Oral Sessions

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Ageing and dementia 1

OS1101

Assessing brain system dysfunction in amnesic mild cognitive impairment through MRI-based connectomics

F. Agosta1, E. Canu1, S. Galantucci1, A. Meani1, G. Magnani1, A. Marcone1, A. Falini2, G. Comi2, M. Filippi1,2
1Neuroimaging Research Unit, Institute of Experimental Neurology, 2Department of Clinical Neurosciences, 4Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To investigate the topological organization of functional brain network connectivity in patients with amnesic mild cognitive impairment (aMCI).

Methods: Graph theoretical analysis was applied to resting state fMRI from 45 aMCI patients and 32 healthy controls. Functional connectivity between 90 cortical and subcortical brain regions was estimated using bivariate correlation analysis and thresholded to construct a set of undirected graphs. Measures of global and local network organization were obtained.

Results: Small-worldness was verified in both groups. Functional brain networks in aMCI patients were characterized by a significantly higher hierarchy compared with controls. Compared to controls, aMCI patients did not show hub regions in the right hippocampus, anterior cingulate and calcarine cortices bilaterally, and left putamen and caudate nucleus. Compared with controls, aMCI patients showed increased betweenness centrality in the posterior cingulate cortex bilaterally, left angular, inferior parietal and supramarginal gyri, and right superior medial frontal cortex.

Conclusions: The global organization of functional networks is relatively preserved in aMCI, except for an increased hierarchy of the brain functional networks. High hierarchy suggests a high sub-modular decomposition of the functional networks, which is thought to be negatively related with the span of control acted by the central module. On the contrary, local functional network organization is altered in aMCI showing a loss of major hubs in the regions typically hit by the disease and evidence for increased connectivity locally within the parietal and frontal lobes. Graph analysis provides additional insights into the physiology of early changes in Alzheimer’s disease.

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OS1102

Cytokine gene expression in peripheral cells from patients with frontotemporal lobar degeneration due to GRN and C9ORF72 mutation

C. Fenoglio1,2, M. Serpente1,2, R. Bonsi1,2, S.M. Cioffi1,2, A. Arighi1,2, L. Ghezzi1,2, A. Callea1,2, C. Donelli1,2, M. Mercurio1,2, E. Scarpi1,2, D. Galimberti1,2
1University of Milan, 2Fondazione Ca’ Granda, Ospedale Policlinico, Milan, Italy

Introduction: Mutations in progranulin (GRN) and C9ORF72 genes are common causes of familial Frontotemporal Lobar Degeneration (FTLD). Our main aim is to evaluate the expression of inflammatory factors in peripheral cells from GRN and C9ORF72 carriers as compared with sporadic FTLD and controls.

Methods: Sabiosciences PCR array containing 84 common cytokines was used to investigate the expression profile of cytokines in 3 C9ORF72 FTLD symptomatic expansion carriers, 3 GRN symptomatic mutation carriers, 3 GRN asymptomatic carriers, 3 sporadic FTLD patients and 3 age-matched controls.

Results: We observed a general down-regulation of cytokines expression levels in C9ORF72 symptomatic expansion carriers compared with controls. In particular, IL8, IL4 and TNFSF4 expression levels showed a significant downregulation (-8.03; -2.55 and -2.32 fold regulation, respectively, p<0.05) compared to controls. The same trend characterized GRN mutation carriers compared to controls, even in a stronger fashion. On the contrary, considering cytokine profiling of sporadic cases compared to controls, the opposite trend was observed. Results showed a general up-regulation of cytokines expression levels compared to controls, the opposite trend was observed. Results showed a general up-regulation of cytokines expression levels, in particular, IL12A, IL5 and VEGFA expression levels were significantly over-expressed in sporadic cases (1.81, 3.59 fold and 1.51 fold regulation over controls, respectively, p<0.05). No de-regulated cytokines were observed in asymptomatic GRN carriers.

Conclusions: This is the first attempt to characterize the cytokine profile of GRN and C9ORF72 expansion carriers. Preliminary results showed opposite trend of cytokines expression levels between GRN and C9ORF72 FTLD and controls.
carriers and sporadic patients compared with controls, suggesting different pathogenic pathways between mutation carriers and sporadic FTLD.

Disclosure: Nothing to disclose

OS1103
Mild cognitive impairment with suspected non AD pathology (SNAP): prediction of progression to dementia

A. Caroli¹, A. Prestia², S. Galluzzi², C. Ferrari², W.M. van der Flier³,4, R. Ossenkoppele³, B. Van Berckel³, F. Barkhof³, C.E. Teunissen⁶, A. Wall⁷, S.F. Carter⁸, M. Scholl⁹, I.H. Choo¹⁰, T. Grimmer¹¹, A. Nordberg¹¹,¹², P. Scheltens³, A. Drzezga¹³, G.B. Frisoni¹³,¹⁴
¹Medical Imaging Unit, Bioengineering Dept, IRCCS Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, ²LENITEM - Laboratory of Epidemiology and Neuroimaging, IRCCS Centro San Giovanni di Dio - Fatebenefratelli, Brescia, Italy, ³Alzheimer Center and Dept of Neurology, ⁴Dept of Epidemiology & Biostatistics, ⁵Dept of Radiology & Nuclear Medicine, ⁶Neurochemistry Laboratory and Biobank, Dept of Clinical Chemistry, VU University Medical Center, Amsterdam, Netherlands, ⁷PET-Center, Section of Nuclear Medicine & PET, Dept of Radiology, Oncology and Radiation Sciences, Uppsala University, Uppsala, ⁸Alzheimer Neurobiology Center, Karolinska Institutet, Stockholm, ⁹MedTech West, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden, ¹⁰Dept of Neuropsychiatry, School of Medicine, Chosun University College of Medicine, Gwangju, Korea, Republic of, ¹¹Dept of Psychiatry and Psychotherapy, Klinikum rechts der Isar, Technische Universitaet Muenchen, Munich, Germany, ¹²Dept of Geriatric Medicine, Karolinska University Hospital Huddinge, Stockholm, Sweden, ¹³Dept of Nuclear Medicine, University of Cologne, Cologne, Germany, ¹⁴Dept of Internal Medicine and Psychiatry, University Hospitals and University of Geneva, Geneva, Switzerland

Introduction: Alzheimer’s disease (AD) is believed to feature amyloid deposition, followed by neurodegeneration, and clinical symptoms. However, a minority of patients show neurodegeneration but no amyloidosis (“suspected non-AD pathophysiology”- SNAP). Aim of this study was to investigate AD biomarker predictors of progression to dementia in SNAP patients with mild cognitive impairment (MCI).

Methods: CSF Abeta-42, hippocampal volume on MRI, and cortical metabolism on FDG-PET were measured in 188 MCI patients followed for at least one year. MCI patients were categorized based on biomarker abnormality: biomarker negative (MCI-BN), MCI-SNAP (no amyloid pathology, with neurodegeneration), and MCI-AD (amyloid pathology, with or without neurodegeneration). In MCI-SNAP and MCI-AD groups, risk and time to progression to AD dementia were assessed.

Results: 36 MCI-BN, 27 MCI-SNAP and 125 MCI-AD were included. MCI-SNAP showed lower prevalence of APOE-ε4 carriers (p=0.011) and progressors (p=0.185) than MCI-AD. In MCI-SNAP, hypometabolism was comparable to MCI-AD, while hippocampal atrophy was more severe (p<0.0001) (Table 1). MCI-SNAP and MCI-AD had comparable MMSE score loss and risk of progression to dementia (HR=4.04 vs 5.36). In MCI-AD, hypometabolism predicted risk of progression (HR=3.32, p<0.0001) and hippocampal atrophy predicted risk (HR=1.86, p=0.009) (Table 2) and time-to-progression (p=0.009). In MCI-SNAP, hypometabolism predicted risk (HR=6.71, p=0.008) and time-to-progression (p=0.044). Unexpectedly, shorter time-to-progression was predicted by less atrophic hippocampi (p<0.001) (Table 3).

Conclusions: Our findings suggest that in MCI neurodegeneration with no amyloidosis is associated with a specific risk progression profile, and confirm the high-value of FDG-PET as biomarker of progression in MCI, independent of amyloid pathology.

Disclosure: Nothing to disclose

OS1104
Abnormalities of fixation, saccade and pursuit in posterior cortical atrophy

D. Kaski¹, T. Shakespeare², J. Schott³, S. Crutch²
¹Imperial College London, ²University College London, London, United Kingdom

Introduction: Patients with posterior cortical atrophy have impairments in visuo-perceptual and visuo-spatial processing associated with atrophy of the parietal and occipital lobes. Here we present the first detailed and systematic study of oculomotor function in this patient group, describing the particular characteristics of oculomotor abnormalities in posterior cortical atrophy.

Methods: We recorded fixation, saccade and smooth pursuit eye movements in 20 patients with posterior cortical atrophy using an infrared pupil tracking system, 12 patients with typical Alzheimer’s disease, and 22 healthy controls.

Results: Posterior cortical atrophy patients showed a higher frequency of large saccadic intrusions during fixation compared to both healthy controls and typical Alzheimer’s patients. Saccades were hypometric, significantly shorter than those of healthy controls and typical Alzheimer’s patients, and smooth pursuit significantly impaired in PCA.

Conclusions: This study establishes the oculomotor abnormalities present in posterior cortical atrophy for the first time, describing features unique to this condition and features in common with typical Alzheimer’s disease. The cognitive mechanisms and neurological basis for this impairment are discussed, with the features observed suggesting that both visual cognition and automatic oculomotor mechanisms can be impaired in this patient group.

Disclosure: Nothing to disclose
OS1105
Early diagnosis of dementia – a campaign in a population of elderly people in Athens

P. Sakka1, F. Kalligerou1, P. Zoi2, A. Efthymiou2, E. Dimakopoulou2
1Brain Neurodegenerative Diseases Department, Memory Clinic, Hygeia Hospital, 2Memory Clinic, Athens Association of Alzheimer’s Disease and Related Disorders, Athens, Greece

Introduction: Athens Association of Alzheimer’s Disease and Related Disorders in collaboration with the Memory Clinic of HYGEIA hospital organized a project to promote early diagnosis of dementia. Free memory screening was offered to people over 65 years living in the community and without a diagnosis of dementia.

Methods: Neurologists and cognitive psychologists examined the participants. Demographics, medical history and reasons for taking the examination were recorded. Cognitive tests performed were: Mini Mental State Examination (MMSE), Clock Drawing Test (CDT), MOCA 5 words and Geriatric Depression Scale (GDS).

Results: 1800 elderly people participated in memory testing. Mean age was 73 years (60–93 years). 70.1% reported memory dysfunction as the reason for taking the examination. Mean MMSE score was 26.5 (±3.5) and 82% of the participants scored over 24. Mean CDT was 5/10 (±3.3). Age and education level were significant predictors of MMSE score. According to GDS scores, 66% of the participants had no depression, 22% had mild depressive symptoms while 12% showed severe depression. Those diagnosed with cognitive decline or depression were referred to Memory Clinics.

Conclusions: Memory complaints of the participants on the project were not related to actual memory deficits but more to bad mood and anxiety. Age had a negative impact on MMSE scores while higher education was associated with increased MMSE scores.

Disclosure: Nothing to disclose

OS1106
Overview on the clinical development of the PET imaging agent florbetaben to assist in the clinical diagnosis of cognitively impaired subjects

A. Stephens
Clinical Research and Development, Piramal Imaging GmbH, Berlin, Germany

Introduction: The clinical diagnosis of Alzheimer’s Disease is wrong in up to 30% as detected by autopsy studies. Efforts have been taken to reliably detect beta-amyloid (Aβ) plaques in the brain during life. The 18F-labelled stilbene-derivative florbetaben binds to Aβ with high affinity and can be used for PET imaging. The clinical development program comprised the investigation of florbetaben in 884 subjects to study its safety, diagnostic performance and efficacy.

Methods: Regulatory approval required the proof of florbetaben binding to Aβ-plaques. A phase 3 study was designed accordingly: Elderly end-of-life subjects, who consented to donate their brains post mortem, were imaged with florbetaben during life. The correlation of the cortical grey matter PET signal to the presence or absence of Aβ-plaques was investigated post mortem.

Results: In this histopathology study, 216 subjects with diagnoses of AD, other or no dementia were enrolled. In 74 autopsied subjects, a sensitivity of 98% and specificity of 89% was determined. Out of 57 subjects with a clinical diagnosis of AD, 44 subjects (77%) showed presence of Aβ in histopathology. In 43 of these 44 subjects Aβ-plaques were detected by PET. In 11/13 subjects with clinical diagnosis of AD and in 13/14 subjects with other or no dementia but without Aβ-plaques, the PET images were correctly read negative.

Conclusions: Although the detection of Aβ-plaques does not establish a diagnosis of AD, the reliable exclusion of Aβ should encourage the physician to search for other causes of cognitive decline and tailor available treatment options.

Disclosure: Andrew Stephens is employee of Piramal Imaging. Florbetaben (NeuraCeqTM) is an investigational PET amyloid imaging agent currently under review by the U.S. Food and Drug Administration and recommended for approval in the European Union by the CHMP.
Cognitive neurology and neuropsychology

OS1107

Predictors of driving performance in individuals with MCI: preliminary results

S.G. Papageorgiou1, L.N. Beratis1, N. Andronas1, A. Economou2, D. Pavlou3, A. Bonakis1, G. Tsivgoulis3, L. Stefanis1, G. Yannis3

12nd Department of Neurology, University of Athens, Medical School, Attikon University Hospital, 2Department of Psychology, National and Kapodistrian University of Athens, 3Department of Transportation Planning and Engineering, National Technical University of Athens, Athens, Greece

Introduction: Mild Cognitive Impairment (MCI) represents a transitional stage between normal aging and dementia with no or only minimal impairment in everyday activities. Recent research suggests that individuals with MCI may have altered driving abilities. The scope of the present research is to investigate the association of neurological and neuropsychological measures with indexes of driving performance in individuals with MCI.

Methods: A CDR score of 0.5 was required for the diagnosis of MCI. Additional inclusion criteria were the presence of a valid driver’s license and regular car driving. Sixteen individuals with MCI attending our Memory Clinic participated in the study. The collection of the data included:
(a) detailed clinical, medical and neurological assessment,
(b) extensive neuropsychological assessment, and
(c) a driving simulation experiment.

Outcome measures were driving speed, number of crashes, and reaction time in unexpected incidents.

Results: A regression model that included as predictors general cognitive functioning (MMSE) as well as balance and movement coordination explained 55.9% of the variance in driving speed, \(R^2=0.559, F(2,13)=8.25, p=0.005\). Measures of general cognitive functioning (MMSE), visuospatial memory and processing speed explained 77.3% of the variance in number of crashes, \(R^2=0.773, F(3,10)=11.35, p=0.001\). Measures of general cognitive functioning (MMSE), processing speed as well as as balance and movement coordination explained 73.2% of the variance in reaction time, \(R^2=0.732, F(3,12)=10.92, p=0.001\).

Conclusions: Preliminary results show that neurological and neuropsychological measures are useful predictors of driving competence in individuals with MCI and could be used for detecting MCI patients at risk for car accidents.

Table 1. Summary of multiple regression analyses for driving speed, number of crashes and reaction time

<table>
<thead>
<tr>
<th>Predictor</th>
<th>(\beta)</th>
<th>t</th>
<th>p</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TW (Balance/Mov. Coordination)</td>
<td>0.63</td>
<td>3.22</td>
<td>0.007</td>
<td>Driving Speed</td>
</tr>
<tr>
<td>UFV_1 (Processing Speed)</td>
<td>0.48</td>
<td>2.58</td>
<td>0.027</td>
<td>Number of crashes</td>
</tr>
<tr>
<td>BVMT_Rec (Visuospatial Memory)</td>
<td>0.40</td>
<td>2.16</td>
<td>0.056</td>
<td>Number of crashes</td>
</tr>
<tr>
<td>SDMT (Processing Speed)</td>
<td>0.60</td>
<td>2.87</td>
<td>0.014</td>
<td>Reaction time</td>
</tr>
<tr>
<td>TW_RNC (Balance/Mov. Coordination)</td>
<td>0.54</td>
<td>3.21</td>
<td>0.007</td>
<td>Reaction time</td>
</tr>
</tbody>
</table>

TW=Tandem Walking; UFV_1=Useful Field of View Subtest; BVMT_Rec=Brief Visuospatial Memory Test Recognition Trial; SDMT=Symbol Digit Modalities Test; TW_RNC=Reverse Number Counting

Disclosure: Nothing to disclose

OS1108

Structural connectivity in patients with major depression with or without generalized anxiety disorder comorbidity

E. Canu1, M. Kostić2, F. Agosta1, A. Munjiza2, D. Pesić2, A. Peljto2, D. Lecic Tosevski2,3, M. Filippi1,4

1Neuroimaging Research Unit, Institute of Experimental Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy, 2Institute of Mental Health, School of Medicine, University of Belgrade, Belgrade, Serbia, 3Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: According to the diagnostic criteria for Major Depressive Disorder (MDD), a common overlap occurs between depression and Generalized Anxiety Disorder (GAD). Aim of this study is to assess white matter (WM) alterations in MDD patients with or without GAD comorbidity (MDD-GAD).

Methods: 55 MDD patients (including 16 MDD-GAD cases) and 21 controls underwent a diffusion tensor (DT) MRI. DT MRI metrics were obtained from the major interhemispheric and long association WM tracts. Between groups comparisons and multiple regressions with the Hamilton depression and anxiety scale sub-scores were performed.

Results: Compared to controls, MDD and MDD-GAD patients showed WM alterations in the corpus callosum (CC) and right superior longitudinal fasciculus (SLF). Compared to controls, MDD patients showed further abnormalities in the right inferior longitudinal fasciculus, while MDD-GAD in the body of CC. The alterations of the body of CC in the MDD-GAD group was positively related to insomnia and gastrointestinal symptoms. When compared to each other, MDD patients showed alterations of the left SLF, while MDD-GAD of the left uncinate fasciculus. Left SLF and uncinate abnormalities were related with patient depression and anxiety symptoms, respectively.

Conclusions: Although MDD and MDD-GAD share a common pattern of WM alterations of the frontoparietal and interhemispheric tracts, they also show different damage involving the fronto-temporal-occipital connections in MDD patients, and the connections to the motor/ somatosensory and frontal cortices in the MDD-GAD group. The relationships between WM alterations and the clinical symptoms might increase our understanding of the pathophysiology of these disorders.

Disclosure: Nothing to disclose
OS1109
Differences in spatial navigation among patients with various neurodegenerative dementias
J. Laczó1,2, J. Cerman1, R. Andel2,3, I. Gazova1,2, K. Vlcek2,4, M. Vyhna1,2, I. Mokr1,2, E. Hyncicova1, O. Lech1, M. Parizkova1, K. Sheardova2, J. Hort1,2
1Department of Neurology, Charles University in Prague, 2nd Faculty of Medicine, Prague, 2International Clinical Research Center, St. Anne’s University Hospital Brno, Brno, Czech Republic, 3School of Aging Studies, University of South Florida, Tampa, FL, United States, 4Department of Neurophysiology of Memory, Institute of Physiology Academy of Sciences of the Czech Republic v.v.i., Prague, Czech Republic

Introduction: Spatial navigation impairment may play an important role in loss of self-sufficiency in patients with dementia. Reliable tests that capture possible differences in real-space navigation among patients with different types of dementia are still lacking. The aim was to compare differences in real-space navigation among patients with three common types of neurodegenerative dementias—Alzheimer’s disease (AD), frontotemporal lobar degeneration (FTLD), and dementia with Lewy bodies (DLB).

Methods: There were 78 patients (61 with AD, 9 with FTLD [including 5 with behavioral variant and 4 with primary progressive aphasia], and 8 with DLB). All patients were tested in the real-space human analogue of the Morris Water Maze, which allows to measure performance in each of the three spatial navigation components—cued navigation (using a close orientation cue), egocentric navigation (using a position of the body at the starting position) and allocentric navigation (using a distant orientation cue). One-way analysis of variance was used.

Results: In the cued navigation test, the FTLD group performed better than the AD (p=0.030) and DLB (p=0.006) groups. In the egocentric navigation test, the DLB group had worse scores than AD (p=0.012) and FTLD (p=0.012) groups. Group differences in allocentric navigation were not significant (p=0.069).

Conclusions: Overall spatial navigation impairment may be least pronounced in FTLD and most pronounced in DLB patients. There are qualitative differences in spatial navigation impairment among patients with AD, FTLD and DLB that can be measured with the real-space human analogue of the Morris Water Maze.

Disclosure: Dr. Laczó has consulted for Pfizer and holds shares of Polyhymnia-TS. Dr. Hort has consulted for Pfizer, Janssen, Merck, Novartis, Elan, Zentiva, Ipsen and holds shares of Polyhymnia-TS.

OS1110
Long-term correlates of future incident AD in prospective population cohorts according to education. Longitudinal neurocognitive data
J.-M. Orgogozo1,2, H. Amieva1, H. Jacqmin-Gadda1, Y. Stern3, J.-F. Dartigues1,2
1Inserm, U 897, Bordeaux University, 2Department of Neurology, University Hospital, Bordeaux, France, 3Cognitive Neuroscience Division, Columbia University, New York, NY, United States

Analyzing long-term trajectories of cognitive decline is key to the understanding of the process leading to dementia. Level of education is a major modulator for the occurrence of sporadic Alzheimer’s disease (AD). We compared the pattern and duration of neuro-cognitive trajectories before dementia in elderly subjects with low and high education (LES and HES respectively) followed within the PAQUID cohort over 20 years. There were 442 cases of incident AD (27.2% men), 171 LES (age=86.2; SD=5.3) and 271 HES (age=86.5; SD=5.4) and 442 controls matched for age, sex and education. Cases of AD were diagnosed clinically and comprehensive cognitive and clinical measures were repeatedly collected. The evolution of these measures in pre-demented subjects and matched controls was analyzed with a semi-parametric extension of the mixed effects linear model.

In HES a decline in the IST and DSST began 15-16 years before dementia, with no memory or functional complaints during the first 7-8 years. About 7 years before dementia, global cognitive abilities begin to deteriorate, along with difficulties with complex activities of daily living. By contrast, LES presented a single period of decline lasting about 7 years before dementia, with more global cognitive impairment along with alteration in functional abilities.

These data show a latent phase of 7-8 years in HES who will become demented 15-16 years later, objectived on sensitive neuropsychological tests. LES present a single period of decline lasting about 7 years before dementia, with more global cognitive impairment along with alteration in functional abilities.

Disclosure: Nothing to disclose
OS1111

Patterns of regional gray matter and white matter atrophy in “cortical multiple sclerosis”

G.C. Riccitelli1, M.A. Rocca1-2, L. Parisi1, F. Mattioli3, R. Capra4, M. Filippi1,2
1Neuroimaging Research Unit, Institute of Experimental Neurology, 2Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, 3Clinical Neuropsychology, 4Multiple Sclerosis Centre, Spedali Civili of Brescia, Brescia, Italy

Introduction: “Cortical” multiple sclerosis (cort-MS) is a rare form of the disease characterized by a severe progressive cognitive impairment, focal cortical syndromes, cortical signs with a relative sparing of motor, sensory and cerebellar functions. We used voxel-based morphometry (VBM) to investigate the patterns of regional gray matter (GM) and white matter (WM) atrophy in patients with cort-MS in comparison to classical MS (c-MS) to elucidate the contribution of GM and WM damage to cognitive and psychiatric symptomatology.

Methods: Eighteen MS patients (9 cort-MS and 9 c-MS) and 9 age-matched healthy controls (HC) were enrolled. MS patients underwent neurological and neuropsychological evaluations. All subjects underwent a brain MRI exam, including a fluid attenuation inversion recovery (FLAIR) and a high-resolution T1-weighted scans. VBM was used to assess between group differences of GM and WM volumes (SPM8, p<0.001, uncorrected). T1-lesion probability maps (LPMs) were obtained.

Results: Performance at each neuropsychological test was significantly worse in cort-MS vs c-MS patients (p ranging from <0.0001 to 0.01). Compared to HC, MS patients had cortical and subcortical GM atrophy and WM atrophy of the corpus callosum and bilateral corticospinal tracts. No GM/WM area was more atrophied in c-MS vs cort-MS patients. Compared to c-MS, cort-MS patients had GM atrophy of fronto-temporal-parietal areas and cingulum, and WM atrophy of the cingulum, bilateral cerebral peduncles, right inferior and left superior longitudinal fasciculus.

Conclusions: Higher susceptibility to neurodegenerative processes in key brain regions known to be related to cognitive functions could underlie the clinical presentation of cort-MS.

Disclosure: MAR speakers honoraria from Biogen Idec and Serono Symposia International Foundation. MF received compensation for consulting and/or speaking from Bayer, Biogen Idec, Merck Serono, and Teva.

OS1112

Relationship between cognitive impairment and physical disability in MS patients

A.M. Silva1-2-3, I. Moreira2, C. Pinto2, E. Santos1,3, I. Moreira1, R. Samões1, A. Gonçalves1, A. Bettencourt3, X. Montalban4, S. Cavaco2,3
1Neurology Department, 2Laboratory of Neurobiology of Human Behavior, Centro Hospitalar do Porto - Hospital de Santo António, 3UMIB, ICBAS-UP, Porto, Portugal, 4Unitat de Neuroimmunologia Clinica, Vall d’Hebron University Hospital, Barcelona, Spain

Objectives: To investigate cognitive functioning in a Portuguese MS population and to examine its relationship with physical and clinical course characteristics.

Methods: 419 MS patients (266 women; mean age=40 sd=13; mean education=11 sd=5; mean disease duration=9.92, sd=8.47; 332 RRMS, 44 SPMS and 43 PPMS) and 159 healthy comparison subjects (HC; women; mean age=41 sd=13; mean education=12 sd=5) performed a series of neuropsychological (NP) tests (i.e., Attentive Matrices-AT, Digit Span-DS, Wisconsin Card Sorting Test-WCST, Corsi Block-Tapping Test-CB, Auditory Verbal Learning Test-AVLT, Sentence Repetition-SR, Letter Word Fluency-LWF) and answered the Hospital Anxiety and Depression Scale-HADS. Based on HC group’s multiple linear regression coefficients, MS patients’ NP scores were adjusted for gender, age and education. Univariate and multivariate logistic regressions were used to compute the odds of deficit among MS subjects.

Results: Among MS patients, deficit on NP measures AT, AVLT, CB, and SR was statistically related (p<0.05) with EDSS, MSSS and SP course. The associations with EDSS and MSSS (separate regression models) remained statistically significant for AT, AVLT and CB, while adjusting for other covariates (gender, age, education, disease duration, disease course, and depression scores). Deficit on AVLT, CB, and SR remain significantly associated with secondary progressive course (p<0.05), even after adjusting for others covariates (gender, age, disease duration, depression scores, and EDSS or MSSS).

Conclusions: These results suggest that the likelihood of cognitive dysfunction in MS increase with higher severity of physical symptoms and with SP course. These associations appear to be independent of demographic and psychopathological features.

Disclosure: Nothing to disclose
Multiple sclerosis and related disorders 1

**OS1113**

**Contribution of spinal cord MR to the diagnosis of patients with clinically isolated syndromes suggestive of multiple sclerosis**

G. Arrambide¹, M. Tintoré¹, A. Rovira², C. Tur¹, E. Simon¹, J. Sastre-Garriga¹, J. Castilló¹, J. Río¹, A. Vidal-Jordana¹, I. Galán¹, F. Palavra¹, L. Negrotto¹, C. Nos¹, M. Comabella¹, E. Huerga², C. Auger², X. Montalban¹

¹MS Centre of Catalonia (Cemcat), Hospital Universitari Vall d’Hebron/VHIR, Universitat Autònoma de Barcelona, ²Magnetic Resonance Unit (IDII), Hospital Universitari Vall d’Hebron, Barcelona, Spain

**Introduction:** Spinal cord (SC) topography is used to determine dissemination in space (DIS, 2010 criteria). The added value of SC magnetic resonance (MR) at 3.0 and 1.5T in the diagnosis of multiple sclerosis (MS) was evaluated.

**Methods:** From a clinically isolated syndrome (CIS) cohort, 100 patients with brain and SC MR at 3.0T and 107 with MR at 1.5T were identified. Baseline characteristics were compared. As there were no significant differences, the 3.0T (N=76) and 1.5T (N=67) non-SC CIS groups were merged to identify the proportion of patients fulfilling DIS, first assessing brain MR and then both brain and SC MR, to determine DIS and dissemination in time (DIT) in each case and the number needed to scan (NNS) to diagnose one additional MS case. Hazard ratios were calculated for four CIS subtypes.

**Results:** When additionally reading SC MR in non-SC CIS (N=143), 4 (2.8%) more patients fulfilled DIS and DIT (NNS=36). This analysis was repeated for pathological brain MR (N=90, NNS=23) and pathological brain MR not fulfilling DIS and DIT (N=70, NNS=18) Presence of SC lesions posed a higher risk of developing clinically definite MS in: all cases, non-SC CIS, and non-SC CIS with pathological brain MR, whereas a trend was observed in non-SC CIS with pathological brain MR not fulfilling DIS and DIT

**Conclusions:** Although the added value of SC MR appears to be modest when analysing MR at 3.0 and 1.5T together, the prognostic impact of SC lesions seems relevant in all CIS subtypes.

**Disclosure:** G Arrambide: travel expenses for scientific meetings from Merck-Serono. M Tintoré, A Rovira, J Sastre-Garriga, M Comabella, and X Montalban: speaker honoraria from Bayer Schering Pharma, Sanofi-Aventis, Bracco, Merck Serono, Teva Pharmaceuticals, Biogen Idec, Novartis, Sanofi, Genentech, Genzyme, and Almirall. Other authors: no disclosures.

**OS1114**

**Proportion of multiple sclerosis patients with brain volume loss comparable to healthy adults in the phase 3, placebo-controlled fingolimod studies, FREEDOMS and FREEDOMS II**

N. De Stefano¹, D. Tomic², D. Haering³, G. Francis³, E.W. Radue¹, T. Sprenger⁴, L. Kappos⁴

¹University of Siena, Siena, Italy, ²Novartis Pharma AG, Basel, Switzerland, ³Novartis Pharmaceutical Corporation, East Hanover, NJ, United States, ⁴University Hospital Basel, Basel, Switzerland

**Introduction:** In healthy adults up to age 55, the mean yearly rate of brain volume loss (BVL) reported in the literature is approximately -0.2% to -0.3%. The mean annual rate of BVL observed in multiple sclerosis (MS) patients is approximately -0.6% to -1.0%. BVL has been correlated with increasing measures of disability progression. Fingolimod significantly reduced BVL vs. active comparator/placebo in all three, pivotal phase 3 studies. We have conducted an analysis of the pooled 2-year FREEDOMS and FREEDOMS II study data in relapsing-remitting MS, to assess the proportion of patients on fingolimod 0.5mg with annual rates of BVL comparable to that reported in healthy adults.

