Symposia

Saturday, 28 May

Symposium 1
MDS-ES/EAN: Update in movement disorders

SYMP01-1
Essential tremor
G. Deuschl
Kiel, Germany

**Background and purpose:** Essential tremor is so far only clinically defined and the separation from dystonic tremor, some cerebellar tremors and psychogenic tremor may be difficult. Consented differential diagnostic criteria are lacking. Therefore, a classification on the basis of surrogate data would be helpful. Despite significant efforts attempts to classify the patients on the basis of clinical description, pathology, biochemistry, neurophysiology or genetics did unfortunately not lead to a generally accepted consensus. This is in particular surprising as twin studies are suggesting a strong hereditary component for ET. There is still a controversy if ET represents a neurodegenerative entity or only a slowly progressive functional disturbance. Certainly a proof for neurodegeneration needs convincing signs for earlier death or at least a progressive clinical decline apart from the motor disturbance. There are data suggesting that ET can be subdivided on the basis of the age at onset, as the vast majority develops after the age of 50 years. Indeed the early and the late onset cases differ in the amount of patients with alcohol-sensitivity and a positive family history for tremor. Only the late onset cases seem to have a shorter life expectancy and evidence for a more rapid cognitive decline. This needs to be confirmed in prospective studies. The currently reached consensus is that the new definition should include very careful phenotyping of each patient clinically and if possibly with additional methods.

**Disclosure:** Nothing to disclose.

SYMP01-2
Non-motor symptoms in Parkinson's disease
K.R. Chaudhuri
London, United Kingdom

**Background and purpose:** Non-motor symptoms (NMS) have emerged as a key component of Parkinson’s disease (PD) from a possible role as clinical biomarker in the premotor phase to a range of symptoms that complicate the whole journey of a person with Parkinson’s. The burden of NMS as a whole is recognised as one of the defining constituent of health related quality of life of people with Parkinson’s. NMS also substantially increases the cost of care of PD and leads to increased hospitalisation, and treatment of NMS poses one of the biggest challenges to health care professionals dealing with PD. However, in the clinic and in clinical practice NMS continues to be regarded as a peripheral issue compared to motor symptoms management of PD. NMS are now the key component of “pre motor “ PD and new evidence suggest evidence of discrete non motor subtypes in PD. This could led to “subtype specific” treatment packages. Evidence also suggest that conventional non oral dopaminergic therapies may help motor and non motor aspects of PD while NMS also may form of the spectrum of acute medical presentations in PD. In part this has led the international Parkinson and Movement Disorder Society (IPMDS) task force to attempt a re-definition of PD incorporating NMS and not base the diagnosis solely on motor symptoms. While motor subtypes within PD have been recognized and researched, recent, clinical and neurobiological research suggests the existence of discrete non-motor subtypes in PD, particularly in untreated (drug naïve) and early PD patients. Several independent observers have reported specific “clusters of NMS dominant PD” using a data driven approach in early and untreated PD patients while others have reported on the burden of NMS in untreated PD and specific NMS dominant phenotypes in untreated or treated PD using observational case series based data. We have reported specific NMS dominant phenotypes of PD as described in the literature using clinical observational studies and address pathophysiological concepts. This is the basis of for several NMS subtypes combining clinical reports with, where possible, evidence base supporting probable biomarkers.

**References:** Chaudhuri KR, Schapira AHV. The non motor symptoms of Parkinson’s disease: dopaminergic pathophysiology and treatment. Lancet Neurol 2009; 8: 464-474. Todorova A, Jenner P, Ray Chaudhuri K. Non-motor Parkinson’s: integral to motor parkinson’s, yet often neglected. Practical Neurology:2014 doi:10.1136/practneur-2013-000741 A Sauerbier, P Jenner, A Todorova, K Ray Chaudhuri. Non motor subtypes and Parkinson’s disease. Parkinsonism and Related Disorders 22 (2016) S41eS46

**Disclosure:** Nothing to disclose.
SYMP01-3

Dystonia

E. Dietrichs

Oslo, Norway

Background and purpose: According to the proposed new classification we distinguish isolated (previously called primary) and combined (secondary) dystonias. The causes of most dystonias have remained enigmatic, but novel genetic findings as well as new insights concerning plasticity in basal ganglia and other neural networks may give clues to dystonia pathophysiology. Botulinum toxin represents a good option for symptomatic treatment in many patients, especially for those with focal or segmental dystonia. Deep brain stimulation is also well documented, with good results also for long-term treatment.

Disclosure: Nothing to disclose.

SYMP01-4

PSP/MSA

M. Stamelou

Athens, Greece

Background and purpose: Update in Movement Disorders: PSP/MSA

Progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) are atypical parkinsonian syndromes with largely unknown etiology, and no available effective treatments. However, the recent years a plethora of new evidence both in terms of etiology/pathophysiology and treatment options as well as clinical trials have become available. A genome-wide association study in PSP has provided risk-loci, which have been shown to have a direct association to tau pathology in vitro. The first gene (CoQ2) possibly associated with autosomal dominant MSA has been described. In terms of diagnosis, new clinical criteria are under development for PSP, while tau-PET imaging is intensely being studied. In terms of treatment, the largest double-blind placebo controlled trials have been published in both disorders providing important information for further clinical trials. Currently, a plethora of neuroprotective agents are being tested in double-blind, placebo-controlled trials for both disorders.

Disclosure: Nothing to disclose
Symposium 2
Neurostimulation, what can be achieved in...

SYMP02-1
...movement disorders
M.J.D. Vidailhett
Paris, France

Backround and purpose: Deep brain stimulation has been an major breakthrough in the treatment of movement disorders including dystonia, tremor and severe Tourette syndrome. Indication, efficacy and long term follow-up results will be reviewed from the literature and illustrated by videos and clinical observations. Targets will be discussed (thalamus, pallidum, STN). A few examples of Parkinson’s disease treated by subthalamic nucleus deep brain stimulation will be provided, including positive effects and adverse effects (freezing of gait, eyelid apraxia).

Disclosure: Nothing to disclose.

