge through subacute inflammatory demyelinating polyradiculoneuropathy with CIDP. GBS may show early recurrence after treatment but eventually recover and sometimes CIDP has an acute onset. Painstakingly constructed, but arbitrary, diagnostic criteria have served the research community for epidemiological studies and recruitment into randomised trials. Astute clinical observations have added Fisher syndrome, Lewis-Sumner syndrome and multifocal motor neuropathy to the clinical spectrum. Within GBS, detailed pathological studies, characteristic antibodies and animal experiments have largely explained the pathogenesis of acute motor axonal neuropathy and distinguished it from acute inflammatory demyelinating polyradiculoneuropathy. Other characteristic antibodies distinguish and explain Fisher syndrome. Work continues to identify biomarkers and explain the pathogenesis of the rest of the GBS and CIDP spectrum. Paraprotein associated chronic inflammatory neuropathies with antibodies to minor myelin proteins or gangliosides inform this research. Differences in treatment response of different members of the spectrum, most notably to corticosteroids, indicate different underlying mechanisms and complicate treatment of these, often very disabling, diseases.

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1685
WFN15-1804
Plenary Lecture 11
Can MRI replace clinical neuro-ophthalmology?

C. Kennard. *Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom*

Historically clinical neuro-ophthalmology was an area of neurology, par excellence, where the history and the clinical examination, which required a detailed knowledge of neuroanatomy, would usually provide the localization of the site of the pathological lesion and some indication of its underlying aetiology. In many cases MRI can, often with even more accuracy, do as good a job of localization and pathological diagnosis. But there is far more to being a clinical neuro-ophthalmologist than merely ordering an MRI scan. Firstly, clinical assessment needs to precede scanning to ensure that the appropriate scan is requested. Secondly, there are many patients with neuro-ophthalmological disorders in whom the imaging is normal, who require a full history and detailed examination to enable the patient to be directed to other more timely and appropriate investigations. Thirdly, the neuro-ophthalmologist is essential to correctly interpret for the patient the relevance of non-specific or benign findings, which are often reported on MRI. Finally, whatever the MRI scan may reveal a well trained neuro-ophthalmologist is then required to direct the patient to the most appropriate therapeutic procedure, be it a neurosurgical intervention, some pharmacological agent or masterly inactivity.

Using a variety of neuro-ophthalmological patient histories the case will be made that despite the advent of MRI the clinical neuro-ophthalmologist is still essential for the provision of safe patient care and rapid diagnosis.

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1686
WFN15-1881
Regional North American Symposium
Management of Acute Strokes – evolving approaches

J. Biller. *Neurology, Loyola University Chicago Stritch School of Medicine, Maywood, USA*

Management of Acute Strokes – Evolving Approaches
José Biller, MD, FACP, FAAN, FANA, FAHA

Management of patients with acute ischemic stroke (AIS) is multifacetic. This presentation focuses on recent data, and evidence-based recommendations, on the timely restoration of blood flow using new generation mechanical thrombectomy stent retrievers for highly selected subgroup of patients with AIS due to large artery occlusive disease of the proximal anterior circulation.

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1687
WFN15-1780
Regional Pan-Arab Symposium
Epilepsy

H. Hosny, A. Ashmawi. *Neurology department, Cairo University, Cairo, Egypt*

Prognosis of Newly Diagnosed Patients with Epilepsy
Hassan S.Hosny MD
Prof of Neurology , Cairo University

Background: Although Epilepsy is one of the most common neurological conditions**,** Limited data are available on the clinical patterns of treatment response in newly diagnosed epilepsy.
Objective: To identify the different clinical pattern of outcome of epilepsy in the newly diagnosed patients and the strong predictors of failure to achieve 2 years seizure remission.

Methodology: In this retrospective study we collected the data of **239** patients from all ages with newly diagnosed epilepsy between the year 1994 and 2008 that were diagnosed by single senior epileptologist and followed up for at least four years at specialized epilepsy center in Egypt. The patients were divided into two groups (poor and good control) and compared for clinical characteristics.
Results: A total of 239 patients with newly diagnosed epilepsy were included. Early remission was achieved in (**73.6**%) while (**12.1**%) entered late remission. Thirty four patients (**14.2**%) failed to achieve 2 years seizure remission. Twenty six patients (**10.9**%) have drug resistant epilepsy.Terminal remission uninterrupted by relapse was noted (**25.1**%) indicating a remitting course of epilepsy. Out of (85.5%) patients who achieved a two years remission, the events of relapse occurred in (**60.7**%), indicating a remitting–relapsing course of epilepsy. **10.1** % of the patients had remission which was followed by relapse and never regained terminal remission with a worsening course of epilepsy. The prognosis for patients with 6 seizures before starting treatment and bad response to the first AED is unfavorable.
Conclusion: The prognosis of the majority of patients with newly diagnosed epilepsy is good and the clinical pattern of epilepsy during treatment is complex and dynamic. Predictors for failure of achievement of 2 years seizure remission were high pre-treatment seizure frequency (≥6) and bad response to first AED.

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1688
WFN15-1871
Regional Pan-Arab Symposium
Movement disorders

S. Bohlega. *Neurosciences, King Faisal Specialist Hospital & Research Centre, Riyadh, Kingdom of Saudi Arabia*

Parkinson Disease in the Arab World

There are scares reports originating from the Middle East regarding the epidemiology and genetic data of various movement disorders among Arabs. The incidence of PD reported from Libya, Saudi Arabia, Tunisia, Egypt and Palestinians in Israel are remarkably lower than other parts of the world. As most of the Arab population is young which may explain the low incidence and prevalence which ranges from 27 to 43. The incidence of PD is reported at 4.5 per 100,000.

Most of the responsible genes described in Arabs are inherited as autosomal recessive like Parkin and PINK1, ATP13A2, DJ-1, and PLA2G6. The G2019S LRRK2 mutation is more common in both familial (37-42%) and apparently sporadic PD (41%) in North African Arabs than in European and North Americans (2-3%). This frequency is the highest reported anywhere in the world so far. However, recent study from other Middle Eastern Countries did not show similar findings. Methodological issues and population age structures could partially explain the differences in incidence and prevalence studies among different Arabic countries. Additional epidemiological and genetic studies from the majority of Arabic countries are needed to enhance our understanding of PD.

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1689
WFN15-1866
Regional Pan-Arab Symposium
Genetics of recessive ataxia

C. Mhiri. *Neurology, Habib Bourguiba Hospital, Sfax, Tunisia*

Recessive ataxia: Study of Tunisian series and literature review Autosomal recessive cerebellar ataxias (ARCA) are a group of little known and often neglected diseases. Cerebellar ataxia is the prominent sign (movement incoordination, unsteady gait…) and has a progressive and unremitting course (chronic).

In our department we reviewed all cases of progressive ataxia occurring during childhood or adolescence with a pedigree suggestive of autosomal recessive mode of inheritance. We excluded acquired causes of progressive ataxia (tumor…). Using these criteria, we collected 107 cases belonging to 56 families (56 index cases and 51 secondary cases, 60 are male and 47 female). The mean age of onset was 11.2 + 6.8 years (range: 2.5 – 32). The prevalence of ARCA in our population is about 4 cases/100.000. Forty two patients had Friedreich ataxia (FA) phenotype. In this group, genetic study demonstrated that 25 cases are ataxia with vitamin E deficiency, 12 are FA, 3 are ataxia with ocular apraxia (AOA) type 2 and unknown genetic abnormality in two. 28 cases presented ataxia with telangiectasia (AT) and/or ocular apraxia. Genetic testing showed that 17 cases are AT, 8 AOA2, one AOA1 and no linkage to known loci in 2 case. 37 cases had spastic ataxia, 8 patient linked to ARSACS gene, 3 to SAX2, 6 to SPG11, 5 to SPG 46 and 15 patients are not linked to known genes.

ARCA usually occurs during childhood or adolescence however the onset of autosomal dominant ataxias is late over the age of 30 years. Clinical picture permit to orientate genetic study.

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1690
WFN15-1696
Regional Asian-Oceanian Symposium
Evolution, current status and way forward for AOAN

M. Mehndiratta[a], P. Mehndiratta[b], C. Tsai[c], R. Kaji[d], N. Gulati[e], M. Wasay[f]. *[a]Neurology, Janakpuri Superspecialty Hospital, New Delhi, India; [b]Neurology, Vascular Neurology Fellow University of Virginia VA 22908, Charlottesville, USA; [c]Neurology, Chief of the Neurological Institute at Taipei Veterans General Hospital and National Yang-Ming University, Taipei, Taiwan; [d]Neurology, Professor and Chairman Department of Neurology Institute of Health-BioscienceTokushima University, Kuramoto-cho, Japan; [e]Pathology, Janakpuri Superspeciality Hospital, New Delhi, India; [f]Neurology, Aga Khan University, Karachi, Pakistan*

Evolution, Current Status and Way Forward for AsianOceanian Association of Neurology (AOAN)

AOAN was established in 1961 with the primary aim of promotingneurological advancement via the exchange of ideas for development of educationprograms in Neurology and to encouragescientific research geared towards neurological diseases that are a majorhealth burden in the Asian-Oceanian countries.

Over the years, AOCN has consistently brought togetherneurologists from the various member countries and has thus established itselfas an academic congress serving the needs of physicians in the Asian andOceanian realm. The membership of the association has grown over the years.

Education and training of physicians inNeurology, is a top priority for AOAN. Developing standardized trainingprograms and courses for countries where there is an undersupply ofneurologists are top priorities. AOAN is extending financial and expertisesupport for CME in Afghanistan. We have plannedto use this model for other developing Asian countries especially Myanmar,Cambodia, and Laos etc.

AOAN in collaboration with the WFN envisions holding CME programs in the countriesthat have limited resources with a long-term goal to uphold standardsof neurologic care provided in these areas like Central Asian countries.

The challenges are many, but at the same time great opportunityexists for AOAN to implement strong and productive initiatives. Publicawareness and advocacy related to neurological diseases, development ofregional and local Neurology forums, and facilitation of training andmentorship efforts are important areas of work in the present Asiancontext.

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1691
WFN15-1797
Regional Asian-Oceanian Symposium
Evaluation and management of ALS

M.C. Kiernan. *Clinical Neurosciences, Brain and Mind Centre University of Sydney, Sydney, Australia*

Amyotrophic lateral sclerosis (ALS), colloquially known as Lou Gehrig's disease, is a rapidly progressive and universally fatal neurodegenerative disorder of the human motor system, first described in the mid-19th century. Although ALS is clinically characterized by progressive neurological deterioration and co-existence of upper and lower motor neuron signs, recent discoveries have indicated a heterogeneous nature of ALS. Despite the clinical heterogeneity, median survival of ALS remains 3 years, with 10% of patients surviving over 8 years.

Over the past decade, evidence has emerged of unique pathophysiological processes, including glutamate-mediated excitotoxicity, which has resulted in development of novel diagnostic investigations and uncovered potential therapeutic targets. Advances in genetics, including the recently discovered C9orf72 gene, have radically changed the pathological mind-set, from ALS being classified as a neuromuscular disease to one that ALS forms a continuum with other primary neurodegenerative disorders, including frontotemporal dementia.

In the absence of a curative therapy, the management of ALS remains focused on symptom control, with the primary aim of maintaining quality of life. Evidence-based management guidelines advise a multi-disciplinary model of care, led by a neurologist and clinical nurse consultant working together with physical therapists, occupational therapists, speech pathologists, respiratory physicians, gastroenterologists, psychologists and social workers to guide patient management, and such an approach has profoundly impacted on the patients quality of life and survival.

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1692
WFN15-1837
Regional Asian-Oceanian Symposium
Burden and genetics of Parkinson's disease in Asian Oceanian Region

H. Mizusawa. *Neurology, National Center Hospital National Center of Neurology and Psychiatry, Tokyo, Japan*

Parkinson's disease (PD) is the second most common neurodegenerative disorder which is characterized by not only movement abnormalities including tremor, akinesia, muscle rigidity, dyskinesia and fluctuation of these symptoms, but also non-motor symptoms such as dementia, depression, hallucination, anosmia and autonomic dysfunction. These signs and symptoms cause disability and disturb quality of life. Therefor PD places a heavy burden on patients themselves of course and on caregivers in addition. In Asia Oceania region where about 60% of the world's population resides, the burden of PD is tremendous while the prevalence and incidence of PD may be slightly lower than those in Western countries. Furthermore, our society's population is rapidly ageing and it is estimated number of PD patients in 2005 would be doubled by the year 2030 in the world.

Genetic aspects appear very important in order to elucidate regional characteristics. Currently reported have been many monogenic loci/PD (Park1 to Park20) and more than 10 risk loci of which GBA and LARK2 showed higher odds ratios about 3 and 2 respectively. In many other risk loci including SNCA, odds ratios are relatively low. G2385R variant of LARK2 seems unique to east and south Asian population and is not found in European people. R1628P variant of LARK2 may be a risk only in Chinese. The epidemiological and genetic studies in Asia Oceania region would contribute a lot to better understand characteristics of PD not only in the region but also in other areas, and to develop better strategies to overcome PD.

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1693
WFN15-1782
Regional Asian-Oceanian Symposium
National stroke registries: what can we learn from them?

N. Bornstein. *Neurology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel*

Clinical registries play an important role in measuring healthcare delivery and supporting quality improvement for individuals with cardiovascular disease and stroke. Well-designed clinical registry programs provide important mechanisms to monitor patterns of care, evaluate healthcare effectiveness and safety, and improve clinical outcomes. The use of clinical registries is likely to grow given the increasing focus on measuring and improving healthcare delivery and patient outcomes by stakeholders in both the private and public sectors.

The focus of clinical registries is to capture data that reflect "real-world" clinical practice in large patient populations. The data from clinical registries do not replace the need for traditional randomized controlled trials. Rather, registries and trials are complementary approaches, each with unique advantages and imperfections.[2] Such clinical registries do not solely contain claims or administrative data yet may be linked to such data sources.

Clinical registries also provide the opportunity to identify and evaluate healthcare disparities within a broad patient population in community practice outside of the structured research protocol setting. This promotes the ability to examine important issues involving patient access and outcomes in subpopulations, including racial and ethnic minorities, women, the elderly, individuals with multiple comorbidities, and individuals with congenital heart conditions.

National Acute Stroke Israeli Survey (NASIS) ia a tri-annual prospective national registry conducted over a period of two consecutive months in order to assess trends in incidence, characteristics, management, and outcome of hospitalized patients with acute stroke and TIA. Includes all stroke patients admitted to hospitals nationwide, thus avoiding institution and patient selection bias. NASIS registry intotal over 8,000 patients (2004-2013).

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1694
WFN15-1777
Regional Pan-African Symposium
Neuro-HIV

W. Howlett. *Internal Medicine, Kilimanjaro Christian Medical Centre, Moshi, Tanzania*

It is estimated that 35 million people are infected with HIV globally of whom >70% live in SSA. Neurological disorders (NDs) are common affecting at least 70% of HIV infected persons in SSA. They are caused mostly by opportunistic infections (OIs) and primary HIV infection. The main CNS/OIs (24%) are meningitis (14%) and focal brain lesions (10%). Primary HIV infection of the nervous system mainly results in HIV associated neurocognitive disorders (HAND) (49%), neuropathy (52%) and vacuolar myelopathy (16%). Neuropathies arising from autoimmune based inflammation also occur but are uncommon (<1%). The main causes of meningitis are: *cyrptococcus (CM) 52%, tuberculous meningitis(TBM) 20%, acute bacterial meningitis (ABM) 14% & others 14%.* Focal brain lesions are caused mostly by infections: *toxoplasmosis (9%) and tuberculosis (1%).* In 2013, a total of 1.5 million deaths from HIV were reported globally, of which 1.1 million were from SSA. The leading causes were tuberculosis: (*pulmonary/systemic)*, pneumonia and bacteraemia (>40%) followed by CNS/OIs (20-25%). The case fatality rate (CFR) in treated HIV/meningitis is 62-69% with approximately 10% reduction post ART in CM and TBM and no reduction in ABM. CFR in treated toxoplasmosis is 22%. The immune reconstitution inflammatory syndrome (IRIS) occurs in CM 21% (13-45%) and in TB 12% (5-47%) in ART treated patients. The excess mortality attributable to IRIS in CM is 20% (13-36%) and TBM is 30% (13-70%).