**Methods:** Percentage change from baseline in BV was estimated at 6-, 12- and 24-months using the Structural Image Evaluation using Normalisation of Atrophy (SIENA) methodology. We present proportions of patients whose annual rate of BVL did not exceed -0.2%, an arbitrary cut-off value based on a literature-based mean estimate of BVL in healthy adults. Patients were categorised by treatment-group during months 0-24 and according to the following age-groups: 17-30, 31-40, 41-50, and 51-60 years, given the known positive correlation of age with BVL.

**Results:** In all age strata, more fingolimod patients exhibited BVL of less than -0.2% per annum than patients on placebo.

**Conclusions:** The proportion of patients having the least degree of global BVL, comparable to the reported mean of cohorts of healthy adults, was greater with fingolimod than placebo over 2 years. This result was consistent across the age categories assessed.

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OS1115
How to treat MS patients after the 24th natalizumab administration: the TY-STOP trial

1Ospedale S. Luigi Gonzaga Department of Neurology, Orbassano, 2Biostatistics Unit Department of Health Sciences (DISSAL), University of Genoa, Genova, 3University Division of Radiology, Ospedale S. Luigi Gonzaga Department of Oncology, Orbassano, 4Department of Neurosciences, Reproductive and Odontostomatological Sciences, 5Biostructure and Bioimaging Institute of Naples, National Research Council, Federico II University, Napoli, 6Department of Neurology II, A.O.S.Anatone Abate di Gallarate, Multiple Sclerosis Studies Centre, 7Department of Neurology II, Multiple Sclerosis Studies Centre, A.O.S.Antonio Abate di Gallarate, Gallarate, 8Department of Experimental Biomedicine and Clinical Neuroscience, University of Palermo, Section of Neurology, Palermo, 9Hospital of Crema, Crema, 10University of Reggio Emilia, Center for Demyelinating Diseases, Modena, 11Department of Neuroscience, University of Turin, Neurology Division-MS Center, 12Department of Basic Medical Sciences, Neurosciences and Sense Organs. University of Bari Aldo Moro, Bari, Italy

Introduction: Natalizumab is the most effective drug for relapsing-remitting MS but could be associated with progressive multifocal leukoencephalopathy (PML), whose risk increases after 24 natalizumab administrations.

Methods: Spontaneous, prospective, multicenter, observational study to evaluate disease course after the 24th natalizumab administration. Primary outcome: annualized mean relapse rate. Secondary outcomes: annual MRI activity, mean confirmed EDSS at 1 year. Groups of treatment:

(a) 1 relapse while on treatment and radiological activity (≥1 T2-hyperintense or ≥1 gadolinium-enhancing lesions), or
(b) unchanged or increased relapse rate in the 1 year prior to entry into DEFINE/CONFIRM compared with the preceding 2 years.

Results: A total of 475 patients fulfilled IFNβ “non-responder” criteria, including 162, 156, and 157 in the placebo and delayed-release DMF BID and TID groups, respectively. In these patients, at 2 years, the annualized relapse rate was reduced significantly by delayed-release DMF BID (rate ratio [95% confidence interval]: 0.570 [0.388−0.836]; p=0.004) and TID (0.471 [0.316−0.701]; p=0.0002), compared with placebo. Other definitions of IFNβ “non-responders” were defined as having ≥12 months prior treatment with IFNβ and

Conclusions: Patients who interrupted natalizumab developed clinical and radiological disease activity more frequently than those who continued it beyond 24 administrations. Therapeutic decision must take into account two types of risk: disease resumption if natalizumab is stopped; PML development if natalizumab is continued. If PML risk is high, natalizumab should be reasonably stopped; otherwise it should be continued carefully monitoring PML subclinical occurrence.

Disclosure: Nothing to disclose

OS1116
Efficacy of delayed-release dimethyl fumarate for relapsing-remitting multiple sclerosis (RRMS) in “non-responders” to prior treatment with interferon beta

1Department of Neurology, IBIMA (Instituto de Investigacion Biomédica de Málaga), Hospital Regional Universitario, Universidad de Málaga, Málaga, Spain, 2Blizard Institute, Queen Mary University of London, London, United Kingdom, 3Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH, United States, 4Department of Neurology, St Joseph Hospital, Ruhr University, Bochum, Germany, 5Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, TX, 6Biogen Idec Inc., Cambridge, MA, United States

Introduction: A post-hoc analysis of integrated data from the Phase 3 DEFINE and CONFIRM studies was conducted to assess the efficacy of delayed-release dimethyl fumarate (DMF) over 2 years in RRMS patients who were considered “non-responders” to prior treatment with interferon beta (IFNβ) before randomization in DEFINE/CONFIRM.

Methods: Eligibility criteria for DEFINE and CONFIRM included age 18-55 years, RRMS diagnosis (McDonald criteria), and EDSS score 0-5.0. Patients were randomized to receive placebo (n=771), delayed-release DMF 240mg twice (BID; n=769) or three times daily (TID; n=761), or glatiramer acetate (CONFIRM only; n=350), for up to 96 weeks. For this analysis, IFNβ “non-responders” were defined as having ≥12 months prior treatment with IFNβ and

Conclusions: These results suggest that delayed-release DMF demonstrates significant efficacy in IFNβ “non-responders.” The magnitude of the effect is similar to that seen in the overall intent-to-treat population of DEFINE/CONFIRM.

Disclosure: Study supported by: Biogen Idec, Inc.
OS1117

Cortical thickness and cortical surface area relate to specific symptoms in early multiple sclerosis


1Dept of Neurology, Oslo University Hospital, 2Institute of Clinical Medicine, 3Institute of Psychology, University of Oslo, 4Dept of Radiology, Oslo University Hospital, Oslo, Norway, 5Dept of Neurobiology, Karolinska Institutet, Stockholm, Sweden

Introduction: The relation between the clinical manifestations of early relapsing remitting Multiple Sclerosis (RR MS) and structural cortical changes are poorly characterised. Our objectives were to investigate the difference in cortical structure between recently diagnosed RR MS patients and healthy controls, and to investigate the relation between cortical structure and the different manifestations of the disease.

Methods: Patients diagnosed with RR MS within the last three years underwent MRI, neurological and neuropsychological examinations. Cortical surface area, thickness and volumes were estimated based on 3D T1 MRIs from 61 RR MS patients and 61 matched controls. General linear models were used to compare the patients and controls and to study the relation between neurological disability, cognition, fatigue and depressive symptoms and cortical structure within the patient group.

Results: We found widespread differences in cortical thickness and a 6.5 % (p<0.001) smaller cortical volume, but no difference in cortical surface area, between the groups. Within the patient group we identified large regions, mainly of the frontal lobes, with higher depression scores related to a smaller cortical surface area and volume. Neurological disability was related to regionally reduced cortical thickness, while better verbal memory was associated with regionally larger surface area. Fatigue was associated with regionally smaller cortical volume.

Conclusion: Cortical thickness reduction represents the primary change of cortical morphology in RR MS. We identify specific structural correlates to the main clinical manifestations in early RR MS, emphasizing the relevance of both cortical thickness and surface area in explaining these symptoms.

Disclosure: Nothing to disclose

OS1118

A subgroup meta-analysis of multiple sclerosis clinical trials

A. Signori, M.P. Sormani

Department of Health Sciences, University of Genova, Genova, Italy

Introduction: The object of this work was to evaluate whether there are subgroups of relapsing-remitting (RR) multiple sclerosis (MS) patients that are more responsive to treatments.

Methods: We collected all published randomized clinical trials in RRMS reporting a subgroup analysis, that is, an assessment of the treatment effect in different subgroups of patients defined according to baseline characteristics (sex, age, baseline Expanded Disability Status Scale (EDSS), relapse history, previous treatments, presence of Gadolinium enhancing lesions and T2 lesion volume on the baseline MRI scan). The primary outcome of the analysis was the treatment effect on the annualized relapse rate (ARR). The treatment effect in each subgroup was rescaled to the overall treatment effect size and reported as a relative contribution to the treatment specific effect. The subgroup specific treatment effects were combined in a meta-analysis weighted by the inverse of variance.

Results: Seven trials including a total of 7037 RRMS patients were included in the meta-analysis. Pooled treatment effects on ARR resulted to be significantly higher in younger subjects (p<0.0001), in patients with lower baseline EDSS (p=0.013), in patients with baseline Gd+ enhancing activity (p<0.001) and with high T2 lesion load (p=0.04). No differences of treatment effect was detected among groups defined by different gender, relapse history or history of previous treatment.

Conclusions: This study shows in a formal way that in RRMS, higher treatment effects are associated to characteristics of an earlier (age and EDSS) and more active (Gd+ and T2 activity) disease.

Disclosure: Nothing to disclose
Neurorehabilitation I

OS1119

Brain structural and functional changes after action observation therapy in Parkinson's disease patients with freezing of gait

F. Agosta¹, E. Canu¹, E. Sarasso², M. Gemma³, A. Meani¹, M.A. Volontè¹, L. Sarro¹, S. Galantucci¹, A. Falini⁴, G. Comi³, R. Gatti², M. Filippi¹,³
¹Neuroimaging Research Unit, Institute of Experimental Neurology, ²Laboratory of Movement Analysis, ³Department of Neurology, ⁴Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To assess brain functional and structural changes following action observation therapy (AOT) in Parkinson's disease patients with freezing of gait (PD-FoG).

Methods: 20 PD-FoG patients underwent a 4-week (W4) rehabilitation training. Subjects were randomized into 2 groups: in AOT-group, therapy consisted of AO combined with practicing the observed actions; control-group performed the same training combined with landscape-videos observation. At baseline (T0) and W4, patients underwent: clinical evaluations, 3D-T1-weighted and functional MRI (fMRI tasks: foot simple-movement; observation of videos showing a man in circumstances precipitating FoG; motor imagery as in observation task). Clinical assessments were repeated at week 8 (W8).

Results: At W4, both groups showed reduced FoG severity and walking speed improvement. AOT-group showed additional UPDRSIII, balance, and QoL improvements. At W8, motor improvements were confirmed in both groups, while positive effects on UPDRSIII and QoL were observed in AOT-group only. At W4, AOT was associated with increased cerebellar and parietal grey matter (GM) volumes; in control-group, an increased primary motor cortex (PMC) volume was observed bilaterally. FMRI showed that AOT was associated with increased recruitment of PMC/premotor cortex, mirror neuron system (MNS) and caudate nucleus bilaterally during simple-motor/imagery tasks. At W4, control-group showed reduced PMC recruitment during all tasks. In both groups, structural and functional brain changes correlated with W4 clinical improvements and predicted clinical evolution at W8.

Conclusions: AOT has a positive additional effect on walking ability recovery of PD-FoG patients. In PD, AOT promotes brain structural/functional plasticity of both the primary sensorimotor and MNS.

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OS1121

Systematic review of the influence of spasticity on quality of life in adults with chronic neurological conditions

K. Milinis¹, C.A. Young¹,², Trajectories of Outcome in Neurological Conditions (TONiC)
¹University of Liverpool, ²The Walton Centre NHS Foundation Trust, Liverpool, United Kingdom

Introduction: Spasticity is a common and often long term symptom in several chronic neurological conditions. Our aim was to conduct a systematic review of the published evidence on the relationship between spasticity and quality of life (QOL).

Methods: MEDLINE, Embase, CINAHL and PsycINFO databases were searched using keywords ‘spasticity’ and ‘quality of life’.

Results: 17/551 studies met inclusion criteria for review. These examined the relationship between spasticity and QOL in multiple sclerosis (MS), spinal cord injury (SCI) and stroke. Spasticity was found to be associated with significantly lower scores on health status measures, namely SF-12, SF-36 and EQ-5D, in MS and SCI, but less so in stroke. Spasticity was associated with considerably lower scores on physical components of the health status questionnaires, but with only marginally lower scores on mental components. The studies that employed global QOL measures such as the World Health Organisation Quality of Life - BREF found no significant relationship between spasticity and QOL. Spasticity was often associated with pain, sleep problems, fatigue and urinary dysfunction. A single study in spinal cord injury found spasticity to be an insignificant predictor of HRQOL after accounting for these factors.

Conclusions: Spasticity is associated with worse health status, but not with overall QOL. The relationship between spasticity and QOL is confounded by associated other symptoms. Future studies should account for this, in these conditions and also in the many other spasticity-causing disorders not yet studied.

Disclosure: Nothing to disclose

OS1122

Comparing unilateral and bilateral computer-supported arm training for the severely affected arm after stroke

C.I.E. Renner, C. Brendel, R. Ludwig, H. Hummelsheim Neurologisches Rehabilitationszentrum Leipzig-Bennewitz, Universität Leipzig, Bennewitz, Germany

Introduction: Functional recovery after stroke depends on brain plasticity. Ipsilesional and bihemispheric reorganization have been documented. In addition stroke patients experience an increased inhibitory influence from the contralesional to the ipsilesional motor cortex. Yet there is evidence that patients benefit from both bilateral and unilateral arm training. Therefore we compared the effects of bilateral versus unilateral computer-supported arm training on motor recovery in severely affected subacute stroke patients.

Methods: 38 patients with a severe arm paresis (Fugl-Meyer-Score for the arm (FMA) less than 18) were recruited for this randomized single-blinded study. The bilateral arm training entailed a repetitive training on an “arm-bicycle” followed by synchronized bilateral repetitive hand training. The unilateral arm training was identical but performed by the paretic limb only. Both trainings were administered twice daily over six weeks and incorporated shaping elements. Main outcome measures included the FMA and biomechanical parameters (hand grip-, hand extension-, elbow flexion- and elbow extension isometric force and rate of force generation), assessed at the beginning, after 6 and 8 weeks.

Results: Both groups improved significantly over time regarding the FMA and all biomechanical parameters. There was a significantly greater improvement following the bilateral training in FMA (p= 0.04) and isometric force of hand grip and hand extension (p= 0.04) compared to the unilateral training.

Conclusions: Bilateral computer-supported arm training followed by repetitive bilateral hand training leads to greater improvements in motor control and force of the severely paretic upper limb compared to the unilateral version of the same training.

Disclosure: Nothing to disclose
OS1123

Social networks and multiple sclerosis: an Italian experience

L. Lavorgna1, M. de Stefano1, D. Buonanno1, S. Eboli2, A. Gallo1, S. Bonavita1, G. Tedeschi1
1Dipartimento di Scienze Mediche, Chirurgiche, Neurologiche, Metaboliche e dell’Invecchiamento, Second University of Naples, 2Private, Naples, Italy

Introduction: The aim of blogs and websites on Multiple Sclerosis (MS) is connecting people and sharing information that acquire assertive importance even not referring to scientific references. Social-network MS users/patients are generally informed about the disease but are also influenced by false hopes arising from wrong information, myths and not scientifically proven therapeutic approaches. Our aim was to create a MS web-community to facilitate the sharing of information, monitored by a doctor and based on scientific rigor.

Methods: www.smsocialnetwork.com gives the opportunity to its users to publicly or privately interact using chat, messages and community wall. All the users can even contact doctors, psychologists and, through the streaming page, watch outpatient visits and medical conferences.

Results: Started in March 2012, our web-community includes over 5,500 visitors and over 800 registered users. The total number of pages viewed is 132,937. After 19 months, we can clearly distinguish two macrogroups of users: A (leaders) and B (receivers). In group A there are users who propose innovations and suggestions and in group B there are users who share, partially approve or reject these standpoints.

Conclusions: The aim of the team of smsocialnetwork.com was to monitor and promote interactions between patients, controlling that information sharing was based on current medical science. In line with our aim, we have obtained that Group A is driven by common sense and wise use of the network. In the internet emotions often prevail on rationality, but we have tried not to make them necessarily acquire a clinic value.

Disclosure: Nothing to disclose

OS1124

Living independently with intensive support (WmI): long-term results of a new housing project for people with severe disabilities in Germany

K. Wolf-Ostermann, J. Gräske
Alice Salomon University Berlin, Berlin, Germany

Introduction: In 2009 the Fürst-Donnersmarck-Foundation launched a new housing project in Berlin/Germany for people with severe disabilities caused by acquired brain injuries. Residents from a permanent residential living facility (LTC) are offered the opportunity to move into newly built supported living accommodations (SLA) with a 24/7 individual support. The aim of the study is to investigate effects of SLA on residents’ social and health-related outcomes.

Methods: In a longitudinal design residents in two SLA and one LTC were surveyed at baseline and follow-up after 6, 12 and 36 months. Considered outcomes are perceived disability (WHODAS II), ADL-functioning (EBI), needs of assistance (Metzler), quality of life (WHOQoL-Bref, EQ-5D), anxiety and depression (HADS-D), sense of mastery (Pearlin Mastery Scale) and social contacts.

Results: 40 residents (average age 46.2 years) were included into the study, 29 of them moved into SLA. During the study perceived disability (WHODAS II) as well as ADL-functioning (EBI) worsened significantly but we could not show differences between groups (mixed model p>0.05). Changes in quality of life (WHOQoL-Bref, EQ-5D) could not be shown in general (mixed models p>0.05). The perceived sense of mastery (Pearlin Mastery Scale) increased significantly and showed more positive developments in SLA. Everyday activities in SLA increased to a large extent.

Conclusions: Some positive but no overall effects of moving into SLA could be shown. The new housing project offers residents of LTC with multiple severe disabilities the chance of a more self-determined life and of active participation in new social networks.

Disclosure: Nothing to disclose
Sleep disorders

OS1125

The evolution of REM sleep behaviour disorder in Parkinson’s disease patients with Parkin mutations: a report from the DeNoPa cohort

F. Sixel-Doering¹, M. Canelo¹, K. Lohmann², C. Klein², B. Mollenhauer³, C. Trenkwalder¹

¹Neurology, Paracelsus-Elena-Klinik, Kassel, ²Neurology, University of Lübeck, Lübeck, Germany

Objective: We analyzed the occurrence of REM sleep behaviour disorder (RBD) and REM without atonia (RWA) in Parkinson’s disease (PD) patients with heterozygous Parkin mutations at baseline and at follow up after 2 years.

Patients and methods: In 159 de novo PD patients (DeNoPa cohort) we performed multiplex ligation-dependent probe analysis to test for exon rearrangements in various genes frequently associated with PD. In individuals found to carry an exon rearrangement in the Parkin gene in the heterozygous state, all 12 Parkin exons were sequenced. Video-supported PSG (vPSG) was performed in all patients on two consecutive nights at baseline and after 2 years for identification of RBD and for measuring REM without atonia (RWA).

Results: We identified 6/159 (4%) de novo PD patients with heterozygous Parkin mutations. At baseline, mean age was 63.3±11.5 yrs. (range 48 - 76) and Hoehn & Yahr stage was determined at 1.3±0.27 (range 1.0 - 1.5). At baseline, none of the Parkin mutation carriers, but 40 out of 152 (26%) non-carriers were identified with RBD, RWA values were 5.9±3.9% (range 0.7 - 11.1%). After 2 years, 1/6 Parkin PD patients showed mild RBD and one Parkin PD patient had developed excessive RWA measured at 55.7%.

Conclusion: In this small cohort of 6 patients with heterozygous Parkin mutations we identified a possibly smaller proportion of RBD both at baseline and after 2 years compared to the remaining 152 PD patients of the DeNoPa cohort.

Disclosure: Nothing to disclose

OS1126

Resting muscle sympathetic activity and blood pressure during wake in narcolepsy with cataplexy patients

V. Donadio¹, R. Liguori², S. Vandi², F. Pizza², Y. Dauvilliers³, M.P. Giannoccaro², V. Leta¹, A. Baruzzi¹, G. Plazzi²

¹IRCCS Istituto delle Scienze Neurologiche, ²Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy, ³Centre de Référence National sur les Maladies Rares, Service de Neurologie, Unité des Troubles du Sommeil, Hôpital Gui-de-Chauliac, INSERM U 1061, Montpellier, France

Introduction: Conflicting data have been reported on resting autonomic tone in narcolepsy with cataplexy (NC) including both reduced or increased sympathetic activity. If confirmed, increased sympathetic activity may represent an additional cardiovascular risk factor for NC patients usually presenting obesity, diabetes, sleep apnea and metabolic syndrome. In order to settle this important point we aimed to measure the resting sympathetic and cardiovascular activities in NC patients by direct microneurographic monitoring of muscle nerve sympathetic activity (MSNA) during wakefulness.

Methods: We studied 19 untreated patients with established criteria for NC and hypocretin deficiency, and 19 sex and age matched healthy subjects. Subjects underwent resting microneurographic recording of MSNA from peroneal nerve whereas blood pressure (BP) was measured with a sphygmomanometer after the end of microneurographic recording. The awake state was continuously monitored by an ambulatory polygraphic recorder.

Results: NC patients displayed significantly lower resting MSNA, HR and BP values than controls. Pearson regression analysis showed a significant correlation between CSF hypocretin-1 level and MSNA or HR whereas no correlation was found with BP; however patients with virtually absent hypocretin-1 displayed lower BP than patients with the highest hypocretin-1 value.

Conclusions:

1) NC patients displayed decreased resting MSNA, HR and BP during wakefulness lowering their cardiovascular risk profile;
2) a positive correlation supported a direct effect of CSF hypocretin-1 deficiency on MSNA or HR regulation;
3) although hypocretin-1 was not correlated with BP, patients with absent hypocretin-1 had lower BP.

Disclosure: Nothing to disclose
OS1127
Selective activation of LH GABA->RTN circuit induces rapid arousal
C. Gutierrez Herrera1,2, S. Jego2, J. Colby-Milley2, A. Adamantidis1,2
1Neurology, University of Bern, Inselspital Bern, Bern, Switzerland, 2Psychiatry, McGill University, Montreal, QC, Canada

Introduction: The sleep-wake cycle is a highly conserved physiological process across all vertebrates that result from a complex, yet undefined, inhibitory/excitatory balance between neural circuits distributed throughout the brain. Here, we investigate the role of inhibitory cells from the lateral hypothalamus (LH) on sleep-wake states.

Methods: We targeted the expression channelrhodopsin-2 (ChETA) to the LH-GABA cells in VGAT::Cre mice. Chronic EEG/EMG recordings were use to characterize changes in their sleep/wake cycles in response to bilateral optogenetic stimulation.

Results: First, we identified anatomical and functional connections between LH-GABA neurons and neurons located in the septum, periaqueductal grey area, ventral-tegmental area, locus coeruleus, ventral tegmental area and reticular thalamic nucleus (RTN). We then, using a semi-chronic activation (1-20 Hz, 10 s every minute over 1 h), show that LH-GABA cells at 20 Hz, but not 1 Hz, resulted in a 2-fold increase in wake duration. We further found that a 10 s single stimulation of LH-GABA cells at 1-20 Hz, induces a rapid switch from NREM, but not REM, sleep to wakefulness (<2 s) in ChETA compare to control animals. Local optical activation of LH GABA terminals in the RTN induced GABAA-mediated IPSCs in reticular neurons in vitro, and desynchronisation of cortico-thalamic loops.

Conclusion: Collectively, our results suggest that activation of a subpopulation of LH-GABA neurons induces rapid arousal from sleep, through inhibition of RTN cells and subsequent re-activation of thalamo-cortical loops, revealing a new hypothalamic -thalamic circuit for modulation of arousal, as well as somatosensory inputs during sleep.

Disclosure: Nothing to disclose

OS1128
Impact of sleep apnea on mean blood pressure and blood pressure variability in patients with acute and chronic ischemic stroke or TIA (SAS-CARE study)
T. Horvath1, U. Fischer1, S. Ott2, S. Schroth1, C. Cereda3, M. Manconi3, G. Moschovitis4, C.L. Bassetti1
1Department of Neurology, Sleep-Wake-Epilepsy and Stroke Centers, University Hospital Inselspital, 2Department of Pneumology, University Hospital Inselspital, Bern, 3Department of Neurology, 4Department of Cardiology, Stroke Center, Lugano, Switzerland

Introduction: Sleep apnea (SA) is an independent risk factor for both stroke and hypertension. Previous studies have shown a correlation between severe SA and increased blood pressure (BP) after acute stroke in small cohorts. The aim of this multicenter prospective study (SAS-CARE) was to assess the impact of SA on mean BP and BP variability in patients with stroke/TIA.

Methods: We assessed 115 patients with acute (within 96 hours) and 115 patients with chronic (after 60-90 days) stroke/TIA from two centers (Bern/Lugano). Polysomnography and 24-hour-BP-monitoring were performed within 7 and after 60-90 days. SA was defined by an apnea-hypopnea-index (AHI) ≥10/h. Mean, maximum and minimum systolic and diastolic BP readings were assessed. Short-term BP variability was defined as standard deviation (SD) and coefficient of variation (CV). Non-dipping-state (NDS) was defined as ratio >0.9 of mean systolic diurnal/mean systolic nocturnal.

Results: SA was detected in 72 patients (63%) in the acute and in 69 (59%) in the chronic phase. NDS was present in 75 patients (65%) in the acute and in 72 (63%) in the chronic phase. Mean systolic BP correlated with AHI in the acute phase (r=0.191; p=0.042), mean and maximum systolic BP with AHI in the chronic phase (mean: r=0.344, p=0.001; max: r=0.313, p=0.001). Systolic BP-variability and AHI correlated in the chronic, but not in the acute phase (r=0.240, p=0.01).

Conclusion: There is a correlation of mean systolic BP and BP-variability with AHI in patients with chronic stroke/TIA. This correlation has potential clinical implications on early intervention strategies.

Disclosure: Nothing to disclose
OS1129
Role of DA-ergic therapy on REM sleep behaviour disorder in a large population of PD patients

L. Laccu1, P. Congiu1, M. Figorilli1, A. Cannas2, G. Gioi1, F. Marrosu1, M. Puligheddu1, Sleep Center Neurophysiology Unit University of Cagliari, Italy
1Sleep Center Neurophysiology Unit, 2Extrapyramidal Disease Unit, 3Neurology and Neurophysiopathology Department, Cagliari, Italy

Introduction: Patients with Parkinson’s disease usually complain of a wide range of parasomnia most of them related to rapid eye movements sleep behaviour disorder (RBD). This study is aimed to investigate clinical features of RBD which allows to report its prevalence in these patients and whether DA-ergic therapy plays a role in its pathophysiology.

Methods: 261 subjects (mean age 68.7±13.4) affected by Parkinsonism were consecutively recruited. Among them, 86 patients were Naive without any DAergic treatment. Clinical sleep scoring was realized by using PDSS, the RBD screening questionnaire, UPDRS and H&Y scores. According to treatment, patients were grouped in non-DAergic therapy (n=86); only L-dopa (n=87); exclusively Dopamine-agonist (n=30) and combined L-dopa + Da-agonist therapy (n=58). Non-parametric Kruskal-Wallis test was used for the four categories.

Results: Parasomnias were evident in 70.2% of the total patients and specifically 62.45% were positive to RBD score. No significant correlation was found between DAergic and non-DAergic therapy in the RBD group, neither significant correlation was found in respect to H&Y score. As expected, RBD is not related to stage of PD. Nonetheless, therapy stratification surprisingly showed direct effect connected with L-dopa therapy, with a significant highest RBD-score in respect to no-therapy subjects (p=0.019).

Conclusions: The role of L-DOPA treatment seems crucial in this observational study with an enhancing/inducing effect; however, Da-agonists seem to modulate and attenuate clinical manifestations of RBD. Further studies, longitudinal follow up monitor and possible investigations on animal models are required for the adequate comprehension of the subtended mechanism.

Disclosure: Nothing to disclose

OS1130
A novel NREM and REM parasomnia with sleep breathing disorder associated with antibodies against IgLON5: a case series, pathological features, and characterization of the antigen

J. Santamaria Cano1,2, L. Sabater3, C. Gaig3,4, E. Gelpi3,5, L. Bataller6, A. Iranzo7,9, J. Lewerenz7, E. Torres-Vega8, A. Contreras9, B. Giometto10, Y. Compta4, C. Embid11, I. Vilaesc3,3, J. Dalmau13,14, F. Graus1,3
1Department of Neurology, Hospital Clinica de Barcelona, 2Multidisciplinary Sleep Disorders Unit, Hospital Clinic, 3Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 4Department of Neurology, Hospital Clinic, 5Neurological Tissue Bank of the Biobanc-Hospital Clinic-IDIBAPS, Barcelona, 6Department of Neurology, Hospital Universitari i Politécnic La Fe, Valencia, Spain, 7Department of Neurology, Ulm University, Ulm, Germany, 8Instituto de Investigación Sanitaria La Fe, Valencia, 9Department of Neurology, Hospital Morales Meseguer, Murcia, Spain, 10Department of Neurology, Regional Hospital ‘Ca’ Foscari’, Treviso, Italy, 11Department of Respiratory Diseases, Hospital Clinic, 12Department of Ear Nose and Throat, Hospital Clinic, Barcelona, Spain, 13Department of Neurology, University of Pennsylvania, Philadelphia, PA, United States, 14Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Introduction: We describe the clinical, video-polysonmographic and neuropathological features of an unrecognized disorder characterized by prominent sleep symptoms and antibodies against a novel cell-surface protein named IgLON5.

Methods: Eight patients with antibodies showing similar reactivity with neuropil of rat brain underwent PSG and two had brain postmortem examination. Immunoprecipitation and mass spectrometry identified the novel antigen.

Results: All eight patients (five women; age range: 52-76 years) had abnormal sleep movements and behaviors along with obstructive sleep apnea. Five patients underwent video-polysomnography showing stridor, obstructive sleep apnea, undifferentiated NREM sleep and poorly structured N2 sleep with frequent simple movements and finalistic-purposeful behaviors and REM sleep behavior disorder. Normalization of NREM sleep characteristically occurred in the last part of the night. Clinical course was protracted in 6 (median: 5 years, range 2-12 years); in four the sleep disorder was the initial symptom, and in two it was preceded by progressive gait instability, and subsequently accompanied by dysarthria, dysphagia, and chorea. Two patients had a rapid presentation of the sleep disorder (2-6 months) with disequilibrium, dysarthria, dysphagia, and central hypoventilation. Sudden death occurred in six patients (median time from symptom onset: 3.5 years). Neuropathological examination showed a novel neuronal taupathy mainly involving the tegmentum of the brainstem and hypothalamus. All patients had serum and CSF antibodies against an extracellular epitope of IgLON5, a cell-adhesion molecule involved in synaptogenesis.

Conclusions: IgLON5-antibodies identify a unique NREM and REM parasomnia with sleep breathing dysfunction and pathological features suggesting a novel tauopathy, linking autoimmunity and neurodegeneration.