SYMP02-2
...epilepsy
K. Vonck
Ghent, Belgium

Backround and purpose: Neurostimulation is an emerging treatment for neuropsychiatric disorders. Excitability-reducing neurostimulation is pursued as an alternative therapeutic strategy for refractory epilepsy when drugs and surgery fail or are not indicated. For intracranial neurostimulation, stimulation electrodes are inserted into intracerebral targets in ‘deep brain stimulation’ (DBS) or placed over the cortical convexity for ‘cortical stimulation’ (CS) to administer electrical pulses to central nervous system structures. These modalities of neurostimulation are not entirely new for neurological indications. Some have been extensively applied in movement disorders and pain. Several new indications such as obsessive compulsive behaviour and cluster headache are being investigated with promising results. In the past DBS and CS of different brain structures such as the cerebellum, the locus coeruleus and the thalamus were performed mainly in patients with spasticity or psychiatric disorders who had epilepsy as a comorbidity. The vast progress in biotechnology along with the experience in other neurological diseases in the past ten years has led to a renewed interest in intracerebral stimulation for epilepsy. Several epilepsy centers around the world have recently conducted trials with DBS in different intracerebral structures such as the thalamus, the subthalamic nucleus, the caudate nucleus and medial temporal lobe structures. Also CS has been investigated in a multicenter trial in a so-called closed-loop system. Especially CS of eloquent cortex may be developed into a valuable alternative for resective surgery to treat refractory partial focal seizures arising from eloquent cortex.

Disclosure: Nothing to disclose.

SYMP02-3
...chronic pain
S. Boccard
Oxford, United Kingdom

Backround and purpose: Deep Brain Stimulation (DBS) is an invasive neurosurgical intervention established in movement disorders, reported also to improve symptoms of depression, Obsessive Compulsive Disorder, epilepsy, obesity and pain. Over time, several brain structures have been targeted to relieve pain, including the periventricular/periaqueductal gray area (PAG) and the ventral posterior medial and lateral nuclei of the sensory thalamus (VPL). In our long-term case series, DBS has been used with varying degrees of success for facial pain, post-stroke pain, brachial plexus injury, and phantom limb pain. Pain is a multifaceted phenomenon, and some patients, with widespread pain, may benefit from targeting regions involved in its affective dimension, such as the anterior cingulate cortex (ACC). We recently demonstrated that DBS of the ACC can significantly alleviate the suffering of patients with treatment resistant chronic pain. This provides a promising avenue for patients for whom other treatments including PAG and VPL DBS are ineffective.

Disclosure: Nothing to disclose.
Symposium 3
The changing landscape of coma treatment

SYMP03-1
Amantadine, benefit-risk balance in severe brain injury
J.T. Giacino
Charlestown, USA

Background and purpose: This presentation will describe the results of a 12-site randomized, double-blinded, placebo-controlled trial of amantadine hydrochloride (AH) completed in 184 patients with prolonged post-traumatic disorders of consciousness. Patients were in a vegetative or minimally conscious state, between 4 and 16 weeks post-injury and were undergoing inpatient rehabilitation. Following baseline examination, patients were randomized to 4 weeks of amantadine or placebo and followed for 2 additional weeks after drug discontinuation. Rate of functional recovery was monitored on the Disability Rating Scale (DRS) and the Coma Recovery Scale- Revised (CRS-R) during the treatment window, and over a two-week washout period. Mixed-effect regression models were used to analyze the results. During the four week treatment period, the amantadine group recovered significantly faster on the DRS compared with the placebo group (0.24 points/week faster; p=0.007). In a pre-specified subgroup analysis, the treatment effect was similar for patients in both the vegetative and minimally conscious states. The rate of improvement in the amantadine group slowed after treatment discontinuation, so that improvement in the amantadine group was slower than in the placebo group for study weeks 5-6 (.30 DRS points/week slower; p=.02). Degree of improvement in DRS scores between baseline and week 6 (2 week post treatment discontinuation) was similar in the placebo and amantadine groups. There were no significant differences in the incidence of serious adverse events. In conclusion, amantadine accelerated the pace of functional recovery during active treatment in patients with post-traumatic disorders of consciousness.

Disclosure: The National Institute on Disability and Rehabilitation Research (NIDRR Award # H133A031713) provided all support for this study, including funds to purchase amantadine hydrochloride.

SYMP03-2
Deep brain stimulation in the minimally conscious state: which targets?
J.-J. Lemaire
Clermont-Ferrand, France

Background and purpose: The modulation of consciousness processes with deep brain stimulation (DBS) in minimally conscious state is challenging. Indeed the clinical knowledge is still limited relying on 7 studies published between 1968 and 2016 reporting effects in 58 vegetative or minimally conscious patients. Although very inhomogeneous they harvested clues that electric stimulation of deep gray structures, particularly of the thalamus, can provoke overt conscious behaviors. The role of thalamus in consciousness processes is well documented, notably of intralaminar nuclei as relay-control between the upper brainstem (tegmentum) and the cortex. Nowadays there is a growing body of evidences that consciousness, close to cognition as far as they are different, brings into operation different elements of the overall brain circuitry, such as input relay-controllers within the brainstem and cortices, thalamic nuclei, basal ganglia and the executive-behavioral system. Within such an extended network DBS could potentially modulate deeply located nodes, as it does in movement and neuropsychiatric disorders, which could be relevant for future clinical applications; this therapeutic-driven application could also help to decipher the altered dynamics of neural correlates of disorder of consciousness.

Disclosure: Nothing to disclose.

SYMP03-3
Modulating the anterior forebrain mesocircuit in disorders of consciousness
N.D. Schiff
New York, USA

Background and purpose: This presentation will discuss the “mesocircuit hypothesis” for the key role of the human anterior forebrain mesocircuit in recovery from disorders of consciousness following multi-focal brain injuries. The mesocircuit model makes several specific predictions for the co-variation of measures reflecting progressive restoration of cellular and circuit-level functional integrity following severe deafferentation produced by brain injuries. The talk will focus primarily on modulation of the mesocircuit in studies of human subjects and experimental animal. Testing of model predictions using quantitative measurements of local and global dynamics of the human electroencephalogram (EEG), and measurements from neuroimaging studies of patients with disorders of consciousness will be highlighted. Validation of the predictions derived from this large-scale brain network model may provide a set of measures useful to track recovery and predict the impact of different therapeutic inventions in the injured brain on an individual basis.

Disclosure: Nothing to disclose.
SYMP03-4
Transcranial direct current stimulation: a promising new avenue
S. Laureys
Liege, Belgium

Background and purpose: The past 15 years have provided an unprecedented collection of discoveries that bear upon our scientific understanding of recovery of consciousness in the human brain following severe brain damage. Highlighted among these discoveries are unique demonstrations that patients with little or no behavioral evidence of conscious awareness may retain critical cognitive capacities and the first scientific demonstrations that some patients, with severely injured brains and very longstanding conditions of limited behavioral responsiveness, may nonetheless harbor latent capacities for recovery (Laureys & Schiff, NeuroImage 2012; Giacino et al Nature Reviews Neurology 2014). We will here discuss the potential therapeutic efficacy of transcranial direct current stimulation (tDCS) in disorders of consciousness. tDCS was recently shown to improve the level of consciousness in patients in a minimally conscious state (MCS) (Thibaut et al, Neurology 2014). tDCS delivers a weak (usually 1–2 mA) electrical current through the brain using two electrodes, an anode (target electrode) and a cathode (reference electrode) placed on the scalp. It is presumed that anodal tDCS strengthens synaptic connections through a mechanism similar to long-term potentiation and an increase in NMDA receptor excitability, which could improve and strengthen cortical excitability within the stimulated area. We recently identified that responders to tDCS (stimulation over the left prefrontal cortex) showed more grey matter preservation and residual metabolic activity, as compared to non-responders, in the stimulated area (i.e., left prefrontal cortex), in the precuneus, and in the thalamus, all areas known to be involved conscious processes (Thibaut et al, Brain Stimulation 2015).