Conclusion: CNS/OIs are a leading causes of death in HIV in SSA. Contributory causes include advanced immunosuppression, late clinical presentation, IRIS and concurrent systemic tuberculosis.

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1695
WFN15-1903
Regional Pan-African Symposium
Neuro-Brucellosis

R. Gouider. *Neurology, Razi Hospital, Tunis, Tunisia*

NEUROBRUCELLOSIS IN AFRICA

Pr. Riadh GOUIDER
Department of Neurology, Research Unit 12SP21- Razi Hospital-Tunis, TUNISIA

Brucellosis is the most common zoonotic bacterial infection in the world with 500,000 infections/ year worldwide and a real incidence 10–25 times superior to the notified. It prevails in the Mediterranean Basin, especially in the Maghreb, and sub-Saharan Africa (SSA). The epidemiology of brucellosis in Africa is not well described. In SSA, the mean bovine prevalence in 21 countries varied from0,034% in Botswana to30% in Niger. In Guinea, the prevalence of brucellosis in humans is 30%. In Tunisia, where the disease is endemic in some areas, its incidence is 4,5/100000 with two epidemics in 1992and2006 because of the introduction of infected animals from neighboring countries. In fact, the major “moving” pattern of animal husbandry (transhumance, divagation and nomadism) in Africa facilitates the expansion of the disease from one country to another. Brucellosis is a multisystem disease with a broad spectrum of clinical manifestations including nervous system involvement or neurobrucellosis(NB) in 3-7%. The diagnosis is confirmed by detection of specific antibodies in cerebrospinal fluid. Delayed diagnosis is common in Africa. For instance, in Tanzania, only 22% of patients with probable brucellosis are reported to health facilities within 1 month, and 20% presented after 1 year of symptoms. There are no specific guidelines on antibiotic regimens and duration of treatment of NB. Vaccination of animals against Brucella and pasteurization of milk are not routinely practiced in endemic areas in Africa, where cultural practices and lack of resources may limit their application. Prophylaxis and control of brucellosis requires contextual adaptation in the African continent.

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1696
WFN15-1906
Regional Pan-African Symposium
Tuberculosis of the nervous system

O.A. Seidi. *Neurosciences, University of Khartoum, Khartoum, Sudan*

Tuberculosis (TB) is an ancient disease that has crippled mankind since prehistoric times.

Its involvement of the nervous system carries moribund consequences with high mortality and devastating morbidity. As yet the real extent, the pathogenesis and long term preventative measure of this disease needs further exploration. The HIV epidemic, the use of powerful immunosuppressive agents in organ transplant recipients and continued immigration increased awareness about TB of the nervous system and other forms of mycobacterial infection. The prevalence and incidence are variable in different parts of the world and the majority of cases are in the underdeveloped countries where poverty, malnutrition, crowding, and rudimentary health services are common particularly in the HIV stricken African region. Mycobaterium tuberculosis affects humans mainly while other species can be zoonotic like M. bovis and M. avium intercellulare. The pathology involves direct invation of the neural tissues, their surrounding coverings , the meninges , bones of the skull and more commonly the spinal canal as well as the blood vessels. The involvement includes tuberculous meningitis (TMB), tuberculomata, tuberculous brain abscess, Pott’s disease of the spine, vasculitis and entrapments leading to hydrocephalus or basal cranial nerve neuropathties. Common clinical presentations, complications and outlines of diagnostic tests will be discussed. Cerebrospinal fluid (CSF) examination and neuro-imaging modalities will be highlighted. Standard therapies and supportive measures are aso covered as well as recent advances in diagnostic testing, imaging techniques and therapies. Illustrative clinical material will also be shown.

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1698
WFN15-1935
Regional European Symposium
Imaging tools at the forefront of clinical studies and practice in Europe

F. Fazekas. *Department of Neurology, Medical University of Graz, Graz, Austria*

Careful history taking and a detailed neurologic and clinical examination are still essential when approaching a patient to define the likely site and cause of a suspected neurologic disorder. From this information CT and even more so MRI often can be used to directly view the underlying pathologic process which helps to rapidly come to an accurate diagnosis and to institute a specific treatment. While imaging thus has become indispensable for clinical practice the possibility to visualize pathologic changes and their dynamics over time has also made neuroimaging an important tool to substantiate treatment effects in clinical studies including patient selection. Two of the best examples are Multiple Sclerosis (MS) and Stroke. MRI nowadays can allow diagnosing MS already at the time of the first clinical symptom and morphologic markers such as contrast enhancing or new lesions are important outcome markers in clinical trials. Such findings have also proven important for patient

management and treatment decisions. In stroke CT and MRI are needed to select patients for intravenous thrombolysis and have been instrumental to develop and prove the efficacy of mechanical thrombectomy. Multimodal imaging may help to better define the window of opportunity for efficacious intervention. With these developments there is increasing need that neurologists understand neuroimaging techniques and are able to interpret their results for the best of their patients.

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1699
WFN15-1923
Regional European Symposium
How to organize stroke research and services in Europe

D. Leys. *Neurology, Stroke centre, INSERM U 1171, Lille, France*

Background: Stroke is a major public health issue. It is the 1st cause of physical disability in adults, the 2nd cause of dementia and the 3rd cause of mortality. Because of aging of European populations, with an increase in life-expectancy of 3 months every year, the social and economic burden of stroke will considerably increase in the next 50 years. For these reasons, stroke research should be a priority in Europe.
Objectives: To identify (i) sources of funding for stroke research in Europe, (ii) funding of stroke research compared to other fields in Europe, (iii) the weight of Europe in Stroke research and its evolution over time.
Results: Sources of funding in Europe are mixed, private and (mostly) institutional. There is a marked underfunding of stroke research in Europe, consistent between countries, compared with coronary disorders and cancer, by a factor of about 10. This phenomenon seems to be also present in other parts of the world, especially in the USA. In terms of scientific production, European countries have similar results than the USA, with huge variations between countries. Most studies published in high impact factors journals are multicenter and multinational studies, leading to difficulties in evaluating the weight of every individual countries.
Conclusion: Stroke research in Europe is mainly institutional. There is a clear underfunding of stroke research compared with coronary diseases and cancers, the other two major killers in Europe, but this seems to be part of a worldwide problem.

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1700
WFN15-1698
Regional European Symposium
European contribution to MS treatment algorithms: benefits and risk stratification

P.S. Sorensen. *Neurology, University of Copenhagen Rigshospitalet, Copenhagen, Denmark*

The first-line injectable treatments,interferon-beta and glatiramer acetate, have been used for decades and areknown to be safe although only moderately effective.

The new first-line oral treatments,teriflunomide and dimethyl fumarate, seem to match the first-line injectablesregarding efficacy. The drugs appear to have a good safety profile, although progressive multifocal leukoencephalopathy (PML) hasbeen reported as a rare complication to dimethyl fumarate.

Among the second-line therapies, natalizumab hasa profound therapeutic effect, but more than 500 MS patients treated wit-hnatalizumab have developed PML. Fortunately, reliable and validated assaysfor detection of antibodies directed against JC virus make it possible toidentify persons who are at risk of developing PML.

Fingolimod has proven more effective thanIFN-beta, but therapy can be associated with herpes virus infections. After the first administration of fingolimodsome patients may develop bradycardia or heart block. A few cases of PML havebeen reported in patients treated with fingolimod.

Alemtuzumab is a very effective monoclonalantibody shown superior to interferon-beta. However, a substantial proportionof patients develop secondary immune mediated disorders; thyroid diseases in morethan 30% of patients and thrombocytopenic purpura (ITP) in a few per cent.

Hence, disease-modifying drugs with higherefficacy carry the risk of more serious adverse effects, and the treatmentshould be tailored to the individual patient in order provide sufficientlyeffective treatment with the lowest possible risk.

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1701
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Regional European Symposium
Rare diseases in Europe

A. Federico Chair Scientific Committee EAN. *Dept Medicine Surgery and Neurosciences University of Siena, Siena, Italy*

Neurologic Rare Diseases (RND) and European Academy of Neurology (EAN)
Antonio FEDERICO, Dept Medicine, Surgery and Neurosciences, University of Siena, Italy
Chair Scientific Committee EAN

Rare Neurological diseases are a Pandora Box for Neurology.

The list of the Rare diseases encloses more then 5000 disorders, half of them with a neurological interest, involving Central and Peripheral nervous system or Muscle or all. They are underdiagnosticated and a global effort is necessary to improve their knowledge, the possibility to have a correct diagnosis by dissemination of informations and research, leading to possible treatments (the majority of them are without treatments and in all countries a cooperative effort for “orphan drugs” development has started).

Since Neurology, as speciality, has the major role in the diagnosis and care of these diseases, and Basic and Applied Neurosciences are involved in researching their pathogenesis, EAN has the main responsibility for the promotion of the knowledge of these disorders, of the informations and of the research within the european neurologic community.

For these reasons, EAN promoted a Working Group on Rare Neurologic Disorders, under the responsaibility of the Scientific Committee and formed by members from the different SubSpecialistic Panels and by delegates of the Patients’Associations.

The aims of the WorkingGroup will be

- Stimulation the redaction of a list of Rare Neurological Diseases, with main symptoms and diagnostic criteria and guidelines for diagnosis
- Evaluation of the facilities for diagnosis of RND in Europe, with the indication of the main centers, where is possible to perform the genetic, biochemical and other laboratory tests, etc
- Analysis of the attitude of European Neurologists to RND and which is the state of the art of this issue in the different European countries;
- Promotion of registries for RND, data bank and biobanks.
- Creation of European Networks for RND for diagnosis and research.
- Promotion of Teaching courses in Europe.

- Information Service for RNDs, new findings, research founds, treatments, etc. Discussion on Rare Cases, within the Section on Webpage. With this activity, the EAN recognizes the primary role of neurologists in the care of RNDs, the necessity to improve the level of the organization of Neurological Units in Europe and of the formation of neurologists expert in the care of RNDs. But also we will stimulate a better integrated relationship with Patient Associations and other Rare Diseases related Associations.

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1702
WFN15-0001
Palatucci Advocacy TC 20
Advocacy in resource limited world

A.G. Diop. *Department of Neurology, University of Dakar, Senegal*

In the developing world, increasing cases of non-communicable diseases are reported (i.e. epilepsy, stroke, dementias, cancers, movement disorders, and pain). The scarcity of specialized health staff, financial and/or geographical unavailability of diagnostic means and major drugs, has led to difficulty and delays in management of these issues. As a result, original methods of advocacy would be recommended. The focus should be on preventive communication, education, and activities to raise awareness among the community and key-leaders. New initiatives must be taken to reach the disfavored population by any means necessary. Specialists should leave the capital cities, their respective universities, and hospitals, and be more proactive in the field. Simple, clear and pertinent messages, adapted to the human and cultural environment, should be elaborated and shared with primary health personnel, and the community. Strong partnership is to be developed between specialists of both public and private sectors in order to establish a community-based and holistic approach, which would lead to greater efficiency. The experiences and perspectives shared are directed towards young neurologists in this communication.

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1703
WFN15-1895
Channelopathies T 9.1
Presynaptic channelopathies causing ataxia and migraine

D.M. Kullmann. *UCL Institute of Neurology, University College London, London, United Kingdom*

Several dominantly inherited disorders of ion channels underlie familial hemiplegic migraine. These include mutations of CACNA1A, which encodes the P/Q-type voltage-gated calcium channel (FHM1), ATP1A2, which encodes a sodium-potassium ATPase (FHM2), and SCN1A, which encodes the NaV1.1 sodium channel (FHM3). Of these, the disease mechanisms of FHM1 have been studied most extensively, in part through the availability of mouse models that show enhanced cortical spreading depression, which is related to migraine aura. P/Q calcium channels play an important role in neurotransmitter release throughout the nervous system. FHM1 is allelic with spinocerebellar ataxia type 6 and episodic ataxia type 2. Another form of episodic ataxia (type 1) is caused by dominant mutations of the potassium channel gene KCNA1, which is also expressed presynaptically. Mutations of KCNA1 result in increased neurotransmitter release, similar to the mutations in CACNA1A in FHM1, although the phenotypes are distinct. Recently, mutations in PRRT2, which encodes a presynaptic protein of unknown function, have been identified in families with dominantly inherited paroxysmal kinesigenic choreoathetosis (PKC), but also in a wide spectrum of disorders including migraine and episodic ataxia. Although genetic advances have shed light on the molecular causes of a wide range of mainly paroxysmal neurological disorders, many sporadic patients remain genetically undiagnosed. Understanding the detailed mechanisms of these diseases may lead to an improved understanding of commoner forms of episodic neurological diseases such as migraine and epilepsy.

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1704
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Channelopathies T 9.1
Muscle channelopathies - clinical trials

R. Griggs. *Department of Neurology and the Center for Human Experimental Therapeutics, University of Rochester, Rochester NY, USA*

Of the over 100 inherited neurological channelopathies at least 12 cause muscle disease: the periodic paralyses (6 or more), the dystrophic and nondystrophic myotonias (5 or more) and malignant hyperthermia. All are rare and pose challenges for investigators designing and conducting clinical trials. Many channelopathies have in common the fact that they are episodic with normal or near-normal baseline function with intermittent symptoms suggesting that the underlying mutation in necessary but not sufficient to cause symptomatic disease. Many patients with chanelopathies develop persistent and progressive deficits that appear to be cummulative and possible the result of the episodic symtoms. The presence of triggering or exaccerbating factors suggests the possibility of treatment to prevent or modify such triggers. Clinical trials for channelopathies have been greatly benefited by the discovery of their molecular defects permitting diagnosis and identification of cases. However, this has also led to the recognition that there is wide variation in the genotypes/mutations that cause "the same" disease making it impossible to assemble a large number of cases with identical mutations. Despite the limitations, clinical trials in the muscle channelopathies have proceeded rapidly over the past decade with the development of outcome mesures and the successful completion or initaition of multicenter clinical trials. A randomized, placebo-controlled crossover clinical trial in both dominant and recessive myotonia congenita caused by chloride and sodium channel mutations found mexilitine to be highly beneficial to both patient reported and clinical outcome measures as well as to the electrophysiologic abnormalities of the the diseases. Moreover, a recent parallel group, randomized placebo-controlled trial of dichlorphenamide in both hypokalemic and hyperkalemic periodic paralysis showed significant benefit in hypokalemic periodic paralysis leading to regulatory (FDA) approval of the treatment. Finally, a phase 1 multicenter trial of antisense oligonulcleotide-based

treatment is underway in myotonic dystrophy type 1. The muscle channelopathies thus are in the vangard of treatment for the neurological channelopathies and will likely inform advances in many other diseases.

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1705
WFN15-1800
Neuroepidemiology T 2.1
Dementias across continents: the Global Burden of Disease study

G. Logroscino. *Neurodegenerative Disease Unit, Department of Basic Medicine, Neuroscience, and Sense Organs, University of Bari "Aldo Moro", Bari, Italy; Department of Clinical Research in Neurology, University of Bari Aldo Moro, "Pia Fondazione Cardinale G. Panico", Tricase, Lecce, Italy*

About 25% of the total global burden of disease (GBD) worldwide is due to disorders/ risk factors in subjects 65 years old and older. A significant part of this burden is due to dementia and other cognitive disorders. Almost forty million of people live with dementia and there are 4.5 millions of new cases every year.

Based on GBD data, there is little variation within continent but the prevalence of dementia in Sub saharian Africa and Asia is relatively lower to Europe and North America. The burden of disease of dementia as for other age-related conditions is clearly determined more from disability than from mortality.

Incident studies from three different communities indicate a possible decline in incidence in the last decades. A possible role of the treatment of vascular risk factors, including hyperthension, as possible origin of this trend has been suggested.

Overall half of the attributable risk of dementia is probably due to modifiable risk factors. Therefore, a substantial contribution to the diminution of the health problems related to dementia and similar conditions will be based on prevention policies that need to be implemented both in younger cohorts and among the elderly. The role of primary prevention will be compared with secondary and tertiary prevention.