Disclosure: Nothing to disclose
Ageing and dementia 2

OS1201

Selective affection of hippocampal subfields in pre-dementia is related to spinal fluid amyloidbeta and tau

I.S. Almdahl¹, P. Selnes¹, K.K. Johansen¹, J. Saltye-Benth²,³, T. Fladby¹,³

¹Department of Neurology, ²Akershus University Hospital, ³Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Introduction: Early etiological diagnosis of cognitive impairment depends on precise characterization of regional neurodegenerative changes. We hypothesize that hippocampal subfields are selectively affected in subjective and mild cognitive impairment (SCI and MCI), and that it's related to established pathological mechanisms in Alzheimer's disease.

Methods: 159 cases, 81 MCI, 32 SCI and 46 controls (NC) were included in this cross-sectional study. MRI volume measures of hippocampal subfields were obtained using FreeSurfer, and patients underwent lumbar puncture for spinal fluid biomarkers (CSF Abeta42, T-tau and P-tau). Cluster analysis was performed on MRI data, and MANOVA-tests used for multiple comparisons. Subsequently, regression analyses were used to predict effects of CSF biomarkers on volumes in the subgroups.

Results: CSF Abeta42 was a significant predictor of presubiculum (p<0.005), subiculum (p<0.05) and hippocampal volumes (p<0.05) in SCI, whereas T-tau was the best predictor for subfield volumes in MCI. Volumes of hippocampus (p<0.001), presubiculum (p<0.001), subiculum (p<0.001), CA2-3 (p=0.002) and CA4-DG (p=0.005) and entorhinal cortex thickness (p<0.001) were significantly different between MCI and NC. CA1 volumes did not differ between groups, and no volumes were significantly different between NC and SCI.

Conclusions: No significant volume loss is observed at the SCI stage (as compared to NC), but hippocampal subfield volumes are best predicted by levels of CSF Abeta42. Volume loss has occurred at the MCI stage and is best predicted by levels of tau. This is in accord with amyloid dysmetabolism as an early event in cognitive impairment and dementia.

Disclosure: Nothing to disclose

OS1202

The effect of age of onset on the brain functional connectivity in Alzheimer's disease: a graph analysis study

E. Canu¹, F. Agosta¹, S. Galantucci¹, A. Meani¹, G. Magnani², F. Caso¹, A. Marcone³, A. Falini¹, G. Comi², M. Filippi¹,²

¹Neuroimaging Research Unit, Institute of Experimental Neurology, ²Department of Neurology, ³Department of Clinical Neurosciences, ⁴Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To examine the relation between the topological organization of functional brain networks and the age of onset in patients with Alzheimer’s disease (AD) using a network-based approach.

Methods: Graph theoretical analysis was applied to resting state fMRI from 36 late onset AD (LOAD) patients, 23 early onset (EOAD) patients and two groups of old and young healthy individuals. Measures of global and local network organization were obtained.

Results: Small-worldness was verified in controls and patients. Globally, the functional brain networks of LOAD patients were characterized by a significantly lower local and global efficiency, lower clustering coefficient and higher assortativity compared with age-matched controls. In contrast, functional brain networks of EOAD patients were characterized by a significantly higher hierarchy and lower assortativity compared with age-matched controls. Locally, lower nodal degree and local efficiency, and higher betweenness centrality were observed in both AD groups compared to the age-matched controls. However, while LOAD showed local alterations (in terms of decreased nodal degree and increased betweenness centrality) in the medial temporal, parietal and occipital lobes, EOAD patients showed a widespread pattern of damage involving also the frontal regions.

Conclusions: Graph analysis showed that global functional network organization was abnormal in AD patients. Compared to LOAD, the EOAD patients showed a widespread pattern of local network alterations involving also the frontal regions. The topological differences between patient groups may represent the effect of age of onset on functional connections.

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OS1203

Cardiovascular medication burden in dementia disorders: a nationwide study of 19,743 dementia patients included in the Swedish Dementia Registry (SveDem)

P. Cermáková1,2, S.-M. Fereshtehnejad3, K. Johnell4, M. Eriksdotter3, D. Religa1
1KI-ADRC, NVS, Karolinska Institutet, Stockholm, Sweden, 2ICRC, Brno, Czech Republic, 3Division of Clinical Geriatrics, NVS, Karolinska Institutet, 4Aging Research Center, Karolinska Institutet and Stockholm University, Stockholm, Sweden

Introduction: We aimed to investigate whether there are differences in the use of cardiovascular (CV) medication (as a proxy for CV disease) between different dementia disorders

Methods: Data come from Swedish Dementia Registry (SveDem). Patients were diagnosed with one of following dementia disorders: Alzheimer’s disease (n=8,139), mixed dementia (n=5,203), vascular dementia (n=4,982), Lewy body dementia (n=605), frontotemporal dementia (n=409) and Parkinson’s disease dementia (n=405). Multivariate logistic regression analysis was performed to investigate the association between dementia disorders and the use of CV medication, after adjustment for age, gender, living condition, MMSE score and total number of drugs (a proxy for overall co-morbidity).

Results: Seventy percent of all patients use CV medication. CV drugs are prescribed to more than 50% of patients diagnosed with each dementia disorder. The use of CV medication has been found related especially to vascular and mixed dementia compared to other dementia disorders. On the other hand, the use of CV drugs lowers the probability of being diagnosed with Alzheimer’s disease and Parkinson’s disease dementia. Male gender correlated with a higher risk of using CV medication compared to women. Living alone has been found negatively associated with the use of CV drugs.

Conclusions: In clinical reality, the burden of CV disorders in dementia is large in all dementia types, with predominance in vascular and mixed dementia.

Disclosure: Nothing to disclose

OS1204

Circulating and intrathecal miRNAs as potential biomarkers for Alzheimer’s disease

D. Galimberti1,2, C. Fenoglio1,2, C. Villa1,2, M. Serpente1,2, R. Bonsi1,2, S.M. Cioffi1,2, L. Ghezzi1,2, A. Arighi1,2, P. Basilico1,2, A. Callea2, E. Scarpini1,2
1University of Milan, 2Fondazione Ca’ Granda, Ospedale Policlinico, Milan, Italy

Introduction: Circulating micro(mi)RNAs have been reported as promising biomarkers with great accuracy for neurodegenerative disorders and processes affecting the central nervous system (CNS), especially in aging, Parkinson’s disease and multiple sclerosis. Aim of this study is to identify specific circulating miRNAs in serum as possible biomarkers for Alzheimer’s disease (AD).

Methods: A specific PCR array containing 84 common miRNAs was initially used to screen miRNA serum levels in 7 patients with AD and 6 non-inflammatory neurological controls (NINDCs). Best hits were first validated by real time PCR in an independent cohort consisting of 15 serum samples from AD patients and 12 NINDCs, comparing them also to 10 subjects affected by frontotemporal lobar degeneration (FTLD) and 8 inflammatory neurological controls (INDCs). Finally, the same analysis was conducted also in samples of cerebrospinal fluid (CSF).

Results: Statistically significant decreased levels of miR-125b, miR-223, miR-23a and miR-26b were observed in AD patients compared to NINDCs (-5.5, -4.5, -5.0 and -6.3 fold regulation over NINDCs respectively, p<0.050). MiR-125b, miR-223 and miR-26b were then validated both in serum and CSF (p<0.050), while miR-23a failed to be replicated in CSF. Moreover, miR-223 was also found down-regulated both in serum and CSF from FTLD patients (p<0.050).

Conclusions: Our findings suggest a potential use of circulating miRNAs, along with other markers, as non-invasive, relatively inexpensive and peripheral biomarkers for AD diagnosis.

Disclosure: Nothing to disclose
OS1205

Beyond visual deficits: motor features and associated atrophy patterns in posterior cortical atrophy

N.S. Ryan¹, T.J. Shakespeare², M. Lehmann², S. Keihaninejad², J.M. Nicholas²-³, K.K. Leung², N.C. Fox², S.J. Crutch²
¹Dementia Research Centre, University College London (UCL) Institute of Neurology, ²Dementia Research Centre, UCL Institute of Neurology, ³Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom

Introduction: Posterior cortical atrophy (PCA) is a neurodegenerative syndrome which is typically but not exclusively caused by Alzheimer’s disease (AD). Clinically, it is characterised by impaired higher visual processing, literacy and numeracy skills, however motor features more commonly associated with corticobasal syndrome (CBS) may also occur. This study investigated the frequency, clinical characteristics and neuroimaging correlates of motor features in a cohort of 44 PCA patients.

Methods: Clinical, neuropsychological, genetic and pathological data from the cohort were reviewed and the presence of prominent limb rigidity used to define a PCA+CBS subgroup. MRI brain scans of the two patient subgroups and 30 healthy controls were compared using voxel-based morphometry, cortical thickness and subcortical region of interest volumetric analyses.

Results: In this PCA cohort, 30% (13) had PCA+CBS; all demonstrating asymmetrical left upper limb rigidity. Limb apraxia was more frequent and asymmetrical in PCA+CBS, as was myoclonus. Tremor and alien limb phenomena only occurred in this subgroup. The subgroups did not differ in neuropsychological test performance or Apolipoprotein E4 allele frequency. Greater asymmetry of atrophy occurred in PCA+CBS, particularly involving right frontoparietal and peri-rolandic cortices, putamen and thalamus. The nine patients (including four PCA+CBS) with pathology or CSF all showed evidence of AD.

Conclusions: Our data suggest that PCA patients with motor features have greater atrophy of contralateral sensorimotor areas but are still likely to have underlying AD. Appreciation that PCA presentations of AD may include motor aspects of CBS is important to ensure that these patients receive appropriate treatment options.

 Disclosure: Nothing to disclose

OS1206

Abstract withdrawn
Movement disorders I

OS1207

Brain functional connectomics in early Parkinson’s disease

S. Galantucci1, F. Agosta1, I. Stankovic2, A. Meani1, I. Petrovic1, M. Svetel2, V.S. Kostic2, M. Filippi1,3
1Neuroimaging Research Unit, Institute of Experimental Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy. 2Clinic of Neurology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 3Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To explore the integrity of the functional brain connectome in patients at different stages of Parkinson’s disease (PD).

Methods: Graph theoretical analysis was applied to resting state fMRI data from 212 PD patients (100: Hoehn and Yahr score [HY]=1-1.5; 54: HY=2-2.5; 44: HY=3-3.5; 14: HY=4-5) and 46 controls (HC). Measures of global and regional network properties were obtained. Correlations between UPDRSIII score and network metrics were tested.

Results: Functional brain networks in PD and HC showed the same hub organization, with differences only in the right cingulum, left postcentral gyrus and precuneus bilaterally (hubs only in patients), and right fusiform gyrus (hub only in HC). However, all global network metrics were altered in PD patients. At a regional level, PD patients showed nodal degree reduction and betweenness centrality increase compared with HC. Such local abnormalities were relatively focal in patients with HY=1-1.5, involving the globus pallidus, putamen, supplementary motor area, cingulum, and gyrus rectus bilaterally, spreading to the frontal, temporal, parietal and occipital cortical regions in the more advanced disease stages. In PD, network metrics showed significant correlations with UPDRS III.

Conclusions: In PD, functional brain networks are characterized by an imbalanced structure, with a loss of efficiency in information exchange between both close and distant brain areas. Abnormal functional network connectivity occurs even at the earliest stages of the disease and is an important factor contributing to PD motor deficits.

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OS1208

The first data on retinal optical coherence tomography parameters in Huntington’s disease

S. Kopishinskaya, S. Svetozarskiy, V. Antonova, A. Gustov
Nizhny Novgorod Medical Academy, Nizhny Novgorod, Russian Federation

Introduction: Huntington’s disease (HD) is a severe progressive neurodegenerative disorder. Optical coherence tomography (OCT) is a non-invasive method for retinal structure visualization. The aim of this study was to evaluate the number of retinal OCT parameters in patients with HD.

Methods: We examined 90 participants divided into three groups. The first group consisted of 30 patients with HD clinic expanded, the second group included 30 patients - carriers of the mutant HD gene, the third - control group of 30 healthy patients. The excluding criteria were diabetes mellitus and diagnosed ophthalmological pathology. Three groups of parameters were assessed by the retinal OCT (Cirrus HD-OCT 4000): peripapillary Retinal Nerve Fiber Layer (RNFL) thickness, Ganglion Cell Layer (GCL) characteristics and Macular Thickness.

Results: The healthy control group had no significant pathological changes. Peripapillary RNFL thickness was decreased in 70% patients from the first group and in 40% from the second. GCL damage was registered in both groups with equal frequency (30%). The macular thickness was also decreased in 53% HD clinic expanded patients and in 57% gene carriers. All the patients from the first two groups had abnormalities at least in one of the three retinal parameters, mostly symmetrically.

Conclusions: We have identified a number of pathological changes in the retina in both groups - carriers of the mutant HD gene and patients with HD clinic expanded. Thus, retinal OCT can be served as a new biomarker for neurodegenerative diseases in an early stage.

Disclosure: Nothing to disclose
OS1209

Sensory attenuation in functional movement disorders

Sobell Department of Motor Neuroscience and Movement Disorders, University College London (UCL) Institute of Neurology, London, United Kingdom

Introduction: Sensory attenuation (SA) is the phenomenon whereby self-produced sensation is perceived as reduced in intensity compared to an identical externally produced sensation. This phenomenon has previously been linked to sense of agency for movement.

Objective: Assessment of SA through measurement of sensory evoked potentials (SEPs) at the onset of movement. We hypothesised that patients with functional movement disorders (FMD) have loss of SEPs suppression at the onset of movement as consequence of loss of SA.

Methods: 17 right-handed patients with FMD and 17 right-handed age-matched healthy participants were studied. SEPs were elicited after electrical stimulation of the median nerve at the wrist. EEGs were recorded over the scalp at three sites according to the International 10-20 System (F3, C3 and P3). SEPs were recorded in two conditions: at rest and at the onset of movement.

Results: A repeated measures ANOVA with SEPs ELECTRODE (F3, C3 and P3) as within-subjects factors and DIAGNOSIS as between group factor revealed that there was a significant main effect of GROUP (F(1, 21)=0.8, p=0.000). Post Hoc exploration of this effect revealed it to be due to an absence of SEPs suppression in patients (ratio>1 for all the SEP components) compared to controls, who had SEPs gating (ratio<1 for all the SEP components).

Conclusions: We demonstrate abnormal SEPs suppression at the onset of movement in patients with FMD. We suggest that these results could reflect abnormalities in sensory predictions relating to the expected sensory consequences of voluntary movement, which could be directly related to deficits in sense of agency seen in patients with FMD.

Disclosure: Nothing to disclose

OS1210

Olfactory assessment for predicting transition to neurodegenerative parkinsonian disorders in subjects with idiopathic rapid-eye-movement sleep behaviour disorder: a prospective cohort study

P. Mahlknecht1, K. Seppi1, A. Iranzo2,3, J. Santamaría2,3, E. Tolosa2,3, M. Serradell2,3, B. Högl1, B. Frauscher1, V. Gschliesser1, T. Mitterling1, W. Poewe1, SINBAR (Sleep Innsbruck Barcelona) Group
1Department of Neurology, Medical University Innsbruck, Innsbruck, Austria, 2Neurology Service, Hospital Clinic Barcelona, 3Centro de Investigación Biomédica en Red Enfermedades Neurodegenerativas, Barcelona, Spain

Introduction: Olfactory dysfunction is present in approximately 80% of patients with Parkinson’s disease (PD) and may antedate the onset of classical motor symptoms by years. The latter is also true for idiopathic rapid-eye-movement sleep behaviour disorder (iRBD) and the aim of the present study was to determine the predictive value of olfactory dysfunction for conversion into PD or other types of neurodegeneration in subjects with iRBD.

Methods: A total of 35 polysomnography-confirmed iRBD subjects underwent olfactory testing using the Sniffin’ Sticks test assessing odour-identification, odour-discrimination and threshold at baseline. Subjects were routinely followed-up including a thorough neurological examination for a mean of 4.4 ±standard deviation 0.7 years. The diagnosis of PD and other neurodegenerative parkinsonian disorders was based on current clinical diagnostic criteria.

Results: Overall, 9 subjects developed a neurodegenerative parkinsonian disorder (6 PD and 3 Lewy-body dementia). Receiver operating characteristic curve analysis revealed that baseline olfactory function was predictive for their development with areas under the curve of 0.82 [95% confidence interval (CI), 0.66-0.99] for the entire Sniffin’ Sticks, 0.82 [95%CI, 0.66-0.97] for odour-identification, 0.77 [95%CI, 0.56-0.97] for odour-discrimination and 0.65 [95%CI, 0.39-0.91] for threshold. The relative risk for a neurodegenerative parkinsonian disorder in the lowest tertile of olfactory function was 7.4 [95%CI, 1.9-29.2] compared with the top two tertiles.

Conclusions: Assessment of olfactory dysfunction may help to predict the development of a neurodegenerative parkinsonian disorder in iRBD patients over a short time period.

Disclosure: Nothing to disclose
OS1211

On the basis of reflexive saccadic eye (RS) movements responses machine learning (ML) predicts UPDRS in individual Parkinson’s disease (PD) patients

A.W. Przybyszewski1,2, S. Szlufik3, J. Dutkiewicz3, P. Habela2, D. Koziorowski3

1Neurology, University of Massachusetts Medical School, Worcester, MA, United States, 2Informatics, Polish Japanese Institute of Information Technology, 3Neurology, Faculty of Health Science, Medical University Warsaw, Warsaw, Poland

Introduction: L-DOPA as well as DBS has been shown to improve peripheral motor abnormalities in PD measured as UPDRS. We propose to measure RS in order to find if their parameter correlate with UPDRS.

Methods: We conducted horizontal RS measurements in nine patients with Parkinson’s disease (PD) in four sessions: S1: MedOffDBSOff, S2: MedOffDBSOn, S3: MedOnDBSOff, S4: MedOnDBSOn. Changes of motor performance, behavioral dysfunction, cognitive impairment and functional disability were evaluated in each session according to the UPDRS. RS were recorded by head-mounted saccadometer (Ober Consulting, Poland). ML method was based on RSES 2.2 (Rough System Exploration Program).

Results: The mean age was 51.1±10.2(SD) years, mean disease duration was 11.3±3.2 years, mean UPDRS: S1: 66.6±16.3; S2: 22.3±13.6; mean RS latencies: S1:291.2±93.1ms, S2: 199.6±39.5ms, S3: 232.9±82.7ms; S4: 183.2±30ms. Differences between latencies: S1-S2, and S1-S4 were stat sig (t-test p<0.01), S1-S3 - not stat sig. Similar to differences between UPDRS: S1-S2, and S1-S4 were stat sig (t<0.001) and S1-S3 - not stat sig. Prediction of individual UPDRS values only from RS latencies was not possible (ML). But patient’s age, RS: latency, amplitude, duration give global accuracy in UPDRS prediction 83.3% (ML: cross-validation-method).

Conclusions: ML approach is more precise and powerful than popular statistical methods.

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OS1212

All in the blink of any eye: insights into the pathophysiology of DYT1 and DYT6 dystonia


National Hospital for Neurology and Neurosurgery, Sobell Department of Motor Neuroscience and Movement Disorders, London, United Kingdom

Introduction: Traditionally dystonia has been considered a disorder of basal ganglia dysfunction however recent research has advocated a more complex neuroanatomical network. In particular, there is increasing interest in the pathophysiological role of the cerebellum. Patients with cervical and focal hand dystonia have impaired cerebellar associative learning using the paradigm eye blink conditioning. This is perhaps the most direct evidence to date that the cerebellum is implicated in patients.

Methods: We examined eleven patients with DYT1 dystonia and five patients with DYT6 dystonia and compared rates of eye blink conditioning to age-matched controls. In addition we studied brainstem circuit excitability by testing blink reflex recovery in the same groups.

Results: Patients with DYT1 and DYT6 are both able to acquire eyeblink conditioning to the same ability as age-matched controls. There was evidence of enhanced blink reflex recovery excitability in DYT1 but this effect was not seen in DYT6.

Conclusions: If the cerebellum is an important driver in DYT1 and DYT6 dystonia our data suggest that there is specific cerebellar dysfunction such that the circuits essential for conditioning function normally. In addition, these data are contrary to observations in focal dystonia and suggest that the cerebellum may have a more dominant role in focal subgroups of dystonia. We do not find evidence of enhanced blink reflex recovery in all patients with dystonia and recent studies calling for the blink recovery reflex to be used as a diagnostic test for dystonic tremor may require further corroboration, especially in genetically proven dystonia.

Disclosure: Nothing to disclose
Muscle and neuromuscular junction diseases

OS1213
Myofiber HLA-DR expression: a distinctive biomarker for antisynthetase myositis
J. Aouizerate1, M. De Antonio1, Y. Baba Amer1, R.K. Gherardi1, G. Bassez1, F. Berenbaum2, L. Guillemin1, T. Maisonobe1, O. Benveniste1, F.J. Authier1
1Paris Est University-Creteil, Creteil, 2Université Paris 6, 3Université Paris 5, 4Hôpital Pitié Salpêtrière, Paris, France

Introduction: Idiopathic autoimmune myopathies (IIM) mainly include dermatomyositis (DM), polymyositis (PM), and necrotizing autoimmune myopathy (NAM). Anti-RNA- amino-acylsynthetase (anti-synthetase, AS) autoantibodies are characteristics of a subset of IIM associated with extramuscular features and perimysial pathology. Current diagnostic approaches of IIM require histopathological evaluation of immunological parameters including lymphocyte phenotype, myofiber MHC-1 expression and complement activation (C5b9 formation). In routine practice, we observed myofiber HLA-DR expression seems specifically associated with antisynthetase myositis. In the present work, we evaluated the reliability of HLA-DR expression as a biomarker of antisynthetase myositis.

Methods: We investigated HLA-DR expression in muscle biopsies from 33 patients with AS syndrome (anti-Jo-1: n=26; anti-PL7: n=2; anti-PL12: n=4; anti-EJ:n=1), 16 DM, and 10 histologically normal muscle. For each case, we evaluated (i) the percentage of positive fibers on the whole fascicle, and (ii) the percentage of contiguous positive perifascicular fibers.

Results: HLA-DR myofiber expression was found in 84.8% (28/33) AS patients (anti-Jo1: 88.4%) and in 4/17 (23.5%) patients with DM (p<0.0001). No myofiber HLA-DR expression was found in normal muscles. The mean percentage of positive fibers was 36.3% in AS (40.5% in anti-Jo1) and 6.8% in DM (DM vs AS: p=0.001; DM vs Jo1: p<0.001). All DM had less than 10% DR-positive myofiber. Myofiber HLA-DR expression was observed in perifascicular areas with ribbon-like pattern. The percentage of DR-positive perifascicular contiguous myofibers was 33.4% in AS and 2% in DM (p<0.001).

Conclusions: Myofiber HLA-DR expression is a specific biomarker of anti-synthetase myopathy suggesting a role for INF-γ in its pathophysiology.

Disclosure: Nothing to disclose

OS1214
Autologous transplantation of bone marrow-derived CD133+ stem cells in facioscapulohumeral dystrophy
Y. Torrente1, P. Razini1, M. Belicchi1, A. Mazza2, A. Schiavetta2, R. Giordano3, M. Marconi3, N. Bresolin4
1Department of Pathophysiology and Transplantation, Stem Cell Laboratory, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Centro Dino Ferrari, Università di Milano, Milan, 2Ospedale ‘Santa Corona’ Pietra Ligure, Savona, 3Department of Regenerative Medicine, Center of Transfusion Medicine, Cellular Therapy and Cryobiology, Foundation IRCCS Cà Granda Ospedale Maggiore Policlinico, 4Department of Pathophysiology and Transplantation, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Centro Dino Ferrari, Università di Milano, Milan, Italy

Introduction: Facioscapulohumeral muscular dystrophy is the third most common muscular dystrophy, exhibits autosomal dominant inheritance and has no cure. FSHD typically arises with a reduction of facial and shoulder girdle muscle mass. The disease may extend to abdominal and pelvic girdle muscles impairing the ability to walk. The aim of this open pilot study was to establish the profile of tolerability and clinical response of autologous bone marrow-derived CD133+ stem cells in a cohort of patients affected by facioscapulohumeral muscular dystrophy (FSHD).

Methods: Thirteen patients between 30 and 56 years of age were included in this study and two of them treated with two serial infusions of autologous bone marrow-derived CD133+ stem cells and followed for 1 year. All patients were longitudinally assessed using the 6 minutes walking test (6MWT) and isometric/isokinetic quantitative muscle test (QMT) 6 months before treatment started (T0), at baseline (T1) and 6 and 12 months later.

Results: In treated patients there was no significant change in function between T0 and T1 assessments, but the quantitative scores recorded after 6 and 12 months of treatment were significantly higher than those recorded at baseline (p=0.006). Moreover, the treatment is related to a gain of muscle force unobserved in untreated FSHD patients.

Conclusions: Our results suggest that bone marrow-derived CD133+ stem cells may be beneficial to facioscapulohumeral dystrophic patients without producing any major side effect. Larger prospective randomized, double-blind, placebo controlled trials are needed to confirm these preliminary findings.

Disclosure: Nothing to disclose
OS1215

CD4+ T-cell produced IL17 is essential for loss of B-cell tolerance in experimental autoimmune myasthenia gravis (EAMG)

H. Schaffert1, A. Meisel1, A. Thiel2, S. Kohler1
1Neurocure, 2Berlin Center for Regenerative Therapies (BCRT), Charité Universitätsmedizin Berlin, Berlin, Germany

Introduction: An important contribution of CD4+ T-cell produced IL-17 to autoantibody mediated autoimmune disorders like Myasthenia Gravis has recently been suggested, but never been directly demonstrated.

Methods: We used Experimental Autoimmune Myasthenia Gravis (EAMG) induced by repetitive immunizations with torpedo AchR (tAChR) as a model for a classical autoantibody mediated disease in order to dissect the role of Th17 cells in disease pathogenesis.

Results: We show that in wildtype (WT) mice significant numbers of IL17-producing tAchR-specific CD4+ T-cells can be observed after immunization. Interestingly, IL17ko mice develop less or no EAMG symptoms, although frequencies of tAchR-specific CD4+ T-cells secreting IL2, IFNγ or IL21 as well as percentage of FoxP3+ Treg cells are similar. On the other hand anti-tAChR antibody levels are equal, while pathogenic anti-murine AChR antibody levels are significantly lower in IL17ko mice. These results were confirmed in a system with IL-17 deficiency restricted to CD4+ T-cells, created by the reconstitution of TCR β/δko mice with CD4+ T-cells of either WT or IL17ko origin.

Conclusions: Taken together we show here that numbers and differentiation of antigen specific CD4+ T-cells as well as the level of immunization antigen specific antibody titers are not affected by IL17-deficiency in the EAMG model. However, breaking of B-cell tolerance resulting in pathogenic anti-murine AChR specific antibodies and subsequent disease induction are dependent on IL17 produced by CD4+ T-cells.

Disclosure: Nothing to disclose

OS1216

‘Core rod’ congenital myopathy with foot-drop associated with nebuline (NEB) gene mutations

1Institute of Myiology, Paris, France, 2Hospital Nacional de Pediatría J.P Garrahan, Buenos Aires, Argentina, 3Department of Medical Genetics, University of Helsinki, Helsinki, Finland, 4Department of Translational Medicine, IGBMC, Strasbourg, 5Institute of Myology, Paris, France

Introduction: ‘Core rod’ myopathy is a rare congenital myopathy presenting with cores and rods as distinctive morphological picture. Up to now, recessive mutations of the nebulin gene (NEB) associated with cores and rods lesions have been described in only two patients with early onset distal myopathy.

Objectives: To describe two patients presenting early onset distal muscle weakness with bilateral foot drop associated with never reported recessive NEB mutations.

Methods: Clinical, histoenzymological, and ultrastructural analysis of one 15 years old male patient (P1) and another 21 years old female patient (P2). Molecular screening for NEB gene was effectuated combining Exome sequencing coupled with dHPLC/Sanger sequencing.

Results: P1 presented delayed gait acquisition, frequent falls, and mainly lower limb distal weakness with bilateral foot-drop. P2 showed frequent falls from the age of 1 years. She successively developed slowly progressive distal lower limbs weakness with bilateral foot-drop. P1 and P2 muscle biopsy analysis showed a homogenous pathological picture characterized by the association of distinct and separated cores with nemaline bodies (rods). P1 harbored one intron 106 mutation (c.16909-2A>G), and one exon 171 duplication (c.24392_24395dup). P2 harbored one exon 129 mutation (c. 19944G>A), and one exons’ 74-144 deletion.

Conclusions: We describe two novel patients presenting a distal ‘Core rod’ myopathy with foot drop associated with novel NEB heterogeneous mutations. Our report suggests that NEB gene should be routinely screened in patients presenting early onset ‘Core rod’ myopathy with foot drop and should be considered in the differential diagnosis of early onset distal neuromuscular conditions.

Disclosure: Nothing to disclose
**OS1217**

**Bulbar myasthenia gravis: why are treatable patients needing admission to hospital - are neurologists doing something wrong?**

M. Niestrata-Ortiz\(^1\), J. Sussman\(^2\)

\(^1\)Neurology, Chelsea and Westminster Hospital, London, \(^2\)Neurology, Greater Manchester Neuroscience Centre, Manchester, United Kingdom

**Introduction:** Some patients with autoimmune myasthenia gravis (MG) deteriorate despite treatment. We analysed the demographics and management of patients requiring hospitalisation to identify treatable factors associated with clinical deterioration.

**Methods:** The study included admissions for MG to the regional neuroscience centre in Greater Manchester, England 2002-2012. Records were obtained for 108 admissions of 78 patients, including characteristics of MG using Myasthenia Gravis Foundation of America (MGFA) clinical classification, and details of treatment changes before each hospital admission.

**Results:** Disease severity increased leading up to hospitalisation. Bulbar weakness increased from 38.46% at onset, to 82.57% at diagnosis and 91.67% at hospital admission. Of patients with bulbar disease at diagnosis, 42% had class IV-V severity by the time of admission, while only 16.7% of patients without bulbar involvement at diagnosis developed class IV-V disease. 90% of patients requiring ICU admission and 84% of patients with multiple admissions had bulbar involvement at diagnosis.

From the start of deterioration to admission patients were managed with increased Prednisolone of only 0.16 mg/kg on average, with no change in dose in 45% of cases. Of patients with bulbar involvement at diagnosis, 46% had not received immunosuppressants by the time of admission and 35% were receiving drugs but in low doses.

**Conclusions:** Bulbar symptoms are a marker for severe MG, however, neurologists do not increase treatment despite patient deterioration. Patients would benefit from guidelines based on evidence combined with expert opinion in areas lacking evidence, confirmed by trials. The authors will discuss developments in this direction.

**Disclosure:** Nothing to disclose

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**OS1218**

**Disease-related symptoms and activities of daily living: a novel survey of patients with nonsense mutation Duchenne muscular dystrophy**

A. Reha, J. Barth, G.L. Elfring, R. Spiegel

PTC Therapeutics, Inc., South Plainfield, NJ, United States

**Introduction:** Health-related quality of life in Duchenne muscular dystrophy (DMD) is not well understood, and there is a need for a sensitive disease-specific questionnaire. A novel survey of symptoms and activities of daily living (ADL) was developed and piloted in an ongoing open-label study of ataluren 40mg/kg/day in nonsense mutation DMD (nmDMD). We describe the survey design and provide a summary of interim data from 47 patients with nmDMD.