Disclosure: Nothing to disclose.
Symposium 4
Evolving concepts in the management of gliomas

SYMP04-1
How to integrate molecular markers of prognostic significance in the new WHO classification?

J. Kros
Rotterdam, The Netherlands

Background and purpose: Over the past decade a flood of genetic data on primary brain tumors became known. Part of the various genetic aberrations was tested in retrospective and prospective settings for either diagnostic, prognostic or predictive significance. Particularly, codeletion of the chromosome arms 1p and 19q and mutation of IDH1 appeared to have significant impacts on prognosis. The codeletion 1p/19q is diagnostic for oligodendroglioma and were found mutually exclusive with mutations of ATRX, which are associated with astrocytic lineage of tumor cells. Importantly, the codeletion predicts better responsiveness to alkylating chemotherapy. Mutations of IDH are present in 70% of all diffusely infiltrating gliomas and are found in both oligodendrogliomas and astrocytomas. The prognostic impact of IDH mutation reportedly overrides grading of these tumors. The majority of non-IDH mutated gliomas overlap with primary glioblastomas, which usually have a set of additional aberrations like amplification of EGFR. Further, particular astrocytoma subtypes do not have IDH mutations but carry other genetic characteristics: the pilocytic astrocytomas usually come with the KIAA1549-BRAF fusion gene while the relative infrequent midline gliomas show mutations in histone H3-K27M. Also for ependymomas and medulloblastomas genetic characteristics have become definers for behavior and therapy responsiveness. In the 2007 edition of the WHO classification of CNS tumors for only few tumors genetic hallmarks were mentioned in the definitions, a big leap forward is made in the 2016 revision where the above mentioned genotypes have been incorporated into the definitions of the tumors. Diagnoses therefore should provide layers of classic histology and molecular data. To accommodate centers without access to molecular diagnostics the term NOS should indicate that only a histopathological diagnosis was provided.

Disclosure: Nothing to disclose.

SYMP04-2
Will new forms of immunotherapy improve the outcome of glioblastomas?

M. Weller
Zurich, Switzerland

Background and purpose: 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)-ß 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. A phase III trial comparing the PD-1 antibody nivolumab with bevacizumab in glioblastoma at first relapse has completed accrual. 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.

Disclosure: Nothing to disclose.
SYMP04-3
From chemotherapy to targeted therapy in low grade gliomas

R. Soffietti
Turin, Italy

Background and purpose: Several issues regarding the optimization of chemotherapy in newly diagnosed low grade gliomas (grade II WHO) are still debated: association with radiotherapy or initial treatment alone; best regimen and duration; role of molecular factors to predict response and outcome; role of neuroimaging to predict response and outcome.

RTOG 9802 has recently reported a significant advantage in terms of PFS and OS for the addition of PCV chemotherapy to radiotherapy in the postsurgical treatment of high risk grade II gliomas. Phase II trials on chemotherapy (temozolomide) alone as initial treatment, delaying RT as salvage, have reported a response rate of about 40-60% with significant seizure reduction. 1p/19q codeletion is so far the unique molecular marker with a predictive value.

Commonly used to evaluate the response are the RANO criteria, but a more precise qualification of tumor volume on MRI and/or metabolic evaluation by PET with aminoacids are increasingly adopted. Ongoing studies are evaluating the role of an adjuvant RT+TMZ or of preoperative chemotherapy with TMZ. Targeted agents to inhibit specific molecular changes (m-TOR pathway, IDH1/2 mutations, etc) are entering the area of clinical trials.

Disclosure: Nothing to disclose

SYMP04-4
New developments in neuroimaging to monitor response and toxicity following antiangiogenic agents

W. Wick
Heidelberg, Germany

Background and purpose: Disease status evaluation in brain tumors is complicated by treatment-induced changes, which may be desired (as with immunotherapies) or potentially not desired (as with radiotherapy). Similarly, discordance between enhancing and non-enhancing tumor may complicate the assessment of objective responses.

Measures to assess pseudoprosess or pseudoresponse have been developed with algorithms reducing imaging bias of calling progression too early. In addition, advanced magnetic resonance imaging (MRI) with T1 subtraction, susceptibility-weighted, dynamic perfusion and diffusion images have been used to reduce the level of uncertainty in the early treatment phase after chemoradiotherapy, but also to substantiate responses in cases, in which contrast-enhancement alone is not sufficient to assess the tumor growth or regression. Data on progression patterns, progression types, the value of new MRI techniques and an outlook on metabolic imaging is presented.

Disclosure: Nothing to disclose.
Monday, 30 May

Plenary Symposium 2
Neuroimaging of dementia

PLEN02-1
Imaging of cerebral small vessel disease
R. Schmidt
Graz, Austria

Background and purpose: Cerebral small vessel pathology is heterogeneous and results in lacunar strokes, microinfarcts, white matter lesions, microbleeds, and microstructural abnormalities detectable by advanced MRI techniques. Acute small subcortical infarcts only partly become lacunes. The factors that influence cavitation are widely unknown. Incident lacunes localize preferentially at the edge of white matter abnormalities. It has been suggested that the „white matter hyperintensity penumbra“ - the area of microstructurally altered surrounding tissue plays a role in the occurrence of lacunes closely related white matter abnormalities. White matter abnormalities represent a plethora of changes with varying clinical significance. Nonetheless, the magnitude of the diffuse microstructural damage of the white matter rather determines cognitive impairment than the extent of visible white matter foci per se. Another important determinant of cognitive impairment is atrophy. There is increasing evidence that cortical atrophy may have a pure vascular basis. The change of small vessel disease-related lesions might serve as secondary outcome measures in clinical trials in patients with vascular cognitive impairment. Yet, the validation status of lesion change as a surrogate endpoint is incomplete. It is best established for confluent white matter lesions. However, if the expected change in cognitive performance resulting from treatment effects on lesion progression is used as an outcome, the sample size needed to show treatment effects becomes very large. Validation of surrogate endpoints for trials in subcortical vascular cognitive impairment has high priority to foster establishment of treatment options in this heavily understudied endemic of the aging brain.