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1706
WFN15-1832
Neuroepidemiology T 2.1
Sex, gender, and the brain

W.A. Rocca. *Division of Epidemiology Department of Health Sciences Research and Department of Neurology, Mayo Clinic, Rochester, USA*

Background: Invited lecture.
Objective: To discuss new concepts related to differences between men and women in their experience of neurological diseases. As an example, I use dementia or Alzheimer's disease (AD), and I focus on risk and protective factors.
Material and methods: This is a narrative review of the literature; therefore, Institutional Review Board (IRB) approval was not necessary. First, I introduce the concept of dimorphic neurology and the distinction between sex (biological) and gender (social-cultural). Second, I provide three examples of risk factors related to sex and gender from the literature.
Results: Apolipoprotein E genotype is equally common in men and women but increases the risk of AD more strongly in women than in men. Apolipoprotein E genotype is a biological factor that may not be modified directly, but it interacts with sex or gender related factors that may be modified. Low education increases the risk of dementia in both men and women; however, women historically have had less access to education. Education is a social-cultural factor related to gender that may be modified. Finally, bilateral oophorectomy is a factor restricted to women. Bilateral oophorectomy is a surgical practice related to sex that may be modified.
Conclusions: Consideration of risk and protective factors in men and women separately may accelerate etiologic research for neurological diseases in general, and for dementia in particular. In addition, future preventive interventions for dementia should consider both sex and gender factors (Mielke et al., *Clin Epidemiol* 2014; Rocca et al., *Maturitas* 2014).

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1707
WFN15-1891
Neuroepidemiology T 2.1
Neuroepidemiology in Africa

A. Ogunniyi. *Medicine, University of Ibadan, Ibadan, Nigeria*

Neuroepidemiology is the study of the distribution and the determinants of neurological disease. With respect to Africa, there has been a rapid increase in the number of community-based studies of these disorders when compared with the situation about three decades ago. Data from INTERSTROKE, different Governorates of Egypt, KEMRI (Kenya), Agincourt (South Africa), Hai District (Tanzania), Mali and Nigeria etc. have substantially contributed information on the burden and the putative risk factors. With regards to stroke, the age-adjusted prevalence rates vary between 15 and 1230 (per 100,000) in Ethiopia and Kegbara community in Nigeria respectively. The important risk factors are hypertension, diabetes mellitus and lack of physical activity. Dyslipidaemia is emerging as an important risk factor for cardiovascular diseases from the Africa Middle East Cardiovascular Epidemiologic Study. Low incidence of active epilepsy was reported from Agincourt while exposure to multiple parasites and cysticercosis are important contributors to the burden of this condition that is still highly stigmatized. The neurologic sequelae of severe malaria, malnutrition and exposure to neurotoxins are prevalent in many communities. Conditions once thought to be rare like Dementia and Multiple Sclerosis are adding to the neurologic disease burden. The prevalence of dementia ranges between 2.3 and 10.1%. Vascular risk factors apart from age are important. Nodding syndrome in parts of Uganda, Tanzania and Sudan remains an enigma. With respect to Neuroepidemiology in Africa, "the world is a global village" The presentation will include country-by-country presentation of diseases and their peculiarities.

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1708
WFN15-1862
Intraoperative Neurological Monitoring T 27.1
The impact of intraoperative monitoring in adult and pediatric neurosurgery: does it make a difference?

F. Sala. *Neurological Sciences and Movement, Neurosurgery, Verona, Italy*

Over the past twenty years new intraoperative neurophysiological monitoring (IONM) techniques have been introduced, and evidence has accumulated on the role of IONM as a tool not merely to predict but rather to prevent or mitigate an injury to the nervous

system during high-risk neurosurgical procedures. The key question then became whether or not IONM is evidence-based according to the standards of evidence-based medicine. Nowadays there is strong evidence than IONM can document and therefore predict an injury to the brain and spinal cord (level I and II), whereas there is much weaker evidence (level II and III) that IONM can prevent such an injury. Yet, it should be acknowledged that the vast majority of current neurosurgical practice is not supported by evidence-based medicine standards either, but even in the absence of class I data, many neurosurgical interventions are firmly established as the standard of care for their respective conditions. Therefore, the evidence for the benefit of IONM is no less than the evidence we have for most of the neurosurgical practice.

A second matter of debate is the cost effectiveness of IONM. A number of studies support the cost effectiveness of IONM, even when the incidence of severe neurological injury is rather low, and this ratio becomes more favorable for neurosurgical procedures where the risk of neurological injury is significant.

This presentation will review and discuss the most controversial aspects on the value of IONM in adult and pediatric neurosurgery, highlighting the need for credentialing and training in IONM.

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1709
WFN15-1795
Intraoperative Neurological Monitoring T 27.1
Intraoperative monitoring in spinal deformity surgery: a paradigm on the evolution and future perspectives

D.B. MacDonald. *Neurosciences, King Faisal Specialist Hospital, Riyadh, Kingdom of Saudi Arabia*

Because spinal deformity surgery is the oldest and still most common indication for intraoperative neurophysiologic monitoring, it has been a paradigm for the evolution of monitoring techniques also applicable to other types of surgery. At first, non-invasive somatosensory evoked potentials (SEPs) were used alone; invasive spinal SEPs did not gain widespread use. SEPs proved to halve the incidence of paraplegia, but observations of motor injury without SEP warning and of SEP deterioration without motor deficit accumulated. The addition of motor evoked potential (MEP) monitoring progressed through now-discredited 'neurogenic' MEPs to D-waves that eventually produced some false results and finally muscle MEPs. Along the way, total intravenous anesthesia (TIVA) became recognized as optimal for SEP-MEP monitoring, triggered electromyography (EMG) was validated for pedicle screw testing, and free-running EMG became a questionable ancillary modality for nerve root irritation or acute spinal cord compression. More recently, optimized SEP techniques have been developed to speed surgical feedback by minimizing averaging. Future perspectives include the demonstration of a further reduction of motor deficits with the addition of MEPs, the widespread adoption of SEP optimization and TIVA, and the establishment of monitoring as a standard of care.

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1710
WFN15-1892
Child Neurology T 14.1
Co-morbidities of epilepsy in children - a major management challenge

J. Wilmshurst. *Paediatric Neurology, University of Cape Town, Cape Town, South Africa*

Co-morbidities of epilepsy in children - A major management challenge

Children with epilepsy are at increased risk of comorbidities, especially behavioural and cognitive. This talk will address the epidemiology and aetiologies of the comorbidities which affect children with epilepsy. The talk will focus on common and challenging aspects. Greater understandings into comorbidities have arisen through the exploration of epilepsy syndromes. Leading on from this further expansion of information has occurred with insight into genetic syndromes. The talk will address where these insights aid patient management, and will include data relating to outcome.

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1711
WFN15-1893
Child Neurology T 14.1
An approach to epilepsy in mitochondrial disorders of childhood

I. Tein. *Division of Neurology, The Hospital for Sick Children University of Toronto, ON, Canada*

Mitochondrial epilepsy is commonly seen in certain mtDNA mutations such as mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged red fibres (MERRF) syndromes. They are also seen with mutations in the mtDNA maintenance gene polymerase gamma (*POLG*) which may manifest with Alpers or Alpers-Huttenlocher syndrome, mitochondrial recessive ataxia syndrome (MIRAS), spinocerebellar ataxia with epilepsy (SCAE), and myoclonus, epilepsy, myopathy, sensory ataxia (MEMSA) syndromes. They are also seen in disorders of Coenzyme Q10 biosynthesis, Complex 1 deficiency and disorders of mitochondrial translation such as with *RARS2* gene mutations. The mechanisms for the epileptogenesis may relate to impaired mitochondrial sequestration of calcium, decreased intracellular ATP generation, increased glutamate release into synaptic clefts, increased reactive oxygen species arising from defects in Complex I and Complex III of the respiratory chain, and "stroke-like episodes" as seen in MELAS syndrome. Mitochondrial epilepsy may be characterized by generalized, focal, multifocal or myoclonic seizures in semiology and is critical to control given the further exacerbation of the bioenergetic insufficiency by the heightened energy requirement of seizing neurons. Treatment often consists of a combination of multiple standard anticonvulsants along with vitamins, cofactors, antioxidants and electron donors to enhance mitochondrial function which may be only partially successful. The ketogenic diet is promising but warrants prospective clinical trials. It is important to try to avoid use of mitochondrial toxins such as valproic acid which also exacerbates cellular carnitine deficiency requiring supplementation and which has been associated with rapid neurodegeneration and liver failure in Alpers-Huttenlocher disease.

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1712
WFN15-1793
Genetics and Neurology T 26.1
Impact of next generation sequencing in neurology practice

S. Tsuji. *Neurology, The University of Tokyo Hospital, Tokyo, Japan*

Recent advances in molecular genetics have revealed a number of causative genes for diseases with Mendelian trait, accelerating development of disease-modifying therapies for these diseases. In particular, the availability of massively parallel sequencing technologies employing next-generation sequencers are revolutionizing the

neurogenomics view of neurological diseases. These advances in next generation sequencer technologies have been accelerating our effort to elucidate molecular bases of not only hereditary neurological diseases but also sporadic neurological diseases. Given increasing number of genes associated with neurological diseases, we are facing with difficulties to perform mutational analyses for a number of genes to establish the diagnosis for individual cases. For example, we may need to analyze as many as 35 genes to establish the diagnosis for "leukodystrophy". In our laboratories, we have established molecular diagnoses for 132 of the 393 cases of hereditary spastic paraplegia, and 10 of the 24 cases of leukodystrophy. These results indicate that we can establish molecular diagnoses for approximately one third of the cases, emphasizing the utility of next generation sequencing technologies. It should also be noted that we observe numerous variants with undermined significance (VUS). To improve interpretation of these VUS, worldwide collaborative effort to share information on mutations and variants of our genome will be urgently needed. The results also emphasize that there remain diseases where the causative genes are yet to be elucidated. Since these diseases are mostly rare diseases with limited number of families, we need to accelerate our collaborative efforts to elucidate molecular bases of these diseases.

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1713
WFN15-1827
Genetics and Neurology T 26.1
The role of noncoding regions modifications in neurodegenerative disorders

I. Lopes-Cendes[a], D.B. Dogini[a], H.M. Tavares[b], M. França Jr.[b]. [a]*Medical Genetics, University of Campinas - UNICAMP, Campinas, Brazil;* [b]*Neurology, University of Campinas - UNICAMP, Campinas, Brazil*

Currently, it is well recognized that mutations and dysregulations of noncoding RNAs are linked to many human diseases, and noncoding RNAs have been implicated in the molecular pathogenesis of some neurodegenerative disorders. The expansion of trinucleotide repeats is now recognized as a major cause of neurological disorders. Studies of fragile X-associated tremor ataxia syndrome have established that the sequestration of RNA-binding proteins due to the expression of pathogenic RNAs with expanded repeats is involved in disease pathogenesis. In pathological samples from patients with spinocerebellar ataxia type 8 (SCA8) the observed bidirectional expression of *SCA8* CTG · CAG expansion produces toxic noncoding RNAs. Furthermore, in polyglutamine (polyQ) neurodegenerative disorders there is evidence suggesting that the mutant repeat RNA formed plays a pathogenic role in polyQ toxicity. In addition, recent studies have suggested that alterations in small regulatory RNAs, such as miRNAs, could contribute to the pathogenesis of several neurodegenerative disorders, such as Huntington disease, myotonic dystrophy type-2 and amyotrophic lateral sclerosis (ALS). Indeed, we have recently shown increased expression of **hsa-miR-424** and **has-miR-206** in skeletal muscle and plasma of patients with ALS. Baseline expression levels of these two microRNAs are significantly correlated with disease progression and might be useful as prognostic markers. However, the mechanism by which modified RNAs are generated and how these affects disease processes are still unclear.
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1714
WFN15-1865
Genetics and Neurology T 26.1
Huntington's disease: towards paradigmatic molecular based treatment

J.M. Burgunder. *University of Bern, Department of Neurology, Bern, Switzerland*

Huntington's disease, a monogenetic disorder complex phenotype encompassing motor, cognitive and behaviour changes, presents with a variable age after a long presymptomatic phase. This opens a window of opportunity for therapeutic strategies aimed at postponing disease onset and progression. The mutation, a CAG triplet elongation, leads to impairment of numerous cellular functions involving the protein, and also to accumulation after a process of abnormal protein conformation. A profound knowledge of the numerous aspects of these intricate pathophysiological mechanisms has now opened the path for rational therapies aimed at decreasing the burden of the disease. This can be done in decreasing the amount of abnormal protein and by modifying downstream processes at different cellular levels. These strategies have been tested in cellular and animal models and first studies are now starting to be tested in human.

On the other hand, recent large cohort studies have made major advances in our understanding of presentation and course of Huntington's disease, specifically in the prodromal and early symptomatic phases. These have involved novel tools to measure the complex patterns of signs and symptoms, which have allowed to shed light about phenomenology, including apathy and selective cognitive impairment as well as specific psychiatric symptoms. Moreover, these studies represent a real progress in the development of biomarkers needed to perform therapeutic trials for disease modifying treatments. Huntington's disease can be considered a model in the development of such strategies, since it is a monogenetic, fully penetrant disorder with a long presymptomatic period opened to interventions.

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1715
WFN15-1834
Nutrition and Toxins T 18.1
Analysis of motor pathway involvement in Konzo disease

R. Ali Ekangu[a], J. Kambale Kikandau[b], G. Vumbi Lelo[b], R. Kalala Lunganza[b], M. Yandju Marie-Claire[c], P. Takaisi Kikuni[d], D. Okitundu Luwa E-Andjafono[e], D. Mumba Ngoyi[f], J. Michael Boivin[g], D. Tshala-Katumbay[h]. [a]*Biology, University of Kinshasa & INRB, Kinshasa, Democratic Republic of Congo;* [b]*Biomedical Sciences, University of Kinshasa, Kinshasa, Democratic Republic of Congo;* [c]*Biology, University of Kinshasa, Kinshasa, Democratic Republic of Congo;* [d]*Pharmacy, University of Kinshasa, Kinshasa, Democratic Republic of Congo;* [e]*Neurology, University of Kinshasa, Kinshasa, Democratic Republic of Congo;* [f]*Tropical Medicine, University of Kinshasa & INRB, Kinshasa, Democratic Republic of Congo;* [g]*Neurology & Psychiatry, Michigan State University, East Lansing, USA;* [h]*Neurology, Oregon Health & Science University & University of Kinshasa & INRB, Portland, USA*

Objectives: To elucidate the biomarkers of cassava-associated neurological disease, konzo children from the Democratic Republic of Congo (N = 123; mean age 8.7 years) were compared to those with no konzo (N = 87; mean age 9.1 years) on the KABC-II battery for cognition, and BOT-2 battery for motor proficiency; and levels of serum F2-isoprostanes (oxidant markers measured by LC-MS/MS; in 40 children). **Results:** Using a Kruskal-Wallis test, children with konzo did worse on the KABC-II Simultaneous Processing (visual-spatial analysis)

(K (1) = 8.78, P = 0.003) and Mental Processing Index (MPI) (K (1) = 4.56, P = 0.03). Both konzo and non-konzo children had poorer performances relative to the normative group from a non-konzo region (K (2) = 75.55, P < 0.001). KABC-II MPI and BOT-2 total scores were predictive of konzo status in a binary logistic regression model: odds ratio = 1.41, P < 0.013; 95% confidence interval 1.13 – 1.69. Within regression models adjusting for age, gender, motor proficiency, and other biochemical variables, the level of 8,12-iso-iPF2α-VI isoprostane was significantly associated with the overall cognitive performance (β = -32.36 (95% CI: -51.59 to -13.03; P < 0.001).

Conclusion: Both konzo and non-konzo children have impaired cognition compared to control children from a non-outbreak area. This may evidence a subclinical neurocognitive form of the disease, extending the human burden of konzo with dramatic public health implications. Cognitive deficits and, possibly, brain injury associated with cassava poisoning is mediated in part by oxidative stress.

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1716
WFN15-1861
Neurological Education T 15.1
Assessments and examinations in neurology

W. Grisold. *Department of Neurology, Kaiser Franz Josef hospital, Vienna, Austria*

Training of specialists is one of the most important tasks of a scientific society and aims to produce a specialist, who has knowledge, skills, competence and also an adequate attitude to treat neurological patients. A defined board certification finalizes the training process and the trainee becomes a fully certified neurologist.

The training duration is usually defined and has a neurological core curriculum. Within the curriculum trainee needs to be exposed to all aspects of neurology, in different neurological settings including emergency, acute, subacute, chronic, rehabilitation, and palliation. Experience has to be acquired in outpatients, inpatients, and as consultants. The training of skills such as neurophysiology, and ultrasound are recommended, but depend on the local structure. Training should also include working with interdisciplinary and multiprofessional teams. Knowledge in administrative aspects and in regard to resources is necessary. Early subspecialty training should be avoided.