**Methods:** The survey was administered by site personnel to the same respondent (patient/parent/caregiver) throughout the study. At each 12-week site visit, respondents were asked whether there were any changes in ADL/disease symptoms compared with baseline, within six pre-specified categories. If yes, respondents were asked to self-report specific ADL/disease symptom terms (within the identified categories) and rate the change from baseline on a 5-point Likert scale.

**Results:** Patients representing various degrees of ambulatory disability were included. The most common improvements during ataluren treatment occurred in the domains of physical functioning (e.g. walking, stair climbing, swimming, upper extremity activity, self-care). Approximately 80% of reports reflected stability or improvement in physical functioning over time with ataluren 40mg/kg/day (week 12, 87.2%; week 24, 82.9%; week 36, 78.3%; week 48, 80.0%).

**Conclusions:** Survey data describing changes in ADL/disease symptoms may be used to complement functional outcome measures. Given that the natural history of DMD indicates a progressive decline in physical function, stabilization of this domain may be regarded as a positive effect.

**Disclosure:** AR, JB, GLE and RS are all employees of PTC Therapeutics, Inc., which has developed ataluren. Medical writing support was provided by Dr Jonathan Morton of Oxford PharmaGenesis™ Ltd and was paid for by PTC Therapeutics, Inc.
Neuroimaging

OS1219

Computation based diagnosis reveals intermediate Alzheimer’s disease phenotypes

J. Cui1, V. Zufferey1, S. Muller1, S. Klöppel2, A. Abdulkadir1, R. Frackowiak1, B. Draganski1, F. Kherif2
1CHUV BH07 Department of Neurology, Centre Hospitalier Universitaire Vaudoise, Lausanne, Switzerland, 2Department of Psychiatry and Psychotherapy, Freiburg, Germany

Introduction: A definitive diagnosis of Alzheimer’s disease (AD) can only be confirmed with pathology. In-vivo clinical criteria alone can lead to 35% misdiagnosis rate. We present a new diagnostic tool for AD based on in-vivo neuroimaging patterns, which predicts pathological proven (PP) AD. We inspected imaging and cognitive patterns from individuals and explored reasons for diagnostic mismatch based on clinical criteria and the results of MR structural neuroimaging based automated classification. We suggest that such individuals have differential patterns of brain atrophy associated with memory loss.

Methods: We trained a Support Vector Machine (SVM) classifier on grey matter volume (GMv) estimations from post-mortem proved AD and healthy controls (HC). Using this classifier, we relabelled ADNI individuals (clinically diagnosed). Training: 15 HC / 18 AD T1-weighted ante-mortem MRI from PP individuals (Klöppel et al, 2008). ADNI set: T1-weighted MRI from 359 HC / 284 AD patients (defined by MMSE, CDR scores) at baseline time. We normalized all GMv images to MNI space using a template generated from PP individuals using SPM12.

Results: SVM classified the 33 PP individuals with 87% accuracy (leave-one-out cross-validation). ADNI individuals were classified either AD or HC and then stratified into 4 subgroups: AD_AD, AD_HC, HC_AD, HC_HC (formatted as clinical_SVM, Table 1). Comparisons of GMv and MMSE scores between these groups are shown in Figure 1-2.

Conclusion: Clinical / neuroimaging mismatch labeled individuals (AD_HC & HC_AD) showed intermediate characteristics in both anatomy patterns and memory performance. This result suggests different mechanisms of clinically AD-type dementia syndrome.

Disclosure: Nothing to disclose

OS1220

Iron deposits in post-mortem brains of patients with neurodegenerative and cerebrovascular diseases: a semi-quantitative 7.0 Tesla magnetic resonance imaging study

Université Lille Nord de France, Lille, France

Objectives: Accumulation of iron (Fe) is often detected in brains of people suffering from neurodegenerative diseases. However, no studies have compared the Fe load between these disease entities. The present study investigates on T2*-weighted gradient-echo 7.0 T magnetic resonance imaging (MRI) the Fe content in post-mortem brains with different neurodegenerative and cerebrovascular diseases.

Methods: Hundred-fifty two post-mortem brains, composed of 46 with Alzheimer’s disease (AD), 37 with frontotemporal lobar degeneration (FTLD), 11 with amyotrophic lateral sclerosis, 13 with Lewy body disease, 14 with progressive supranuclear palsy, 16 with vascular dementia (VaD) and 15 controls without a brain disease were examined. The Fe load was determined semi-quantitatively on T2*-weighted MRI serial brain sections in the caudatum, putamen, globus pallidus, thalamus, subthalamic nucleus, hippocampus, mammillary body, lateral geniculate body, red nucleus, substantia nigra and dentate nucleus. The disease diagnosis was made on subsequent neuropathological examination.

Results: Only in the caudatum, putamen nuclei and putamen of FTLD brains a highly significant Fe load was observed, while also present to a lesser degree in the globus pallidus, thalamus and subthalamic nucleus. In the other neurodegenerative diseases no Fe accumulation was observed, except for a mild increase in the caudate nucleus of AD brains. In VaD brains no Fe increase was detected.

Conclusions: Only FTLD displays a significant Fe load, suggesting that impaired Fe homeostasis plays an important role in the pathogenesis of this heterogeneous disease entity while cerebrovascular lesions are not implied.

Disclosure: Nothing to disclose
Diagnostic performance of ioflupane I123 injection (DaTSCAN™) in patients with movement disorders and dementia


1 University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, 2Philipps-University of Marburg, Marburg, Germany, 3Newcastle University, Newcastle upon Tyne, 4University of Glasgow, Glasgow, 5University College London, London, United Kingdom, 6Municipal Hospital Karlsruhe, Inc., Karlsruhe, Germany, 7University of Barcelona, Barcelona, Spain, 8GE Healthcare, Princeton, NJ, United States

Introduction: Early and accurate diagnosis of movement disorders and dementia is critical to ensuring optimal clinical management. Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (123I)) is approved to visualize loss of striatal dopamine transporter in a subset of patients with dementia and movement disorders.

Methods: Four clinical trials were pooled to determine the overall sensitivity and specificity of ioflupane (123I) images in detecting or excluding a striatal dopaminergic deficit (SDD), which is associated with Parkinsonian syndrome and dementia with Lewy bodies. Patients with either a movement disorder or dementia, and healthy volunteers were administered ioflupane (123I). Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (123I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (123I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDD. Ioflupane (123I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

Disclosure: Drs. Sherwin and Grachev are employees of GE Healthcare

DWI intensity values for the prediction of time from stroke onset in acute stroke


1Centre for Stroke Research Berlin, Charité Universitätsmedizin Berlin, Berlin, 2Max-Planck-Institute for Neurological Research, Cologne, 3Department of Radiology, Lüdmillenstift, Meppen, 4Fraunhofer MEVIS, Bremen, Germany

Introduction: In acute stroke, the DWI-FLAIR mismatch allows for the identification of patients eligible for thrombolysis. FLAIR-lesions, however, are difficult to analyze. In comparison, DWI alone may be a suitable biomarker. We analyzed whether a relative DWI intensity threshold (rSI) can identify stroke patients imaged within the thrombolysis time-window.

Methods: We retrospectively included patients according to the following criteria:
1) proven stroke,
2) symptom-onset <12h,
3) confirmed lesion in DW-imaging.

Patients were dichotomized into two groups (stroke-onset-time [SOT] <4.5h/>4.5h). MR-imaging hardware: 1.5T Intera Master (Philips Medical Systems). A DWI lesion-volume was created and
a) mean (DWmean),
b) minimum (DWmin) and
c) maximum voxel-values (DWmax) of the volume was calculated.

Values were normalized: [value/mean value of a representative slice from the unaffected hemisphere]%.

DWI-rSIs were correlated with SOT. The ability of DWmin-, DWmean- and DWmax-rSI values to allocate patients to the thrombolysis window was analyzed using receiver operating characteristics (ROC) curve analysis.

Results: 44 patients were included (in median: stroke-onset-time=2.3 h; age=62 a; NIHSS=8 points; lesion volume=23 ml). 31 patients were imaged within 4.5h after stroke-onset. Correlation of SOT with DWmin, DWmean and DWmax was 0.05, 0.46 and 0.43. Area under the curve (AUC) for DWmean and DWmax was 0.75 and 0.81. DWmin performed poorly (AUC: 0.53). Optimal rSI-thresholds with sensitivity/specificity were: for DWmean 162% with 58%/85%; for DWmax 239% with 71%/93%.

Conclusion: DWI-rSIs identified patients within the 4.5h time-window with high specificity. This finding is promising for the use of DW-rSI in acute stroke.

Disclosure: Nothing to disclose
OS1223

Thalamic dysfunction is associated with fatigue in patients with multiple sclerosis: a graph theory study

M.A. Rocca¹,², P. Valsasina¹, A. Bisecco¹, A. Meani¹, L. Parisi¹, M.J. Messina², F. Mele¹,², B. Colombo², A. Falini³, G. Comi², M. Filippi¹,²

¹Neuroimaging Research Unit, Institute of Experimental Neurology, ²Department of Neurology, ³Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To explore abnormalities of large-scale brain networks (connectome) in MS patients with fatigue.

Methods: Graph theoretical analysis was applied to RS fMRI data from 64 MS patients with fatigue (F) according to the Fatigue Severity Scale. As control groups, 60 MS patients without fatigue (NF) matched for disease duration and brain T2 lesion volume with F-MS patients and 59 gender and age-matched healthy controls (HC) were included. Functional connectivity between 116 cortical and subcortical brain regions was estimated using a bivariate correlation analysis. Small-worldness properties were tested by comparison with matched random networks. Between-group differences of global and local network metrics were investigated using ANOVA models.

Results: Small-worldness was verified in all study groups. All global network parameters were significantly altered in F-MS patients and NF-MS patients compared with HC, with no significant differences between F- and NF-MS patients. The cerebellum (right lobule VI and bilateral crus I), and bilateral middle and inferior temporal gyri were hubs in all study groups. F- and NF-MS patients lost hubs in the bilateral anterior cingulate cortex and cerebellar regions (lobule VII-VIII, crus II). F-MS patients also lost hubs in the thalami and middle cingulate cortex. Compared to HC, F- and NF-MS patients had a decreased degree in the bilateral caudate nucleus. F-MS patients also experienced a decreased degree in the bilateral thalamus.

Conclusions: Fatigue in MS is related to a functional disruption of the thalamic connector, which should be the target of potential therapeutic interventions.

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OS1224

Preoperative memory fMRI predicts verbal memory decline after left anterior temporal lobe resection


Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, United Kingdom

Introduction: Anterior temporal lobe resection brings remission in up to 80% of patients but up to 30% of temporal lobe resections in the speech dominant hemisphere cause significant verbal memory decline. The purpose of this study was to develop a robust memory fMRI method as a clinically applicable tool for predicting post surgical memory outcome in individual patients.

Methods: 23 patients with left TLE and 26 controls performed an explicit fMRI memory encoding paradigm of words with a subsequent out of scanner recognition assessment. Neuropsychological assessment was performed pre-operatively and 4 months after anterior temporal lobe resection, and at equal time-intervals in controls. An event related analysis was used to explore brain activations for words remembered and change in verbal memory scores 4 months post-operatively was correlated with pre-operative activations. Individual lateralisation indices were calculated within a medial temporal and frontal region and compared with other clinical parameters (hippocampal volume, pre-operative verbal memory, age at onset and duration of epilepsy) as a predictor of verbal memory outcome.

Results: Greater left than right anterior medial temporal and frontal activations on remembering words correlated significantly with greater verbal memory decline post-operatively. In a step wise regression model, left lateralised memory lateralisation index (>0.5) within a medial temporal and frontal mask was the best predictor of verbal memory outcome.

Conclusion: We propose a robust, clinically applicable memory fMRI method where both temporal and extra-temporal activations predict post-operative verbal memory decline in individual patients.

Disclosure: Nothing to disclose
Neurotraumatology & Neuro-oncology

OS1225

Identification and quantification of CSF malignant T-cells by the CellSearch® technology in patients with lung leptomeningeal metastasis

M. Blonski1, B. Wittwer1, G. Faure2, L. Simon1, M. De Carvalho Bittencourt2, Q. Tu3, D. Larrieu4, E. Le Rhun4, L. Taillandier4

1Neuro-Oncology Unit, Nancy University Hospital, 2Immunology Laboratory, Nancy University Hospital, Nancytomique, Nancy, 3Neurology Department, Poitiers University Hospital, Poitiers, 4Neuro-Oncology Unit, Lille University Hospital, Lille, France

Introduction: Diagnosis of lung leptomeningeal metastasis (LM) remains difficult. The usual diagnostic methods of cytomorphological assessment of cerebro-spinal fluid (CSF) and gadolinium-enhanced MRI lack both specificity and sensitivity. The Veridex CellSearch® technology is validated in detection of circulating tumor cells (CTC) in blood and in the follow-up of breast, prostate and colorectal cancer. Our aim was to adapt this technology for detection and quantification of tumor cells in the CSF of lung cancer patients with LM.

Methods: Patients with suspected lung LM from a french neuro-oncological center (Nancy) were prospectively included. The CSF samples were collected on traditional cytology tubes (1 mL) and on CellSave® Preservative tubes (4mL).

Results: 11 patients with clinical symptoms and/or radiological criteria suggestive of lung LM (5 at diagnosis / 6 at recurrence) underwent CSF analysis with conventional cytology and with Veridex CellSearch® technology. Conventional CSF cytomorphological analysis was positive in 5 patients (with a median of 13 tumor cells/mm²; range 10 to 25 tumor cells/mm²) whereas the assessment with Veridex CellSearch® technology was positive in 11 patients. Quantitative analysis with the Veridex CellSearch® technology showed a median of 203 tumor cells / 5mL of CSF (from 1 to 1500 tumor cells per 5ml CSF).

Conclusions: In contrast to the current gold standard cytomorphological analysis, this new approach seems more sensitive and allowed a quantification of CSF tumor cells in lung LM.

This methodology could be useful for earlier diagnosis of lung LM and for follow-up. A large prospective study is required.

Disclosure: Nothing to disclose

OS1226

Long-term survival in patients with brain metastasis (BM): frequency and accompanying neurological status

D. Suki, R. Sawaya

Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

Introduction: BM patients die within an average of eight months following treatment. Little is known about long-term survivors and their neurological status.

Methods: 2,170 patients treated with resection or radiosurgery at M.D. Anderson Cancer Center between 1993 and 2008 for a newly-diagnosed BM were grouped according to their survival status five years from BM diagnosis date. Factors impacting long-term survival (LTS; ≥5 years) and neurological status were reviewed under an IRB-approved protocol.

Results: The median age of the 163 patients with LTS was 53 years. 47% were males. The primary cancer was lung in 30%, melanoma in 20%, breast in 18% and renal in 11%. The interval from primary to BM diagnosis was 14.3 months. 77% had a stable primary or no evidence of disease at treatment time. 72% of BM were in or near eloquent brain; 80% were single. The median largest tumor volume was 4.5 cm³. 71% were treated with a resection. In the multivariate analysis comparing the 163 patients with the 2094 patients who were known to have died before five years, a KPS ≥70 and a non-progressing primary had the strongest associations with LTS. The effect of treatment type and adjuvant radiation within different patient subgroups and data on neurological status will be presented.

Conclusions: LTS was observed in all typically unfavorable categories. However, good functional status and non-progressing primary most strongly impacted survival duration. Modern treatments may have enabled BM patients with good functional status and a controlled primary to survive for prolonged periods.

Disclosure: Nothing to disclose
OS1227

Optogenetic inhibition of primary human malignant glioma

F. Yang, J. Tu, Y. Liu, L. Wang
Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China

Introduction: Glioblastoma are aggressive cancers with low survival and poor prognosis because of their highly proliferative and invasive capacity. It is not clear whether precise regulation of membrane depolarization and ion channels can inhibit glioma growth.

Methods: In the current study, we used optogenetics, an ideal tool to precisely control membrane depolarization and neural circuits, to inhibit the in vitro and in vivo growth of human malignant glioma.

Results: We showed that the engineered opsin gene (ChETA) expression in primary human glioma cells and light stimulation could reduce the viability of glioma cells. We further demonstrated that light illumination inhibited subcutaneous/intracranial glioma growth in vivo.

Conclusions: We demonstrated for the first time that precise regulation of membrane depolarization using optogenetics inhibited the proliferation and growth of glioma, thus providing new insights into glioma biology and the regulation of the proliferative capacity of malignant human glioma.

Disclosure: Nothing to disclose

OS1228

Autologous skin derived stem cells and platelet-rich plasma as treatment for traumatic spinal cord injury

Y. Torrente1, N. Grimoldi2, M. Belicchi1, S. Erratico3, M. Pluderi2, R. Giordano2, F. Tiberio2, M. Marconi4, P. Rampini2, N. Bresolin5

1Department of Pathophysiology and Transplantation, Stem Cell Laboratory, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Centro Dino Ferrari, Università di Milano, 2Neurosurgery, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Università di Milano, 3System, s.r.l., 4Department of Regenerative Medicine, Center of Transfusion Medicine, Cellular Therapy and Cryobiology, Foundation IRCCS Ca’ Granda Ospedale Maggiore Policlinico, 5Department of Pathophysiology and Transplantation, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Centro Dino Ferrari, Università di Milano, Milan, Italy

Introduction: Traumatic spinal cord injury (SCI) results in a devastating loss of neurological function and in psychologically shattering condition that affects young healthy people that are in their most productive years. Currently, there are over 2 million SCI patients worldwide and at present, there are no universally accepted treatments for this neurological disorder. Recently, particular attention is paid to the potential of stem cells in treating SCI, but there are only few clinical studies and insufficient data. This clinical study explored the feasibility and efficacy of autologous skin derived stem cells (SDSCs) transplantation in two patients with complete and chronic spinal cord injury.

Methods: We hypothesized that the combination of autologous SDSCs as accessible sources of stem cells combining with platelet-rich plasma (PRP), rich of growth factors, was a possible treatment of SCI. PRP behave as natural scaffold and is able to improve stem cells survival, proliferation and axon regeneration and remyelination.

Results: Preoperative and postoperative neurological functions were evaluated with neurological clinical examination, MRI, and electrophysiological studies every two months after the treatment for one years.

Conclusions: Results showed that in the treated patients had a clinical improvement in terms of pin prick sensory and sphincter control. No signs of adverse events such as wound infection, and no sign of tumor were evident until 6 months postoperatively.

Disclosure: Nothing to disclose
OS1229
Abnormalities of the attentional network following traumatic brain injury in pediatric patients: an fMRI study
M.A. Rocca\textsuperscript{1,2}, S. Strazzer\textsuperscript{1}, P. Valsasina\textsuperscript{1}, E. De Meo\textsuperscript{1,2}, E. Molteni\textsuperscript{1}, M. Recla\textsuperscript{1}, S. Galbiati\textsuperscript{1}, A. Bardoni\textsuperscript{1}, G. Comi\textsuperscript{2}, M. Filippi\textsuperscript{1,2}
\textsuperscript{1}Neuroimaging Research Unit, Institute of Experimental Neurology, \textsuperscript{2}Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, and \textsuperscript{3}Neurorehabilitation Unit, Sci. Inst. IRCCS E. Medea, Bosisio Parini (LC), Italy

Introduction: To assess abnormalities of fMRI activity during a sustained attention task in pediatric patients with traumatic brain injury (TBI).

Methods: FMRI scans were acquired from 22 pediatric TBI patients (mean age=14.3 years; mean time from TBI=1.96 years) and 7 healthy controls (mean age=10.8 years) during the administration of the Conners’ CPT. Patients underwent the Wechsler Intelligence Scale for Children (WISC-IV) and the Functional Independence Measure (FIM) evaluation.

Results: In both groups, significant activations during the different conditions of the CPT task were found in the right somatosensory cortex, supplementary motor area, middle cingulate cortex, inferior frontal gyrus (pars opercularis) and left cerebellum. With increasing task difficulty (“load effect”) both groups had increased fMRI activity in the bilateral middle occipital gyrus. During this condition, compared to TBI patients, controls also had an increased recruitment of the middle occipital gyrus as well as temporal and parietal regions. Patients having better performances at the CPT, better scores at WISC-IV and FIM scales and a longer time from TBI showed a reduced activity of the anterior cingulate cortex, superior frontal and middle frontal gyri during the CPT task. Patients having better scores at WISC-IV and a longer time from TBI showed also higher activity of frontal and temporal regions during the “load” condition.

Conclusions: Pediatric TBI patients experience an inability to optimize the recruitment of the attentional network, which might contribute to explain the attentional deficits frequently observed in this condition.

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OS1230
Decreased apparent diffusion coefficient in pituitary is correlated with hypopituitarism in patients with traumatic brain injury
P. Zheng
Shanghai Pudong New Area People’s Hospital, Shanghai, China

Introduction: To identify the role of the apparent diffusion coefficient (ADC) using a diffusion-weighted imaging technique and to evaluate the association of such changes with hypopituitarism (HPT) in TBI patients.

Methods: Diffusion weighted images were performed in 164 consecutive patients with TBI within 2 weeks after onset to generate the pituitary ADC as a measure of microstructural change. Patients with TBI were further grouped with or without HPT based on the secretion status of pituitary hormones at six months post injury. Patients with TBI were further grouped with or without HPT based on the secretion status of pituitary hormones at six months post injury. MRI data and laboratory findings were analyzed blindly. 30 healthy controls were enrolled. Mean ADC values were compared among the control, TBI with and without hypopituitarism group, and correlational studies were also performed. The neurological outcome was assessed with the Glasgow outcome scale (GOS) scores at 6 months post injury as well.

Results: Our study included 84 TBI patients with HPT and 80 TBI patients with normal pituitary function. The pituitary ADC in TBI patients was significantly less than that in controls (1.83±0.16 vs. 4.13±0.33, p<0.01). Furthermore, the mean ADC was much less in TBI patients with pituitary dysfunction compared to those without HPT (1.32±0.09 vs. 2.28±0.17, p<0.05). In addition, the ADC value was positively correlated with the neurological outcome at 6 months following TBI (r=0.602, p<0.05).

Conclusions: We confirm that the ADC in pituitary is correlated with the hormone-secreting status in TBI patients. We also demonstrate that the pituitary ADC may become a novel biomarker to predict the pituitary function in patients with TBI.

Disclosure: Nothing to disclose
Clinical neurophysiology

OS2101

The significance of dorsal sural nerve recordings in early detecting oxaliplatin-induced peripheral neuropathy


Introduction: To study the capability of monitoring dorsal sural nerve conduction study (DSN) to predict the neurological outcome at end of chemotherapy. Our objective was to assess its ability to early detect oxaliplatin-induced peripheral neuropathy (OXAIPN).

Methods: A total of 116 colorectal cancer patients were evaluated before, at mid-point and at the end of chemotherapy. Standard nerve conduction studies plus DSN were performed. The Total Neuropathy Score-clinical version (TNSc) was used to assess OXAIPN. Elaborating a tree regression, cut-offs for z-score of DSN amplitude were individuated to subdivide at mid-treatment subjects at high versus low risk to develop neurotoxicity at the end of chemotherapy.

Results: At baseline all patients had no preexisting neuropathy. At mid-treatment, 11 (9.5%) patients had abnormal sural nerve amplitudes and 24 (20.7%) abnormal DSN amplitudes. At the end of treatment, 37 (32%) patients had grade I neuropathy and 37 (32%) had grade II/III. Forty-four (38%) patients had abnormal sural nerve amplitudes and 55 (47.4%) had abnormal DSN amplitudes. The -0.815 cut-off for the z-score of DSN amplitude was able to individuate the probability of patients to develop OXAIPN, better than sensory nerves conventionally studied, e.g., sural nerve.

Conclusions: DSN recording might be a useful objective outcome measure to individuate patients at higher risk to develop neurotoxicity during chemotherapy. It might also be a significant end-point in neuroprotection trials.

Disclosure: Nothing to disclose

OS2102

Defective inhibition of exteroceptive cutaneo-muscular reflexes during focal ballistic movement execution in multiple sclerosis

C. Cabib, S. Llufriu, A. Saiz, J. Valls-Solé

1EMG Unit, Neurology Department, Hospital Clinic of Barcelona, 2Center of Neuroimmunology, Neurology Department, IDIBAPS, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain

Introduction: Cutaneous reflexes may be enhanced in patients with multiple sclerosis (MS) reflecting lack of supraspinal inhibitory control over spinal motoneurons. Cutaneo-muscular reflexes (CMR) to exteroceptive stimuli are usually recorded on pre-activated muscles. In the context of a unilateral simple reaction time paradigm (sRT), the execution of ballistic movements requires focusing excitatory inputs to motoneurons involved in execution of the task and inhibitory inputs to avoid unwanted activity. We hypothesized that CMR may be abnormally present in MS patients during sRT.

Methods: In 13 healthy subjects (HS) and 21 mildly disabled relapsing-remitting MS patients, we recorded bilaterally wrist-extensors activity using surface EMG. The sRT consisted on performing ballistic wrist-extension movements at perception of an electrical somatosensory low-intensity imperative stimulus (IS) given to either ipsilateral or contralateral index fingers. CMR were identified when a response was consistently obtained in the wrist-extensors of the side receiving the IS at a latency of 50-70ms.

Results: In HS, CMR were present in 4 (31%) during ipsilateral trials but never during contralateral trials. In patients, ipsilateral CMR was present in 13 (62%; $\chi^2 = 0.077$) and most of them were larger than in HS. In contralateral trials, CMR were consistently seen in 5 patients (24%; $\chi^2 = 0.056$ vs HS). All of them had also CMR in ipsilateral trials.

Conclusions: Unwanted release of reflex responses to cutaneous inputs occurs more frequently in patients with MS than in healthy volunteers. This may be related to a defective supraspinal control of inhibitory commands during sRT paradigms.

Disclosure: Nothing to disclose

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OS2103

Tafamidis meglumine and nerve fiber function in Portuguese patients with transthyretin familial amyloid neuropathy


1Department of Neurosciences, Centro Hospitalar Lisboa Norte-Hospital de Santa Maria, Translational and Clinical Physiology Unit, Instituto de Medicina Molecular, Faculty of Medicine, Lisbon. 2Familial Amyloid Polyneuropathy Clinical Unit and Neurophysiology Department, Hospital Santo António, Centro Hospitalar do Porto, Porto. 3Department of Neurology, Hospital Garcia de Orta, Almada, Portugal

Introduction: Transthyretin familial amyloid polyneuropathy (TTR-FAP) is an inherited amyloidosis that presents as a progressive sensorimotor and autonomic polyneuropathy. Class II evidence suggests that Tafamidis dampens clinical progression and preserves nerve function. Neurophysiologic parameters, including sensory and motor nerve amplitudes and motor nerve velocities, have been used to assess TTR-FAP nerve function.

Objectives: To describe the effect of one year of Tafamidis treatment on nerve conduction studies of TTR-FAP patients.

Methods: Nerve conduction data from patients on Tafamidis for 12 months was analyzed retrospectively, in the two major centers of TTR-FAP in Portugal. Sympathetic skin response, as well as motor and sensory composed scores were obtained after summing the respective nerve amplitudes. Patients were also evaluated with clinical scales, namely Neuropathy Impairment Score (NIS), Karnofsky index and Norfolk Quality of Life-Diabetic Neuropathy total score (TQOL). Paired-samples t-tests were used; a p value<0.01 was considered significant.

Results: We collected data from 118 patients (54 female) with an age of 38.4±10.0 years. The sensory score was the only neurophysiological parameter that changed significantly over time from 44.9 to 40.9. Clinical scores showed no significant change in the same period of time.

Conclusions: A significant decrease of the sensory score over time is consistent with subclinical progression of axonal sensory nerve fiber dysfunction. Stabilization of motor nerve fiber function on nerve conduction studies correlates with clinical stabilization of patients assessed by NIS score. Further studies on nerve fiber function comparing different forms of treatment need to be conducted.

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OS2104

Deep repetitive transcranial magnetic stimulation with H-Coil in Parkinson's disease: a randomized, double blind, placebo-controlled study


1San Raffaele Scientific Institute, Institute of Experimental Neurology, Milan, Italy. 2Ben-Gurion University, Beer Sheva, Israel. 3Neurology, San Raffaele Hospital, Milan, Italy

Introduction: Parkinson’s disease-PD is characterized by a widespread alteration of cortico-subcortical circuits. The H-coil allows a wider and deeper stimulation field compared with traditional coils. We evaluated safety and efficacy of deep repetitive transcranial magnetic stimulation (rDTMS) with H-Coil as add-on treatment for motor symptoms in PD in a double-blind, randomized placebo-controlled study.

Methods: 60 patients underwent 12 sessions (3 sessions/week) of 10 Hz rDTMS, after randomization into 3 groups: Group 1 (real rDTMS on primary motor-M1 and prefrontal-PF areas); Group 2 (M1-real/PF-sham), Group 3 (M1-sham/PF-sham). Primary outcome was percent reduction of Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part III, OFF therapy. Secondary outcomes were: changes in UPDRSIII sub-scores; improvement in timed tests (Hand Tapping-HT, Foot Tapping-FT, Walking Time-WT, Nine Hole Peg Test-NHPT). Statistical analysis was performed using Mann-Whitney or t-test. Outcomes were tested in hierarchical order, by comparing the two real groups (1-2) only if their pooled data significantly differed from sham.

Results: No drop-outs or serious adverse effects were recorded. Both real groups improved significantly more than sham in UPDRSIII (p=0.010 and p=0.045 respectively), while they did not significantly differ between them. Pooled real groups showed a significant improvement vs sham in UPDRSIII (p=0.007), tremor (p=0.011) and lateralized sub-scores (p=0.042 and p=0.012 for worse and better side respectively). Timed tests significantly improved more in the real group vs sham on the worse side (HT p=0.041, FT p=0.012, NHPT p=0.003).

Conclusion: rDTMS with H-Coil appeared safe and effective on motor symptoms as add-on treatment in PD.

Disclosure: Nothing to disclose.
OS2105

Visual evoked potentials and optic coherence tomography in monitoring multiple sclerosis

San Raffaele Hospital, Institute of Experimental Neurology (INSPE), Milan, Italy

Introduction: In the assessment the involvement of visual pathways in Multiple Sclerosis-MS, optical coherence tomography-OCT and visual evoked potentials-VEPs are mainly used. The aim of our study was to investigate their value in longitudinal monitoring of the disease.

Methods: Eighty people with MS patients (13 clinically isolated syndrome-CIS, 55 relapsing-remitting-RR, 9 secondary progressive-SP, 3 primary progressive-PP) underwent neurological and neurophysiological evaluation with OCT and VEPs, with repeated clinical assessment after a mean follow-up of one year, when 50 patients also repeated OCT-VEPs.