Disclosure: Nothing to disclose

PLEN02-2
Imaging of Alzheimer's disease
P. Scheltens
Amsterdam, The Netherlands

Background and purpose: In this overview I will detail how imaging has changed the landscape of diagnosis of dementia. Starting with MRI and followed by PET imaging of glucose consumption and amyloid and tau has made possible to diagnose the underlying disease even before dementia is present. The presence of imaging biomarkers has enabled new criteria to appear and be implemented in clinical trials. Thus, by using imaging as biomarker for diagnosis and staging of disease, clinical trials are now being carried out, creating hope for the patients of the future

Disclosure: Nothing to disclose

PLEN02-3
Imaging of frontotemporal dementia
M. Filippi
Milan, Italy

Background and purpose: Frontotemporal dementia (FTD) is a genetically and clinically heterogeneous syndrome that is characterized by overlapping clinical symptoms involving behaviour, personality, language and/or motor functions and degeneration of the frontal and temporal lobes. The term frontotemporal lobar degeneration (FTLD) is used to describe the proteinopathies associated with clinical FTD. An improved reliability in distinguishing FTD syndromes using neuroimaging techniques may become important in the near future, as etiology-specific modifying treatments are likely to be developed and thus enter the clinical arena. Emerging evidence from network-based neuroimaging studies, such as resting state functional MRI and diffusion tensor MRI studies, have implicated specific large-scale brain networks in the pathogenesis of FTD syndromes, suggesting a new paradigm for explaining the distributed and heterogeneous spreading patterns of pathological proteins in FTLD. Furthermore, measurement of white matter tract involvement seems to be a valid biomarker to provide further in vivo insight into disease progression. Preliminary studies in genetically proven cases suggest that key MRI signatures occur in relation to the different FTD-related genes. However, open questions remain with regard to how and where pathological protein propagation is initiated and the characterization of the major factors playing a role in the modulation of pathology spreading in these conditions. Future longitudinal studies of multimodal imaging datasets, involving subjects in the preclinical phase of the disease, will help understanding the apparent selective network vulnerability of brain regions in various FTD syndromes and predicting disease spread.

Disclosure: Nothing to disclose
Monitoring treatment response in dementia trials

N.C. Fox
London, United Kingdom

Background and purpose: Trials in dementia are changing and so are the roles of imaging in those trials. Historically most trials were in mild-to-moderate Alzheimer’s disease and imaging was only used for inclusion/exclusion. Subsequently imaging has been adopted to assess effects of therapy as a safety read and importantly as an outcome measure. The aims of including imaging as an outcome were to show evidence of disease modification and/or to provide an alternative, more powerful, means of assessing efficacy than clinical scales. Natural history studies estimated that fewer subjects were needed to show a given effect on imaging measures such as rates of brain/hippocampal atrophy. The anti-amyloid immunotherapy trials challenged assumptions about the effects on therapies on brain volume with studies showing that therapies could increase volume losses without cognitive worsening. At the same time amyloid imaging using novel PET ligands started to be included in trials providing the opportunity to “see” the effects of therapy on the molecular pathology. The move to trials aimed at pre-manifest disease (especially AD but also FTD or HD) raises new challenges for monitoring treatment effects. Imaging and other biomarkers become more important in “preclinical” trials as clinical outcomes may take years to detect. The range of imaging modalities available to address these challenges is growing. Novel MR methods are being validated, amyloid PET quantification improved, and now tau-PET offers new possibilities for monitoring treatment response in AD and other tauopathies. These new methods and trials will help provide new insights – and hopefully new therapies.

Disclosure: UCL has received payment for image analyses or consultancy from Biogen, Eli Lilly, GSK, Janssen, Novartis, Pfizer, Roche and Sanofi. NF receives no personal compensation for this. NF gratefully acknowledges support from the NIHR, the Queen Square BRU in dementia, the Leonard Wolfson Experimental Neurology Centre, the MRC, the Alzheimer’s Society and Alzheimer’s Research UK.
Symposium 5  
New perspectives in the treatment of neuromuscular diseases: therapies on the horizon

SYMP05-1  
Amyotrophic lateral sclerosis: still far from an effective therapy?

V. Silani
Milan, Italy

ALS is a neurodegenerative disease characterized by progressive deterioration mainly involving both the corticospinal tract and the anterior horn cells of the brainstem and spinal cord. Patients develop focal and then generalized weakness leading to paralysis. As recently stated (Mitsumoto et al., 2014), there is no disease-modifying therapy for ALS, though riluzole slows the rate of progression and prolongs survival by 2 or 3 months. It also quite evident that ALS is a complex, multifactorial disease with variations in individual susceptibility and phenotype: the clinical and biological complexities of ALS have probably hindered development of effective therapeutic drugs. Precision medicine may be an innovative approach that applies recently developed biomedical technologies to optimize and individualize treatment to the molecular drivers of an individual’s disease. It involves not creation of treatments that are unique to a patient, but rather classification of individuals into subpopulations that differ in their susceptibility, in the biology and/or prognosis of ALS or in their response to a specific treatment. This approach of using tailored, mechanism-based therapies has been applied to cancer care and gained progressively greater impact, but it is only beginning to be considered in ALS. The key elements of phenotypic classification, comprehensive risk assessment, detecting a presymptomatic period, studying potential molecular pathways, developing disease models, discovering biomarkers, and tailoring interventions to molecular specifics probably embody the most modern therapeutic approach to ALS.

Disclosure: Nothing to disclose.

SYMP05-2  
Myasthenia gravis: new therapies for new antibodies?

TBA

SYMP05-3  
Immune mediated neuropathies: monoclonal antibodies and what else?

E. Nobile-Orazio
Milan, Italy

Chronic immune-mediated neuropathies, including chronic inflammatory demyelinating neuropathy (CIDP), multifocal motor neuropathy (MMN), neuropathies associated with monoclonal gammopathy, are a group of disorders deemed to be caused by an immune response against peripheral nerve. Several immune therapies are effective in these neuropathies including steroids, plasma exchange and high-dose intravenous immunoglobulins (IVIg) in CIDP, IVIg in MMN and plasma exchange in neuropathy associated with IgM monoclonal gammopathy but not all patients respond to or tolerate these therapies. A number of immunosuppressive agents have been used in these neuropathies but their efficacy was not confirmed in randomized trials. More recently, new biological agents such as Rituximab have proved to be effective in patients with neuropathy associated with IgM monoclonal gammopathy. This therapy is currently under consideration in other immune neuropathies even if the preliminary results on their efficacy in CIDP and MMN are less promising than expected. Another monoclonal antibodies, Eculizumab, that inhibits terminal complement activation, has been used in MMN showing a minimal effect in some patients. Other therapies currently used in multiple sclerosis has been recently tested in CIDP. Natalizumab was initially found ineffective in a patient with CIDP even it had some effect on three other patients. The positive response to fingolimod in a patient with demyelinating neuropathy awaits confirmation from an ongoing controlled trial in CIDP. Despite the frequent beneficial effect of currently used immune therapies, new therapies are on the horizon for these neuropathies even if their efficacy needs to be proved in controlled studies.