To assess the trainees several possibilities can be chosen: 1) several time points during training, 2) a final examination where several methods of examinations can be used and 3) practical skills examination. The purpose of the examination is to guarantee a level of educational knowledge and skills, qualifying the trainee to work independently as a board certified neurologist.

Worldwide, several examination types and systems exist, and for this presentation the European Board examination in neurology (UEMS) European Board of Neurology is presented.

The development of examinations requires resources as manpower and finances. The use professional educationalists for the development of examinations is recommended.

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1717
WFN15-1814
Neurological Education T 15.1
Transition from adolescent to adult neurological care

P. Camfield. *Pediatrics, Dalhousie University, Halifax, Canada*

Increasing numbers of children with chronic neurological disorders are surviving into adulthood. Some of their disorders are straightforward and some highly esoteric and virtually unknown to adult neurology. Many of these youth have additional serious social problems and it would appear that few have mastered the skills to successfully benefit from adult medical care. Disorders associated with intellectual disability and/or multiple co-morbidities are particularly vexing because the family or other caretakers must remain central to care throughout adult life. A transition program should begin in early adolescence to allow these vulnerable youth to understand their disorder, to develop independent coping strategies and to develop the self confidence needed to navigate the individual focus of adult care. This approach is very different than the family oriented care offered in pediatrics. A simple transfer letter is insufficient. Some form of a joint pediatric-adult transition clinic appears optimal to ensure that transfer to adult care is successful. Youth with disorders that involve multiple specialists require a "medical home" that can co-ordinate and direct adult care. A highly motivated primary care provider is likely the best person for this task. Much more research is needed to outline the adult natural history of many childhood onset neurological disorders. With this type of information, adult neurological care may be able to anticipate serious issues that may shorten life or negatively impact quality of life for youth who have had a huge investment in comprehensive care during childhood.

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1717A
WFN15-1946
Neurological Education T 15.1
International videoconference rounds: sharing expertise across the globe

M. Freedman. *Medicine (Neurology), Baycrest Health Sciences and University of Toronto, Toronto, Canada*

Since 2005, my colleagues and I have used television quality videoconferencing to bring together health care professionals from across the globe within a virtual auditorium for an international series of behavioural neurology rounds. The initial goal was to build bridges through health education involving colleagues in Canada, Israel, Jordan and the West Bank. The rounds have now expanded to a wider audience, and there has been participation from American, Canadian,Cuban, Israeli, Jordanian, Russian, Saudi Arabian, South African, Spanish and Swiss (WHO) hospitals. The audiences are multidisciplinary and include neurologists, psychiatrists, geriatricians, family physicians, nurses, occupational therapists, psychologists, and social workers, as well as trainees in these disciplines. A key feature to the success of the rounds is that they are collaborative with all sites being equal partners.

Another important development is the international neurology resident initiative, i.e., the Neurology International Residents Videoconference and Exchange (NIRVE), that promotes international collaboration among neurology residents. Participating sites have included Brazil, Canada,Chile, Ethiopia, France, Jordan, Nigeria, and Russia.

Challenges include language barriers, time zones, eLearning-based interactivity, and evaluation that takes into account geographical and cultural needs. Future plans include development of innovative techniques for interactivity, and obtaining resources to assist developing countries to participate in the videoconference rounds.

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1718
WFN15-1831
Psychiatry for Neurologists T 16.1 - Challenging mental disorders of adult and childhood
Bipolar disorder

P. Ruiz. *Psychiatry and Behavioral Sciences, University of Miami, Miami, USA*

Will be participating in symposium presentation. No abstract required.

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1719
WFN15-1823
Psychiatry for Neurologists T 16.1 - Challenging mental disorders of adult and childhood
Depressive and anxiety disorders for the clinician: challenges in diagnosis and treatment

L. Küey. *Psychiatry, Istanbul Bilgi University, Istanbul, Turkey*

Depressive and anxiety disorders constitute a major health problem. Categorical approach in the classification of mental disorders had reached a point where the dilemma of comorbidity became a crucial matter of concern. The overlapping and discriminating features of depressive and anxiety states have both conceptual and clinical importance.

In clinical practice, the common co-existence of these two states makes it difficult to keep them as complete distinct entities. The dilemma of comorbidity may be discussed in different levels of description: distinct disorders, comorbid disorders, overlapping syndromes, shared symptoms, and common personality traits and psychosocial stress. Depending on the level of description these conditions may be reviewed (i) as independent two distinct clinical entities; (ii) as comorbid conditions; (iii) as one having the primary diagnosis associated with the other syndrome; (iv) as mixed states where both conditions have concomitant sub-threshold symptoms; (v) as related personality traits and psychosocial stresses. Researches have shown that, the distinction is more prominent at the level of disorders, where the overlap becomes more prominent at the levels of symptomatology and personality traits and psychosocial stress.

Depressive and anxiety states are strongly associated with one another. To some extent, methodological problems may be responsible for their co-occurrence; but explanations are insufficient to reveal the strong observed correlation. The differences between these two states are best viewed as relative, rather than absolute.

This presentation will focus on the implications for clinical practice and future research.

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1720
WFN15-1879
Psychiatry for Neurologists T 16.1 - Challenging mental disorders of adult and childhood
Psychiatric disorders in childhood

E. Belfort. *Secretary for Education, World Psychiatry Association, Caracas, Venezuela*

Psychiatric disorders in childhood

From a clinical perspective, understanding the patient's illness needs, helps determine our assessment, diagnosis and our treatment plan in the population of child and adolescents. The effective evaluation of different dimensions: Psychosocial Features: expectations, perceptions, and needs; Health Features: reference source, symptoms, quality of life impact; as well as geographic and linguistic diversity, cultural framework, must be also considered.

The review of the two main diagnostic and classification systems in the field of psychiatry: the ICD-10 (chapter on mental and behavioral disorders) and the DSM-IV, represents the most important challenge, especially for the diagnostic and assessment in Child & Adolescent Psychiatry.

The diagnostic classification should include additional information or dimensions that, while not a part of diagnosis per se, are important for making decisions about patient care, such as associated disability, acuity, exacerbating psychosocial factors, level of social support, and cultural factors.

Clinical symptoms based on international classifications, allows identifying clinical entities in the population of children and adolescents, such as, substance use and abuse, emotional disorders especially bipolar disorders, attention deficit disorder and high prevalence of psychiatric comorbidity among themselves, hindering further diagnosis.

In this speech, an overview of these conditions, particularly bipolar disorder in children and adolescents and their comorbidity, will be presented.

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1721
WFN15-1806
Autonomic Nervous System T 1.1
Central and/or peripheral autonomic disorders – an overview

E. Benarroch. *Neurology, Mayo Clinic, Rochester MN, USA*

Central and Peripheral Autonomic Disorders: and Overview
Eduardo E. Benarroch, M.D.

Abstract: Autonomic disorders may reflect processes affecting any ofthe central or peripheral nervous system. They may manifest with autonomicfailure or autonomic hyperactivity involving the sympathetic, parasympathetic,or enteric nervous system (ENS), either selectively or in various combinations.

Autonomic failure manifests primarily with orthostatic hypotension (OH), impaired sweating, impaired gastric emptying, urinary retention, or erectile dysfunction, in several combinations. Disorders causing autonomic failure can be classified according to the presence or absence of associated neurologic manifestations, their temporal profile (acute/subacute,chronic progressive, static, or episodic. Effect of medications or comorbid conditionsshould always be considered. Subacute isolated autonomic failure affecting sympathetic, parasympathetic and ENS function, in various combinations, occurs in autoimmune (including paraneoplastic) autonomic ganglionopathy. Autonomic failure may be an important manifestation of sensorimotor peripheral neuropathies (such as those associated with diabetes or amyloidosis); sensory ganglionopathy (such as occurs in paraneoplastic or Sjögren disease), or distal painful peripheral neuropathies (including those associated with diabetes; amyloidosis;vasculitis; Fabry disease; or sodium channelopathies). Progressive autonomic failure associated with motor or cognitive manifestations, or both, occurs in neurodegenerative synucleinopathies such as multiple system atrophy (MSA) or Lewy body disorders. Autonomichyperactivity typically involves the sympathetic output producing tachycardia, hypertension and hyperhidrosis. This can occur in traumatic or hypoxic brain injury,subarachnoid hemorrhage, limbic encephalitis, Guillain-Barré syndrome, autonomic dysreflexia, or toxidromes. Disorders of orthostatic tolerance, such as postural tachycardia syndrome

(POTS), occasionally reflect a peripheral autonomic neuropathy or ganglionopathy.

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1722
WFN15-1842
Autonomic Nervous System T 1.1
Assessment and treatment of male and female sexual dysfunction

M. Hilz. *Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany*

In the USA, 43% of women and 31% of men report sexual dysfunction. Assessment of sexual dysfunction should be patient-specific, including a detailed history, physical, genital and neurologic examination, neurophysiologic testing, such as genital quantitative sensory testing, endocrine and psychological work-ups. Treatment of female hypoactive sexual desire disorder is mainly non-pharmacologic. For sexual arousal disorder, various treatment options have been tested, for example transdermal testosterone substitution which is not approved in the USA. Treatment of orgasmic disorders may require a combination of therapies. Patients with sexual pain require specific treatment depending on the particular cause.

Male erectile dysfunction (ED) probably affects 20 to 30 million men in the USA. Diagnosis may include nocturnal tumescence testing or Doppler sonographic measurements of penile perfusion. PDE5 inhibitors are one of the pharmacologic treatment options in ED patients. However, in patients with reduced nitric oxide production, such as diabetics, PDE5 inhibitors may fail. Patients with high cardiovascular risk should defer sexual activity. PDE5 inhibitors are contraindicated in these patients and in patients on nitrates.

Premature ejaculation (PE) is the most common male sexual dysfunction affecting up to 21% of men between 18 and 59 years of age in the USA. Patients with PE may benefit from behavioral, cognitive therapy, “squeeze techniques”, serotonin reuptake inhibitors (SSRIs), and topical anesthetics. In several countries, the short-acting Dapoxetine is approved while most drugs are not officially approved for PE therapy. SSRI treatment should be used with caution due to the risk of a life-threatening serotonin syndrome.

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1723
WFN15-1932
Ethics T 10.1
Huntington's disease and ALS - the ethical challenges for families and professionals facing genetic disease

C. Shaw. *Department of Basic and Clinical Neuroscience, Institute of Psychiatry Psychology and Neuroscience King's College London and King's Health Partners, London, United Kingdom*

Huntington’s disease (HD) and amyotrophic lateral sclerosis (ALS) are both relentlessly progressive neurodegenerative disorders for which diagnostic and predictive gene testing have been available for ~20 years. HD is a single gene autosomal dominant disorder whereas ALS is highly heterogeneous and complex. ALS is familial in ~10% of cases and currently 13+ genes account for 60% of familial cases but the same genes are also present in 10% of sporadic cases due in large part to incomplete penetrance. Significant differences in the rate and effects of symptomatic progression have influenced the uptake of predictive gene testing. This talk will discuss the major issues that face affected individuals and families with HD and ALS and our current practice for diagnostic and predictive gene testing, pre-implantation genetic diagnosis and the prospects for gene therapy.

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1724
WFN15-1779
Ethics T 10.1
Withdrawal and withholding of treatment - at the end of life

D. Oliver. *Tizard Centre, University of Kent, Canterbury, United Kingdom*

As a patient with a progressive neurological disease deteriorates there may be an increasing need to consider new options for the management of symptoms, including the consideration of withdrawing existing treatment options or withholding treatments. Ethically the withdrawal or withholding of treatment are similar – as the goals of any medical treatment should be to benefit the patient by restoring or maintaining health, maximising benefit and minimising harm. If a treatment is felt not to provide net benefit to the patient it may be, legally and ethically, withheld or withdrawn, with the goals of care shifting to the palliation of symptoms.

These issues can be seen when there is consideration of the withdrawal of non-invasive ventilation (NIV) in a patient with amyotrophic lateral sclerosis. There may be consideration of a tracheostomy, to maintain ventilation, although this may often seem to be too burdensome. However as the disease progresses and the patient continues to deteriorate they may ask for the NIV to be withdrawn. This is ethically acceptable, at the clear request of the patient or in the presence of a clear advance directive. There is a need to ensure that symptoms are adequately treated and distress avoided and there may be complex discussion within the team with the patient and family.

The complex discussion and involvement at these times is a crucial part of the palliative care of a person with a progressive neurological disease, ensuring that all aspects of care – physical, psychological, social and spiritual – are considered and supported.

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1725
WFN15-1868
Neuro-Otology T 12.1
Diagnosis of acute vertigo

A. Bronstein. *Clinical Neuro-otology, Imperial College London/ Charing Cross Hospital, London, United Kingdom*

Acute vertigo and dizziness is common in emergency departments. It creates confusion amongst emergency doctors as a very similar presentation can be due to a very benign self-limiting condition (e.g. vestibular neuritits, BPPV, migraine) or to a life threating disease (e.g. posterior fossa stroke). The majority of cases are due to benign peripheral vestibular disorders or migraine that can be easily treated so in this lecture we will emphasise the ‘red flags’ that, in the presence of acute vertigo, suggest structural, central disease and warrant acute MRI. These red flags can be summarised as follows (Seemungal and Bronstein, in *Practical Neurology*): 1) acute unilateral deafness (may be Meniere’s disease but suspect AICA stroke), 2) acute occipital headache (may be migraine but suspect posterior fossa stroke), 3) any central neurological symptoms or signs (ask for them, look for them) and 4) a negative (i.e. normal) head-impulse test.

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1726
WFN15-1808
Neuro-Otology T 12.1
Current pharmacotherapy of vertigo and nystagmus

M. Strupp. *Neurology, University Hospital Munich, Munich, Germany*

Current pharmacotherapy of vertigo, dizziness and nystagmus

Michael Strupp, MD, FANA. FEAN
Department of Neurology and German Center for Vertigo and Balance Disorders
Michael.Strupp@med.uni-muenchen.de

There are currently 8 groups of drugs for the pharmacotherapy of vertigo, nystagmus and cerebellar disorders: antiemetics; anti-inflammatory, anti-menières, and anti-migraineous medications; anti-depressants, anti-convulsants, aminopyridines and acetyl-DL-leucine ("the 8 A's"). In acute unilateral vestibulopathy corticosteroids improve the recovery of peripheral vestibular function without sufficient current evidence for a general recommendation; recent animal studies show that betahistine, acetyl-DL-leucine and 4-aminopyridine have an effect in acute unilateral vestibulopathy. There is insufficient evidence that 16 mg tid or 48 mg tid betahistine has an effect in Menière's disease. Therefore, higher dosages are recommended; in animal studies it was shown that betahistine increases cochlear blood flow. In vestibular paroxysmia oxcarbazepine was effective (one randomized controlled trial (RCT)). Aminopyridines are recommended for the treatment of downbeat nystagmus (2 RCTs) and episodic ataxia type 2 (EA2, 1 RCT). There are so far no RCTs on vestibular migraine so currently no treatment can be recommended (recenet Cochrane Review). Acetyl-DL-leucine improves cerebellar ataxia (3 observational studies); it also accelerates central compensation in an animal model of acute unilateral lesion but RCTs on central compensation were negative. Perspectives: There are ongoing RCTs on vestibular paroxysmia with carbamazepine ("VESPA-trial"), acute unilateral vestibulopathy with betahistine ("BETAVEST-trial"), vestibular migraine with metoprolol ("PROVEMIG-trial"), BPPV with vitamin D ("VitD@BPPV-trial"), EA2 with 4-aminopyridine vs acetazolamide ("EAT-2-TREAT-trial") and cerebellar ataxias with acetyl-DL-leucine ("ALCAT-trial").