Results: VEPs were more sensitive vs OCT in eyes with recent (<3 months) optic neuritis-ON at baseline (80.0% Vs 6.7%, p=0.001), the two sensitivities were similar in chronic ON eyes (78.4 %). Comparing eyes with and without previous ON, VEP latency and RNFL thickness were respectively significantly higher (131.2 ms Vs 118.8 ms, p=0.008) and lower (78.15µm Vs 90.00µm, p<0.001) in the first subgroup. Significant longitudinal changes at follow-up, consisting in improved VEPs (-15.3 ms) and worsened RNFL thickness (-7.7 µm), were found only in eyes with baseline recent ON. No significant correlation was found between OCT-VEPs parameters and disease activity. Similar results were found when considering only RR and CIS patients.

Conclusions: These results would exclude recommending OCT and VEPs as surrogate biomarkers in short-medium term monitoring as in Phase II studies, with the exception of acute ON. However, these findings cannot exclude the usefulness of these techniques for longer follow-ups and/or large phase III studies.

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OS2106

Contact heat evoked potentials and quantitative thermal testing in a patient with Hansen's disease

A. Mirallave Pescador¹, M. Agredano Jiménez², M. Neves Cardoso³, C. Cabib⁴, M. Morales⁴, J. Valls-Solé⁴
¹Clinical Neurophysiology, Hospital Universitario Nuestra Señora de Candelaria, La Laguna, Spain, ²Medicina de Rehabilitación, Centro de Rehabilitación Integral SNDIF, Guadalajara, Mexico, ³Clinical Neurophysiology, Centro Hospitalar do Porto - Hospital de Santo António, Porto, Portugal, ⁴Neurología-Unidad de EMG, Hospital Clinic de Barcelona, Barcelona, Spain

Introduction: Leprosy is one of the most common causes of non-traumatic peripheral neuropathy in the developing world, rarely diagnosed in Europe. We had the opportunity to study a full blown case of multifocal sensory neuropathy with small fiber involvement in a 38 year old Colombian woman in our center.

Methods: The patient was first seen after a 6 years history of slowly progressive distal thermoalgesic hypoesthesia on all four limbs, with a lower limb predominance as well as pain related to distal skin lesions (ulcers) in fingers and toes. Physical examination showed distal lesions with nail loss and toes deformities, eyebrow and eyelash alopecia, normal tendon jerks and normal motor balance. We performed motor, sensory and mixed nerve conduction studies on all 4 limbs, recorded long latency evoked potentials to contact heat (CHEPs) and electrical stimuli with simultaneous recording of the SSR and assessed quantitative thermal testing (QTT).

Results: A skin biopsy showed histiocytic cell accumulates in dermis with normal epidermis and was positive for Hansen’s disease. Nerve conduction studies showed a severe asymmetric sensory neuropathy. Evoked potentials were normal to electrical stimuli but CHEPs were absent. QTT showed misperception of heat and cold with increased thresholds to all thermoalgesic sensations in all 4 limbs.

Conclusions: The absence of CHEPs to stimuli in an area where electrical stimuli induced normal evoked potentials documents the clinically suspected involvement of the small fibers conveying thermoalgesic sensations in sensory neuropathy of Hansen’s disease.

Disclosure: Nothing to disclose
Oral Sessions      51

Headache and pain

OS2107

Correlation between habituation of visual evoked potentials and magnetophosphene thresholds in migraine

A. Ambrosini1, A. Kisialiou2, E. Iezzi1, A. Perrotta1, A. Nardella1, A. Berardelli1,3, F. Pierelli1, J. Schoenen4
1IRCCS Neuromed, Pozzilli, Italy, 2University of Glasgow, Glasgow, United Kingdom, 3University of Rome ‘La Sapienza’, Rome, 4University of Liège, Belgium

Introduction: An interictal habituation deficit of visual evoked potentials (VEP) and a reduced threshold (PT) of magnetophosphenes have been reported in migraine in separate studies. While the habituation deficit was attributed to reduced preactivation level of the visual cortex, the reduced PT likely indicates cortical hyperexcitability. Both phenomena have not yet been explored in the same patients.

Methods: We assessed PT by transcranial magnetic stimulation (TMS) in 15 healthy volunteers (HV) and in 13 episodic migraineurs without aura between attacks (MO), whereafter we recorded pattern-reversal VEP (6 blocks of 100 responses) and measured habituation. Results were compared using Mann-Whitney U test. Interrelationships were examined using Spearman’s correlation.

Results: Phosphene thresholds was not significantly different between HV and MO. By contrast, MO patients had a reduced VEP habituation compared to HV (p=0.001). There was no correlation between PT and habituation in neither group of subjects.

Conclusions: This study confirmed that migraineurs present interictally a deficit of VEP habituation, but failed to find decreased PT in these patients. VEP habituation and phosphene threshold values are not reciprocally correlated in healthy volunteers or in migraine patients, which suggest that they index different aspects of cortical excitability, i.e. a punctual measure of cortical activation threshold for PT, as opposed to a dynamic response pattern to repeated stimuli for VEP habituation.

Disclosure: Nothing to disclose

OS2108

White matter abnormalities in chronic migraine patients are located in anterior corpus callosum: study using a new automatic tractography selection method

C. De la Cruz1, A.L. Guerrero1, M.L. Peñas2, D. Argibay3, J. Sierra1, S. Aja-Fernandez2, R. de Luis-García3
1Hospital Clínico Universitario, Valladolid, 2Hospital Virgen de la Concha, Zamora, 3ETS University of Valladolid, Valladolid, Spain

Introduction: Diffusion tensor imaging techniques may detect white matter abnormalities in migraine patients. We analyzed microstructural changes in some tracts using a new automatic selection method and compared them between episodic and chronic migraineurs.

Methods: 30 patients (3 male, 27 females) were selected. We gathered demographic and nosological characteristics. Episodic (Group A) and Chronic migraine (Group B) was diagnosed accordingly to ICHD III edition. Streamline tractography was performed on the tensor data; we automatically extracted six major fiber tracts using geometrical constraints specific for each fiber bundle: corpus callosum (CC), cingulate gyrus, corticospinal tract, inferior frontooccipital fasciculus, inferior longitudinal fasciculus and uncinate fasciculus. Tracts belonging to CC were also separated into five sectors according to Hofer criteria and a volumetric segmentation of CC and its five sectors was automatically performed. We analyzed Fractional Anisotrophy (FA), Mean Diffusivity (MD), Tensor Mode (TM) and Linear Measure (LM).

Results: 11 patients (2 male, 9 females, 33.2± 7.3 years) in Group A, and 19 (1 male, 18 females, 38±13.4 years) in Group B. Chronic migraine patients showed significantly lower values of FA (0.6855±0.0229 vs 0.7051±0.0171, p: 0.02), TM (0.8407±0.0138 vs 0.8558±0.0254, p: 0.04) and LM (0.6621±0.0172 vs 0.6809±0.0184, p: 0.008) in the anterior CC (Hofer first sector). No significant differences were found in the rest of CC sectors or the other tracts studied.

Conclusions: Results indicate that white matter alterations in chronic migraine are concentrated on the anterior CC.

Disclosure: Nothing to disclose
OS2109

Greater occipital nerve blocks with bupivacaine in the treatment of chronic migraine. Randomized, multicenter, double-blind, parallel, placebo-controlled study

L. İnan¹, N. İnan², Ö. Karadağ³, H.L. Gül⁴, A.K. Erdemoğlu⁵, Y. Türkel⁶, A. Akyol⁶
1Ankara Education and Research Hospital, 2Algology, Gazi University Faculty of Medicine, 3Mevki Hastanesi, Ankara, 4Neurology, Lütfi Kirdar Research and Training Hospital, Istanbul, 5Neurology, Kirikkale University, Kirikkale, 6Neurology, Aydın Menderes University, Aydın, Turkey

Introduction: Background Our aim was to assess the efficacy of greater occipital nerve (GON) blocks at chronic migraine (CM). There is not randomized, multicenter, double-blind, parallel, and placebo-controlled study with GON blocks; headache days, headache duration and VAS scores were evaluated.

Methods: 72 patients who have CM according to IHS Criteria 2004 were enrolled from 6 clinics. After 4 weeks pretreatment headache diary. Patients were divided in two groups randomly as “A” (placebo) and “B” (bupivacaine). 33 patients as “A” and 39 patients as “B” completed the study. Blocks were applied 4 times with saline or bupivacaine one week intervally. After four weeks blindness is opened; in “A”, GON were blocked by bupivacaine as “B”, then blocks were done monthly and followed for two months. “B” for three months. The primary endpoint was the difference in headache days, headache duration and VAS scores during bupivacine blocks.

Results: 72 patients completed the study. Headache days decreased from 16.9±5.7 to 13.2±6.7 in “A” (0.035); 18.1±5.3 to 8.8±4.8 (<0.001) in “B”; headache duration is decreased from 24.2±13.7 to 21.2±13.4 (0.223) in “A”; 25.9±16.3 to 19.3±11.5 in “B” (<0.001) and VAS decreased from 8.1±0.9 to 6.7±1.1 in “A” (<0.001); 8.4±1.5 to 5.3±2.1 in “B” (<0.001) in the first mounth. After blindness is opened, Group “A” showed similar results as “B” after bupivacine blocks. No severe adverse effects were reported only local pain, vertigo and nausea to stop treatment.

Conclusions: GON blocks with bupivacaine can be effective treatment in CM.

Disclosure: Nothing to disclose

OS2110

Anodal transcranial direct current stimulation alleviates pain in trigeminal neuralgia

M. Obermann, V. Bude, S. Naegel, D. Holle, H.-C. Diener, T. Hagenacker
Department of Neurology, University of Duisburg-Essen, Essen, Germany

Introduction and objective: To investigate the efficacy of transcranial direct current stimulation (tDCS) of the primary motor cortex on pain and trigeminal nociceptive processing in subjects with classical trigeminal neuralgia (TN).

Methods: Seventeen subjects with TN were recruited in the study. Patients stimulated daily for 20 minutes over two weeks using anodal (1mA) or sham tDCS in a randomized cross-over design. Primary outcome variable was pain intensity on a verbal rating scale (VRS). VRS and attack frequency were assessed daily for one month before and after tDCS using an individual patient diary. The impact on trigeminal pain processing was assessed with pain-related evoked potentials (PREP) and the nociceptive blink reflex (nBR) following electrical stimulation on both sides of the forehead (V1) before and after tDCS.

Results: Anodal tDCS reduced pain intensity more effectively than sham stimulation after two weeks of treatment. The attack frequency reduction was not significant. PREP showed an increased N2 latency and decreased peak-to-peak amplitude after anodal tDCS. No severe adverse events were reported. Patients with concomitant chronic background pain do not seem to benefit from tDCS as described previously for medical therapy and surgical intervention.

Conclusions: Daily anodal tDCS over two weeks ameliorates trigeminal pain in TN. It may become a valuable treatment option for patients unresponsive to conventional medical treatment or on wait for surgical procedures. International, multicenter, randomized controlled trials are needed with higher patient numbers before a definite recommendation can be proposed.

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OS2111

**Visual induced analgesia in the face in healthy subjects and migraineurs**

S.L. Sava, R. Baschi, E. Vecchio, V. de Pasqua, D. Magis, J. Schoenen

*Department of Neurology, University of Liège, Liège, Belgium*

**Introduction:** Visually induced analgesia (VIA) is the reduction of pain perception when seeing the stimulated body site, due to interplay between the brain’s pain network and a posterior visual network. VIA was not demonstrated in the face and migraine is associated with abnormal connectivity in visual areas. We performed a comparative study of facial VIA in healthy subjects (HS) and migraine without aura patients (MO).

**Methods:** CHEPs were analyzed in 10 HS and 12 MO (interictal) with stimuli of 53°C applied to the right forehead with or without observation of the face with a mirror. For comparison, we recorded CHEPs by stimulating the right wrist. 20 averaged sweeps were partitioned in 5 blocks of 4 responses to measure latency, amplitude and habituation of the cortical response. Pain was rated with a visual analog scale (VAS).

**Results:** Seeing the face decreased latency of N2 (p=0.04) and amplitude of P1-N2 (p=0.03) and N2-P2 (p=0.006) in HS; P1-N2 habituation increased in HS (p=0.02), but decreased in MO (p=0.002). There was no effect of the mirror CHEPs at wrist, on facial or wrist pain perception, nor in pain perception between HS and MO.

**Conclusion:** Seeing the stimulated face attenuates thermonociceptive potentials but leaves pain ratings unchanged in healthy subjects, which contrasts with extracephalic sites where both pain perception and cortical potentials are reduced. We found no visually induced effect on heat pain evoked in migraineurs between attacks, possibly because of changes in connectivity of visual areas with the pain network.

**Disclosure:** Nothing to disclose

OS2112

**Headache yesterday - Analysing a new approach for estimating the burden of headache in children and adolescents**

C. Wöber-Bingöl¹, C. Wöber², D. Uludüz Uğurlu¹, U. Uygunoğlu¹, T.S. Aslan³, M. Kernmayer¹, G. Wagner¹, M. Kaya¹, H.-E. Zesch¹, A. Siva³, T.J. Steiner⁴

¹Child and Adolescent Psychiatry, ²Neurology, Medical University of Vienna, Vienna, Austria, ³Neurology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey, ⁴Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway

**Introduction:** Within our process of developing a questionnaire for a global study on burden of headache in children and adolescents we focus here on headache yesterday as a new approach for estimating the impact of headache (IoH) and quality of life (QoL) in headache sufferers.

**Methods:** In this pilot study, we administered a structured questionnaire (1) to pupils in Vienna (age 6-11 yr) and Istanbul (age 14-18 yr). The questionnaire included 45 questions, 14 on IoH and 13 on QoL. Six IoH questions and all QoL questions were rated on a 4-point Likert scale.

**Results:** We analysed 491 questionnaires: 122 from Vienna (49% girls, age 8.7±1.3 yr) and 369 from Istanbul (53% girls; age 15.8±0.9 yr). Headache yesterday was recorded by 27% of the children and by 30% of the adolescents and was associated with statistically significant differences from headache sufferers without headache yesterday: headache frequency was higher, duration longer, intensity more severe and use of abortive headache medication more common. Children and adolescents with headache yesterday more days with loss of own activities and with parental work loss. The IoH sum score was significantly higher in adolescents but not in children with headache yesterday compared to other headache sufferers. QoL was poorest in children and adolescents with headache yesterday, intermediate in other subjects with headache and best in headache-free controls.

**Conclusions:** This pilot study suggests that headache yesterday is a frequent problem and a useful predictor for the burden of headache in children and adolescents.

**Disclosure:** Nothing to disclose
Movement disorders 2

OS2113

Clinical and genetical analysis of Wilson’s disease families with pseudo-dominant inheritance

K. Dzieżyc¹, T. Litwin¹, G. Chabik¹, A. Członkowska¹,²
¹Second Department of Neurology, Institute of Psychiatry and Neurology, ²Department of Experimental and Clinical Pharmacology, Medical University of Warsaw, Warsaw, Poland

Introduction: Wilson’s disease (WD) is an autosomal recessive inherited disorder of copper metabolism caused by mutation of the ATP7B gene, which leads to copper accumulation and presents with hepatic, neurological symptoms. The prevalence of WD in most populations in previous studies is calculated as 1 in 30,000, the carrier frequency 1 per 90, so the risk of the offspring is 0.5%. The aim of the study was to establish frequency of pseudo-dominant inheritance among our WD patients. We also performed clinical and genetic analysis of affected members in families with pseudo-dominant inheritance.

Material and methods: In our registry by the end of October 2013 we had 742 WD confirmed cases. For the present analysis, we selected families where WD was diagnosed through consecutive generations. Diagnosis of WD was based on copper metabolism tests results, genetic testing and in uncertain cases radiocopper study was used.

Results: Between 1957 and October 2013, 1043 (623 siblings, 288 offspring, 103 parents) relatives of affected members were examined by family screening. Pseudo-dominant inheritance was observed in 8 non-consanguineous families. We identified 9 affected offspring of 7 probands. Eight of 9 diagnosed offspring were presymptomatic, 1 presented hepatic symptoms.

Conclusion: Our study showed higher (3.1%) than expected (0.5%) incidence of WD among offspring. This is in accordance with some recent studies which suggested higher WD gene prevalence in European population. Because WD is a treatable disorder, family screening should also be performed among probands’ offspring.

Disclosure: Nothing to disclose
OS2115

Skin nerve α-synuclein deposits: a biomarker for idiopathic Parkinson's disease

R. Liguori¹, A. Incensi², V. Leta², M.P. Giannoccaro¹, C. Scaglione², S. Cappellari¹, P. Avoni¹, A. Baruzzi², V. Donadio²
¹Dipartimento di Scienze Biomediche e Neuromotorie, Università di Bologna, ²IRCCS Istituto delle Scienze Neurologiche, Bologna, Italy

Introduction: To investigate
1) whether phosphorylated α-synuclein deposits in skin nerve fibers might represent a useful biomarker for idiopathic Parkinson's disease (IPD);
2) the underlying pathogenesis of peripheral neuropathy associated with IPD.

Methods: 21 well-characterized IPD patients were studied together with 20 patients with parkinsonisms assumed not to have α-synuclein deposits (PAR: 10 patients fulfilling clinical criteria for vascular parkinsonism, 6 for taupathies and 4 with parkin mutations) and 30 controls. Subjects underwent: nerve conduction velocities from the leg to evaluate large nerve fibers; skin biopsy from proximal (i.e. cervical) and distal (i.e. thigh and distal leg) sites to study small nerve fibers and deposits of phosphorylated α-synuclein, considered the pathological form of α-synuclein.

Results: IPD patients showed a small nerve fiber neuropathy prevalent in the leg with preserved large nerve fibers. PAR patients showed normal large and small nerve fibers. Phosphorylated α-synuclein was not found in any skin sample in PAR patients and controls but it was found in all IPD patients in the cervical skin site. Abnormal deposits were correlated with leg epidermal denervation.

Conclusions: The search for phosphorylated α-synuclein in proximal peripheral nerves is a sensitive biomarker for IPD diagnosis helping to differentiate IPD from other parkinsonisms. Neuritic inclusions of α-synuclein were correlated with a small fiber neuropathy suggesting their direct role in peripheral nerve fiber damage.

Disclosure: Nothing to disclose

OS2116

Abnormal tactile and proprioceptive temporal discrimination in psychogenic tremor

A. Peretti¹, A. Fasano², F. Bove², A. Conte³,⁴, C. Dall’Occhio⁵, C. Arbasino⁵, G. Defazio⁶, M. Fiorio¹, A. Berardelli³,⁴, M. Tinazzi¹
¹Department of Neurological and Movement Sciences, University of Verona, Verona, ²Department of Neurology, Catholic University, ³Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, ⁴Neuromed Institute, Pozzilli, ⁵Neurology Unit, Hospital of Voghera, Voghera, ⁶Department of Neurological and Psychiatric Science, University of Bari, Bari, Italy

Objectives: Tactile (TDT) and proprioceptive (TDMT) temporal discrimination thresholds, defined as the shortest interval at which two tactile stimuli and two passive movements are perceived as temporally separate, are reliable measures of somatosensory processing. We recently reported abnormal TDMT and normal TDT in patients with essential tremor of the upper limbs and the opposite pattern in patients with tremor associated with dystonia.

Methods: In the present study we assessed TDT and TDMT in 11 patients with psychogenic tremor of the upper limbs (Psy-T) and compared the results with those assessed in 11 patients with essential tremor (ET) and in 13 healthy subjects matched for age and sex.

Results: We found that Psy-T had significantly higher TDT values compared to ET and control subjects, while TDMT was significantly higher in both Psy-T and ET than in control subjects.

Conclusion: Our study, demonstrating a more widespread impairment of temporal processing of somatosensory (both tactile and proprioceptive) inputs in psychogenic than in essential tremor, highlights the involvement of different mechanisms in the two diseases.

Disclosure: Nothing to disclose
OS2117

Validation of “laboratory-supported” criteria for functional tremor

P. Schwingenschuh1, T.A. Saifee2, P. Katschnig-Winter1, M. Kög-Wallner1, A. Macerollo2, V. Culea1, Ç. Ghadery1, T. Pendl1, S. Seiler1, U. Werner1, E. Hofer1, N. Maurits3, M.A. Tijssen3, J.C. Rothwell2, R. Schmidt1, K. Bhatia2, M.J. Edwards2

1Medical University of Graz, Graz, Austria, 2Sobell Department, Institute of Neurology, UCL Institute of Neurology, London, United Kingdom, 3Department of Neurology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

Introduction: In a small group of patients, we have previously shown that a combination of electrophysiological tests was able to distinguish functional (FT) and organic tremor (OT) with excellent sensitivity and specificity. Here we aimed to validate this electrophysiological test battery as a tool to diagnose patients with FT based on a “laboratory-supported” level of certainty.

Methods: We prospectively recruited 40 patients with FT (mean age 37.3±24.7 years; mean disease duration 5.7±8.9 years) and 72 patients with OT (mean age 56.1±24.7 years; mean disease duration 16.1±17.8 years). Tremor was recorded at rest, posture (+loading), and action, while performing three tapping tasks, and while performing ballistic movements with the less affected hand. Analyses were performed as previously described (Schwingenschuh et al. Mov Disord 2011) by raters blinded to the clinical diagnosis. A subset of recordings was analyzed by three blinded raters and another subgroup of patients was tested twice on different days.

Results: Patients with FT had a higher average score on the test battery, compared to patients with OT (3.5±1.5 points versus 1.0±0.8 points; p<0.001). The predefined cut-off score for a diagnosis of laboratory-supported FT with 3 out of 10 points yielded a test sensitivity of 85.0% and a specificity of 95.8%; p<0.001. We demonstrated good interrater-reliability and test-retest-reliability.

Conclusions: We propose this test battery as the basis of laboratory-supported criteria for the diagnosis of functional tremor and we now encourage its use in the work-up of patients with presumed FT.

Disclosure: Nothing to disclose

OS2118

Phenotypic spectrum of SNCA G209A mutation carriers for familial Parkinson’s disease in Greece

D. Papadimitriou1,2, R. Antonelou3, M. Stamelou3, M. Bozi3, M. Maniati1, N. Papagiannakis1, S. Bostantjopoulou4, A. Leonardos4, S. Papageorgiou5, G. Hadjigeorgiou6, E. Kapaki4, G. Tagaris7, A. Papadimitriou8, A. Athanassiadou8, L. Stefanis1,3

1Biomedical Research Foundation of the Academy of Athens, 2Henry Dunant Hospital, 3University of Athens, Medical School, Attikon University Hospital, Athens, 4Aristotle University of Thessaloniki Medical School, Thessaloniki, 5University of Athens, Medical School, Aiginito Hospital, Athens, 6University of Thessaly, Medical School, Larissa, 7G. Gennimatas General Hospital, Athens, 8University of Patras Medical School, Patras, Greece

Introduction: The G209A mutation in the SNCA gene encoding for alpha-synuclein was the first Mendelian genetic defect identified in Parkinson’s Disease. The mutation occurred in families of Italian and Greek origin with an autosomal dominant pattern of inheritance.

Methods: As part of the FP7 Project MEFOPA, we are attempting to
1) identify living carriers of the G209A SNCA mutation in Greece,
2) register demographic and clinical information,
3) perform relevant questionnaires and scales,
4) obtain biological samples in order to establish the phenotype of the disease, and to examine questions regarding its biological underpinnings.

Results: We have so far registered 30 mutation carriers and we have followed them for at least two years. Of the 30 carriers, 8 are asymptomatic. 7 probands belong to new families, apparently unrelated to those already known to carry the G209A SNCA mutation. Mean age of disease onset is 44.8±10.3 years (range 30-65), and mean disease duration is 7.1±4.3 years (range 0.5-18). There is a large variability in the clinical phenotype ranging from a still asymptomatic carrier at age 90 to subjects presenting with early disease onset and either a relatively benign clinical course or rapid progression to dementia. There is also a varied range of presentation of Non-Motor symptoms such as depression, psychosis and dementia.

Conclusions: G209A SNCA carriers demonstrate a wide clinical phenotypic spectrum. Greek PD patients with a compatible inheritance pattern should be screened for this mutation. The biggest challenge now is to identify the biological basis of this variability providing a foundation for novel therapeutics.

Disclosure: Nothing to disclose
Multiple sclerosis and related disorders 2

OS2119

Are GABA levels abnormal in progressive MS?

N. Cawley1, B. Solanky2, N. Muhlert3, C. Wheeler-Kingshott4, A. Thompson4, O. Ciccarelli4
1Department of Brain Repair & Rehabilitation, 2Department of Neuroinflammation, UCL Institute of Neurology, London, 3Cognitive Neuroscience, Cardiff University, Cardiff, 4NIHR UCL-UCLH Biomedical Research Centre., London, United Kingdom

Introduction: Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the human brain. Given the possible involvement of GABA in motor impairment and cognitive problems in MS, we sought to develop 1H Magnetic Resonance Spectroscopy (MRS) at 3T to measure GABA in the sensorimotor cortex (SMC), pre-frontal cortex (PFC) and, for the first time in MS, in the hippocampus (HPC). These have been identified as key areas in cognitive and motor function and correlate with performance on clinical tests. We looked at secondary progressive MS patients, as it is crucial to understand the mechanism underlying progressive disease.

Methods: Written informed consent was obtained from 21 patients with SPMS (15F, 6M), mean age 50.42 yrs (SD 8.80), and 16 healthy controls (9F, 7M), mean age 43.80 (SD 12.5).

Results: Patients showed reduced [GABA+] in the HPC (mean=0.99mM (patients) vs. 1.44mM (controls), p=0.044) and a trend towards reduced [GABA+] in the SMC (mean=1.30mM (patients) vs. 1.52mM (controls), p=0.068) compared to healthy controls. No statistical difference in [GABA+] in the PFC was seen between groups. In patients, reduced right upper and lower limb power measured using the MRC (Medical Research Council) scoring system, was associated with lower [GABA+] levels in the left SMC (rs=0.45, p=0.013).

[Coronal images depicting the right hippocampus, pr]

Conclusions: Using the MEGA-PRESS 1H MRS at 3T, this study provides the first evidence that [GABA+] is reduced in the hippocampus and sensorimotor cortex in secondary progressive MS patients when compared to healthy controls. In patients, reduced [GABA+] in the sensorimotor cortex correlates with motor dysfunction.

Disclosure: Nothing to disclose

OS2120

Serum biomarkers predict IFNb treatment response in patients with multiple sclerosis

H. Hegen1, R. Axtell2, Y. Hu2, A. Millonig1, A. Bertolotto1, M. Comabella2, G. Giovanonni2, M. Gugger4, M. Hoelzl1, M. Khalili7, J. Killestein3, R. Lindberg6, S. Malucchi1, M. Mehling8, X. Montalban4, D. Rudzik1, F. Schautzer9, F. Sellebjerg11, P.S. Sorensen11, L. Steinman12, F. Deisenhammer3
1Department of Neurology, Innsbruck Medical University, Innsbruck, Austria, 2Department of Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, United States, 3Centro Riferimento Regionale Sclerosi Multipla, AOU San Luigi Gonzaga, Turin, Italy, 4Centre d’Esclerosis Multiple de Catalunya, Hospital Universitari Vall d’Hebron, Barcelona, Spain, 5Blizard Institute of Cell and Molecular Science, Barts and The London School of Medicine and Dentistry, London, United Kingdom, 6Department of Neurology, Allgemeines Krankenhaus Linz, Linz, 7Department of Neurology, Medical University of Graz, Graz, Austria, 8Department of Neurology, VU Medical Center, Amsterdam, Netherlands, 9Department of Biomedicine and Neurology, Clinical Neuroimmunology, University Hospital Basel, Basel, Switzerland, 10Department of Neurology, Landeskrankenhaus Villach, Villach, Austria, 11Department of Neurology, Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark, 12Beckman Center for Molecular Medicine, Stanford University, Stanford, CA, United States

Introduction: A considerable proportion of multiple sclerosis (MS) patients do not respond to interferon-beta (IFNβ) treatment. Apart from neutralizing antibodies there are no biomarkers that predict IFNβ treatment response.

Objective: To investigate whether serum markers can predict IFNβ treatment response.

Methods: Patients with MS or clinically isolated syndrome receiving de novo IFNβ treatment were included in this prospective multicenter study. Number of relapses two years prior to and two years after IFNβ initiation were monitored. Serum samples were collected at baseline and after 3 months on therapy. Cytokines were assessed by Luminex multiplex assay. Baseline samples were grouped using Gene Cluster software. Clinical outcome in these groups were assessed by relapses pre- and post-initiation of therapy.

Results: Baseline cytokine profiles of patients were clustered into three groups. Group 1 had elevated IL-8, CXCL1/Gro-α, CD40L and Eotaxin concentrations. Group 2 showed elevated CD40L and Eotaxin but low IL-8 and CXCL1/Gro-α levels. Group 3 were low for all cytokines. 24 months after therapy, 34.8% of patients in group 1 were relapse free, whereas 70.3% and 50.8% of patients in group 2 and group 3, respectively, remained relapse free. Patients in group 2 and group 3 had reduced relapses after IFNβ treatment. Group 1 had no difference in relapses pre and post treatment.

Conclusions: Patients with elevated baseline serum CD40L and Eotaxin, but low IL-8 and CXCL1 are more likely to respond to IFNβ treatment compared to patients with high IL-8 and CXCL1/Gro-α.

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OS2121

Dynamics of brain iron accumulation differ between clinically isolated syndrome and multiple sclerosis: a longitudinal 3T MRI study

M. Khalil¹, C. Langkammer¹, A. Pichler¹, D. Pinter¹, A. Mader¹, G. Bachmaier², S. Ropele³, S. Fuchs³, C. Enzinger¹, B. Alfano¹
¹Department of Neurology, ²Institute for Medical Informatics, Statistics and Documentation, ³Department of Radiology (Division of Neuroradiology), Medical University of Graz, Graz, Austria

Introduction: Increased iron concentration in cerebral deep grey matter is a consistent finding in multiple sclerosis (MS) while respective results have been controversial in patients with a clinically isolated syndrome (CIS). This suggests a temporal dynamic of iron accumulation.

Methods: We studied 76 CIS and 67 MS patients with baseline and follow-up 3T MRI (median follow-up CIS 2.6 yrs, MS 3.0 yrs; p=n.s.). Iron deposition in caudate nucleus, globus pallidus, putamen and the thalamus was assessed by automated, regional calculation of R2* rates. We further determined T2 lesion load and percentage of brain volume change (PBVC).