Disclosure: Nothing to disclose.
SYMP05-4

Genetic treatment in muscular dystrophies: hope or reality?

F. Muntoni
London, United Kingdom

The improved understanding of the genetic basis and molecular events leading to muscle degeneration in muscular dystrophies, coupled with advances in small molecules aimed at interfering with gene transcription and translation, has very rapidly moved in the last decade from proof of concept studies to phase I; II; and III clinical trials in Duchenne muscular dystrophy (DMD). These approaches take advantages of antisense oligonucleotides to target pre-mRNA and induce redirection of splicing in DMD patients with out of frame deletions; and of small molecules to induce read through of nonsense mutations. Clinical trials in myotonic dystrophy have also rapidly advanced, aimed at using antisense oligonucleotides to target the mutant DMPK allele which characterize this condition. The pace of the development of these novel genetic approaches to treat muscular dystrophies is exciting and one of the fastest in recent drug development program. Nevertheless the outcome of recently completed clinical trials in DMD has been variable, with clear signal of clinical efficacy, especially in specific ranges of age and functional abilities, but also failures to meet endpoints in several phase III trials. The field has learned several lessons, especially on optimal disease cohorts to demonstrate clinical efficacy, importance of harmonization of standards of care and strength and weaknesses of different outcome measures used. The indispensable interface with regulatory authorities in USA and Europe for these rare diseases has also demonstrated that more mutual education is necessary. In my presentation I will summarise the status of the art of these developments

Disclosure: Francesco Muntoni has served on scientific advisory boards for AcceleronPharma, Genzyme, Sarepta, Debiopharma Group, GlaxoSmithKline, Prosensa, Servier, Italfarmaco, Summit and Santhera Pharmaceutical, received research support from GlaxoSmithKline and Summit, and has received funding for trials from PTC, Biomarin, Sarepta, Pfizer. He also serves in the Pfizer Rare Disease SAB.
Symposium 6
ESO/EAN: Acute stroke: new opportunities and challenges for neurologists

SYMP06-1
Intracranial large vessel occlusions: how to recognize them as fast as possible
P. Michel
Lausanne, Switzerland

First, stroke has to be recognized or at least suspected, both by patients, bystanders and paramedics. This is probably best achieved by using simple preshospital scales such as the FAST or Cincinnati Prehospital Scale, and will decrease the rate of stroke mimics (false positives) and stroke chameleons (false negatives). Patients with suspected stroke and preshospital thrombolysis criteria should be transferred directly to a thrombolysis-capable hospital (usually stroke units) where imaging can also rapidly determine LVO:
- Onset of symptoms < 4h
- Potentially disabling deficit
- Patient relatively independent
- No rapid resolution of symptoms.

Preimaging prediction of LVO can be done with scores quantifying stroke severity, and other items may be added. Such scores may determine which patients are sent directly to an endovascular hospital (usually stroke centers):
- Motor symptoms alone (Los Angeles Motor Scale) à cut-off ≥4 points
- Motor and other symptoms
  - Cincinnati Prehospital Stroke Severity Scale à cut-off ≥2 points
  - Rapid Arterial oCclusion Evaluation (RACE) à cut-off ≥5 points
  - NIHSS
    - < 6h: cut-off ~10 points
    - > 6h: cut-off ~7 points
  - NIHSS plus other items (ASTRAL-Occlusion score), i.e.
    - Female
    - No prestroke handicap
    - Atrial fibrillation
    - Hemineglect
    à cut-off ≥16 points

Such prediction models can also be used upon hospital arrival or with telemedicine. Given their limited reliability, rapid non-invasive imaging should always be sought, preferably CT-angiography (CTA) or MR-angiography (MRA). Combined with clinical information, CTA and MRA are highly accurate. Images may be transferred by teleradiology to an endovascular center before or during patient transfer. CTA can also be performed in an ambulance (“mobile thrombolysis unit”). Once LVO is documented or highly suspected, the patient should be treated immediately by an experienced endovascular team given the low rate (~10%) of rapid recanalisation with thrombolysis alone.

Disclosure: Nothing to disclose.

SYMP06-2
Anterior and posterior circulation: mind the differences
D. Strbian
Espoo, Finland

Posterior circulation strokes account for approximately 1/5 to ¼ of all strokes, which affect cerebellum, brainstem, mesencephalon, thalamus, and occipital cortex. Vascular supply of these anatomical structures is covered by the vertebrobasilar system (in comparison of carotid system and anterior circulation).

Most acute stroke trials include majority of anterior stroke patients, which is not only given by higher aforementioned natural proportion of these stroke types. Another reason for this selection bias arises from recognition of posterior circulation strokes. Corroborating this, clinical signs of the posterior circulation strokes are underrepresented in the classic and widely-used tool for evaluation of an acute stroke patient – the NIHSS score. The problem of posterior stroke recognition does concern both in-hospital setting as well as emergency medical services, including paramedics. The recognition tools used for prehospital recognition (e.g., FAST) are more sensitive for anterior than posterior circulation. These factors usually translate into longer treatment delay for patients suffering from posterior circulation strokes as compared to anterior circulation strokes. This presentation will cover some facts about pre- and in-hospital recognition, clinical features, imaging, and treatment of anterior vs. posterior circulation strokes.

Disclosure: Nothing to disclose.