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1727
WFN15-1790
Neuropathology T 21.1
Serum/CSF-diagnostics in neurodegenerative diseases

G.G. Kovacs. *Institute of Neurology, Medical University of Vienna, Vienna, Austria*

Molecular classification of neurodegenerative diseases is based on the evaluation of pathological protein depositons in the brain. Morphological subclassification of protein deposits implicate functional differences, or different capabilities to co-aggregate further proteins or to reach body fluids at a detectable level that would be relevant for biomarker assays. Recent studies revealed that 1) there are modifications of proteins intrinsic to disease (e.g. phosphorylation, nitration, oligomers, proteinase-resistant, and cleavage products); and 2) disease forms characterized by accumulation of a single protein only are rather the exception than the rule. In the diagnostic practice currently three protein-related markers (Amyloid-beta, tau, phospho-tau) complemented by surrogate markers (e.g. 14-3-3 protein) are the most widely examined variables in the cerebrospinal fluid. Evaluation of alpha-synuclein also reveals promising results. Moreover, there are attempts to evaluate these proteins in the plasma also. Due to the high number of combinations of diseases, it would be pivotal to evaluate modifications of at least the five most relevant proteins (amyloid-beta, prion protein, tau, a-synuclein, TDP-43) simultaneously with different methods. When complemented by the detection of biomarkers associated with pathogenetic processes, and also neuroimaging and genetic analysis, a highly personalized diagnostic profile could be obtained. However, the importance of standardized pre-analytical steps must be emphasized to avoid discrepant results and misinterpretations. This complex approach may have higher prognostic predictive value; may be useful for monitoring therapy; and may open new avenues for research on pathogenesis.

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1728
WFN15-1880
Neuropathology T 21.1
Translating brain tumor biomarkers into diagnostic use

J.A. Hainfellner. *Institute of Neurology, Medical University of Vienna, Vienna, Austria*

Brain tumor biomarkers considered nowadays as candidates for clinical use, mainly comprise tissue-based genetic and epigenetic markers, such as chromosome arms 1p/19q co-deletion, mutations in *IDH*, mutations in *TERT* promoter*n* and methylation of the *MGMT* promoter. In a recent international effort, substantially driven by The Cancer Genome Atlas (TCGA) Research Network, some of these markers have emerged to be useful for grouping of diffuse gliomas, providing the basis for biological classification of this important brain tumor category. Some markers have additionally proven useful for prognosis (indicating patient outcome) and/or prediction (indicating response to a given therapy), e.g. *MGMT* promoter methylation status as prognostic and/or predictive marker in glioblastoma.

Although these recent advances strongly argue for the use of molecular brain tumor biomarkers in clinical practice, translation into routine clinical use is still rather protracted. This is due to a number of limiting factors, including methodological, infrastructural, organisational, and also scientific issues (e.g. lack of prospective clinical trials specifically designed for investigation of analytical and clinical performances of candidate biomarkers). Nevertheless, the WHO has started to integrate molecular markers into its international brain tumor classification system, which will lead to a paradigmatic shift in brain tumor typing, necessitating the integration of histopathological assessment and molecular analysis of brain tumor biopsies.

It will be the task of Neuropathology as medical and academic discipline to handle this highly complex change-management in the coming years, for the sake of optimized and personalized treatment of patients suffering from brain tumors.

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1729
WFN15-1812
Public Policy and Health Economics T 3.1
A learning collaborative for implementation science in neuroscience

D. Silberberg[a], E. Ewart-Pierce[b], R. Sturke[b]. [a]*Department of Neurology, University of Pennsylvania, Philadelphia PA, USA;* [b]*Division of International Science Policy Planning and Evaluation, Fogarty International Center National Institutes of Health, Bethesda MD, USA*

Background: Where scientifically proven health innovations from neuroscience promise improved outcomes there is a persistent gap between this promise and successful implementation in low- and middle-income country contexts. Fogarty International Center together with others at NIH including: NINDS, NICHD, NIMH and NIA, as well as the Society of Neuroscientists of Africa gathered diverse stakeholders including: grantees of the NIH Global Brain Disorders Program, program implementers, policy-makers, and other stakeholders for a one day event in Durban, South Africa in March 2015.
Objective: The group identified an unmet implementation science (IS) agenda within the discipline and prioritized deepening connections between multiple stakeholders, improving stakeholder engagement in research, and extending reach of successful interventions.
Methods: In order to advance these priorities the assembled group is launching the Learning Collaborative for Implementation Science in Global Brain Disorders (The Collaborative). The Collaborative provides a platform for communication, collaboration, and learning among members to raise awareness of implementation science strategies, promote research priorities informed by stakeholder communities, and support identification and resolution implementation challenges.
Results: This group is currently executing a needs assessment and developing a work plan to achieve for collaborative learning and improved capacity in IS.
Conclusion: The group is seeking input and discourse about three key questions: 1) What are the opportunities for improved connection between research, practice and policy? 2) What is the experience of the neuroscience community in engaging diverse stakeholders? 3) How can the Learning Collaborative support the neuroscience community in moving the implementation science agenda forward?

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1730
WFN15-1931
Public Policy and Health Economics T 3.1
The cost of neurological disorders in Europe

J. Olesen. *Neurology, The national hospital Glostrup, Glostrup Copenhagen, Denmark*

The cost of neurological disorders in Europe

Supported by the European Brain Council I have led two huge studies of the cost of disorders of the brain in Europe. It included both neurological and psychiatric disorders. The first was published in 2005 and the next in 2011. The total cost in a population of around 500 million was 386 billion euros in the first study which was far from complete. The next study found a staggering 798 billion. Of this one third or 266 billion was ascribed to neurological disorder. The rank order of these disorders was dementia, stroke, headache, sleep disorders, traumatic brain damage, Diseases traditionally occupying neurologists such as epilepsy, movement disorders and multiple sclerosis were also very costly but much less than those mentioned first.This raises issues about the future use of resources in neurology.

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1731
WFN15-1938
Neurological Diseases and Pregnancy T 13.1
Epilepsy and antiepileptic drugs in pregnancy and beyond

C. Harden. *Epilepsy Services Mount Sinai Health System, Mount Sinai Beth Israel Phillips Ambulatory Care Center, NY, USA*

Many women with epilepsy have well-controlled seizures and lead lives that are for the most part unrestricted by the illness. Therefore, many women with epilepsy need expert guidance to achieve the optimal pregnancy outcome. Antiepileptic drugs (AEDs) must often be maintained throughout pregnancy in order to prevent seizures. There is a range of safety among AEDs in terms of their teratogenic risk. Valproate, phenobarbital and topiramate carry the greatest risks, with a rate of major congenital malformations (MCMs) in the range of 4-9% for offspring exposed within the first trimester in utero. Many other AEDS including levetiracetam, oxcarbazepine, lamotrigine, carbamazepine and phenytoin have lower rates of teratogenesis at approximately 2-3%. To put this in perspective, the expected rate of MCMs in the general population is 2%. There is a prominent dose effect with valproate, and maternal doses of up to 500 mg per day are associated with malformation rates of approximately 4%. A dose-to-malformation rate relationship is present with all AEDs however. Effects of AEDs on intellectual outcome are not confined to first trimester exposure, and are also most at risk for being adverse with valproate exposure. Folic acid supplementation provides some protection against cognitive teratogenesis, but not clearly so for the risk of MCMs. The safety of breast feeding while taking several AEDs has been established. During pregnancy, most women have little change from their pre-pregnancy seizure frequency, but the individualized therapeutic AED level should maintained to minimize the risk of seizures.

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1732
WFN15-1886
Neurological Diseases and Pregnancy T 13.1
Demyelinating diseases and pregnancy

D. Sadovnick. *Medical Genetics and Neurology, University of British Columbia, Vancouver, Canada*

This talk will focus on reproduction and multiple sclerosis (MS). Current knowledge and future directionsneeded in this area will be discussed and will range from contemplating apregnancy (father or mother with MS) to post-partum (e.g. post-partumdepression in men and women with MS) and the need for a disease-specific ratherthan a therapy specific pregnancy registry(ies).

MS is themost common cause of neurologic disability, other than trauma, among youngadults. MS affects women and men in the prime of their reproductive lives.Childbearing is a major goal of many with MS. The concurrent demands of livingwith MS and bearing/ parenting a child(ren) can exert considering concern to coupleswhen 1 parent has MS.

Historically, women with MSwere advised not to become pregnant but today the decision is made by theperson with MS and his/her partner. They are encouraged to make informeddecisions on many issues including parental disease course, disease therapies, recurrencerisks and psychosocial issues. Unfortunately,little prospective data are available. Wehave thus established the **M**ultiple **S**clerosis**C**entre of **E**xcellence on **R**eproduction and **C**hild **H**ealth (MS-CERCH), a ***virtual*** international multidisciplinaryresearch consortium in response to an increasing need by individuals with MSand their partners for evidence-based, up-to-date, and personalized informationsurrounding childbearing and child rearing. Comprised of a diverse team ofinternational clinicians and researchers, the MS-CERCH mandate is “to provideevidence-based strategies in reproductive decision-making and parenting-relatedissues to individuals with MS, their partners, and their health careproviders”.

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1733
WFN15-1945
Neurosurgery for Neurologists T 24.1
Strategies on the treatment of intracranial arteriovenous malformations

Y. Tu. *Neurosurgery, World Federation of Neurosurgical Societies, Taipei, Taiwan*

Surgical treatment of intracranial arteriovenous malformation (AVM) is one of the most difficult tasks for neurosurgeons, especially, for patients with large size AVM or AVM at the eloquent and deep location. Recent advent of endovascular treatment and radiosurgery may replace the role of surgery and decrease the difficulty of treatment of AVM to some extend but not all. Surgical excision with or without preoperative embolization remains the main modality of treatment of intracranial AVMs. However, the procedure of embolization itself also carries certain percentage of risk. Selection of this treatment modality needs to be carefully evluated.

For small deep seated AVM and small AVM at the eloquent area, radiosurgery is another therapeutic option. However, the efficacy to achieve obliteration of the AVM by radiosurgery is only 60%-70% in general. Combined embolization and radiosurgery has been advocated as an option for treating large complex AVM. However, current treatment results failed to demonstrate any superiority of the result from this combined treatment.

Palliative treatment with partial obliteration of the AVM nidus to reduce arteriovenous shunting is considered to be useful for the decrease of the occurrence of steal phenomenon, however, it may also increase shear stress of the abnormal vascular architecture and resulted in increase rate of hemorrhage.

From 1989 to 2011, a total of 367 patients with cerebral AVM were treated at the National Taiwan University Hospital and its' affiliate hospitals. Of these 367 patients, 143 patients underwent microsurgery as the solo treatment and 214 patients received embolization. In the later group, 25 patients had their AVMs cured after one or multiple sessions of endovascular treatment. The other 189 patients in this group, endovascular treatment can only be applied for the reduction of the flow and the size of the AVM. These patients finally underwent microsurgery as the definite treatment. The treatment morbidity was 11% in microsurgical group and 9% in endovascular group. There were 2 mortalities in surgical group (o.6 %) and 2 in endovascular group (0.9 %).

Our current selection criteria for different therapeutic modality and surgical strategy for intracranial AVM will be discussed.

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1734
WFN15-1943
Sports Neurology T 5.1
Chronic traumatic encephalopathy

B. Jordan. *Neurology, Burke Rehabilitation Hospital, White Plains, USA*

Chronic traumatic brain injury (CTBI) represents a spectrum of disorders associated with long term consequences single or repetitive traumatic brain injury (TBI). Although, the prototypic CTBI is chronic traumatic encephalopathy (CTE), other chronic brain injuries can be encountered. These include chronic neurocognitive impairment (CNI), chronic postconcussion syndrome (CPCS) and posttraumatic dementia (PTD). CTE represents the long term neurological consequences of repetitive concussive and/or subconcussive blows, presumably secondary to a progressive tauopathy. Dementia pugilistica represents a subtype of CTE and is typically reserved for cases of severe end-stage dementia secondary to a long boxing career. The exact incidence and prevalence of CTE in modern era sports is unknown. Although, CTE represents a distinct neuropathological entity, the causation has yet to be clearly established. Exposure to repetitive mild TBI has been associated with CTE and is speculated to be an important risk factor for CTE. The genetic risk factors for CTE have yet to be determined but apolipoprotein E ε4 (APOE ε4) may be an effect modifier of the condition. CTE can present with cognitive, behavioral and/or motorical symptomatology. Traditional structural neuroimaging reveals nonspecific findings such as cavum septum pellucidum (CSP), diffuse atrophy, and ventricular dilatation. Reduced fractional anisotropy (FA) on diffusion tensor imaging (DTI) reflective of decreased white matter integrity can be observed in individuals exposed to repetitive head trauma. Although, molecular neuroimaging may provide assistance in establishing the antemortem diagnosis of CTE, currently the diagnosis can only be definitively ascertained at postmortem.

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1735
WFN15-1671
Sports Neurology T 5.1
Peripheral nerve injuries

M. Hallett. *Human Motor Control Section, NINDS, Bethesda, USA*

Peripheral nerve can be damaged in sports by direct trauma or entrapment and microtrauma over time. It is the latter that will be the focus of this lecture. The ulnar nerve can be damaged at the medial side of the elbow in the throwing motion. This is due to valgus strain of the elbow and damage to the soft tissues near the ulnar nerve. Common in baseball pitchers, this injury is also seen in football, javelin, volleyball and tennis. The lateral side of the elbow is the site of tennis elbow and is most commonly epicondylitis, but there can be an entrapment of the posterior interosseous nerve. Particularly in volleyball, there can be an entrapment of the infraspinatus branch of the suprascapular nerve at the spinoglenoid notch of the scapula. In bicycling the ulnar nerve may be damaged at the wrist and the pudendal nerve can be compressed by the bicycle seat. In joggers, if there is heel pain other than plantar fasciitis, it can be due to entrapment of the tibial nerve in the tarsal tunnel syndrome, or entrapment of its branches, the medial calcaneal branch or the first branch of the lateral plantar nerve. Pain on the medial side of the foot may be due to entrapment of the medial plantar nerve.

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1736
WFN15-1878
Mitochondrial Diseases T 28.1
Nutrition and nutritional signaling as therapy targets for mitochondrial disorders

D. Munoz, M. Troncoso, P. Santander. *Department of Pediatric Neurology, Hospital Clinico San Borja Arriarán, Santiago, Chile*

Mitochondrial disorders are degenerative diseases known to be responsible for a number of heterogenous clinical presentations with multi-systemic dysfunctions that often involves the nervous, endocrine, renal and cardiac system. Impaired oxidative phosphorylation leading to a decrease in cellular energy (ATP) production is the most important cause underlying these conditions.

Despite significant progress made in the field of mitochondrial medicine during the last two decades, defining the specific biochemical defects and underlying molecular mechanisms, the avaliable information about effective treatment approaches is limited.

The goal of nutritional treatment of mitochondrial dysfunction in various neurological syndromes are based primarily in improving the efficiency of the processes of oxidative phosphorylation at the system level. Accumulation of toxic metabolites and reduction of electron transfer activity have prompted the use of new therapeutic agents, such as antioxidants, radical scavangers and cofactors. A literature review of the use of these supplements in mitochondrial disorders is presented.

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1737
WFN15-1901
Mitochondrial Diseases T 28.1
Genome editing to treat mitochondrial DNA disorders

M.A. Avaria, K. Kleinsteuber. *Pediatric Department Pediatric Neurology Unit, Universidad de Chile Facultad de Medicina Campus Norte, Santiago, Chile*

It is estimated that mtDNA mutations resulting in diseases affect 1 in 5,000 children, representing the most common neurometabolic disorder of childhood, and that 1 in 200 women could be a mitochondrial disease carrier.

Currently, there is no cure for mitochondrial diseases, so great effort has been directed to find genetic treatments that can at least ameliorate symptoms and prevent trans generational transmission.

Pre-implantation genetic diagnosis and mitochondrial replacement techniques are currently therapeutic resources, but issues of safety and ethics have been raised.

mtDNA is present in multiple copies per cell. Cells with mtDNA mutations are heteroplasmic, containing different proportions of wild and mutant mtDNA. There is a threshold level of percentage of mutated mtDNA that is important for the clinical expression of disease. Threshold levels for biochemical and clinical defects are generally in the range of 60%–95% mutated mtDNA depending on the severity of the mutation.

Several strategies for genetic manipulation of mtDNA have been developed based in these characteristics. mtDNA editing to inhibit the replication of mutated mtDNA, expecting cells to replace it with normal mtDNA is the most promising. Experiments in somatic cells containing the mutation for NARP /MILS syndromes, have established restoration of normal mitochondrial function. Recently it has been reported that human mutated mtDNA can be reduced in oocytes by mitochondria-targeted nucleases.

A review of key reports on research in this area in scientific literature will be presented.