Results: In CIS, R2* relaxation rates significantly increased over time in the globus pallidus (p<0.001), putamen (p<0.001) and the caudate nucleus (p<0.005), whereas R2* rates within the thalamus decreased (p<0.05). In contrast in MS, R2* rates only slightly increased in the putamen (p<0.05), remained stable in the globus pallidus and caudate nucleus and significantly decreased in the thalamus (p<0.01). Using a hierarchical regression analysis, the change of R2* rates within the globus pallidus independently predicted PBVC in CIS (β=-0.4, p<0.05) but not in MS. There were no correlations with the change in other morphologic variables.

Conclusions: Iron accumulation is an early phenomenon of the disease, which parallels brain volume loss and appears to plateau over time. These dynamics suggest that higher iron concentration in MS is a consequence of ongoing morphologic damage. Whether increased iron concentration exerts detrimental effects of its own deserves separate investigation.

Disclosure: Nothing to disclose

OS2122

Brain atrophy in relapsing-remitting multiple sclerosis patients treated with interferon-beta and atorvastatin (The ARIANNA study)

R. Lanzillo¹, M. Quarantelli², V. Veria¹, G. Orefice¹, M.G. Marrosu¹, M. Trojano², M.P. Amato³, A.M. Francia⁴, C. Florio⁴, G. Tedeschi⁵, P. Bellantoni⁶, P. Annunziata⁷, M. Comerci², A. Brunetti¹, V. Bonavita¹, B. Alfano², S. Marini¹, C. Pozzilli¹, V. Brescia Morra¹
¹Federico II University, ²National Research Council, Naples, ³Cagliari University, Cagliari, ⁴Bari University, Bari, ⁵Florence University, Florence, ⁶Sant’Andrea Hospital, Rome, ⁷Cardarelli Hospital, ²Second University of Naples, Naples, ⁸Neuromed, Pozzilli, ⁹Siena University, Siena, ¹⁰IDC Hermitage Capodimonte, Naples, ¹¹University of Rome Sapienza, Rome, Italy

Introduction: Statin effects on brain atrophy in multiple sclerosis (MS) is still poorly investigated, although a neuroprotective effect has been suggested.

Methods: This multi-center, double-blind, randomized, placebo-controlled, study in 154 RRMS patients in treatment with IFN-beta 1b, compared for 24 months the add-on of atorvastatin 40 mg p.o.daily to placebo, to evaluate efficacy on cerebral atrophy. MSFC score, Rao battery and brain MRI were obtained at baseline and yearly since then. The MRI scans were analysed centrally in a blinded fashion by a core lab. MRI volumes were segmented into Grey Matter, normal and abnormal White Matter, and cerebrospinal fluid using a fully automated relaxometric method.

Results: Intent to treat (ITT) patients were 75 in the atorvastatin arm and 79 in the placebo. Month 24 was reached by 97 patients (63%). Patients clinical and demographic characteristics were not different in the two groups. Brain atrophy over 2 years was not different in the two groups, even when analyzing the two years separately (-0.367% and -0.382 for the atorvastatin and -0.302% and -0.545% for the placebo groups respectively). Stratification of patients for the presence of gadolinium enhancement at baseline MRI did not reveal significant differences in brain atrophy. No differences in secondary endpoints were found between the two groups.

Conclusions: Our data indicate Class I evidence that atorvastatin 40 mg daily as an add-on therapy with IFN-beta 1b, despite being safe, has no effect on brain atrophy changes or on other disease activity and progression parameters.

Disclosure: Nothing to disclose
OS2123

Longitudinal changes of global and compartmental brain atrophy in patients with clinically isolated syndrome and clinically definite multiple sclerosis using 3-Tesla magnetic resonance imaging

A. Pichler1, M. Khalil1, C. Langkammer1, A. Mader1, G. Bachmaier2, S. Ropele1, S. Fuchs1, D. Pinter1, C. Enzinger1, F. Fazekas1
1Department of Neurology, 2Institute for Medical Informatics, Statistics and Documentation, 3Department of Radiology (Division of Neuroradiology), Medical University of Graz, Graz, Austria

Background: Brain atrophy is an important element in the course of multiple sclerosis (MS) but its association with different phases of the disease is still under discussion.

Aim: To determine the rate and clinical association of global and compartmental brain atrophy in patients with a clinically isolated syndrome (CIS) compared to patients with clinically definite MS (CDMS) by long-term follow-up.

Methods: We investigated 63 CIS and 57 CDMS patients at baseline and after 3-4 years with detailed clinical examination and a comprehensive MR imaging protocol at 3T. Imaging assessment consisted of the annual change of brain parenchymal fraction (BPF), grey matter (GMF) and white matter (WMF) fractions, the percentage of brain volume change (PBVC) and change of T2 lesion load (T2-LL).

Results: The age at baseline and mean follow-up time were comparable between CIS and CDMS. During follow-up 33 CIS patients (52.4%) converted to CDMS. While BPF (p=0.018) and WMF (p=0.008) were significantly lower in CIS patients at baseline, the T2-LL in CDMS was significantly higher (p=0.003). CIS and CDMS patients had comparable rates of GMF, WMF and BPF changes over time but the PBVC was significantly higher in CDMS patients at baseline, the T2-LL change (PBVC) and change of T2 lesion load (T2-LL).

Conclusion: The rate of global and compartmental brain atrophy is comparable between CIS and CDMS and especially pronounced in CIS converters, with PBVC being the most sensitive marker. This confirms the importance of brain volume changes to monitor the evolution of MS already early on.

Disclosure: Nothing to disclose

OS2124

The CSF JCV antibody index for diagnosis of natalizumab-associated PML

1University Düsseldorf, Düsseldorf, Germany, 2National Institute of Neurological Disorders and Stroke (NINDS), Bethesda, MD, United States, 3Ruhr University Bochum, St. Josef-Hospital, Bochum, 4German Cancer Research Center (DKFZ), Heidelberg, 5Ludwig-Maximilians-Universität München, München, 6Caritas Hospital, Bad Mergentheim, 7Hannover Medical School (MMH), Hannover, 8Johannes Welsing Hospital Minden, Minden, 9Merheim Hospital, Köln, 10Marienhospital, Hamburg, 11Julius-Maximilians-University, Würzburg, Germany, 12VU Medical Center, Amsterdam, Netherlands, 13Umeå University Hospital, Umeå, 14Karolinska Institutet, Stockholm, Sweden

Introduction: Progressive multifocal leukoencephalopathy (PML), caused by JC virus (JCV), can occur in patients receiving natalizumab for multiple sclerosis (MS). JCV detection by quantitative polymerase chain reaction (qPCR) in cerebrospinal fluid (CSF), or brain biopsy is required for probable or definite diagnosis of PML. However, in some patients only low levels of JCV-DNA (<100 copies/ml) are present in CSF, making the diagnosis challenging.

Objective: To assess the complementary value of a CSF JCV antibody index (AJJC) in the diagnosis of natalizumab-associated PML.

Methods: In 37 cases of natalizumab-associated PML and 89 MS-patients treated with natalizumab without PML AJJC was assessed. Sera and CSF were tested in a capture ELISA, using JCV-VP1 fused to glutathione S-transferase (GST) as antigen. Albumin levels and total IgG concentration were determined by immunonephelometry, and the AJJC was calculated as published.

Results: Twenty-six of 37 (70%) patients with natalizumab-associated PML exhibited an AJJC>1.5, while this was seen in none of the controls (p<0.0001). At time of the first positive qPCR for JCV-DNA, 11/20 (55%) of patients with natalizumab-associated PML had an AJJC>1.5. JCV-DNA levels of <100 copies/ml were seen in 14/20 (70%) of these patients of which 8 (57%) demonstrated an AJJC>1.5.

Conclusions: Determination of the AJJC could be an added tool in the diagnostic workup for PML and should be included in the case definition of natalizumab-associated PML.

Disclosure: Dr. Warnke reports grants and personal fees from European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), during the conduct of the study.
OS2201

Interictal epileptic networks and postsurgical outcome using intracranial EEG-fMRI

U.J. Chaudhary1, D.W. Carmichael2, R. Rodionov1, S. Vulliemoz3, R. Thornton1, M. Pugnaghi4, C. Micallef4, A.W. McEvoy4, C. Scott4, B. Diehl1, M.C. Walker4, J.S. Duncan1, L. Lemieux1

1National Hospital of Neurology and Neurosurgery, Institute of Neurology, University College London, 2Institute of Child Health, University College London London, United Kingdom, 3University Hospital and Functional Brain Mapping Lab, Faculty of Medicine, Geneva, Switzerland, 4University of Modena and Reggio Emilia, Modena, Italy

Introduction: Most advanced localization techniques may fail to reveal the full extent of the epileptogenic zone (EZ), as 30% of patients with refractory focal epilepsy continue having seizures after surgery. In 14 patients with refractory focal epilepsy undergoing invasive presurgical evaluation, we compared the distribution of interictal epileptiform discharges (IED)-related blood-oxygen-level-dependent (BOLD)-changes with the invasively-defined epileptogenic zone (EZ) and postsurgical-outcome, using simultaneous intracranial EEG-fMRI (iEEG-fMRI).

Methods: IEDs were classified according to their field distribution in 13 patients. BOLD changes were assessed using statistical-parametric-mapping (SPM8). SPM[F]-maps were generated for individual IED-types and for all IEDs originating in the EZ (‘combined-EZ-interictal-BOLD-map’) for each patient. The degree-of-concordance of the BOLD-maps was based on the localization of clusters in relation to the EZ. We evaluated the association between BOLD-changes in deep brain structures, degree-of-concordance and postsurgical-outcome.

Results: Fifty three different IED-types, identified across the group, revealed significant BOLD-changes in the EZ, healthy neocortex and deep brain structures. BOLD-changes in deep brain structures were associated with discordant maps. Ten patients who underwent surgery revealed 44 different IED-types and 33 IED-types originated in the EZ. BOLD-maps for 21/33 had a degree-of-concordance with the EZ. ‘Combined-EZ-interictal-BOLD-map’ had a degree-of-concordance with the EZ in 7/10 patients (postsurgical-outcome: ILAE-class-1=6, ILAE-class-3=1). Three patients had discordant ‘combined-EZ-interictal-BOLD-map’ and ILAE class 4 and 5 postsurgical-outcome. The higher level of concordance of ‘combined-EZ-interictal-BOLD-maps’ was significantly associated (rs=0.8; p<0.05) with ILAE-class-1 outcome.

Conclusions: Intracranial-EEG-fMRI can map IED-related BOLD-changes across the whole brain, and their degree-of-concordance with the EZ may help to understand postsurgical-outcome.

Disclosure: Nothing to disclose

OS2202

White matter development in children with benign childhood epilepsy with centro-temporal spikes

C. Ciumas1, M. Saignavongs1, F. Ilski1,2, V. Herbillon1,2, A. Laurent1,2, A. Lothe1, R.A. Heckemann1,4, J.D. Bellescize2, E. Panagiotakaki2, S. Hannoun3, D. Sappey Marinier5,6, A. Montavont2, K. Ostrowsky-Coste2, N. Bedoin2,3, P. Ryvlin1,2

1INSERM U 1028, CNRS UMR 5292, Centre de Recherche en Neurosciences de Lyon, Translational and Integrative Group in Epilepsy Research (TIGER), Universite Lyon-1, 2Department of Paediatric Sleep, Epilepsy and Clinical Neurophysiology and Department of Functional Neurology, Hospices Civils de Lyon, Bron, 3The Neurodis Foundation, Lyon, France, 4Institute for Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden, 5UMR 5220 & INSERM U 1044, CREATIS-CNRS, 6CEIREM - Imagerie du Vivant, 7Laboratoire Dynamique du Langage, CNRS UMR 5596, 8Université Lyon2, Lyon, France

Introduction: Benign childhood epilepsy with centro-temporal spikes (BCECTS) is an age-dependent epilepsy with rare seizures, focal EEG abnormalities, and moderate cognitive dysfunctions. It is hypothesized that interictal EEG discharges might interfere with local brain maturation, resulting in altered cognition. Diffusion tensor imaging (DTI) allows testing this hypothesis by investigating the white matter microstructure.

Methods: We investigated 25 children suffering from BCECTS and 25 age-matched controls and explored changes in white matter (fractional anisotropy (FA) and diffusivity). We used a voxel-based analysis (FSL, SPM8) to detect abnormalities at both the group and individual levels, contrasting patients and controls. FA and diffusivity images were further correlated to neuropsychological and clinical variables.

Results: Group analysis showed significantly reduced FA and increased diffusivity in patients compared with controls, predominantly over the left pre- and postcentral gyri and ipsilateral to the EEG focus. At the individual level, regions of significant differences were observed in ten patients (40%) for anisotropy, and 17 (56%) for diffusivity. There were significant negative correlations between FA maps and duration of epilepsy in the precentral gyri, bilaterally, and in the left postcentral gyrus.

Conclusions: Children with BCECTS demonstrate alterations in the microstructure of the white matter, undetectable with conventional MRI, predominating over the regions displaying chronic interictal epileptiform discharges. The association observed between DTI changes, duration of epilepsy and cognitive performance appears compatible with the hypothesis that interictal epileptic activity alters brain maturation, which could in turn lead to cognitive dysfunction.

Disclosure: Nothing to disclose
OS2203

Surface EEG markers of underlying focal cortical dysplasia: a blinded analysis comparing epilepsy patients with dysplasia and other etiologies

N. Epitashvili1,2, V. San Antonio Arce1, A. Schulze-Bonhage1
1Epilepsy Center, University Hospital Freiburg, Freiburg, Germany, 2MediClubGeorgia, Tbilisi, Georgia

Introduction: Focal cortical dysplasia (FCD) is among the most frequent cortical alterations underlying pharmaco-resistant epilepsy. High diagnostic effort is necessary to identify dysplastic cortical changes in many patients. Here surface EEG recordings were analyzed in patients with FCD with other etiologies to analyze if specific patterns distinguish dysplastic brain areas.

Methods: Surface EEG recordings from 103 patients with pharmaco-resistant focal epilepsy, recorded during wakefulness and sleep, were analyzed retrospectively in a blinded fashion by three certified electrophysiologists. 66 patients had histologically ascertained FCD, 37 patients other etiologies. Surface EEG patterns reported in the literature as well as other visually identified patterns were classified as either present or not in each patient. Statistical analysis was performed using Fisher’s exact test to analyze whether the presence of a specific pattern was associated with an underlying dysplastic brain lesion. Results were considered statistically significant when p<0.01.

Results: Beta bursts, frequent bursting rhythmic epileptiform activity and continuous rhythmic slowing were significantly more frequent in regions overlying cortical dysplasia, whereas other markers were found to be present, but not specific for dysplasia.

Conclusions: Three surface EEG markers were identified which, when present, point to an underlying dysplastic lesion in the patients studied here. Other markers previously reported were not specific for this etiology, showing the need for control groups in the interpretation. Surface EEG may assist to identify not only the region but also the etiology of patients with cortical dysplasia, and may steer specific high resolution imaging in patients with pharmaco-resistant focal epilepsy.

Disclosure: This study was supported by EFNS educational grant

OS2204

Efficacy of antiepileptic drugs on secondary generalized tonic-clonic seizures in patients with drug-resistant partial epilepsy: a meta-analysis

S. Rheims, C. Hemery, P. Ryvlin
Department of Functional Neurology and Epileptology, Hospices Civils de Lyon, Lyon, France

Introduction: There is currently no effective treatment to prevent Sudden Unexpected Death in Epilepsy (SUDEP), apart from optimising antiepileptic drugs (AEDs). In patients with drug-resistant partial epilepsy, secondary generalised tonic-clonic seizures (SGTCS) represent the main risk factor of SUDEP and their prevention might therefore be an important parameter for treatment choice. However, whether or not some AEDs might be more efficacious than other on SGTCS remains unknown.

Methods: We performed a meta-analysis of randomised placebo-controlled trials of adjunctive AED in which information on efficacy outcomes (i.e responder rate and/or frequency per 28 days relative to baseline) were available both for all seizure types and for SGTCS. The primary analysis evaluated the efficacy of AEDs on all types of seizure and on SGTCS by comparing the responder rate in the AED treatment group with that observed in the placebo group.

Results: Responder rate was available both for all seizure types and for SGTCS in 13 of the 72 eligible trials, evaluating seven AEDs. Only three AEDs, lacosamide, perampanel and topiramate, showed significant greater efficacy than placebo on SGTCS. However, confidence intervals of relative risks overlapped for all AEDs. Moreover, there was a non-significant trend toward a lower relative risk of responder rate for SGTCS than for all seizure types, which appeared related to a greater response to placebo for this outcome.

Conclusion: These data did not support robust differences between AEDs to prevent SGTCS. Alternative designs for evaluation of therapeutic interventions in patients at risk of SGTCS-related complications are required.

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OS2205
Clinical- and cost-effectiveness of a nurse led self-management intervention to reduce emergency visits by people with epilepsy
L. Ridsdale¹, P. McCrone², P. Seed³, L. Goldstein⁴, A. Noble⁵
¹Clinical Neuroscience, ²Department of Health Service & Population Research, ³Division of Women’s Health, ⁴Department of Psychology, King’s College, London, London, ⁵Department of Psychological Sciences, University of Liverpool, Liverpool, United Kingdom

Introduction: Some people with chronic epilepsy (PWE) make frequent, costly, and clinically unnecessary emergency department (ED) visits. No studies have examined interventions to reduce them. An intervention delivered by an epilepsy nurse specialist (ENS) might reduce visits. We examined such an intervention’s clinical- and cost-effectiveness.

Methods: Eighty-five adults with epilepsy were recruited from three London EDs. Forty-one PWE recruited from two EDs received treatment-as-usual (TAU). The remaining 44 PWE were recruited from the ED of a hospital that had developed an ENS service for PWE attending ED. They were offered 2 one-to-one sessions with an ENS, plus TAU. Participants completed questionnaires on health service use and psychosocial well-being at baseline, 6- and 12-month follow-up.

Results: Sixty-nine (81%) participants completed follow-up. There was no significant effect on ED visits at 12 months. However, due to less time as inpatients, the average service cost for intervention participants over follow-up was less than for TAU participants’ (adjusted difference £558, 95% CI, £-2409, £648). Covariates most predictive of subsequent ED visits were patients’ baseline feelings of stigmatization due to epilepsy and low confidence in managing epilepsy.

Conclusions: The intervention did not lead to a reduction in ED use, but did not cost more, partly because those receiving the intervention had shorter hospital admissions. Our findings on long-term ED predictors clarifies what causes ED use, and suggests that future interventions might focus more on patients’ perceptions of stigma, and on their confidence in managing epilepsy. If addressed, ED visits might be reduced and efficiency-savings generated.

Disclosure: Nothing to disclose

OS2206
Abstract withdrawn
Motor neurone diseases

OS2207

The distinct genetic pattern of ALS in Turkey

1Neurology Department, Hadassah Hebrew University Medical Center, Jerusalem, 2Felsenstein Medical Research Centre, Tel Aviv University, Tel Aviv, 3BrainStorm Cell Therapeutics, Petach Tikvah, 4Rabin Medical Centre, Tel Aviv University, Tel Aviv, Israel

Introduction: Recently the frequency of ALS mutations has been extensively investigated in several populations, however a systematic analysis has not been reported in Turkey so far.

Methods: A total of 411 Turkish ALS patients, 96 fALS, belonging to 66 families, and 315 sALS cases were screened for mutations in common ALS genes. Patients were genotyped for SOD1 and UBQLN2 gene mutations via conventional PCR; for C9orf72 RP-PCR and Southern blotting were performed. A subset of patients was also subjected to exome sequencing. Haplotype analysis was applied to patients carrying the SOD1-D90A mutation.

Results: SOD1 (12%), C9orf72 (13.5%) and UBQLN2 (6%) gene mutations were found to account for approximately 30% of fALS in Turkey. While no SOD1 mutations were shown so far in Turkish sALS patients; C9orf72 (3.5%) and UBQLN2 (0.7%) explained 4.2% of sALS in the cohort under study. Exomic sequencing revealed FUS, OPTN, SPG11 and PLEKHG5 mutations in four families. SOD1-D90A, known to occur in dominant and recessive pedigrees, behaved as a recessive trait in all three Turkish families in this study with the common Scandinavian founder haplotype.

Conclusions: In the framework of this study we report a systematic screening of Turkish ALS patients for disease-causing mutations. Our results indicate that SOD1, C9orf72 and UBQLN2 mutations are important genetic causes of ALS in the Turkish population. The frequency of SOD1 is consistent with other Mediterranean countries. The spectrum of mutations reflects both the different genetic background and the more heterogeneous nature of the Turkish population.

Disclosure: Nothing to disclose

OS2208

Analysis of patients with amyotrophic lateral sclerosis (ALS) treated with autologous differentiated mesenchymal stem cells: a phase I/II and Ila clinical trial

D. Karussi1, P. Petrou1, D. Offen2, Z. Argov3, M. Goudkin1, Y. Levi1, Y. Gothelf2, L. Kassiss3, A. Vaknin Dembinski1, T. Ben Hur1, E. Melamed4
1Neurology Department, Hadassah Hebrew University Medical Center, Jerusalem, 2Felsenstein Medical Research Centre, Tel Aviv University, Tel Aviv, 3BrainStorm Cell Therapeutics, Petach Tikvah, 4Rabin Medical Centre, Tel Aviv University, Tel Aviv, Israel

Aim: To evaluate the safety and tolerability of treatment with autologous mesenchymal stem cells differentiated to secrete neurotrophic factors (“MSC-NTF”) in ALS patients.

Background: Previous study from our group has shown the safety of IV/IT administration of unmodified MSC in ALS patients. The neuroprotective effects of MSC-NTF have been demonstrated in various animal models of neurodegenerative diseases, including ALS. We are currently conducting the second part of two sequential clinical trials to evaluate the safety and tolerability of autologous MSC-NTF cells in ALS patients.

Methods: MSC were isolated from the bone marrow of 12 ALS patients, expanded ex-vivo and induced to secrete neurotrophic factors such as GDNF and BDNF using BrainStorm’s NurOwn™ technology. These autologous MSC-NTF cells were transplanted by IM or IT injections to ALS patients. All patients were followed up on a monthly basis for a pre-treatment period of 3 months and for 6 months post-transplantation.

Results: During the six-month follow-up of the 12 transplanted patients, no serious treatment-related adverse events were observed. The clinical follow-up revealed a change in the rate of clinical progression (ALSFRS) and respiratory function (FVC) in favor of the IT-treated patients during the six months following treatment.

Conclusions: This trial showed that intrathecal or intramuscular injection of MSC-NTF is safe and revealed some indications of clinical beneficial effects. In the second part of the ongoing Phase Ila, 12 additional ALS patients are currently receiving combined IM and IT treatment with escalating doses of MSC-NTF cells. More detailed and updated data from this trial will be presented.

Disclosure: Nothing to disclose
OS2209
Development of a gene therapy for sporadic ALS by normalizing ADAR2 activity in the motor neurons using a vascular type AAV vector
S. Kwak1, T. Yamashita1, H.L. Chai1, S. Teramoto1, S.-I. Muramatsu2
1University of Tokyo, Tokyo, 2Jichi Medical University, Utsunomiya, Japan

Introduction: Amyotrophic lateral sclerosis (ALS) develops in the middle-aged and elderly and is a fatal disease characterized by progressive muscular weakness resulting from degeneration of motor neurons. There is no known cure preventing patients from death. Downregulation of the RNA editing enzyme ADAR2 is involved in the death of motor neurons of sporadic ALS, which accounts for the great majority of cases of the disease. Therefore, normalization of ADAR2 activity in motor neurons is likely a therapeutic strategy for ALS.

Methods: We developed an adeno-associated virus serotype 9 (AAV9) vector that provides gene delivery to a wide array of central neurons after peripheral administration. Using conditional ADAR2 knockout mice (AR2), which comprise a mechanistic mouse model of sporadic ALS, we investigated whether the delivery of the human ADAR2 gene by the AAV9 vector enabled to enhance ADAR2 activity in the motor neurons to a level sufficient to stop the disease progression.

Results: A single intravenous injection of AAV9-ADAR2 in AR2 mice caused expression of exogenous ADAR2 in the central neurons and effectively prevented progressive motor dysfunction. Notably, AAV9-ADAR2 rescued the motor neurons of AR2 mice from death by normalizing TDP-43 expression. There was no detectable glial reaction in the brains or spinal cords of AAV-treated AR2 mice.

Conclusions: One intravenous injection alone was sufficient to safely bring about long-lasting expression of an effective quantity of the ADAR2 gene in the mouse motor neurons. This AAV9-mediated ADAR2 gene delivery may therefore enable the development of a gene therapy for ALS.

Disclosure: Nothing to disclose

OS2210
Cognitive changes and white matter tract damage in the motor neuron disease spectrum
E.G. Spinelli1,2, F. Agosta1, E. Canu1, P.M. Ferraro1, N. Riva2, M. Copetti3, A. Chiò4, S. Messina5, S. Iannaccone6, A. Calvo4, V. Silani3, A. Falini7, G. Comi2, M. Filippi1,2
1Neuroimaging Research Unit, Institute of Experimental Neurology, 2Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, 3Biostatistics Unit, IRCCS-Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), 4Department of Neuroscience, University of Turin, Turin, 5Department of Pathophysiology and Transplantation, IRCCS Istituto Auxologico Italiano, University of Milan, 6Department of Clinical Neurosciences, 7Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To assess the relationship between white matter (WM) tract abnormalities and cognitive changes in patients within the motor neuron disease (MND) spectrum using diffusion tensor (DT) MRI tractography.

Methods: 81 MND patients (including 40 amyotrophic lateral sclerosis [ALS]), 31 primary lateral sclerosis/pure upper motor neuron, and 10 progressive muscular atrophy [PMA]) and 35 controls were studied. All patients underwent clinical evaluation, neuropsychological assessment, and DT MRI. To fulfill criteria for cognitive impairment, patients had to demonstrate impairment in at least 2 validated executive tasks. The presence of non-executive cognitive impairment was also considered. DT MRI metrics were obtained from corpus callosum (CC), corticospinal tract and extra-motor tracts. Group comparisons were assessed using age-adjusted linear regression models. WM damage contribution to cognitive deficits was assessed using Spearman correlation coefficients adjusted for age and ALSFRS-r.

Results: No PMA patients had cognitive impairment. In the remaining group, seven patients (9.7%) had frontotemporal dementia, six patients (8.6%) had an executive cognitive impairment, and non-executive deficits were found in two patients (2.8%). Relative to controls, ALS patients showed damage to motor and extra-motor tracts (p<0.001-0.49). PMA patients did not show tract damage. In the whole MND group, verbal fluency, attention and executive function performances correlated with DT MRI measures of the CC, cingulum, inferior and superior longitudinal fasciculi, and uncinate bilaterally (R from -0.47 to 0.47; p<0.001-0.049). Correlations remained significant adjusting for ALSFRS-r.

Conclusions: Interhemispheric, limbic and associative WM tract degeneration is associated with neuropsychological deficits in patients with MND.

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OS2211

Genetic epidemiology of ALS in Italy

N. Ticozzi1,2, C. Tiloca1, B. Castellotti1, D. Calini1, V. Pensato1, C. Colombrita1,2, C. Morelli1, F. Verde1, S. Messina1, F. Taroni1, J.E. Landers4, A. Ratti1,2, C. Gellera3, V. Silani1,2
1Dept. of Neurology and Laboratory of Neuroscience, IRCCS Istituto Auxologico Italiano, 2Dept. of Pathophysiology and Transplantation, University of Milan, 3Units of Genetics of Neurodegenerative and Metabolic Disorders, Fondazione Istituto Neurologico ‘Carlo Besta’, Milan, Italy, 4Dept. of Neurology, University of Massachusetts Medical School, Worcester, MA, United States

Introduction: ALS is a genetically heterogeneous disease and causative mutations have been described in ~20 genes. Here we aim to determine the prevalence of mutations in ALS-associated genes in Italian patients with sporadic (SALS) and familial ALS (FALS), and to attempt a genotype-phenotype correlation.

Methods: We screened 925 patients (208 FALS and 717 SALS) for mutations in the C9orf72, SOD1, TARDBP, FUS, and ATXN2 genes. FALS cases were also screened for ANG, PFN1, OPTN, VCP, UBQLN2, SETX, and hnRNP A1-A2/B1.

Results: Pathogenic mutations were identified in 175 individuals (110 FALS and 65 SALS). The most common mutated gene in FALS was C9orf72 (24.5%), followed by SOD1 (8.5%), FUS (5.2%), and TARDBP (4.1%). In SALS patients, C9orf72 repeat expansions accounted for 4.9% and TARDBP mutations for 3.1% of cases. All other genes represented less than 3% of our cohort.

Conclusions: Clinical comparison among mutated patients revealed differences in site of onset (predominantly lower limbs for SOD1, bulbar for C9orf72), phenotype (predominant LMN signs for SOD1 and TARDBP; predominant UMN signs for ANG, OPTN and UBQLN2), age of onset and disease duration (reduced for C9orf72 and FUS), and concurrence of dementia (in C9orf72, TARDBP and FUS). For the most common mutations (C9orf72 repeat expansion; p.A4V, p.L84F, p.F45C, p.G93D, and p.L144F in SOD1; p.A382T in TARDBP; p.R521C in FUS) we could also observe distinct clinical phenotypes. Lastly, we observed a geographical clustering for some mutations, suggesting a founder effect. Our study thus represents a comprehensive survey on genetic epidemiology of ALS in Italy.

Disclosure: Nothing to disclose

OS2212

New data from BENEFIT-ALS: blinded evaluation of neuromuscular effects and functional improvement with tirasemtiv in ALS

J.M. Shefner1, A.A. Wolff2, L.L. Meng2, J.H. Lee2, J. James2, J.A. Andrews2, The BENEFIT-ALS Study Group
1State University of New York, Syracuse, NY, 2Cytokinetics, Inc., South San Francisco, CA, United States

Introduction: Tirasemtiv is a fast skeletal muscle activator that sensitizes the sarcomere to calcium and increases the force of muscle contraction at submaximal contraction rates. In previous studies, it was well tolerated in ALS patients, and dose dependent improvements on measures of muscle strength and patient function were noted.

Methods: ALS patients (N=711) were recruited from 73 centers in North America and Europe. Slow vital capacity was >50% of predicted, at least one handgrip was moderately weak, and ≥ 4 ALSFRS-R items scored 2 or 3. Before randomization, patients received 1 week of open-label tirasemtiv 125mg BID to ensure this dose was tolerated. Patients who tolerated open-label tirasemtiv were randomized 1:1 to double-blind placebo or tirasemtiv beginning at 125 mg BID and escalating weekly based on tolerability to a maximum of 250mg BID for a total of 12 weeks of treatment. ALSFRS-R and quantitative measures of respiratory and extremity muscle strength and endurance were assessed at baseline, after 4, 8, and 12 weeks of treatment, and 1 and 4 weeks after the last dose. Plasma concentrations of tirasemtiv were measured during double-blind treatment.