SYMP06-3
Pathway of acute stroke: how to reduce the ‘pit-stops’ of acute stroke
D. Toni
Rome, Italy

The time between stroke onset and revascularization treatments, either i.v. thrombolysis or/ and endovascular procedures, influences the probability of reaching functional independence, the risk of dying and the risk of symptomatic bleeding complications. The interval time between arrival at hospital and start of treatment (door to needle and door to groin puncture) is the only component we can directly control. Several factors are important for the rapid initiation of treatment:
- Education of dispatchers and EMS personnel: give to stroke a high priority dispatch
- Emergency personnel is prepared via pre-notification from the ambulance, and is ready on arrival; radiology department, laboratory nurse, and stroke unit are alerted
- Blood pressure, pulse, body temperature, blood sugar and oxygen saturation are already checked by the ambulance personnel on the way to hospital, as is information about onset. A large-bore iv catheter is inserted on the way to hospital.
- Preliminary data on level of consciousness (GCS), neurological symptoms, other illnesses and medications as
well as personal identity are transmitted to the ER by the ambulance personnel on the way to hospital
- Patient electronic charts are reviewed, eye-witness interview before/during transportation
- In the emergency room, preliminary data are confirmed, decision taken that the patient is a candidate for thrombolysis/thrombectomy; transfer to CT scanner without delay, blood tests taken (lab technician waiting for the patient, point-of-care INR)
- Thrombolysis infusion prepared in the CT room
- Stroke physician interprets the CT/AngioCT scan
- etc.

**Disclosure:** Nothing to disclose.

**SYMP06-4**

**Who should treat acute large vessel occlusions: neurologists, radiologists or neuro-interventionalists**

C. Kremer

*Malmö, Sweden*

Recent stroke trials showed that endovascular treatment is superior to iv. thrombolysis in stroke patients with large vessel occlusions. In the future there will be an increasing demand of specialists who can perform interventional procedures on stroke patients. The question of training interested colleagues among different medical specializations will become a major one. Up to date there are at least five different specializations involved in the endovascular treatment of stroke patients. The majority of interventions is performed by experienced neurointerventionalists. An overview over the possible advantages and eventual disadvantages regarding the treatment of large vessel occlusions by neurologists, radiologists, and neurointerventionalists will be given. eg. Radiologists are formally certified but often less involved in the treatment of stroke patients and therefore also less sub-specialized in the treatment of occlusions of the intracranial vessels. Neurointerventionalists are more specialized in vascular interventions but less involved in the acute care of stroke patients. Vascular neurologists/strokologists are experienced in acute stroke care and well-trained in meeting the diagnostic and therapeutical challenges in the context of acute stroke treatment. But long-term practical training in performing interventions is lacking. Up to date there are just a few experienced vascular neurologists who can perform endovascular treatments. The presentation will also take into account future perspectives regarding the training of vascular neurologists in performing interventions as a part of their specialization.

**Disclosure:** Nothing to disclose
Topical Symposium
EHF/EAN Topical Symposium: CGRP antibodies: a new class of migraine-specific preventive medication

SYMPTOP-1
Current treatment for migraine: efficacy and safety outcomes
J. Pascual
Santander, Spain
Pharmacological treatment of migraine includes acute medications for the attacks, which all migraine patients need, and preventatives, which are indicated for those patients experiencing ≥3 attacks per month. Nonsteroidals and triptans are the drugs of choice for the acute treatment of migraine attacks. Without objective biomarkers, recommended outcomes for evaluating efficacy of these drugs include pain free at 2 h and sustained pain free over the period of 2-24 h. However, it is possible that these outcome measures do not sufficiently reflect the wishes of patients, who want medications working faster and making them able to function properly. We should not forget that people with migraine have a whole range of potentially disabling associated symptoms, such as nausea/vomiting or photo/phonophobia, which would require outcomes measuring global functional disability. Antihypertensives (beta-blockers and candesartan), antiepileptics (topiramate and valproate), flunarizine and amitriptyline are the drugs indicated for migraine prevention. Recommended efficacy outcomes for preventatives include, in this order, number of migraine days or attacks, 50% improvement in migraine frequency or consumption of symptomatic acute treatment. Adverse events tend to precede efficacy and, in clinical practice, represent a significant problem leading to treatment discontinuation. Globally, no more than 50-60% of migraine patients show a significant improvement in migraine frequency and around 50% of our migraine patients experience at least tolerability problems with these medications. In conclusion, we need new options, having patients experience at least tolerability problems with these medications. In conclusion, we need new options, having patients experience at least tolerability problems with these medications.

Disclosure: Nothing to disclose.

SYMPTOP-2
The role of CGRP in migraine: from molecule to man
M. Ashina
Frederiksborg, Denmark
Calcitonin gene-related peptide (CGRP) is a 37-amino-acid neuropeptide identified in the early 1980s that belongs to a structurally conserved family of peptides that includes calcitonin, adrenomedullin and amylin. CGRP is broadly distributed in the nervous system and in the trigeminal pain pathway. The blood vessels of the meninges are richly innervated by CGRP-containing fibers originating in the trigeminal ganglion, and CGRP is a potent vasodilator both in cranial arteries. Animal models of headache reported release of CGRP from perivascular trigeminal nerve terminals and modulatory role of CGRP in nociceptive transmission. Human studies demonstrated that intravenous infusion of CGRP induces migraine and CGRP antagonism aborts and prevents migraine attacks. The exact pathways involved in CGRP-induced migraine attacks and mechanisms of action of CGRP antagonists/antibodies are not fully clarified but may involve both peripheral and central site of action.

Disclosure: Nothing to disclose.

SYMPTOP-3
CGRP antibodies in treatment of migraine: efficacy and mechanism of action
P.J. Goadsby
London, United Kingdom
Calcitonin gene-related peptide (CGRP) plays a pivotal role in the expression of migraine. Blockade of CGRP mechanisms using monoclonal antibodies provides a way to access this mechanism with high specificity and no off target side effects. I will discuss the antibodies in clinical trials in alphabetical order, using the 50% responder rates as the common endpoint for the top dose tested. All outcomes presented were different from placebo, and each medicine test in episodic (EM) or chronic (CM) migraine. ALD403 is an IgG1 humanised CGRP peptide antibody that was tested in an EM study. A single intravenous dose of 1000mg had a 61% responder rate compared to placebo at 33% for placebo. AMG334 is an IgG2 human CLR/RAMP1- CGRP receptor- antibody that was tested in an EM study. Given sc monthly at 70mg the responder rate was 47% compared to placebo at 30%. LY2951742 is a humanised CGRP peptide antibody that was tested in an EM study. Given sc bi-weekly at 150mg the responder rate was 70% with a placebo rate of 45%. TEV-48125 is a humanised CGRP antibody that was tested in an EM study. Given sc monthly 675mg had a response rate of 59% with a placebo of 28%. In a CM study given sc monthly at 900mg the response rate was 55% with a placebo of 31%. As a group, these medicines are well tolerated with the most common issue being relatively minor injection site reactions. None have produced liver enzyme changes or substantial cardiovascular changes.

Disclosure: Nothing to disclose.
SYMPTOP-4

Can acute and preventive migraine medication pass the blood-brain barrier?