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1738
WFN15-1719
World Health Organization Neurology Initaitives T 25.1
Latin America's strategic plan for prevention and care of epilepsy

C. Acevedo. *Chilean League Against Epilepsy, Director Collaborating Center PAHO/WHO Chile, Santiago, Chile*

- Strategic and plan of action on epilepsy in Latin America is an initiative between International League against Epilepsy (ILAE), International Bureau for Epilepsy (IBE) and Pan American Health Organization (PAHO).
- Approved by PAHO Board in September of 2011, for a period between 2012-2021, and signed by Ministries of Health of Americas countries.
- PAHO, ILAE and IBE-and other partners-will collaborated together to support this plan, and specially work on set priorities, mobilize resources, and encourage the cooperation between countries included in this plan.
- To accomplished these purposes the plan required:
  - Universal access
  - Countries involved solidarity
  - Respect for the human rights of people with epilepsy
  - Social participation
  - Scientific evidence
  - Protection to vulnerable groups
  - Respect for the historical and cultural frameworks of communities
  - Comprehensive care in health units
  - Responsibility and accountability
- Strategic Areas:
  1. Programs and legislation for the care of people with epilepsy and protection of their human rights
  2. Health services network for the treatment of people with epilepsy, with emphasis on primary health care and the provision of drugs
  3. Education and sensitization of the population, including the people with epilepsy and their families
  4. Strengthening of the ability to produce, asses, and use information on epilepsy

This regional initiative in the Americas in unique in the world and has opened up a scenario of cooperation between scientific, social, and governmental world, and PAHO to reduce the huge gap surrounding epilepsy and the stigma associated.

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1739
WFN15-0077
World Health Organization Neurology Initaitives T 25.1
Africa and WHO: fighting non-communicable diseases

A.G. Diop. *Department of Neurology, University of Dakar, Senegal*

In the early 60's, non-communicable disorders such as diabetes, hypertension, obesity and their consequences (stroke, heart infarction, and cancers) were considered as almost nonexistent in Africa. Neurological conditions such as epilepsy, dementia, Parkinson were seldom reported. Nowadays, Africa is in a situation of developmental and sociocultural transition, characterized by a close coexistence of traditions and modernism. Infectious diseases are still occurring, but non-communicable diseases are increasingly the leading cause of morbidity and mortality. Changes in the life style, diet, and rural exodus of poor population to suburban areas of cities, generate co-morbid situations from communicable and non-communicable diseases. In African countries, increasing cases of epilepsy, stroke, dementias, cancers are now diagnosed at any age. African nations and WHO are dealing with a new epidemiological situation in the context of high rates of illiteracy, poverty, but also due to rapid disharmonized urbanization. Usually, the management of these issues is difficult due to the scarcity of specialized health staff, financial and/or unavailability of diagnostic means and major drugs. This led to the set up non-communicable units in the ministries of health, programs and initiatives for tackling such new medical situations. This resulted in the Global Campaign against Epilepsy, and other programs dedicated to diabetes and cancer. There is a need for similar programs for the prevention and management of stroke, pain, dementia and neurodegenerative disorders. All of which are also major, and increasing factors to the public health burden in Africa.

The current state and possible perspectives are discussed in this communication.

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1740
WFN15-1802
Neurology and Special Environments T 5.1
The CNS in lightning

M. Cooper. *Bioengineering and Emergency Medicine, University of Illinois, Chicago, USA*

In developed countries, lightning injury is primarily a neurological, not a burn, injury. It can extend from the nearly harmless simple static discharge similar to walking across a carpet to cardiac arrest with hypoxic bran damage. Between these two extremes, brain injury similar to post-concussion syndrome and nerve injury, with resultant chronic pain, are the main components of lightning injury. The autonomic, and sometimes the endocrine system, can also be affected. Concussive injury from the explosive effect very near a lightning strike or muscle contractions throwing a victim can cause musculoskeletal problems.

Only 3-5% of injuries are from direct strike. The majority are from ground current (40-50%), side flash from another object (20-30%), contact injury (15-25%), or upward streamer (10-15%), all of which deliver only a small portion of lightning's usual energy to the victim. Because of this, thermal injuries occur in less than half of the survivors so that lack of skin markings, burns or scars cannot be used to rule out lightning injury.

Although brain injury with adult attention deficit, memory, executive function, irritability, depression, and other signs have been well described, defining the cellular and tissue level damage has been more difficult due to lack of funding and research trained keraunomedicine practitioners as well as available subjects. Controlled longitudinal studies to determine long term effects have also not been done for similar reasons.

In the US and many other developed countries, lightning injuries and fatalities have been markedly decreased through public education. However, lightning injury continues to be a major concern in lesser developed countries due to lack of lightning-safe buildings and vehicles, poor awareness, and the much higher lightning densities that occur in tropical and subtropical countries.

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1741
WFN15-1817
Neurology and Special Environments T 5.1
The brain in acute mountain sickness and cerebral edema

P. Bärtsch. *Dept. Internal Medicine, Division of Sports Medicine, Heidelberg, Germany*

Ascent to altitudes above 2500 m can cause acute mountain sickness (AMS), which may progress to high altitude cerebral edema (HACE). AMS is characterized by headache, lassitude, anorexia and nausea/vomiting, which are all usually self-limiting with a day of rest and symptomatic treatment. Truncal ataxia and altered consciousness are the cardinal symptoms of HACE, which is often lethal when not treated with oxygen, dexamethasone and descent. Slow ascent, or acetazolamide, or glucocorticosteroids during ascent can attenuate or prevent these illnesses.

The pathophysiology underlying the cerebral symptoms of AMS is unclear. Several mechanisms could activate pain sensitive structures and vegetative centers in the brain. Candidates are brain edema and increased intracranial pressure (ICP), distension of large vessels because of increased cerebral blood flow (CBF) in hypoxia and possibly impaired autoregulation of CBF, restricted venous drainage of the brain, activation of the trigemino-vascular system by hypoxia, or increased permeability of the blood brain barrier (BBB) in hypoxia with release of inflammatory mediators. It is conceivable that several of these factors are involved in the pathophysiology of AMS, since no single factor is strongly associated with the development of AMS.

Increased ICP and vasogenic edema located predominantly in the corpus callosum (CC) are consistent findings in HACE. Hemosiderin depositions in the CC usually detectable by susceptibility weighted MRI after HACE indicate leakage of red blood cells through the BBB and are footprints of HACE. Increased CBF, impaired venous outflow and increased vascular permeability may all contribute to the BBB leak in hypoxia.

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1742
WFN15-1627
Neurological Care During Disasters T 23.1
Acute phase management for neurological patients in a disaster

Y. Ugawa. *Department of Neurology, Fukushima Medical University, Fukushima, Japan*

I summarize what we did at the earthquake on March 11, 2011 and thereafter.

Acute phase (a week or two weeks after the earthquake)

We did our roles as a doctor, not specialists. We triaged emergent, serious patients and cared them in our hospital or transferred them to distant, intact hospitals.

Subacute phase(one month to two months after the earthquake)

We, as neurologists, treated serious patients with encephalitis, MG crisis and MS relapse, who were not able to be managed in other hospitals.

Recovery phase to usual neurology (three months to a half year after the earthquake)

At this phase, we gradually recovered to the usual neurologists. The patients living near our hospital came back to our outpatient clinic.

Chronic phase, usual neurology (several months after the earthquake)

We mostly spent our time the same as before the earthquake. At this stage, we should take care of care givers as well as the patients because some care-givers had some mental problems due to the disaster.

Long term works (one year or more later)

In most areas in Fukushima, people live just like before earthquake because of the same radiation level as the other places in the world. The radiation makes some of us unable to come back to the original living place, which has produced several health problems due to incorrect lifestyles as follows: the higher blood pressure and hyperlipidemia in the people living in the temporary houses, and the cerebrovascular incidence increment after the disaster.

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1743
WFN15-1660
Neurological Care During Disasters T 23.1
Establishing a nationwide disaster management system for neurologically ill patients

R. Kaji. *Neurology, Tokushima University, Tokushima, Japan*

Establishing a nationwide disaster managing system for neurologically ill patients.

RyujiKaji MD Department of Neurology, Tokushima University

Japan and Chile have a common problem of earthquakes and tsunami, which cause amassive national disaster. Critically ill neurological patients such as with amyotrophiclateral sclerosis on a respirator succumbed to death in the last Eastern Japan Earthquake. Some of them died from tsunami, the others of respirator failuredue to power loss. There have been a number of discussions to reduce such casualties. One is to prepare emergency power source driven by oil. The easiest one is tosupply electric power from cars. Of course, continued supply of gasoline or diesel for cars is needed. Local medical personnels have to retain a list of patients with a respirator at home. Japanese government is now promoting these activities to prepare for the expected Southern Japan earthquake, which shouldcome in 50 years with the likelihood of more than 50%.

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1744
WFN15-1667
Neurological Care During Disasters T 23.1
Challenges of mental health care in Latin America in the aftermath of disasters

R.A. Figueroa, P.F. Cortés. *Disaster medicine, National Research Center for Integrated Natural Disaster Management, Santiago, Chile*

Disasters are increasing its frequency in the world and Latin America. Post-traumatic mental disorders are one of the most important consequences of these events, with significant costs for the public health of communities.

During the last decades, the world has designed and organized different models of intervention to prevent and treat post-disaster mental disorders. Latin America - as a region in course of development - has been facing its own local challenges to accomplish this task.

In order to get a glimpse about the key challenges of disaster mental health in Latin America, we surveyed the public health officials in charge of disaster mental health in different countries of the region, asking them the to identify the most important challenges they are facing in their duties. In this keynote, we present the most important results and discuss the implications for future public health actions.

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1745
WFN15-1925
Neurological Care During Disasters T 23.1
Mental health after the Great East Japan Earthquake

M. Mimura. *Neuropsychiatry, Keio University, Tokyo, Japan*

We experienced the Great EastJapan Earthquake on March 11, 2011. This disaster caused unprecedented damage, with nearly 20,000 peopledead or missing. Since March 17, our university dispatched medical rescue teams9 times in total, the last three focused on psychiatric problems and mental supportin Fukushima prefecture. The disaster in Fukushima could be recognized asmultifaceted with tsunami and possible radiation exposure caused by the nuclearaccident in addition to the earthquake damage per se. These complex problems causedtremendous distress to vulnerable people including aged persons, individualswith various medical/neurological/psychiatric conditions, and specificallypeople with cognitive impairment. Psychiatric problems which required forintervention included worsening of original psychiatric diseases, acute stressdisorder, post-traumatic stress disorder, adjustment disorder, suicidal attempt/idea,and alcohol related problems. One exceptional and extraordinary situation in Soma district in Fukushima prefecture was the effect of Nakamura Domainoie-sodo (internal trouble), “Soma Incident” which occurred during 1880’s. Thefeudal lord Tomotane Soma is considered to have had schizophrenia. As adistorted consequence with stigma, there existed no psychiatric facilities inSoma district even before the earthquake, and citizens with psychiatricproblems in Soma had been forced to visit neighboring Minami-Soma and Futabadistricts. However, the psychiatric facilities in Minami-Soma and Futabadistricts were completely destroyed by the nuclear accident. We helped Departmentof Neuropsychiatry, Fukushima Medical University provide suitable mentalsupport for the survivors. In addition, to create new psychiatric services isan urgent issue including outreach activities and remote medical/psychiatriccare.

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1746
WFN15-1848
Neuro-Ophthalmology T 8.1
How can Ocular Coherence Tomography (OCT) Inform the Neurologist?

C. Luco. *Neuro Ophthalmology, Fundacion Oftalmologica Los Andes, Santiago, Chile*

In the 1990's a team from New England Eye Center of Tufts University led by James Fujimoto Ph.D., Joel Schuman M.D. and Carmen Puliafito M.D. was one of the groups that developed the technology of Opthical Coherence Tomography for Opthalmology. The flat retina could now be seen side ways as a histological specimen and differente layers could be measured. OCT is an excellent tool for examining the optic nerve head and the retina. The inner retina, ganglion cells and axons are central nervous system equivalent to the spino-thalamic pathway. As such they can be part of degenerative brain diseases. There are numerous papers dealing with thinning of the inner plexiform, retinal ganglion cells and nerve fiber layers in the macular area and the optic nerve area in different nerurological diseases. The Stratus-Time Domain machine has a definition of 15um., while the Cirrus-Spectral Domain has 7um. definition and the Heidelberg-SD has 10um. definition with 40.000 scans/sec. With these machines it is possible to diagnose a subtle papilledema ophthalmoscopically invisible, a small macular hole that explains a visual loss or fluid under the macular from a disc oedema. In neurodegenerative disorders thinning of the retinal nerve fiber layer in MS or ganglion cell-internal plexiform layer thinning in Parkinson's disease are new elements that contribute to the diganosis and can be part of the prognostic factors. The spatial resolution of the different machines have to be taken in account when different results are compared.

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1747
WFN15-1659
Neuro-Ophthalmology T 8.1
What’s new in idiopathic intracranial hypertension?

V. Biousse. *Neuro-Ophthalmology, Emory University School of Medicine, Atlanta GA, USA*

Idiopathic intracranial hypertension (IIH) is a disorder typically affecting young, obese women, producing a syndrome of increased intracranial pressure without identifiable cause.

Despite a large number of hypotheses and publications overthe past decade, the etiology of IIH is still unknown. Numerous studies have emphasized radiologic abnormalities in IIH, including orbital signs of raised intracranial pressure, empty sella, meningoceles and cerebral transverse sinus stenosis. Identification of subgroups of patients at high-risk for irreversible visual loss, such as black patients, men, morbidly

obese patients, and patients with fulminant IIH, helps determine management approaches and refine follow-upstrategies. There continues to be no evidence-based consensus or formal guidelines regarding management and treatment of the disease. Treatment studies show that the diagnostic lumbar puncture is a valuable intervention beyond its diagnostic importance, and that weight management is critical. The recently completed "idiopathic Intracranial Hypertension Treatment Trial" also showed that acetazolamide is an efficient treatment of papilledema and improves the quality of life of IIH patients. However, many questions remain, regarding theefficacy of cerebrospinal fluid (CSF) shunting procedures, optic nerve sheath fenestration, and cerebral transverse venous sinus stenting.

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1748
WFN15-1658
Neuro-Ophthalmology T 8.1
How can ocular fundus photography inform the neurologist?

N. Newman. *Neuro-Ophthalmology, Emory University School of Medicine, Atlanta, USA*

Ocular fundusexamination is a fundamental component of the neurological examination. However,direct ophthalmoscopy is difficult to perform without pupillary dilation andrequires extensive practice to accurately recognize optic nerve and retinalabnormalities. Although examination of the ocular fundus with a direct ophthalmoscope is an important skill for all neurologists, it is rarely and unreliably performed. Recent studies have suggested that digital retinal photographycan replace direct ophthalmoscopy in many settings.Advances in optical technology have made it easier to obtainhigh-quality retinal imaging, even without pupillary dilation. Retinalphotography has a high sensitivity, specificity, andinterexamination/intraexamination agreement compared with in-personophthalmologist examination, suggesting that photographs can be used in lieu ofophthalmoscopy in many clinical situations. Nonmydriatic retinal photographyhas recently gained relevance as a helpful tool for diagnosingneuro-ophthalmologic disorders in the emergency department. In addition,several population-based studies have used retinal imaging to relate ophthalmicabnormalities to the risk of systemic and neurologic disease. Thepossibility of telemedical consultation offered by digital retinal photographyhas already increased access to timely and accurate subspecialty care,particularly for underserved areas, and holds promise for rapid diagnosis and referral in clinical research settings. Additionally, ocular fundus photography may serve a role in medical education to help improve student confidence in interpretation of ocular fundus findings and improve awareness of the importance of examination of the ocular fundus. The increasing availability of nonmydriatic ocular fundus photography may allow replacement of direct ophthalmoscopy in many clinical, research and educational settings.

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1749
WFN15-1781
Local and Global Histories of Neurology
Making neurology global: the first international neurological congress in Berne, Switzerland 1931

S. Casper. *Humanities & Social Sciences, Clarkson University, Potsdam, USA*

The First International Neurological Congress was held in Berne Switzerland in 1931. New York neurologist Bernard Sachs (1858-1944), the President of the Congress, welcomed an audience of 890 participants from forty nations and six continents, by declaring: "The purpose of this congress is to establish personal contacts and to unite the neurologists of the entire world."

The Congress unquestionably fulfilled that aim. After almost sixteen years of unwavering animosities, neurologists representing all of the belligerent nations of the 1914-1918 conflict gathered together in neutral territory. There they exchanged pleasantries at a steady stream of smokers, high teas, late-night dinner parties, dances, and a host of field trips to nearby cultural attractions, all the while discussing the science and medicine of the nervous system.