Results: The last patient was enrolled on November 27, 2013; the last visit will occur in late March, 2014. Safety and efficacy results related to the dose and plasma concentration of tirasemtiv, and the effects of withdrawing tirasemtiv after 12 weeks of treatment, will be presented.

Conclusions: BENEFIT-ALS tests the hypothesis that tirasemtiv increases skeletal muscle performance to improve function in ALS patients.

Disclosure: Dr. Shefner is a consultant to the sponsor, Cytokinetics, Inc. Drs. Andrews, Meng, James and Wolff and Ms. Lee are employees of the sponsor.
Movement disorders 3

OS2213

Cerebellar continuous theta burst stimulation in essential tremor

M. Bologna, L. Rocchi, G. Leodori, G. Paparella, A. Conte, A. Berardelli
Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy

Introduction: An abnormal cerebello-thalamo-cortical connectivity is thought to be involved in the pathophysiology of essential tremor (ET). In the present study we aimed to investigate whether the severity of postural tremor can be improved by non-invasive stimulation of cerebellum using the continuous theta-burst stimulation (cTBS) protocol. We also aimed to examine whether cTBS-related changes of postural tremor severity are reflected in excitability changes in the contralateral primary motor cortex (M1).

Methods: Fourteen Patients with ET and 10 healthy subjects underwent two experimental sessions: (i) cTBS of the right cerebellar hemisphere (real cerebellar cTBS) and (ii) cTBS over the neck muscles (sham cerebellar cTBS). The two sessions were performed at least one week apart. Postural tremor was rated clinically and objectively measured using kinematic techniques, before and after cerebellar cTBS. The M1 excitability was assessed by recording the input/output curve of the motor evoked potentials from the right first dorsal interosseous muscle.

Results: There were no significant changes in clinical tremor rating after real and sham cerebellar cTBS in patients with ET. Again, cerebellar cTBS did not modify the postural tremor total power assessed with kinematic techniques in patients. Real cerebellar cTBS, but not sham cerebellar cTBS, reduced the excitability in the contralateral M1 only in healthy subjects but not in patients with ET (p< 0.05).

Conclusions: The results suggest that the cerebello-thalamo-cortical connectivity is abnormal in ET and as a consequence cerebellar cTBS does not modify the severity of postural tremor and the M1 excitability in this condition.

Disclosure: Nothing to disclose

OS2214

OPTIPUMP study: impact of apomorphine pump therapy at 6 months on 145 parkinsonian patients' quality of life. A multicentre French observational prospective study

1Neurology, 2CHU Pontchaillou, Rennes, 3CHU, Lille, 4CHU, Marseille, 5APHP, Paris, 6CHU, Aix en Provence, 7CHU, Toulouse, 8CHU, Strasbourg, 9CHU, Grenoble, 10Orkyn, Paris, 11Aguettant, Lyon, 12CHU, Clermont-Ferrand, France

Introduction: Apomorphine pump is used in patients suffering from Parkinson's disease with motor fluctuations and/or dyskinesia. However the efficacy and tolerance of apomorphine pump and the strategies used remain not well known.

Methods: Inclusion criterias were parkinsonian patients ≥18 years with refractory motor fluctuations and/or levodopa-induced dyskinesia. Patient characteristic, dose and duration of all treatment are described. Primary endpoints are PDQ 39 and CGI-Improvement (evaluated both by patient and physician). Secondary endpoints are UPDRS and Ardouin behavioural scale. Endpoints are recorded at baseline, 3 months and 6 months.

Results: 145 patients with apomorphine pump were included (59% female). The average age of patients was 66.8±10.8 years. The average disease duration was 11.6±5.4 years. 97% of patients had motor fluctuations and 86% had dyskinesias. At hospital discharge, 10% of patients were treated without dopamine agonists nor L-dopa (apomorphine pump monotherapy), 57% with L-dopa, 32% with L-dopa and a dopamine agonist. At 6 months, 73% of patients according to neurologist and 70% according to the patient themselves were very much improved, much improved or minimally improved on the CGI-I. According to Ardouin behavioural scale, no more hyperdopaminergic side effects were observed with apomorphine pump. Anxiety, depressive mood, hyperemotivity and non-motor fluctuations (On/Off) were slightly improved. At 6 months, dropout rate was 28%.

Conclusions: Globally, the different treatment strategies used at the apomorphine pump introduction appear to be effective and well tolerated in accordance to previous data. Apomorphine pump presents a good benefit/risk ratio.

Disclosure: Nothing to disclose
OS2215

Prevalence of hypo- and hyperdopaminergic behaviors in PD patients and impact on quality of life

F. Durif¹, J.L. Houeto², B. Pereira³, I. Rieu¹, I. De Chazeron¹, K. Dujardin², P. Krack⁶
¹Neurology Department, CHU Clermont-Ferrand, Clermont-Ferrand, ²Neurology Department, CHU Poitiers, Poitiers, ³Biostatistics Unit, ⁴Psychiatry Department, CHU Clermont-Ferrand, Clermont-Ferrand, ⁵Neurology and Movement Disorders Department, Lille University Medical Center, Lille, ⁶Neurology Department, CHU Grenoble, Grenoble, France

Objectives: To assess the prevalence of behavioral disorders in PD and their impact on quality of life.

Methods: 136 (62% male) patients were assessed with the Ardouin scale and PDQ-39. The Ardouin scale is a new instrument that uses a structured, standardized interview to detect and quantify all the hypo- and hyperdopaminergic symptoms, and the non-motor fluctuations (NMF) in PD.

Results: 97% of PD patients had at least one symptom listed from the Ardouin scale. The prevalence of depressive mood was 42.3%, apathy 31.2%, anxiety 45.0%, compulsive shopping 15.0%, pathological gambling 10.0%, hypersexuality 16.9%, eating behavior 36.5%, dopaminergic addiction 2.7%. Hypodopaminergic disorders (depression, anxiety, irritability, apathy, hyperemotivity) were correlated to the following dimensions of the PDQ-39 (emotional well-being, r=0.55, p<0.01; stigma, r=0.23, p<0.05; social support, r=0.25, p<0.05; cognition, r=0.29, p<0.01 and bodily discomfort, r=0.22, p<0.05). NMF were correlated to dimensions mobility, r=0.25, p<0.05; activities of daily living, r=0.22, p<0.05; communication, r=0.24, p<0.05. No correlation was observed between PDQ-39 and hyperdopaminergic symptoms (behavioral addictions, dopaminergic addiction, nocturnal hyperactivity…).

Conclusions: This study shows the high frequency of behavioral disorders in PD and the main impact of hypodopaminergic symptoms and NMF on quality of life in PD.

Disclosure: Nothing to disclose

OS2216

Microelectrode recording in subthalamic deep brain stimulation for advanced Parkinson's disease

A. Gamaleya¹, A. Tomskiy¹, E. Bri², A. Dekopov³, E. Salova¹, N. Fedorova², V. Shabalov³
¹Burdenko Neurosurgical Institute, Russian Academy of Medical Sciences, ²Russian Medical Academy of Postgraduate Education, Moscow, Russian Federation

Introduction: Microelectrode recording (MER) is used to optimize accuracy of electrode placement during deep brain stimulation surgery (DBS). However, direct advantages of MER for clinical improvement in patients with advanced Parkinson’s disease (PD) are not defined. Our study aimed to reveal the impact of MER on motor and functional outcome in subthalamic DBS.

Methods: We analyzed PD patients operated in the last years using uniform stereotactic procedure. In 40 patients, intraoperative MER was performed for implantation of electrodes into sensorimotor STN. 49 patients were operated without MER. Both groups did not differ significantly in disease duration, severity, age at surgery, and medication dosage. Data available at follow-up of 6-12 months were assessed (surgical tactics, complications, UPDRS, PDQ-39).

Results: MRI-calculated trajectory matched the best neurophysiologically defined track only in 65% of cases with MER; medial track was chosen in 24%, lateral - in 7.5%. Intracranial hemorrhage occurred in 1 case. Without MER, central trajectory was used in 95.1%. In patients with MER, in off-medication state, alleviation of motor disability as well as improvement in activity of daily living appeared to be better (65.4% versus 46.0%, p=0.000355, UPDRS-3, and 61.4% versus 48.6%, p=0.012325, UPDRS-2, respectively). Reduction in levodopa equivalent daily dose was more substantial in group with MER (63.1% versus 45.4%, p=0.009288). Stimulation-related dysarthria and necessity for postoperative electrode correction were higher without MER.

Conclusion: In STN-DBS for PD, MER seems not only to precise electrode placement, but also to improve clinical outcome, and to diminish potential side effects at short-term follow-up.

Disclosure: Nothing to disclose
OS2217

Treatment-induced changes of sensorimotor networks in cervical dystonia: fMRI study of first-time botulinum toxin effect

P. Hluštík1, M. Nevrlý1, P. Otruba1, R. Opavský2, P. Hok1, Z. Tüdös3, P. Kaňovský1

1Neurology, Palacky University and University Hospital, 2Neurology, Palacky University in Olomouc, 3Radiology, Palacky University and University Hospital, Olomouc, Czech Republic

Introduction: Intramuscular botulinum neurotoxin type A (BoNT-A) application has a proven clinical effect on pathological muscle activation in CD but has also been shown to modulate sensorimotor networks. We used functional MRI of sensorimotor networks to describe changes associated with first-time botulinum toxin treatment of CD.

Methods: We studied 12 BoNT-A naïve CD patients using whole-brain functional MRI at 1.5 Tesla during a finger opposition task, before the first BoNT-A application and 4 weeks after application. Clinical treatment response was evaluated with the Tsui score. Functional MRI data were analyzed with FSL. Group mean maps were used to describe task-related activation, BoNT-A treatment effects were tested in linear contrasts (Pre>Post and Post>Pre).

Results: Group maps demonstrated activation of the bilateral sensorimotor network, with lesser extent before BoNT-A therapy. Comparing activations before and after BoNT-A demonstrated bilateral treatment-related increases in local BOLD response in several bilateral frontoparietal areas (primary and association motor and somatosensory cortices), ipsilateral insula and thalamus.

Conclusions: Considering the previously described sensorimotor network hypoactivation during non-dystonic motor task performance in CD (e.g., Oga 2002, also our previous studies, Opavsky et al. 2011, 2012), our observed effect of activation increase after first BoNT-A application may be interpreted as approaching the physiological state. The central effect of repeated BoNT-A applications (Opavsky et al. 2011, 2012) is somewhat different from ours, which likely corresponds to the gradual evolution of the clinical responses to repeated BoNT-A treatment in cervical dystonia.

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OS2218

Apomorphine improves morning akinesia in Parkinson’s disease: interim analysis of the AM-IMPAKT trial

S. Isaacson1, W. Ondo2, F. Pagan3

1Parkinson’s Disease and Movement Disorders Center of Boca Raton, Boca Raton, FL, 2University of Texas Health Science Center at Houston, Houston, TX, 3Georgetown University Medical Center, Washington D.C., WA, United States

Introduction: Motor fluctuations are common with L-dopa treatment in PD and include delayed and/or inconsistent onset of L-dopa effect (delayed-ON). Delayed-ON of the first morning dose of L-dopa manifests as morning akinesia, which may be prolonged and is known to significantly impact patient quality of life.

Methods: In this multicenter open-label study, subjects completed a Baseline Period recording daily time-to-ON (TTO) every 5-minutes following their morning dose of L-dopa for 7 days. After starting trimethobenzamide antiemetic therapy, they were injected with 0.2mg of apomorphine and titrated to an optimal dose, defined as achieving within 15 minutes at least 90% of post-L-dopa UPDRS. Patients then self-injected apomorphine each morning on awakening for a 7-day Treatment Period and recorded TTO following each injection. Efficacy was assessed by comparing baseline vs. apomorphine TTO (primary endpoint), EQ-5D-3L, CGI-S, and PGI-S scales. Safety/tolerability was also assessed.

Results: 50 subjects meeting the “Completer” definition are evaluated in this interim analysis. Change from baseline in TTO and all secondary efficacy measures showed significant improvement (p<0.0001). 94% of patients experienced a reduction in TTO of at least 15 minutes; 84% experienced a 20-minute reduction from baseline. The most common adverse event was nausea (22.0%, not dose-related). Hypotension and orthostatic hypotension were not observed in the 50 Completers included in this interim analysis, but led to 8 discontinuations in the Safety population.

Conclusions: Apomorphine subcutaneous injection significantly reduced TTO in PD patients experiencing delayed onset of their morning L-dopa dose, and was generally well tolerated.

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OS2219

Cerebellar ataxia associated with glutamic acid decarboxylase 65 autoantibodies (GAD65-ab). Long-term impact of immunotherapy

H. Ariño1,2, N. Arribas-Gresa2, E. Martínez-Hernández1,2, S. Llufriu1, Y. Blanco1, J. Dalmau1,3,4, A. Saiz1,2, F. Graus1,2

1Hospital Clinic Barcelona, 2Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 3Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain, 4University of Pennsylvania, Philadelphia (PA), PA, United States

Introduction: Current clinical and immunological knowledge on cerebellar ataxia (CA) associated with GAD65-ab is based on case reports and small series with short-term follow-up. We aimed to describe the clinical profile, presence of additional antibodies, and long-term outcome in a series of 34 patients with CA and GAD65-ab.

Methods: We retrospectively reviewed the clinical features of 34 patients with CA and GAD65-ab, including the long-term (median 5.4 years, IQR 3.1-10.3) outcome of 25. Immunochemistry on rat brain sections, neurones in culture, and HEK cells transfected with the alpha-1 subunit of the glycine receptor (GlyR) or GAD67 were used to identify additional antibodies. Patients with stiff-person syndrome and GAD65-ab (SPS, n=28) served as controls.

Results: Patients’ median age was 58 years (range 33-80); 82% were women. Clinical onset was subacute (weeks) in 13 patients. Five patients were not treated and only one deteriorated. Twenty patients received immunotherapy (11 IVlg, and 9 IVlg and steroids) and 7/20 improved. The only predictor of improvement was the subacute onset of symptoms (OR=13.8, 95%CI 1.5-127.5; p=0.02). The titers of GAD65-ab, predominantly IgG subtype (IgG1), reactivity with linear epitopes, and occurrence of GAD67-ab (in 72% of patients) was similar in patients with CA and SPS. GlyR-ab were identified in 4 patients with CA but in none with SPS. No other cell-surface autoantibodies were detected.

Conclusions: Among patients with CA and GAD65-ab, immunotherapy is more likely to benefit those with a subacute presentation of symptoms. The immunological profile is similar to that of patients with SPS.

Disclosure: Nothing to disclose

OS2220

Charcot-Marie-Tooth neuropathy type 1A associated with chronic inflammatory demyelinating polyneuropathy. Coincidence or immune response to post-translationally modified proteins in inherited neuromuscular disease?

Case report

E. Bilic1, S. Apostolski2, B. Sanader1, B. Anic3, M. Zagar1, D. Vranjes1

1Medical School University of Zagreb, Clinical Hospital Centre Zagreb, Department of Neurology, Zagreb, Croatia, 2Outpatient Neurological Clinic, Belgrade, Serbia, 3Medical School University of Zagreb, Clinical Hospital Centre Zagreb, Department of Clinical Immunology and Rheumatology, Zagreb, Croatia

Introduction: Inherited neuromuscular disorders may be associated with an immune mediated superimposed affection of the same target tissue. If not recognized, this association presents as a deterioration of the primary, inherited, disease.

Methods: We present a patient with Charcot-Marie-Tooth neuropathy type 1A (CMT1A) who developed fifteen years after CMT1A diagnose establishment stepwise worsening of the initial neurologic deficit.

Results: Control neurographic analyses showed multiple conduction blocks and prolonged F-wave latencies. The antiganglioside antibodies were positive. The diagnosis of chronic inflammatory demyelinating polyneuropathy (CIDP) was established. After six months of prednisone treatment (60mg per day) recovery occurred and the patient became ambulatory. The inherited polyneuropathy may expose myelin antigens or the gene duplication may contain genes that modify the immune response. The subgroup with stepwise progression of CMT1A may represent patients in whom a heightened humoral immune response occurs, directed against myelin proteins.

Conclusion: There are times when the presence or absence of post-translational alterations in self-proteins can profoundly affect antigen recognition in immune functions. This is of special interest in the field of inherited neuromuscular diseases in which the congenital change in various proteins may lead to the additional susceptibility to the immune response to the same target tissue. The pathways that control post-translational modifications may become targets of immunotherapeutic strategies to alter the states of autoimmune versus immune tolerance. In patients with inherited neuromuscular disorders the stepwise worsening may be representation of additional underlying autoimmune process and immunosuppressive/immunomodulatory therapy may be a valuable treatment option.

Disclosure: Nothing to disclose
**OS2221**

**Total plasma exchange in neuromyelitis optica patients: single centre experiences**

I.H. Kılıç¹, A. Güler¹, N. Çelebisoy¹, A.N. Yüceyar¹, F. Gökçay¹, H. Şirin¹, A. Dönmez²

¹Neurology, ²Hematology, Ege University Medical School, Izmir, Turkey

**Introduction:** Neuromyelitis Optica (NMO) is an autoimmune demyelinating central nervous system disorder thought to be caused by auto antibodies against Aquaporin-4 that mainly attacks the optic nerves and spinal cord. The most common treatment option against NMO attack is high dose steroids. However, TPE is used effectively in steroid refractory patients. Here we report our patients with NMO, treated with total plasma exchange between 2011 and 2013 in Ege University School of Medicine, Neurology Department and Apharesis Centre. Our goal was to analyze indications, adverse events, responses and outcome of TPE in NMO.

**Methods:** We retrospectively reviewed the medical records of 12 patients who were diagnosed as NMO and recived TPE. The patients were evaluated and compared regarding their age, number of attacks, mean duration between attacks and TPE, number of TPE sessions, baseline EDSS, EDSS on first and third months follow up and responses to TPE.

**Results:** 12 NMO patients were treated with TPE for 14 acute attacks. 9 patients tested positive for NMO antibody. The total number of TPE sessions was 70. The mean number of TPE sessions was 5. 6 patients received TPE on their first attacks. In 1 patient TPE was chosen as first line treatment. The mean baseline EDSS was 3 (0-9). Mean EDSS at acute attacks was 8.5 (7-9.5). In 10 patients TPE was chosen as second line treatment option after high dose intravenous corticosteroids.

**Conclusions:** In steroid refractory NMO patients TPE was found to be beneficial in small studies.

**Disclosure:** Nothing to disclose

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**OS2222**

**Blood brain barrier permeability in limbic encephalitis and neuromyelitis optica**

D. Labunskiy¹, T. Fedotova², S. Kiryukhina³

¹University of Northern California, Santa Rosa, CA, United States, ²Tver State Medical Academy, Tver, ³Mordovian State University, Saransk, Russian Federation

Limbic encephalitis (LE) is characterized by an acute or subacute onset, memory loss, psychiatric features and often seizure. Neuromyelitis optica (NMO), also known as Devic’s disease or Devic’s syndrome, is an heterogeneous condition consisting of simultaneous inflammation and demyelination of the optic nerve (optic neuritis) and the spinal cord (myelitis). It is well documented blood brain barrier (BBB) rupture in limbic encephalitis (LE) and neuromyelitis optica (NMO) both neuroinflammatory brain diseases with autoimmune component, which characterized by autoantibodies (AAB) against membrane-bound, intracellular or secreted proteins (e.g., voltage gated potassium channels VGPC). Little is known regarding autoantibodies targeting such nuclear antigen as antineuronal nuclear AAB type 2 (anti-Ri) and VGPC AAB directed against Aquaporin 4 (AQP4). The aim of our study was comparison between AAB levels against membrane-bound and intracellular proteins targeting nuclear antigen in patients with LE and NMO. We observed 42 LE patients and 37 NMO patients, men aging from 17 to 64 years old. We used ELSA and Western blot analysis for evaluation of AQP4 and anti-Ri AAB in CSF and serum. Control group comprised of 68 relatively healthy donors of same age groups. It was revealed that NMO the level of AQP4 were increased both in CSF and serum. In LE concentration of anti-Ri AAB was higher in CSF than in serum. On the other hand, levels of AQP4 were not increased in NMO. The difference on concentration of AAB against various neuroantigen revealed uneven rupture of BBB, which is especially important for developing of future therapeutic approaches.

**Disclosure:** Nothing to disclose
OS2223

The choroid plexus as a depository for the innate and humoral adaptive immune systems

G.R.W. Moore1,2,3, C. Laule4,5, E. Leung6, V. Pavlova4, B.P. Morgan6, M.M. Esiri7

1Pathology and Laboratory Medicine, University of British Columbia, 2International Collaboration on Repair Discoveries (ICORD), 3Pathology and Laboratory Medicine, Vancouver General Hospital, 4Pathology and Laboratory Medicine, University of British Columbia, ICORD, 5Radiology, University of British Columbia, Vancouver, BC, Canada, 6Cardiff Institute of Infection and Immunity, Cardiff University, Cardiff, 7Neuropathology, University of Oxford, Oxford, United Kingdom

Introduction: Inflammatory cellular infiltrates in the choroid plexus (CP) have been described in a variety of circumstances (Engelhardt et al. Microsci Res Tech 52: 112-129, 2001), including multiple sclerosis (MS) where CP T-cell infiltrates are only modest (Vercellino et al. J Neuroimmunol 199: 133-141, 2008). To our knowledge the roles of the innate and humoral immune systems in the CP have received little attention, aside from a report describing complement receptors (Singhrao et al. Lab Invest 79: 1247-1259, 1999). Thus, the purpose of this study was to examine these systems in the CP in situ.

Methods: Formalin-fixed paraffin-embedded sections of CP from an autopsy series comprising 12 MS cases, 24 cases with other neurological conditions, and 11 cases without neurological involvement were examined for the presence of components of the complement cascade and immunoglobulins (Ig) in an immunofluorescence and confocal microscopy study.

Results: Complement was deposited in the form of C3d, C9 and C9 neo-antigen in focal areas of sclerosis and/or calcification (“concretions”) in the CP stroma. IgM was variably present in the concretions, while IgG and IgA tended to localize in CP epithelial cells or showed a diffuse staining pattern in the stroma.

Conclusions: Complement and immunoglobulins are deposited in the CP in a variety of circumstances; there is no MS-specific pattern. CP concretions appear to be important in trapping immune molecules involved in the early phases of immune responses (complement and IgM), whereas epithelial cells appear important in the CP’s management of IgG and IgA.

Disclosure: Nothing to disclose

OS2224

Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS): insights from the first autopsy case description

J. Moreira1, C. Correia1, C. Cruto2, J.E. Alves3, M. Melo Pires4, R. Taipa4

1Neurology Department, Hospital Geral de Santo António, Centro Hospitalar do Porto, Porto, 2Neurology Department, Centro Hospitalar Cova da Beira, Covilhã, 3Neuroradiology Department, Centro Hospitalar do Porto, Porto, Portugal

Introduction: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently defined inflammatory entity, prominently involving the pons.

Case report: A 76-year-old, diabetic, hypertensive and dyslipidemic woman, developed during 3 weeks headache, VI right and VII left nerves paresis and a cerebellar syndrome. Partially recovered within 3 weeks without treatment. One month later started incoherent speech, visual hallucinations, ophthalmoplegia, left facial and palate paresis, left pyramidal hemiparesis, cerebellar syndrome and depression of consciousness progressing to coma. Brain MRI showed contrast enhancing linear lesions in brainstem, middle cerebellar peduncle and cerebellar deep white matter. Electroencephalogram/electromyography: normal. CSF: 37 monocytes, 0.94g/l proteins, normal glucose; no oligoclonal bands; 14.3.3 protein weakly positive. Infections (including tuberculosis, Syphilis, Whipple’s disease), autoimmune disorders (including sarcoidosis, Devic and Behçet diseases), neoplastic and paraneoplastic disorders were excluded. With 1g methylprednisolone/day during 5days followed by prednisolone 60mg/day she improved consciousness, keeping left eye abduction limitation, cerebellar syndrome and pyramidal tetraparesis. Due to side-effects prednisolone was reduced and immunoglobulins attempted without further improvement. Remained stable during 2 years. Died from an aspiration pneumonia.

Neuropathological study revealed predominantly brainstem white matter perivascular lymphocytic infiltrates, particularly the in pons, accompanied by CD68 positive histiocytes and activated microglia. Involvement was striking localized to superior cerebellar peduncles decussation and white matter surrounding red nucleus.

Conclusions: Clinical, imaging and pathological criteria for CLIPPERS were met. Partial therapeutic response could be attributed to clinical severity, late onset of treatment or low corticosteroid dose. This is the first autopsy case described.

Disclosure: Nothing to disclose

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Neuro-ophthalmology

OS2225

Impaired cortical inhibitory activity - a pathophysiological mechanism of vestibular migraine?

C. Best1, P. zu Eulenburg2, H.H. Krämer3, T. Bauermann4, W. Müller-Forell4, M. Dietrich5
1Department of Neurology, Philipps-University of Marburg, Marburg, 2University Medical Center, Johannes Gutenberg-University, Mainz, 3Department of Neurology, Justus-Liebig-University, Giessen, 4Department of Neuroradiology, University Medical Center, Johannes Gutenberg-University, Mainz, 5Department of Neurology and German Center for Vertigo and Balance Disorders-IFBLMU, Cluster for Systems Neurology (SyNergy), Ludwig-Maximilians-University, Munich, Germany

Introduction: In vestibular migraine (VM), episodic vertigo is accompanied by typical migraine symptoms. The aim of this fMRI study was to investigate the activity of excitatory and inhibitory cortical circuits in VM patients and healthy controls (HC) during visual (optokinetic) stimulation. As a neurophysiological correlate the postural consequences of visual-vestibular interaction were examined by posturography.

Methods: Ten VM patients and 14 matched HC were examined by fMRI during two different visual optokinetic stimulations (6°/s vertical black and white stripes horizontally slowly moving rightward (OKN-L) or leftward (OKN-R)) and a rest condition. Statistical analyses were performed with SPM5. Body sway during visual motion stimulation was examined by static posturography (Kistler, Switzerland).

Results: Compared to HC, in VM patients OKN-L induced significantly increased responses bilaterally within visual and somatosensory areas and the cerebellum. During OKN-R there were significantly reduced activations. The deactivation pattern, in HC typically occurring within the posterior insular cortex, the anterior cingulate cortex, or the superior temporal gyrus, was absent in VM patients: Deactivations were overall significantly reduced. Comparison of OKN-R vs. OKN-L revealed significantly asymmetrical activations, which was not the case in HC. Applying visual motion stimulation during static posturography VM patients showed significantly more instability than HC.

Conclusions: These results confirm the hypothesis of a reduced intracortical inhibition (1, 2) while excitatory activity is increased in VM patients. Moreover, the disturbed visual-vestibular cortical interaction appears to result in an enhanced postural body sway in VM.

Reference: 1: Aurora et al., 2007; 2: Antal et al., 2011

Disclosure: Nothing to disclose

OS2226

Head jolting vertigo and nystagmus: a new vestibular syndrome?

A.M. Bronstein1, D. Kaski2, N. Cutfield3, A. Coelho4, R. Banga4, J. Ray3, R. Irving4
1Neuro-Otology Unit, 2Imperial College London, 3Neuro-Otology, University College London, London, 4ENT, University Hospital Birmingham, Birmingham, 5ENT, Sheffield Teaching Hospitals, Sheffield, United Kingdom

Introduction: 2 patients are reported in whom violent horizontal shaking of the head (head jolting) induced vertigo and nystagmus. The condition cannot be explained as positional vertigo or head-shaking nystagmus.

Methods: Patient 1 was a 58-year-old man and Patient 2 was a 62-year-old man, with no relevant medical history. The main symptom was rotational vertigo after violent and brief oscillations of the head. This triggered violent horizontal nystagmus, with peak eye velocities above 100deg/s, lasting for approximately 45s. Horizontal angular velocities of the head required to induce these episodes could only be achieved by the patients themselves - approximately 700deg/s. Positional manoeuvres for horizontal/vertical canals were negative. Imaging was unrevealing.

Results: On the basis that this syndrome resulted from mechanical excitation of the horizontal canal on the side of the nystagmus beat, Patient 1 underwent canal plugging and his symptoms disappeared immediately. Patient 2 was followed up conservatively and gradually, over a period of 6 years, the episodes disappeared. Triggering an attack became impossible. Videorecordings will be shown at the meeting.

Conclusions: The ‘head jolting’ nystagmus in these two patients illustrate a hitherto undescribed vestibular syndrome that we attribute to mechanically dislodged material within the horizontal semicircular canal causing cupular deflection and excitation. The underlying pathology is unknown but vestibular athelectasis should be considered. Clinical examination, rather than imaging or vestibular testing established the diagnosis. Surgical or conservative treatment appears successful long term but canal plugging can resolve the problem rapidly.

Disclosure: Nothing to disclose
OS2227

Beyond the EYE – behavioral and cortical assessment in posterior cortical atrophy (PCA)

N. Levin, H. Shames, N. Raz
Hadassah Hebrew University Medical Center, Jerusalem, Israel

Introduction: Posterior cortical atrophy (PCA) is a dementing syndrome in which the most pronounced pathologic involvement is in occipito-parietal visual regions. Even though the syndrome has been recognized for more than two decades, PCA is relatively neglected by clinicians and researchers, and the patients are often referred to recurrent ophthalmic evaluation and face considerable delay in diagnosis.

Methods: 6 patients with PCA and 5 age matched controls underwent a comprehensive set of visual and neuro-psychological tests, aimed to differentiate between lower and higher visual functions as well as between dorsal and ventral-related cortical functions affected in the syndrome. Functional MRI (fMRI) was performed on 3 patients addressing the neuronal substrate of the visual dysfunctions.

Results: Higher visual functions deficits were mainly seen within dorsal-related functions including simulant perception, image orientation, figure from ground, closure and spatial orientation. In addition, fine details discrimination was impaired in some patients. Face perception, letter reading and color naming were intact. In accordance with the behavioral findings, fMRI revealed intact activation in ventral visual regions of face and objects perception. Comparing cortical activation during local and global analysis (Navon letters) revealed greater activation for local processing in the Temporo-parietal junction which is usually involved in Gestalt perception.

Conclusions: A myriad of both higher and lower visual functions’ deficits were evident both behaviorally and cortically. Greater awareness of the syndrome is needed to improve diagnostic accuracy, clinical management and design of research studies.

Disclosure: Nothing to disclose

OS2228

White matter microstructure abnormalities in patients with dominant optic atrophy and OPA1 mutations

R. Messina1,2, M.A. Rocca1,2, S. Bianchi-Marzoli1, J. Milesi1, M.L. Cascavilla1, M. Petrolini1, A. Falini2, G. Comi2, M. Filippi1,2
1Neuroimaging Research Unit, Institute of Experimental Neurology, 2Department of Neurology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: Aim of this study was to assess abnormalities of white matter (WM) microstructure in patients affected by dominant optic atrophy (DOA) linked to OPA1 gene mutations, using tract-based spatial statistics (TBSS) analysis.