G.M. Knudsen
Copenhagen, Denmark

It is still debatable to what extent anti-migraine drugs act on receptors located in the brain parenchyma, on the intravascularly located cerebral blood vessels, or affects the nociceptive input from the trigeminal nerves. Whereas the first would require a decent degree of blood-brain barrier (BBB) penetrance and brain retention (at least for acute interventions), the latter two may not. It is important to emphasize that the BBB is not a stable construct; it can be modified in various ways and indeed, some data suggest that the BBB is more leaky under an acute migraine attack. Also, there is accumulating preclinical evidence that inflammatory pain states may be associated with a disrupted BBB function (DosSantos et al, 2014). Even under baseline conditions, however, the BBB is never completely impermeable and the drug concentration that eventually reaches the intraparenchymal receptors, although perhaps in small concentrations, may still be pharmacologically active. That is, arguments for or against central versus peripheral mode of action cannot be based on considerations about concentrations and hardly even on measures of central receptor occupancies as measured with, e.g., positron emission tomography (PET), as long as there is no established dose-occupancy-efficacy relationship. Although the dosing scheme used in the study was less optimal, the so far single PET-studies that investigated the effect of triptans on 5-HT1B receptor binding did not show any significant occupancy of the receptor (Varnás et al, 2013).

Disclosure: Nothing to disclose.
Tuesday, 31 May

Symposium 7
Understanding functional connectivity using MRI

SYMP07-1
Brain functional connectivity assessed using MRI: the basis
B.B. Biswal
Newark, USA

Although long a condition of interest spanning the gamut of neuroimaging modalities, study of the “null”, “fixation” or “resting” state has recently flourished. The fMRI community, in particular, has zealously embraced resting state approaches to mapping brain organization and function. Now, having demonstrated its utility for charting the large-scale functional architecture of the brain, and potential for the identification of biomarkers for clinical conditions, the field is returning to fundamental questions regarding the significance and validity of resting state (intrinsic brain) phenomena. Here, we discuss these challenges, and outline current developments.

Disclosure: Nothing to disclose.

SYMP07-2
Clinical applications in MS
M.A. Rocca
Milan, Italy

In MS, physical and cognitive deficits not only reflect structural damage, but also functional imbalance in and between brain networks. Task-related and resting-state (RS) functional MRI (fMRI) allows to investigate brain activity across the whole brain and to measure the degree of functional correlation between different cortical regions. Functional connectivity (FC) abnormalities have been shown in patients with MS, from the earliest stages of the disease, in patients with clinically isolated syndromes (CIS) suggestive of MS. A comparison between CIS and relapsing-remitting (RR) MS patients has suggested that cortical reorganization might be an early but finite compensatory phenomenon in this condition. FC abnormalities affect also inter-network connectivity and are related to the extent of T2 lesions and the severity of disability. FC abnormalities of cognitive-related networks have been shown to contribute to the presence and severity of cognitive deficits in patients at different stages of the disease. The potential role of fMRI in the monitoring of cognitive rehabilitation treatment in patients affected by MS has been been demonstrated. Overall, fMRI offers a promising venue to investigate the functional impact of MS pathology, complementing structural conventional and quantitative MRI techniques, to understand better MS pathophysiology from the earliest clinical stages of the disease. However, fMRI still require a careful standardization of acquisition and analysis protocols, a careful assessment of scanner stability over time, and normative values as a reference.

Disclosure: Nothing to disclose

SYMP07-3
Implications for clinical trial design and monitoring of drug efficacy
T. Sprenger
Wiesbaden, Germany

Functional connectivity - Implications for clinical trial design and monitoring of drug efficacy

In the past decade, a high number of studies on human brain connectivity have been published. These studies have helped to shed light on the network architecture of the human brain and also helped to improve our understanding of brain plasticity. The according non-invasive techniques also hold some promise for implementations in the setting of clinical trials. In this talk, the potential of connectivity studies, especially resting state studies, for use in clinical trials, i.e. to identify patient populations or for use as outcome measures, is discussed together in the context of potential pitfalls.

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Symposium 8
New diagnostic developments in epilepsy

SYMP08-1
Definition and classification of seizures

J. Peltola
Tampere, Finland

The International League Against Epilepsy (ILAE) has recently presented new important contributions, which have been prepared by international task forces as draft manuscripts and then presented to all for comment. “A practical clinical definition of epilepsy” was published in 2014. The comments made by the epilepsy community have had a major impact on the final version. The task force proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions: (1) At least two unprovoked seizures occurring >24 h apart; (2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; (3) diagnosis of an epilepsy syndrome. In April 2016 a draft version of “Operational Classification of Seizure Types” was posted on the ILAE web site to recognize that some seizure types can have either a focal or generalized onset, to allow classification when the onset is unobserved, to include some missing seizure types and to adopt more transparent names. Changes include: (1) “partial” becomes “focal”; (2) seizures of unknown onset can still be classified; (3) awareness is used as a classifier of focal seizures; (4) the terms dyscognitive, simple partial, complex partial, psychic, secondarily generalized are eliminated; (4) bilateral tonic-clonic seizure replaces secondarily generalized seizure. The new classification does not represent a fundamental change, but allows greater flexibility and transparency in naming seizure types. Comments are still open until 4 June 2016.

Disclosure: Nothing to disclose.

SYMP08-2
Neurophysiological assessment of epilepsies

P.A. Boon
Ghent, Belgium

Electroencephalography (EEG) has an undebated role in confirming the clinical diagnosis of epilepsy in patients with seizures. It is a highly standardized, widely available, un invasive, reliable and cheap method to record field potentials from brain cortex. Interictal epileptiform discharges (IEDs) are the signature of epilepsy, providing information on which part(s) of the brain are involved in the epileptic process. Interpreting EEG signals involves both sound knowledge of recognizable patterns and insight in electro-clinical correlations. The relationship between the occurrence of IEDs and the type and severity of seizures is complex. In some types of epilepsy, EEG allows predicting the natural course or the response to therapy, but this is not the case in many other types of epilepsy. A normal interictal EEG does not exclude epilepsy. EEG recording during photic stimulation or hyperventilation and after sleep deprivation may enhance the sensitivity of EEG in some epileptic conditions. Video-EEG monitoring is a cornerstone diagnostic procedure in patients with medically refractory epilepsy who need a pre-surgical workup. Diagnostic video-EEG may be necessary to rule out (psychogenic) nonepileptic seizures in some patients. A small number of patients, in whom non-invasive EEG does not provide adequate localizing information needs invasive EEG recording. This EEG modality requires EEG electrodes in the subdural space or in the brain parenchyma, using open and/or stereotactic procedures. Magnetoencephalography (MEG) is a non-invasive tool for neurophysiological diagnosis that when compared to EEG, has a higher spatial resolution and does not require contact electrodes. Whether and in which way MEG may be useful for presurgical localization of the epileptogenic zone in refractory epilepsy patients remains a matter of debate. MEG has a clear potential in determining a presurgical strategy for invasive EEG-electrodes in highly selected patients. Moreover, MEG is feasible and useful for functional mapping of eloquent cortical areas.