What was the fundamental purpose of these cultural and intellectual exchanges in Switzerland? What was their legacy? Despite the vast expansion of knowledge about the nervous system and its diseases that occurred between 1880 and 1919, the establishment of institutional settings for neurology in the interwar period had been a haphazard affair. The organizers of the Congress intended it as a global corrective to that situation. In other words, the Congress promoted the specialization of an internationally recognized, autonomous field of medicine. Yet this agenda posed many challenges. Not least, could obvious ideological differences between nations be overlooked temporarily and could the tensions readily remembered from past violence truly be forgotten?

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1750
WFN15-1898
History of Neurology T 22.1 - Local and Global Histories of Neurology
Manganic Parkinsonism in Chile and the introduction of levodopa

M. Miranda[a], M.L. Bustamante[b], F. Mena[c], A. Lees[d]. [a]*Neurology, Clinica Las Condes, Santiago, Chile;* [b]*Faculty of Medicine, University of Chile, Santiago, Chile;* [c]*Neuroradiology, Clinica Las Condes, Santiago, Chile;* [d]*Reta Lila Weston Institute of Neurological Sciences, University College of London, London, United Kingdom*

In 1963 a group of clinicians and researchers led by Dr. Ismael Mena from Chile and George Cotzias began a study on a group of Chilean miners affected by manganism. The collaboration lasted for 7 years and played an important part in the eventual introduction of L-dopa for the treatment of Parkinson's disease (PD) in 1969.

Dr Cotzias was working at that time in Brookhaven Laboratory, Upton, New York, on his initial hypothesis that melanin had a key role in the pathophysiology of Parkinson disease (PD) and the role of manganese as a toxin and its particular affinity to melanin. Cotzias had started in 1967 testing levodopa (L-dopa) treatment for Parkinson´s disease (PD) and the study of chilean manganic patients, who showed parkinsonian features although very atypical, allowed him and his team to further improve the knowledge about how to use L-dopa in PD.

This collaboration led to many seminal papers on clinical and therapeutic aspects of Parkinson´s disease and manganism that were part of the history of the introduction of L-dopa as the main treatment of PD.

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1751
WFN15-1921
History of Neurology T 22.1 - Local and Global Histories of Neurology
Latin American contributions to the WFN

R. Shakir. *President, World Federation of Neurology, London, United Kingdom*

The World Federation was inaugurated in July 1957. There were 38 national delegates of whom 7 were from Latin America. They came from already developed neurological centers. Alfonso Asenjo (Chile), Arana-Iniguez and C. Catell-Diaz (Uruguay), Deolindo Couto (Brazil), Jose Pereyra-Kafer (Argentina) and C. de Rojas (Cuba) and Oscar Montes Trelles (Peru).

Two events shaped Neurology in the sixties the first was the meeting of the Commission on Tropical Neurology held in Buenos Aires in 1961 with four important individual founding members. Oscar Trelles (Peru), Gustavo Poch (Argentina), Webb Haymaker (USA) and Noshir Wadia (India). Their work shaped neurology in the developing world.

The second was the inaugural of the Pan American Congress of Neurology, Lima 20-25 October 1063 under the presidency of Trelles. The congress was attended by 500 delegates and supported by the WFN and NINDB with a grant of US $ 33,000.

The Pan American congresses continued with quarterly meetings with the last one in La Paz Bolivia in 2012.

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1752
WFN15-1888
Motor Neuron Disease T 11.1
New insights into the biological mechanisms of motor neuron injury in ALS

S. Vucic. *Neurology, Westmead Hospital University of Sydney, Sydney, Australia*

Amyotrophic lateral sclerosis (ALS) is the most frequent of the neuromuscular degenerative disorders, with a median survival of 3-5 years. The pathophysiological mechanisms underlying ALS are multifactorial with a complex interaction between genetic factors and molecular pathways. Approximately 10% of all ALS cases are familial, with 40 ALS-associated genes identified to dated. The underlying pathophysiology associated with the genetic mutations appear varied, and include abnormalities of DNA/RNA regulation, RNA metabolism, mitochondrial dysfunction, aberrant axonal transport, and oxidative stress. Recently, increased hexanucleotide expansion in the glutamate c9orf72 gene (9p21.1) was identified as a major caused of familial ALS, resulting in dysregulation of RNA metabolism and toxicity, with resultant neuronal degeneration. Importantly, dysfunction of molecular pathways, including glutamate-mediated excitotoxicity, has been identified in both sporadic and familial ALS, suggesting the existence of a common pathogenic pathway. These pathophysiological insights have provided novel therapeutic approaches, including specific anti-excitotoxic agents such as retigabine, as well as stem-cell and genetic based strategies, providing hope for feasible treatment of ALS.

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1753
WFN15-1694
Motor Neuron Disease T 11.1
ALS/MND: the spectrum of clinical and pathological phenotypes

A.C. Ludolph. *Neurology, University of Ulm, Ulm, Germany*

ALS genotypes and phenotypes

Our epidemiological data show that about 5% of ALS patients in Germany have a family history. The majority carry the C9orf72 mutation (24%), next is the SOD mutation (13%), TBK1, FUS and TDP-43 (each about 5%) follow. Most of these mutations do not only encodemutations in the genome of ALS patients, but also of FTD patients. Therefore, the phenotype – genotype relation is poorly understood.

Recent neuropathlogical findings emphazise that staging ("Braak Staging") for ALS is alsopossible. The results demonstrate that the pathology as shown by the molecular marker TDP-43 spreads from the motor cortex into the direction of the gyrus rectus and the orbitofrontal cortex. In a similar longitudinal fashion it affects the corticofugal tracts, the corticospinal tract (stage 1). the tracts to the precerebellar nuclei (stage 2), the corticostriatal tract (stage 3) and the perforant pathway (stage 4). These findings include ALS in the group of diseases which are characterized by an "initiation and propagation" pattern along anatomically defined pathways.

The translation of these neuropathological findings into phenotypes are at their beginning. However, measurement of fractional anisotropy by DTI shows that the neuropathological staging is mirrored by affection of the respective tracts. Also, spreading of the disease is a characteristic feature clinically and the predominant affection of monosynaptically supplied muscles characterize the disease. Whether these novel findings and these new concepts of ALS can be exploited therapeutically, will be show in the future.

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1754
WFN15-1872
Motor Neuron Disease T 11.1
Monomelic Amyotrophy-Current concepts and natural history

M. Gourie-Devi. *Neurology, Institute of Human Behaviour and Allied Sciences, New Delhi, India*

Monomelic Amyotrophy-Current concepts and natural history

Atrophy and weakness restricted to a single upper or lower limb, sporadic occurrence in the young with male preponderance, benign course, slow progression and spontaneous arrest, are the essential features. In upper limb MMA (Brachial MMA) small muscles of the hand, flexor and extensors of the wrist, innervated by C7-T1 spinal segments are most severely affected with relative sparing of brachioradialis. Contralateral limb involvement occurs in 10 to 80% with persistent asymmetry. However symmetrical bimelic amyotrophy has also been reported in a small number of patients. In the lower limb MMA (Crural MMA) posterior and anterior crural muscles and quadriceps muscles are most commonly affected. Electroneuromyography findings suggest anterior horn cell disorder without conduction block. Focal atrophy of lower cervical cord and high intensity signals localised to the anterior and lateral horns of the gray matter are characteristic features on imaging. Dynamic imaging with flexion of neck may show forward displacement along with flattening of lower cervical cord. Long term follow up studies have unequivocally shown that after the onset of symptoms progression occurs for 5 years in 95% of patients, followed by a stationary course. Multifocal motor neuropathy, post polio progressive muscular atrophy, distal spinal muscular atrophy, intrinsic spinal cord lesions, motor neurone disease and plexopathies have to be considered in the differential diagnosis. Microvascular ischemia, flexion myelopathy, venous stasis have been considered in the pathogenesis but challenged due to lack of robust evidence in support of the hypothesis.

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1755
WFN15-1654
Clinical Neurophysiology T 4.1 - In Collaboration with the International Federation of Clinical Neurophysiology
Disynaptic corticospinal projections to upper limb motoneurons: their role in movement and recovery from stroke

D. Burke. *Department of Neurology, Royal Prince Alfred Hospital and University of Sydney, Sydney, Australia*

Manual dexterity is an evolutionary feature of motor control, reaching its highest expression in humans. It depends on monosynaptic corticomotoneuronal projections, that are densest to the muscles of the hand and forearm and allow discrete movements of the digits. However if a subject cannot get his/her limb to an object, the limb may be next to useless even if manipulative skill is retained - well illustrated by the "man-in-a-barrel syndrome" in ALS.

Voluntary movement mobilises additional systems to control "postural" muscles and to coordinate contractions across joints to place the limb appropriately for the willed movement. One of these is a system of propriospinal neurons located at the C3-C4 level, projecting monosynaptically to motoneurons of multiple muscles across joints. These neurons constitute a premotoneuronal integrating centre that receives descending inputs from corticospinal and other systems from both sides, as well as inhibitory and facilitatory feedback from afferents in the moving limb. Originally described in the cat by Lundberg, Alstermark and colleagues, it has now been demonstrated anatomically and physiologically in higher primates. Pierrot-Deseilligny and colleagues have provided physiological evidence for its importance in humans.

Accordingly in human subjects the corticospinal projection is not exclusively monosynaptic, except for the intrinsic muscles of the hand. Following a stroke Mazevet et al. (2003) found that more of the corticospinal command for movement was transmitted through propriospinal neurons, a conclusion supported by Stinear and Blybow (2004). Unwanted consequences of greater use of this system to restore voluntary movement are "synkinetic contractions".

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1756
WFN15-1621
Clinical Neurophysiology T 4.1 - In Collaboration with the International Federation of Clinical Neurophysiology
Four segments central motor conduction studies in ALS, leukodystrophies and other neurological disorders

H. Matsumoto. *Neurology, Japanese Red Cross Medical Center, Tokyo, Japan*

I would like to introduce four types of stimulation methods that are clinically useful to detect lesions of the corticospinal tract: (i) transcranial magnetic stimulation, (ii) magnetic motor-root stimulation, (iii) magnetic brainstem stimulation, and (iv) magnetic conus stimulation. The central motor conduction time (CMCT) can be measured from the latency differences between cortical stimulation and motor-root stimulation. In brainstem stimulation using a double-cone coil, the cortico-brainstem conduction time (C-BST CT) and brainstem-root conduction time (BST-R CT) can be measured. In conus stimulation using a MATS coil, the cortico-conus motor conduction time (CCCT) and cauda equina conduction time (CECT) can be measured for leg muscles. Based on these developments, central motor conduction can be evaluated more precisely. In my session, I would like to demonstrate the clinical utility of magnetic stimulation in some neurological disorders.

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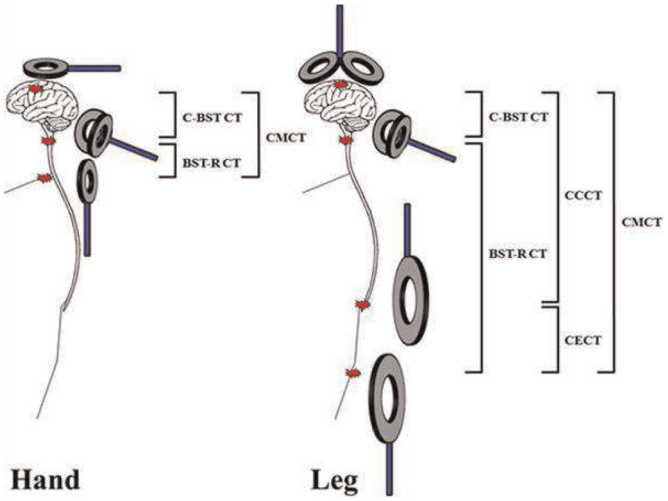

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1757
WFN15-1622
Clinical Neurophysiology T 4.1 - In Collaboration with the International Federation of Clinical Neurophysiology
Motor cortical plasticity in movement disorders and the influence of dopamine

Y. Ugawa. *Department of Neurology, Fukushima Medical University, Fukushima, Japan*

I will show influences of a few anti-Parkinsonian drugs on the neuroplasticity in normal human brain, abnormal plasticity in Parkinson's disease and its improvement by L-Dopa.

Dopamine/Dopamine agonist/Zonisamide and plasticity

It is well known that dopamine enhances both LTP and LTD, and the former is one of D1 effects and the latter is a kind of D2 effects. To study the relation between dopamine and neuroplasticity in humans, we used quadripulse stimulation (QPS), newly developed plasticity induction method in human. We compared LTP/LTD effect between baseline condition and the condition after L-Dopa intake in normal volunteers. Dopamine enhanced both LTP of QPS5 and LTD of QPS50. It is compatible with plasticity induction in animals.

In contrast, dopamine agonists had no significant influence on LTP/LTD like effects induced by QPS. One paper reported LTP was enhanced by D1 agonist and LTD by D1 and D2 agonists together, but D1 agonist alone or D2 agonist alone induced no changes in LTD. The lack of plasticity enhancement by agonist may be explained by the agonist used here is almost purely D2 agonist.

Zonisamide, one anti-Parkinsonian drug, mildly enhanced LTP like effect of QPS in normal subjects. This enhancement may be produced by some dopamine induction by Zonisamide or through some other pathways unrelated with dopamine.

Neuroplasticity in PD

In PD patients, even at early stage, QPS induced neither LTP nor LTD like effects in the motor cortex. This lack of plasticity was normalized by L-DOPA intake in parallel with motor symptoms' improvements.

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1758
WFN15-1887
Clinical Neurophysiology T 4.1 - In Collaboration with the International Federation of Clinical Neurophysiology
Does cortical involvement precede spinal involvement in ALS?

S. Vucic. *Neurology, Westmead Hospital University of Sydney, Sydney, Australia*

Corticomotoneuronal dysfunction has been implicated in the pathogenesis of amyotrophic lateral sclerosis by Charcot. Subsequently, a dying forward hypothesis was proposed whereby anterior horn cell degeneration was postulated to be mediated by corticomotoneuronal hyperexcitability via a transsynaptic glutamate mediated excitotoxic process. Utilising novel threshold tracking transcranial magnetic stimulation techniques, cortical hyperexcitability has been identified as an intrinsic and early feature of sporadic ALS, and linked to the process of neurodegeneration. Importantly, cortical hyperexcitability was also identified in familial forms of ALS, preceding the development of lower motor neuron dysfunction in familial ALS related to mutations in the superoxide dismutase-1 gene. This talk will provide an overview of the role of cortical involvement in ALS pathogenesis, with particular emphasis on the primacy of cortical dysfunction in ALS.

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1759
WFN15-1813
Environmental Neurology T 20.1
Nodding Syndrome: an epileptic disorder restricted to Africa?

P. Spencer. *Department of Neurology, Oregon Health & Science University, Portland OR, USA*

Background: NS is a progressive pediatric epileptic disorder of unknown cause characterized by mental impairment and repetitive head nodding.
Objective: To carry out a 2014 case-control study in post-conflict Uganda to identify environmental factors associated with epidemic NS (1997-2011).
Methods: Enrolled children ages 5-18 included 50 Probable NS cases, 50 Community Controls (CC) matched on age and gender, and 50 Household Controls (HC). A questionnaire was administered. Blood and urine were collected for multimycotoxin analysis.
Results: Mean age of head nodding onset was 7.6 years (range 1-17 years) in 50 NS Cases and 33 Suspect NS. All-year NS onset peaks occurred in April and June (2003-2012). Food shortages spanned November to March. Food at onset of head nodding differed in NS for emergency rations (OR 4.0, CI 1.27-17.6), including moldy maize (OR 4.33, 1.40-18.9, $p = 0.009$). NS cases had a lower BMI ($p = 0.044$). Vaccination history was similar (mostly >90%) for poliomyelitis, tetanus, DPT and measles; however, prior measles infection was higher in NS than CC (OR = 6.0 CI 1.025 to 113; $p = 0.047$). Diverse mycotoxins were present in plasma and urine samples, with no clear-cut differences between NS and CC.
Conclusions: NS is associated with a poor dietary history, low BMI, and exposure to moldy food at onset, which peaked after food shortages. Association with measles raises the possibility of a tardive post-measles disorder akin to subacute sclerosing panencephalitis, with which NS shares several features. Measles cases peaked in 2003 when a warfare truce permitted measles vaccination, with rates dropping precipitously by 2004.