Disclosure: Nothing to disclose.

SYMP08-3
3D multimodal imaging for epilepsy surgery

J.S. Duncan
London, United Kingdom

Brain imaging is critical for successful epilepsy surgery and includes high-resolution structural imaging to reveal underlying lesions, and the relationships of lesions to normal anatomy, tractography to delineate critical pathways, such as corticospinal tract and optic radiation, functional MRI to infer the location of eloquent cortex, and arteriography and venography to indicate the anatomy of vessels that must not be compromised. Further, functional imaging of regional cerebral glucose uptake (PET), ictal blood flow (SPECT), electrical and magnetic source imaging and EEG-fMRI can infer the lateralization and localization of epileptic foci and networks. Viewing all these data simultaneously in a common 3D anatomical reference enhances decision making regarding the strategy of intracranial EEG recording and the precise placement of individual electrodes, and the planning of surgical resections. Software is now being created to semi-automate the placement of electrodes, with template libraries and with programmes for determining electrode trajectories according to preset rules, such as minimum distance from blood vessels, avoiding sulcal pial boundaries, traversing the skull orthogonally and maximising grey matter contact. Resection planning will integrate these data with the output of intracranial EEG, resulting in a 3D resection target that may then be displayed in the eyepiece of the operating microscope, to enable an optimal resection.

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SYMP08-4

Genetic screening

J.M. Serratosa

Madrid, Spain

More than 80 genes have been found to be responsible for either one specific or several epilepsy phenotypes. Genetic testing in the epilepsies is now widely available in most European countries and is helping clinicians reach a precise diagnosis (offering prognostic and genetic counseling information) and select the most adequate treatment. Genetic testing may reduce diagnostic work-up costs and relieve anxiety to families. Most epilepsies in which a gene has been identified are rare. Among these, the epileptic encephalopathies (EEs) of childhood, the progressive myoclonic epilepsies and some familial epilepsies are the most representative groups. In the EEs it is important to test the parents as most mutations occur de novo and this reinforces the role of a variation in the disease. Different genetic screening techniques are now available including classic Sanger sequencing, next generation sequencing (using gene panels or whole exome or genome sequencing), MLPA and CGH karyotyping. The most appropriate test to be performed highly depends on the phenotype of the patient and on local resources and insurance coverage. Selecting the most cost-effective test for each patient and interpreting the results requires expertise in the field of genetic of the epilepsies. Each genetic finding must be correlated with the clinical picture. The presence of a variation in other affected or non-affected family members or parents, the communication of previously similar phenotypes with the same mutation or mutations in the same gene, and the predicted or reported functional effect must all be considered in order to assign causing pathogenicity.

Disclosure: Nothing to disclose.
Untangling inflammatory and degenerative aspects of multiple sclerosis

SYMP09-1

Insights from MS pathology

W. Brück
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There is increasing evidence from morphological studies that inflammatory and neurodegenerative mechanisms are involved in multiple sclerosis. Besides characteristic lesions in the white matter, there is increasing evidence that inflammatory and degenerative events occur also in the grey matter lesions as well as in the normal appearing white and grey matter. Inflammation and degeneration occurs from the start of the disease and strongly depend on each other. The present lecture aims at demonstrating the quantity and quality of inflammation as well as the nature and extent of neurodegeneration in multiple sclerosis from relapsing-remitting to progressive MS as well as within white and grey matter lesions and the normal appearing grey and white matter. The contribution of adaptive and innate immunity as well as the role of peripheral and resident immune cells in mediating neuroaxonal damage in different disease stages will be discussed.

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SYMP09-2

Insights from experimental models

M. Kerschensteiner
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Here, I want to discuss how insights from the in vivo analysis of experimental models can improve our understanding of the relation of inflammation and neurodegeneration in MS. To illustrate this I will use our recent insights into the in vivo pathogenesis of immune mediated axon damage as an example. Such immune-mediated damage to axons plays a crucial role in multiple sclerosis (MS), however we still understand very little about how immune cells can initiate axon damage. In vivo visualization of fluorescently labeled macrophages/microglia and axons recently allowed us to observe the spatially restricted degeneration of axons in mouse models of MS. This “focal axonal degeneration” appears to be a novel type of axonal degeneration that is characterized by intermediated stages that can persist for several days and progress either to the degeneration or full recovery of the affected axons. Refined subcellular and molecular in vivo imaging approaches now further allow us to investigate the molecular mediators that drive axonal degeneration and to better understand the relation between structural and functional axon damage in neuroinflammatory lesions. Finally we can use cortical imaging approaches in models of gray matter pathology to follow up on recent histopathological findings that indicate the presence of widespread synaptic deficits in advanced stages of MS. Using these examples, I hope to illustrate how recent advances in light microscopy can help us to reveal and mechanistically dissect the interactions of activated immune cells and CNS target cells as they happen in the living CNS.

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SYMP09-3
Insights from clinical imaging
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Acute relapses in MS are associated with new, worsening focal inflammation. Clinical symptoms and signs of relapses are frequently associated with appropriately localised Gd-enhancement and new T2-hyperintense MRI lesions. Their frequency is a strong predictor of short-term disability progression and beneficial effects of current anti-inflammatory medicines to slow relapse rate. More recent evidence suggests that measures of cortical lesion evolution also contribute. Nonetheless, the volume or number of T2 lesions, which are related heterogeneously to inflammatory infiltrates and oedema, demyelination and any subsequent glial scar, do not explain disability well in populations sampled cross-sectionally. By contrast, brain volume differences, which have been related largely to loss or atrophy of neurons and their processes, explain a substantial proportion of the variability in disability in the population. Anti-inflammatory treatments for MS slow rates of brain atrophy in patients with relapsing remitting MS, consistent with their impact on relapses and relative rates of relapse related disability progression. However, with one possible exception, these medicines do not slow brain atrophy or disability progression in primary or secondary progressive MS. Recent work using PET with radioligands binding to the 18 kD mitochondrial translocator protein (TSPO) have provided increasingly compelling evidence that chronic, innate immune injury mediated by microglia or astrocyte activation not addressed by most medicines well may be an important factor responsible.
Disclosure: Nothing to disclose.

SYMP09-4
Insights from therapeutic trials
X. Montalban
Barcelona, Spain