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1760
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Environmental Neurology T 20.1
Air pollution and children: barrier breakdown, inflammation, brain immunity and neurodegeneration

L. Calderon Garciduenas[a], G. Melo-Sanchez[b], J. Vargas-Martinez[a], E. Macias-Escobedo[c], V.L. Hernandez-Orona[d], G. Cano-Gutierrez[e], J. Avila-Ramirez[f], R. Torres-Jardon[g]. *[a]Investigacion, Universidad del Valle de Mexico, Mexico DF, Mexico; [b]Investigacion, Universidad del Valle de Mexico, SaltilloCoahuila, Mexico; [c]Psicologia, Universidad Autonoma de Coahuila, Saltillo Coahuila, Mexico; [d]Investigacion, Universidad del Valle de Mexico, Saltillo Coahuila, Mexico; [e]Medicina, Universidad del Valle de Mexico, Mexico DF, Mexico; [f]Neurocirugia, Medica Sur, Mexico DF, Mexico; [g]Quimica de la Atmosfera, Universidad Nacional Autonoma de Mexico UNAM, Mexico DF, Mexico*

Ambient air pollution produces detrimental health effects on millions of people, particularly children and young adults. The neurological effects are an important issue for megacity and small town residents alike and those involved in high risk occupations. New York, Toronto, Los Angeles-South Coast Air Basin, SLC, Paris, Santiago de Chile, Delhi, Beijing, and Mexico City residents share their main sources of pollution: transport, industry and heating. Particulate matter fine particles >100 nm and < 2.5 μm ($PM_{2.5}$) and ultrafine PM <100 nm (nanosize) are target sizes for brain effects.

Early dysregulated neuroinflammation, gene expression changes in oxidative stress, DNA damage and NFκB signaling, and neurodegeneration pathways, brain vascular damage, and breakdown of the neurovascular unit are seen in children and young adults exposed to air pollution. The inducible regulation of gene expression suggests they are evolving different mechanisms in an attempt to cope with the constant state of inflammation and oxidative stress related to their environmental exposures. The accumulation of misfolded hyperphosphorylated tau, alpha-synuclein, and beta-amyloid coincides with the anatomical distribution observed in the early stages of both Alzheimer's and Parkinson's diseases. APOE modulates responses to air pollution in the developing brain and APOE4 carriers could have a higher risk of developing AD if they reside in a polluted environment.

Public health benefit can be achieved by integrating interventions reducing $PM_{2.5}$ and pediatric exposures, establishing pediatric preventative screening programs and young urbanites research could provide new paths toward the unprecedented opportunity for early neuroprotection, AD & PD prevention.

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1761
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Environmental Neurology T 20.1
Multiple Sclerosis: airborne environmental triggers and the 'bacterial toxins hypothesis', a credible synthesis?

J. Reis. *Service de Neurologie, CHU Hautepierre, Strasbourg, France*

Numerous epidemiological studies have reliably detected a number of important environmental factors increasing the risk of MS attacks,

these appear to be diverse in nature and strength and lack a credible synthesis. These risk factors include upper respiratory tract viral infections, low levels of vitamin D, smoking, atmospheric air pollution and solvent exposure, and several 'occupational' studies pointing to farming and exposure to animals. With these recent and topical studies the effect of residence at high latitudes and clear evidence of the seasonality of MS attacks must also be part of any credible synthesis.

The hypothesis that MS is caused by the direct access of bacterial toxins to the CNS generated by the flora of the nasopharynx, appears to provide an epidemiological, pathological, immunological and clinical synthesis to the known risk factors. The demonstration of intrathecal oligoclonal antibody in MS CSF specific for Staphylococcal Aureus (SA) beta-toxin (sphingomyelinase) with the detection of the toxic antigen in primary MS lesions provides direct evidence for the bacterial toxins hypothesis.

Exchanges of bacteria between human and animals are known since a long time. This is well demonstrated for the methicillin-resistant staphylococcus aureus (MRSA). We make the assumption that these airborne environmental factors (viruses, smoking, solvents, air pollution) could trigger a release of exotoxins by specific SA clones is nasal SA carriers.

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1762
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Tropical Neurology T 19.1
Unusual causes of stroke in the tropics: arterial dissections and cortical vein thromboses

A. Arauz. *Stroke Clinic, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City, Mexico*

Cervico-cerebral arterial dissection (CCAD) and cerebral venous thrombosis (CVT) are rare forms of stroke that appear to be most prevalent in the tropics.CCAD occurs by tearing of the wall of the carotid or vertebral artery, which leads to the formation of an intramural hematoma. It represents a major cause of cerebral infarct (CI) in younger patients, accounting for about 25% of cases in this population. The subsequent morbidity is usually the result of distal ischemia caused by the release of an embolus from the damaged arterial site. The angio-CT, angio-MRI and ultrasound Doppler are useful in the diagnosis, evaluation of treatments used and during follow-up. The annual rate of recurrence is estimated close to 1% per year. The currently accepted treatment is antithrombotic, whether anticoagulation or antiplatelet.

CVT accounts for approximately 1% of all strokes, and the majority of these cases occur in people younger than 50 years. In Mexico, in a hospital stroke registry, 3 to 5% of all cases were due to CVT. CVT is characterized by the diversity of its neurologic manifestations, which require a high level of clinical suspicion for diagnosis and prompt, appropriate treatment. Multiple circumstances have been associated with CVT, such as prior medical conditions and transient situations. In developing countries most of the cases are related to pregnancy and puerperium whereas hereditary or acquired protrombotic conditions explain most of the cases in developed countries. For treatment, anticoagulants have become more widely used due to increasing evidence regarding their efficacy and safety.

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1763
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Tropical Neurology T 19.1
Estimating the burden of epilepsy in tropical areas: infections and other environmental factors

P.M. Preux, J. Jost. *Inserm UMR 1094, Institut de neurologie tropicale, Limoges, France*

Epilepsy accounts for 0.5% to 1.0% of the global burden of diseases, even more in tropical developing countries. Globally speaking, the prevalence is 2-10 times higher and the incidence rate 2-5 times higher than in western countries, with disparities across continents. The prognosis in this part of the world is severe (SMR 2-3 times higher than in developed countries) because of a high frequency of seizures, malnutrition, injuries, etc. The treatment gap is over 75%. Tropical areas are deeply impacted by several CNS infections that remain one of the major risk factors with 1 to 5% risk of epilepsy. Survivors are at 7 times higher risk. Among them, the risk after a cerebral bacterial infection is 5 times higher and 40 times higher after a brain abscess. As well, several viruses are strongly involved. In Asia, Japanese encephalitis could lead to epilepsy among up to 20% of survivors. Other arboviruses, herpes viruses and HIV have been identified as important contributors. Parasitoses are also mostly involved. Cerebral malaria and neuro-cysticercosis represent the commonest causes of epilepsy in endemic areas. Rarely, mycoses have been suspected along with immuno-depression but no specific study has been performed. Infections apart, several other risks factors have been identified (stroke, head trauma, tumor, toxics and above all perinatal disorders). All of these could be linked with other environmental factors as nutrition, socio-economic conditions, cultural factors, etc., which are often intricated. Genetic factors and genetic-environment interactions should be mentioned with a high consanguinity rate in some ethnic groups.

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1764
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Tropical Neurology T 19.1
Is tropical neurology specific?

M. Dumas. *Inserm UMR 1094, Institut de neurologie tropicale, Limoges, France*

Only countries situated between the Tropic of Cancer and the Tropic of Capricorn belong to the real tropical parts of the world. But often, the "tropical" concept also concerns regions situated outside of the tropics, because of environmental, cultural and socioeconomic similarities. The neurological affections and their consequences are closely connected to this tropical environment.

Actually, a deep and relatively quick mutation in the environmental conditions and in the neurological practices in tropical countries occurs, that raises the question whether the tropical neurology is still specific.

Indeed, this concept is now obsolete, because of the gradual attenuation or even disappearance of certain environmental conditions such as poor socio-economic status, infectious diseases. Ubiquitous diseases, such as high blood pressure, diabetes, cancer, dementia, are now growing quickly in tropical regions. Moreover, several infectious diseases, such as dengue, formerly encountered only in the tropics, have now become ubiquitous.

Nevertheless, despite these considerations, tropical neurology still remains specific and original because: - cultural peculiarities that have neurological consequences will persist for a long time, - there is a specific common denominator in all tropical regions, and this will not change: the intense solar radiations and UVB rays, which could have many consequences. Among them, the characteristic of

inhibiting the functioning of the dermis Langerhans cells, with all the immunological consequences ensuing, particularly the low prevalence of multiple sclerosis in the tropics.

So YES, we must consider that tropical neurology is still specific, and as such, deserves to be recognized as a speciality of neurology.

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1765
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Advances in Neurosciences T 7.1
Neuron-glia metabolic coupling: relevance for brain plasticity and imaging

P. Magistretti. *BESE (BMI), KAUST (EPFL), Thuwal, Kingdom of Saudi Arabia*

A tight metabolic coupling between astrocytes and neurons is a key feature of brain energy metabolism (Magistretti and Allaman, 2015). Over the years we have described two basic mechanisms of neurometabolic coupling. First the glycogenolytic effect of VIP and of noradrenaline, indicating a regulation of brain homeostasis by neurotransmitters acting on astrocytes, as glycogen is exclusively localized in these cells (Magistretti, 2006). Second, the glutamate-stimulated aerobic glycolysis in astrocytes (Pellerin and Magistretti, 1994). Both the VIP-and noradrenaline-induced glycogenolysis and the glutamate-stimulated aerobic glycolysis result in the release of lactate from astrocytes as an energy substrate for neurons as in the presence of oxygen, lactate after conversion to pyruvate, can generate ATP.

We have recently revealed a second function of lactate, as a signaling molecule for plasticity. We have shown that lactate is necessary for long-term memory consolidation and for maintenance of LTP (Suzuki et al, 2011). At the molecular level we have found that L-lactate stimulates the expression of synaptic plasticity-related genes such as *Arc*, *Zif268* and BDNF through a mechanism involving NMDA receptor activity and its downstream signaling cascade Erk1/2 (Yang et al, 2014). L-lactate potentiates NMDA receptor-mediated currents and the ensuing increases in intracellular calcium. In parallel to this, L-lactate increases intracellular levels of NADH hence modulating the redox state of neurons. NADH mimicks all the effects of L-lactate on NMDA signaling, pointing to NADH increase as a primary mediator of L-lactate effects. These results reveal a novel action of L-lactate as a signaling molecule for neuronal plasticity.

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1766
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Advances in Neurosciences T 7.1
Aging-dependent changes of glial cell function and Alzheimer's disease

R. von Bernhardi, F. Cornejo, L. Eugenín-von Bernhardi. *Neurology, Pontificia Universidad Catolica de Chile School of Medicine, Santiago, Chile*

Aging is the main risk factor for Alzheimer's disease (AD). We propose that age-related impairment of microglia participates in AD pathogenesis. Microglia cytotoxicity is regulated by TGFβ1, but is potentiated in aging despite increased levels of TGFβ1. We studied changes on TGFβ1 signaling during aging that can explain microglia dysregulation. The participation of the TGFβ1-Smad3 pathway on the regulation of microglia activation was evaluated at different ages. The activation of signal transduction pathways, including MAPKs and Smad, as well as modulatory MAPK phosphatases like MKP-1, were analyzed. Astrocytes regulation of microglia cytotoxicity and Aβ removal was mediated by TGFβ1. TGFβ1 decreased IFNy-induced phosphorylation of STAT1 and ERK, which correlated with reduced production of ROS by glia and increased MKP-1. TGFβ1 activation of Smad3 signaling was greatly reduced in adult mice. The reduction on the activation of TGFβ1 signaling was associated with functional changes on the activation of microglia. Whereas NO secretion predominated on microglia from young mice exposed to LPS, induction of ROS predominated in adult mice. TGFβ1 modulated LPS-dependent induction of NO and ROS production. Modulation was partially dependent on Smad3 pathway and was impaired by inflammatory preconditioning. Phagocytosis was induced by inflammation and TGFβ1 only in microglia cultures from young mice, an effect that was also prevented by Smad3 inhibition. Our results show that the TGFβ1-Smad3 pathway regulates the activation pattern of microglia, and is impaired in aging and by inflammatory preconditioning. The impairment could reduce protective activation while facilitating microglia-mediated neurodegenerative changes.
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1767
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Advances in Neurosciences T 7.1
New findings on mirror mechanism

G. Rizzolati. *University of Parma, Dipartimento di Neuroscienze, Parma, Italy*

Mirror neurons are a distinct set of motor neurons that discharge both when the monkey *executes* a specific motor act and when it *observes* another individual doing a similar act. In the first part of my talk, I will review the basic functional properties of monkey mirror neurons. I will show then that mirror neurons encode the goal of motor acts. I will review then their visual properties showing that mirror neurons represent a mechanism that allows a *direct understanding* of what the agent is doing.

Mirror mechanism also exists in humans. I will present fMRI and EEG data proving it and will show that, although there are other mechanisms through which one can understand the behaviour of others, the mirror mechanism is the only one that allows understanding others from the inside providing the observer with a *"first-person"* person grasp of others' motor goals, intentions and emotions.

I will address then some clinical problems and namely the relationship between the mirror mechanism and autism with particular emphasis on Stern's vitality forms, and the neural basis of "action observation" treatment in motor rehabilitation after stroke and other motor disturbances.

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1768
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Clinical Neurophysiology T 4.2
Demyelinating neuropathies

M.C. Kiernan. *Clinical Neurosciences, Brain and Mind Centre University of Sydney, Sydney, Australia*

Clinical neurophysiology plays a critical role in the diagnosis, classification, and prognosis of demyelinating neuropathies. Abnormalities include slowed nerve conduction velocities, prolonged distal latencies, prolonged or absent H reflexes and F-wave latencies, conduction block, and varying degrees of denervation. However, the degree of conduction slowing documented using standard neurophysiological investigation does not correlate well with clinical disability, and even when patients have fully recovered, conduction velocity may

remain permanently slow. Separately, the abnormalities of nerve excitability that underlie conduction slowing, block and ectopic impulse activity are not adequately explored by routine nerve conduction studies.

Acute demyelination lowers the safety margin for impulse conduction, such that axons can become sensitive to shifts in membrane potential, even when those shifts occur through normal physiological mechanisms. In critically conducting axons, impulse conduction can be impaired by the effects of heating and activity and probably by any mechanism that produces a significant shift in membrane potential, whether depolarizing or hyperpolarizing.

The important message is that critically conducting axons are delicately poised. Conduction may block if membrane potential is too far from threshold (i.e., the axon is hyperpolarized) or if the Na^+ current becomes inadequate (because of heating or because of a limitation on the number of functioning Na^+ channels). Significant changes in activity or significant shifts in membrane potential, whether depolarizing or hyperpolarizing, may be sufficient to produce a transient worsening of symptoms.

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1769
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Clinical Neurophysiology T 4.2
Assessment of afferent function

J. Ochoa. *Legacy Health System, Oregon Neve Center, Portland, USA*

Sensation and Neuropathic Pain
Controversial "Neuropathic Pain"

a) **Sympathetically Maintained Pain**: The President of this Congress demonstrated that relief from sympathetic blocks is placebo effect: Down the drain went SMP and its RSD Fairy… but CRPS-I came out of the ashes…

b) **CRPS-I**: There is no demonstrable nerve pathology, nor diagnostic test. In addition, the animal models of CRPS-I are in fact gross CRPS-II models.

Diagnosis? "Criterion #4": "this diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction".

This violates THE principle of scientific diagnosis: Falsifiability or Refutability (Popper): if there is no possibility to prove the statement is false, it is not falsifiable… it is thus pseudoscience.

It is Null Hypothesis by default (Fisher): an assertion which, incapable of being proven false by testing observed data, can never be confirmed: it can only be rejected.

Budapest group popularized their upgraded CRPS-I (last decade), again non-falsifiably: Criterion #4 was their pivot. It is a non-peer reviewable tale.

c) **Secondary Central Neuronal Sensitization**: In 1983, Clifford Woolf demonstrated that sensory nerve injury enhances flexion reflex in the rat. He wrote "I have now developed an animal model where changes occur in the flexor reflex following peripheral injury, that are analogous to the sensory changes found in man (continuing pain; increased sensitivity to noxious stimuli and pain following innocuous stimuli").

There are disabling caveats in the argument (not testable in humans) and criticisms accumulate from distinguished peers of Professor Woolf.

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