Methods: Using a 3.0 Tesla scanner, dual-echo and diffusion tensor (DT) MRI images were derived from 19 patients with DOA (10 females, mean age=43 years, range=22-64) and 20 sex- and age-matched controls. A complete neurological and neuro-ophthalmologic examination was obtained in all patients. TBSS analysis was performed using FMRIB’s Diffusion Toolbox.

Results: Visual acuity was reduced in almost all patients, whereas none of the patients had extra-ocular neurological complications. Focal lesions in the brain WM were identified in ten patients. Three patients presented hyperintense optic nerve lesions on T2 weighted scans. Optic nerve and chiasm atrophy were detected in twelve patients. TBSS analysis showed that compared to controls, patients with DOA had significant lower mean diffusivity, axial and radial diffusivity in WM of the cerebellum, brainstem, thalamus, fronto-occipital-temporal lobes, including the cingulum, corpus callosum, corticospinal tract and optic radiation bilaterally. No abnormalities of fractional anisotropy were detected. DT MRI measures were correlate with ganglion cell complex thickness.

Conclusions: Patients with DOA linked to OPA1 gene mutations present diffuse WM microstructural abnormalities. Clinical expression of DOA could be influenced by the level of mitochondrial impairment and potential compensatory mechanisms, such as increased protein expression. Restricted water diffusion might be explained by a higher macromolecular water binding, due to increased molecular crowding and microviscosity.

Disclosure: MAR speakers honoraria from Biogen Idec and Serono Symposia International Foundation. CG received compensation for consulting and/or speaking from Novartis, Teva, Sanoﬁ, Genzyme, Merck Serono, Biogen, Bayer, Actelion, SSIF. MF received compensation for consulting and/or speaking from Bayer, Biogen Idec, Merck Serono, and Teva.
OS2229

The effect of demyelinative damage on neighboring white matter integrity: an optic neuritis study

N. Raz, A.S. Bick, T. Ben Hur, N. Levin
Hadassah Hebrew University Medical Center, Jerusalem, Israel

Introduction: Neuronal loss following damage is often greater than expected from the severity of the injury to the nerve itself. The visual pathways which comprise a well-defined system, and optic neuritis (ON), which is usually a discrete event, make a fine model to study this phenomenon. This study was aimed to understand the effect of focal optic nerve demyelination on neighboring white matter; in distal segments of the same fiber bundle (optic tract) and in the successive trans-synaptic bundle (optic radiation).

Methods: Diffusion Tensor Imaging and probabilistic tractography were used to identify and characterize the optic tracts and radiations of 17 ON and matched controls. Data were correlated with Retinal Nerve Fiber Layer (RNFL) thickness.

Results: Patients’ optic tracts exhibited reduced axial diffusivity, which correlated with RNFL thickness values. Patients’ optic radiations demonstrated intact axial diffusivity but reduced fractional anisotropy and elevated radial diffusivity, which could be explained by intra-bundle lesions. No correlations were found between diffusivity measurements in patients’ optic tracts and radiations; or between RNFL thickness and optic radiations’ diffusivity.

Conclusions: Following ON, chronic axonal loss develops distally in the optic tracts, demonstrating Wallerian degeneration. Degeneration did not proceed to the optic radiations, opposing anterograde trans-neuronal changes. DTI in ON provides fine in-vivo human model for studying histological abnormalities in normal appearing white matter, localized in close proximity to damaged bundle.

Disclosure: Nothing to disclose

OS2230

The cortical mechanisms of oscillopsia and its suppression in asymptomatic infantile nystagmus and symptomatic nystagmus in neurological patients

Y. Nigmatullina1, V. Ferguson2, N. Yousif1, B.M. Seemungal1
1Brain Sciences, 2Ophthalmology, Imperial College London, London, United Kingdom

Introduction: Patients with acquired nystagmus complain of perceived visual world motion (oscillopsia) concomitant with retinal slip of the visual world. In contrast humans with early onset infantile nystagmus typically report no oscillopsia. Human studies into the mechanisms of oscillopsia have thus far have been purely psychophysical.

Methods: We combined psychophysics, eye movement recording and neurophysiology in six healthy volunteers with normal eye movements and four healthy individuals with infantile nystagmus without oscillopsia. We measured visual cortical spatial updating by applying transcranial magnetic stimulation (TMS) to area V5/MT during gaze fixation. Visual cortex TMS-evoked phosphene phosphene phosphene are retinotopic moving with voluntary gaze.

Results: During a caloric-evoked vestibular nystagmus causing oscillopsia in healthy individuals, there was no updating of phosphene location with eye position ($r^2=0.048$; $p>0.05$ for horizontal eye vs. phosphene position). In contrast in infantile nystagmus subjects fixating upon a perceptually stable target, eye and phosphene position were correlated ($r^2=0.43$; $p=0.006$). When we probed V5/MT excitability (with TMS), we found a continuous modulation of brain excitability across the nystagmus cycle in 3 infantile nystagmus. No such excitability modulation was seen during acute vestibular-nystagmus with oscillopsia.

Conclusions: In summary, both visual spatial updating and a phasic modulation of area V5/MT excitability may contribute to visual perceptual stability during involuntary nystagmus in humans. We are currently extending this work to patients with pendular nystagmus from multiple sclerosis and cerebellar downbeat nystagmus.

Disclosure: Nothing to disclose
Monday, 2 June 2014

Cerebrovascular diseases 1

OS3101

Cerebral amyloid angiopathy-related inflammation. A systematic review of individual reported cases

A. Castro Caldas¹, C. Silva¹, J. Pimentel¹,², J.M. Ferro¹,²
¹Department of Neurology, Hospital de Santa Maria, ²Faculty of Medicine, University of Lisbon, Lisbon, Portugal

Introduction: Cerebral amyloid angiopathy related inflammation (CAA-I) is a rare potentially treatable encephalopathy, characterized by an inflammatory response to vascular deposits of β-amyloid. We aimed to perform a systematic review of all neuropathological-proven CAA-I case reports in order to describe its clinical and pathological features, outcome and effect of different treatment.

Methods: We searched PubMed and Cochrane Library and screened references of included studies and review articles for additional citations. Search results and data extraction were performed independently by 2 reviewers. Outcome was classified at last available follow-up by the modified Rankin Scale (mRS).

Results: A total of 54 publications, reporting on 137 patients, were included. Mean age was 66.9 years, 51.8% were males. The most common clinical presentation was cognitive dysfunction (56.1%) followed by headaches (38.6%), pyramidal signs (18.9%) and confusional syndrome (18.9%). Vasculitis was the most common pathologic pattern (84.8%); granuloma was found in 65.6%. Therapeutic intervention was available in 84.7% of cases: 85.3% were treated with corticosteroids and 28.5% with cyclophosphamide; 31 patients (39.7%) regained independence (mRS 0-2), while 19 patients (24.4%) were left with a severe handicap (mRS 3-5) and 28 (35.9%) died. There were no statistically significant differences (chi²=0.75; p=0.19), between patients treated with corticotherapy alone comparing to those treated with cytostatic agents alone or in combination with corticotherapy.

Conclusions: In our review, the most common clinical manifestation of CAA-I was cognitive dysfunction. The outcome was unfavourable in the majority of the patients, with death in more than 1/3, despite current treatments, mostly steroids.

Disclosure: Nothing to disclose

OS3102

Intravenous thrombolysis for cerebral ischaemia in the North of France region. Impact of the regional health policy at the community level

N. Dequatre-Ponchelle, D. Leys
Lille University Hospital, Lille, France

Introduction: The proportion of patients with ischaemic stroke who are treated by intravenous (i.v.) recombinant-tissue plasminogen activator (rt-PA) is an indicator of quality of stroke care at the hospital level. Little is known about this proportion at the community level, and its evolution over time according to health policies. The objective was to evaluate the impact of a regional health policy on the rate of i.v. thrombolysis in the 13 districts of the North of France region.

Methods: We determined the proportion of residents of the North of France region with ischaemic stroke who were treated by i.v. rt-PA in 2009-2010 (period A; 8 stroke units; no telemedicine) in the region and in each of its 13 districts, and we compared with the same proportions in 2012 (period B; 12 stroke units; telemedicine network between 5 hospitals).

Results: During the study period, 1,563 patients meeting inclusion criteria (period A 835, period B 728) received i.v. rt-PA. For the whole region, the annual rate of thrombolysis per million inhabitants increased from 103 (95% confidence interval [CI] 85 to 125) up to 181 (95%CI 157 to 209) between the 2 periods (relative increase +76%, 95%CI 67% to 83%). This proportion increased in 12 of the 13 districts, and was greater in districts where new stroke units, telemedicine, or both, were implemented.

Conclusions: In a region where the proportion of patients with ischaemic strokes who received i.v. rt-PA was one of the highest ever reported, there was still a possibility of improvement.

Disclosure: Nothing to disclose
OS3103

Stiffer carotids in intracranial atherosclerosis: heart at risk

F.M. Farina, F. Viaro, L. Donà, C. Baracchini
Department of Neurosciences, University of Padova, Padova, Italy

Introduction: Arterial stiffness has been proposed as a surrogate marker of cardiovascular risk, independent of conventional risk factors. Intima-media thickening and carotid plaques are associated with an increased risk of cardiovascular events. The aim of our study was to investigate carotid artery wall dynamics in patients with intracranial atherosclerosis comparing them to subjects with carotid atherosclerosis.

Methods: We enrolled 20 consecutive patients (16 males, 4 females, mean age 74.0±7.4yrs) with a >50% intracranial symptomatic atherosclerotic stenosis detected by TCCD and confirmed by MRA/CTA/DSA. Twenty gender- and age-matched patients with atherosclerotic disease of the cervical arteries but no TCCD evidence of intracranial vessel disease constituted our control group. Every patient underwent a complete bilateral assessment of common carotid artery wall dynamics parameters and IMT. During the follow up period (2009-2013) any vascular event was recorded.

Results: Mean carotid wall stiffness was significantly higher (p<0.01; 6.38±0.30 vs 5.89±0.27) and mean carotid distensibility was significantly lower (p<0.03; 11.52±1.32 vs 13.03±0.98) in study group compared to controls. No significant differences were found in common vascular risk factors, statin use, antithrombotic treatment and mean IMT values between the two groups. There was a significantly higher rate of cardiovascular events in the study group (p<0.05).

Conclusions: According to our data, carotid wall dynamics is significantly more compromised in patients with intracranial atherosclerotic stenoses compared to patients with carotid atherosclerotic disease. This was associated with a higher cardiovascular event rate. Carotid artery wall dynamics is a useful tool to select those patients at a higher cardiovascular risk who might benefit from a more intensive prevention program.

Disclosure: Nothing to disclose

OS3104

Gender aspects of acute stroke care: results from the Austrian Stroke Unit Registry

T. Gattringer1, J. Ferrari2, M. Knoflach3, L. Seyfang4, S. Horner1, K. Niederkorn1, V. Culea1, M. Beitzke5, W. Lang2, C. Enzinger1, F. Fazekas1
1Neurology, Medical University of Graz, Graz, 2Neurology, Hospital Barmherzige Brüder, Vienna, 3Neurology, Medical University of Innsbruck, Innsbruck, 4Danube University of Krems, Krems, Austria

Introduction: Gender differences in quality of acute stroke care are an important concern with limited data available, specifically regarding the stroke unit (SU) setting. We used the prospective nationwide Austrian SU registry to address this issue.

Methods: Our analysis covered an 8-year time period (January 2005 to December 2012) during which all patients with TIA or ischemic stroke admitted to one of 35 Austrian SU had been captured in the registry. These data were analyzed for age-adjusted preclinical and clinical characteristics and quality of acute stroke care in men and women. In addition we assessed the outcome at three months in multivariate analysis.

Results: 47209 individuals (47% females) had received SU care. Women were significantly older (median age: 77.9 vs. 70.3 years), had higher preexisting disability and more severe strokes. Correcting for age, no significant gender differences in quality of care were identified with comparable onset-to-door times, times to and rates of neuroimaging, as well as door-to-needle times and rates of intravenous thrombolysis (14.5% for both genders). Despite equal acute stroke care and a comparable rate of neurorehabilitation, women had a worse functional outcome at 3-months-follow-up (modified Rankin scale 3-5: OR 1.26 (95% CI, 1.17-1.36)), but a lower mortality (OR 0.70 (95% CI, 0.78-0.88)) after correcting for confounders.

Conclusions: We identified no significant differences in quality of care in the acute SU setting between males and females. Further studies on the post-stroke period including socio-economic aspects are needed to get more insights in gender specific prognosis.

Disclosure: Nothing to disclose
OS3105

Combined use of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for stroke prediction in the general population


Introduction: The subclinical atherosclerosis markers coronary artery calcification (CAC), carotid intima-media thickness (CIMT) and ankle-brachial index (ABI) predict stroke in addition to established risk factors in the general population. Whether these markers are surrogates of the same atherosclerotic risk or whether they may be used in combination was unknown.

Methods: 3,289 subjects from the population-based Heinz-Nixdorf-Recall study (45-75 years; 48.8% men) without previous stroke and coronary heart disease were evaluated for incident strokes over 9.0±1.9 years. Cox proportional hazard regressions were used to examine CAC, CIMT and ABI as stroke predictors in addition to established risk factors (age, gender, systolic blood pressure, LDL, HDL, diabetes, smoking).

Results: 84 strokes occurred during the follow-up. In multivariable regressions, CAC (hazard ratio[HR]=1.40 [95%-confidence interval=1.08-1.81]; p=0.011 per 1-standard deviation [SD] increase in log10(CAC+1); SD=1.04), CIMT (1.31[1.07-1.62]; p=0.010 per 1-SD increase; SD=0.127mm) and ABI (1.56[1.32-1.82]; p<0.001 per 1-SD decrease; SD=0.148) predicted stroke when adjusted for established risk factors. When combined with each other, the HR of CAC remained similar when CIMT was also inserted (1.37[1.06-1.77]), but slightly decreased when ABI was inserted (1.28[0.98-1.66]) into the multivariable model. By contrast, the HR of CIMT hardly changed both when combined with CAC (1.29[1.05-1.59]) and ABI (1.28[1.04-1.58]), nor did the HR of ABI when combined with CAC (1.52[1.28-1.79]) and CIMT (1.52[1.30-1.79]).

Conclusions: Despite limitations related to by chance variation of HR in multivariable regression analyses, our observations suggest that CAC, CIMT and ABI preserve their values as stroke predictors in the general population even when combined with each other.

Disclosure: Nothing to disclose

OS3106

Visual hallucinations in acute stroke: a prospective study in 78 patients


Neurology, Hospital de la Santa Creu i de Sant Pau, Universitat Autònoma de Barcelona, Cerebrovascular Disease Unit, Hospital de la Santa Creu i de Sant Pau, Barcelona, Spain

Introduction: Patients with stroke may present visual hallucinations (VH). However the incidence of VH, their clinical characteristics, topographic correlation, underlying physiopathology and prognostic value remain unclear.

Methods: We prospectively recruited 78 patients (mean age 71.09±12.02; 57% were men) with a diagnosis of acute stroke (ischemic/hemorrhagic, any vascular territory). All subjects were admitted within 24h after the onset of symptoms. We excluded patients with previous neurodegenerative/psychiatric disease or previous hallucinations. We collected demographic and clinical data. All subjects had an initial neuroimage study (MRI/CT), and answered (the patient/relatives) a structured hallucination and sleep questionnaire at admission and within the first 15days. A subgroup of patients had also a neuropsychological evaluation (N=50) and an EEG(N=34). Functional outcome was assessed with the Rankin scale.

Results: The incidence of VH was 16.7%. These hallucinations were often complex, began within the first 15days (76.9% within the first 3days) and resolved without medication. VH were associated with lesions in the occipital cortex (4/13vs.5/65;p=0.038), initial visual field defect (6/13vs.8/65; p=0.01), cortical atrophy in neuroimage (7/13vs.15/65; p=0.04) and sleep disturbances during admission (6/12vs.6/58; p<0.01). VH were not related with Rankin scale score at discharge. There were no differences between patients with and without VH in the NIHSS score at admission and discharge, EEG activity, ischemic vs. hemorrhagic etiology, infectious complications or drug/alcohol abuse.

Conclusions: VH are frequent in stroke patients (16.7%). The visualized images are usually complex, appear early in the evolution and are self-limited. VH are more frequent in occipital cortical lesions, and are not associated with functional prognosis.

Disclosure: Nothing to disclose
Neurorehabilitation 2

OS3107

Bilateral deep repetitive transcranial magnetic stimulation (rTMS) on lower limb motor function after stroke: a pilot study with H-coil

R. Chieffo1, S. De Prezzo1, E. Houdayer1, A. Nuara1, L. Straffi1, F. Spagnolo1, D. Dalla Libera1, G. Di Maggio1, E. Coppi1, L. Ferrari1, M. Sessa1, M. Comola1, A. Zangen2, G. Comi1, L. Leocani1
1San Raffaele Hospital, Milan, Italy, 2Ben-Gurion University, Beer-Sheva, Israel

Introduction: Repetitive transcranial magnetic stimulation (rTMS) has been recognized as a promising intervention for treatment of stroke patients. The purpose of this double-blind placebo-controlled crossover study was to assess the efficacy of high frequency (20 Hz) brain stimulation on lower limb motor function in patients with chronic (>6 months) subcortical stroke.

Method: Repetitive TMS (rTMS) was delivered with the H-coil, specifically designed to target deeper and larger brain regions than the figure-of-eight coil. A total of 9 patients received both real and sham rTMS in a random sequence. rTMS treatments (real or sham) were composed of 11 sessions (administered over 3 weeks) and were separated by a four-week wash-out period. Lower limb functions were assessed by the Fugl-Meyer lower limb scale (FM-LL), the 10-meters walking test (10-MT) and the six minutes walking test (6-MWT), before and 1 day after the end of each treatment period, as well as at a 4-week follow-up.

Result: Real rTMS treatment was associated with a significant improvement in FM-LL scores. This effect persisted over time (follow-up) and was significantly greater than that observed with sham stimulation. A significant increase in walking speed was also found after real rTMS but this effect did not reach statistical significance in comparison with the sham stimulation.

Conclusions: These data demonstrated that 3 weeks of high-frequency deep rTMS could induce long-term improvements in lower limb functions in the chronic post-stroke period.

Disclosure: A Zangen is a key inventor of the H-coil and acts as a consultant for Brainsway LTD. The other authors declare no conflicts of interest related to the present study.

OS3108

Stem cell salvage of injured peripheral nerve

N. Grimoldi1, F. Colleoni2, I.G. Vetrale3, A. Cappellari3, A. Costa4, M. Belicchi2, P. Razini5, R. Giordano6, D. Spagnoli7, M. Pluder1, M. Morbin8, S.M. Gaini1, P. Rebulla9, N. Bresolin2, Y. Torrente2

1Neurosurgery, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università di Milano, 2Department of Pathophysiology and Transplantation, Stem Cell Laboratory, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Centro Dino Ferrari, Università di Milano, 3U.O. di Neurofisiopatologia, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, 4Neuroradiology, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, 5Department of Regenerative Medicine, Center of Transfusion Medicine, Cellular Therapy and Cryobiology, Foundation IRCCS Cà' Granda Ospedale Maggiore Policlinico, 6Neurosurgery, Moriggia Pelascini Hospital Gravedona, 7Neuropathology, IRCCS Foundation, ‘Carlo Besta’ Neurological Institute, 8Neuropathology, IRCCS Foundation, ‘Carlo Besta’ Neurological Institute, 9Milan, Italy

Introduction: We previously have developed a polyglycolic acid (PGA)-collagen tube filled with autologous skin-derived stem cells (SDSCs) for bridge long rat sciatic nerves gaps. Here we describe a case report of this graft for repairing poly-injured motor and sensory nerves of upper arms of a human patient.

Method: During the 3-year follow-up period, functional recovery of the injured median and ulnar nerve was assessed by pinch gauge test, static two-point discrimination and touch test with monofilaments, in couple with electrophysiological and MRI examinations.

Results: The motor and sensory function of the median nerve demonstrated an ongoing recovery post-implantation during the follow-up period.

Conclusions: The results indicate that the PGA-collagen/SDSCs artificial nerve graft could be used for surgical repair of larger defects in major lesions of peripheral nerves increasing the quality of life of treated patient by salvage the upper arms from amputation.

Disclosure: Nothing to disclose
OS3109
Voices of patients and physicians in spinal cord pain care – What’s needed!

C. Norrbrink1, M. Löfgren2,3
1Department of Neurosciences, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, 2Clinical Sciences Danderyd University Hospital, Karolinska Institutet, 3Danderyd Hospital, Department of Rehabilitation Medicine, Stockholm, Sweden

Introduction: In our previous study Patients’ perspectives on pain (2012), 18 informants with spinal cord injury (SCI) and neuropathic pain were interviewed. One aim was to explore ideas about how to improve pain treatment for this patient group. The analysis showed that more data was needed on this topic. The present follow-up study sought to deepen our knowledge about how to design future health care for individuals with SCI and neuropathic pain. Sixteen of the former 18 informants participated. Nine physicians working with SCI neuropathic pain rehabilitation from university and regional hospitals were also included as informants.

Methods: The study used focus-group and individual interviews for data collection. Data was analyzed according to content analysis.

Results: Four categories emerged in the preliminary analysis: Structure of SCI pain care, Knowledge, competence and learning to live with pain, Relations between patients and pain care staff, and ‘What’s needed’. All four categories included both patients’ and physicians’ perspectives. The patients want to be met by multi-professional teams specializing in pain with a systematic approach mapping the pain and its consequences. Further, the patients want help and support from health care when learning to live with pain, and also complementary treatments as part of the treatment strategies. The physicians stressed more competence in cognitive behavioural therapy for conducting individual and group activities.

Conclusions: Rehabilitation needs improvements in order to meet the needs both of individuals with SCI and neuropathic pain and of the physicians treating them. We thank the Norrbacka-Eugenia Foundation for financial support.

Disclosure: Nothing to disclose

OS3110
Action observation therapy modifies structural brain plasticity in healthy adult individuals

P. Preziosa1,2, M.A. Rocca1,2, R. Gatti3, M. Petrolini1, R. Messina1,2, G. Salini1, S. Fumagalli1, A. Falini1, G. Comi1, M. Filippi1,2
1Neuroimaging Research Unit, Institute of Experimental Neurology, 2Department of Neurology, 3Laboratory of Movement Analysis, Department of Neuroradiology, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy

Introduction: To assess brain gray (GM) volume changes following action observation therapy (AOT) in healthy controls (HC), and their correlations with improvement of motor performance.

Methods: 36 right (R)-handed HC, without particular manual ability, performed a motor training, consisting in 10 sessions of 10-minute passive mobilization of the R hand, vision of three videos lasting 5 minutes and execution, with the R hand, of three daily-life actions. Subjects were randomized into 2 groups: AOT-group watched videos representing daily-life actions, environmental-group watched videos of landscapes. At baseline (T0) and after a 2-week of training (W2), dexterity and strength measures were assessed and 3D T1-weighted MRI sequences were acquired. Longitudinal GM volume changes were evaluated using Tensor-Based Morphometry.

Results: At W2, both groups showed GM volume increase of the bilateral paracentral lobule, anterior and posterior cingulum, calcarine cortex, and R cerebellum. The AOT-group showed also an increased GM volume of the R cuneus, and R insula. The AOT-group had a reduced GM volume of the R supplementary motor area, while the environmental-group had a decreased GM volume of several fronto-patieto-occipital regions, R middle and anterior cingulum and R cerebellum. Compared to environmental-group, AOT-group had an increased GM volume of the R cerebellum and left insula. In both groups, improvement at motor performance was correlated with GM volumetric changes.

Conclusions: A 10-day manual dexterity training with AOT influences structural reorganization of GM WM volumes in HC, facilitating motor skill improvement and promoting structural brain plasticity.

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Disclosure: MAR speakers honoraria from Biogen Idec and Serono Symposia International Foundation. CG received compensation for consulting and/or speaking from Novartis, Teva, Sanofi, Genzyme, Merck Serono, Biogen, Bayer, Actelion, SSIF. MF received compensation for consulting and/or speaking from Bayer, Biogen Idec, Merck Serono, and Teva.
OS3111

An analysis of sensitivity to change and reproducibility of a functional scale of the upper limb: UL-ADL

M. Rousseaux¹, H.-Y. Bonnin Koang², C. Benaim³, and PRIME² Investigators
¹University Hospital, Lille, ²University Hospital, Le Grau du Roy, ³University Hospital, Dijon, France

Introduction: The upper limb assessment in daily living (UL-ADL) scale analyzes the difficulties of hemiplegic patients in active and passive functions of the upper limb in daily life (questionnaire) and test situations. We analyzed its sensitivity to change and reproducibility.

Methods: In this multicenter study, 92 patients were included for two years. The 15-item UL-ADL scale follows a proximal-distal progression and includes passive and active functions. Each activity is quoted between 0 (cannot perform) and 10 (perform with no difficulty). The scale was presented twice before the 8th week after stroke and after a time of 4-12 weeks. The change was analyzed by classical indexes of change and the sensitivity/specificity with respect to a predefined criterion (an increase in the Motor Index (MI) > 20/100).

Results: The standardized response mean (questionnaire: 0.86; test: 0.71) showed a moderate to good sensitivity, greater than the effect size (0.66, 0.49). These indexes were comparable to those of the Rivermead scale (0.91; 0.63). The area under the ROC curve (sensitivity/specificity) was relatively large, but comparable to that of the Rivermead scale. Correlations were strong (p<0.0001) between changes in the UL-ADL and MI scores. In addition, the intra-observer and interobserver reliability was fair for the questionnaire and the test, as assessed by the intraclass correlation coefficients (>0.80) and the Bland and Altman method.

Conclusions: The UL-ADL scale showed an overall sensitivity similar to that of the reference tests. Reproducibility was fair.

Disclosure: Nothing to disclose

OS3112

Trephined syndrome

L. Sveikata, A. Schneider, B. Leemann
Rehabilitation Clinic, Department of Clinical Neurosciences, University Hospital of Geneva, Geneva, Switzerland

Introduction: Decompressive craniectomy (DC) is frequently used to treat increased intracranial pressure or an intracranial mass effect. Trephined Syndrome (TS) describes a neurologic deterioration, which is attributed to a large craniectomy. It often has an orthostatic component. The incidence of TS has been reported between 7% and 26%. However, it might be underestimated if the course of cognitive functions before and after cranioplasty (CP) were insufficiently documented.

Methods: We evaluated 20 subsequent patients who underwent DC. Neurological and neuropsychological examination and brain CT scan were performed at admission to neurorehabilitation, when TS was suspected, and 1-4 days before and 1-4 days after cranioplasty.

Results: Eight (40%) patients had a clinical course compatible with TS. They had an aggravation of their hemisyndrome or stagnation of clinical evolution, which improved after CP. Five of them also had hemineglect and 1 had severe executive dysfunction, all of which improved rapidly after CP. One patient, who had been in vegetative state for 3 months, started to communicate by writing after CP. Five patients had postoperative complications (4 hematomas, 1 abscess), which may have masked a potential effect of the CP.

Conclusions: Neurologists should consider the presence of a Trephined Syndrome (TS) in patients with DC who worsen or fail to progress. The optimal delay to CP is to be determined.

Disclosure: Nothing to disclose
Peripheral nerve disorders

**OS3113**

**Intra epidermal fiber density (IEFND) in symptomatic transthyretin familial amyloid polyneuropathy (TTR-FAP): patterns of fiber loss and high incidence of amyloid deposit**


1Hospital de Santo António, Centro Hospitalar do Porto, T. Coelho from the Fx1A-303 study on transthyretin familial amyloidosis (TTR-FAP), 2Neurology, Univ Paris Sud/INSERM/APHP/NERF, 3Neuropathology, CHU Bicetre/APHP/INSERM/NERF, 4Neurology, 5Neurophysiology, CHU Bicetre/APHP/NERF, Le Kremlin Bicetre, France

**Introduction:** TTR-FAP are severe and disabling hereditary neuropathy due to a point mutation of TTR gene. Diagnosis is usually difficult and delayed. Main diagnostic tools are nerve biopsy and TTR gene analysis. TTR-FAP present usually as a small fiber polyneuropathy and NCS may be initially normal. Place of skin biopsy by punch in diagnosis procedure is unknown.

**Methods:** We studied distal and proximal lower limb skin biopsies in 58 patients, with symptomatic and genetic proven familial transthyretin (TTR) amyloid neuropathy. They were included with 16 varied TTR mutations including Val30Met in 55%. The mean age was 58.7 yr (20-86); 17 with early onset EO (< 50y)(29%). 3 mm punch skin biopsies were done 10 cm above the lateral malleolus and 20 cm below the anterior iliac spine under local anesthesia. IEFND was calculated on bright-field PGP-immunofluorescence along EFNS guidelines. In addition, Congo red staining was done on each skin biopsy to detect amyloid deposition (AD).

**Results:** Mean delay between the the first symptom and skin biopsy was 3.81 year(0.5-10.3). Decreased IEFND was observed in all patients. 23 pts had complete distal LL IEFN loss (40%); including 7 with complete proximal loss. A non length dependent proximal pattern was seen in 23 pts (40%) including 78% with Late onset (LO), 65% in non met30. Congo positive AD were present in 44/58 (76%) patients; in 100% of EO vs 65% of LO.

**Conclusion:** Symptomatic TTR-FAP are characterized by a severe decreased IEFND or non length dependent pattern with frequent amyloid deposits.

**Disclosure:** Nothing to disclose

**OS3114**

**Long term effects of tafamidis treatment on transthyretin familial amyloid polyneuropathy (TTR-FAP): interim results from the Fx1A-303 study**

T. Coelho, I.M. Conceição, E. Barroso, M. Waddington-Cruz, H.H.-J. Schmidt, G. Rosas, F.S. Mandel, M. Stewart, P. Huertas, O.N. Karayal, 1Hospital de Santo António, Centro Hospitalar Lisboa Norte, Lisbon, Portugal, 2Hospital Santa Maria, Centro Hospitalar Lisboa Norte, Lisboa, Portugal, 3Raul Carrea Institute for Neurological Research, FLENI, Buenos Aires, Argentina, 4Hospital Universitário Clementino Fraga Filho, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, 5Universitätsklinikum Münster, Münster, Germany, 6Pfizer Inc., New York, NY, United States

**Introduction:** Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a progressive disorder associated with both V30M and nonV30M TTR mutations. Tafamidis stabilizes TTR, inhibiting amyloid formation, and delays neurologic impairment in patients with TTR-FAP. This is a preliminary evaluation of safety and efficacy of long-term tafamidis treatment.

**Methods:** Patients were from an ongoing, open-label trial (Study Fx1A-303) and had either received tafamidis in the single-treatment arm Study Fx1A-201 (all nonV30M), or completed an 18-month placebo-controlled trial (Study Fx-005) and then received tafamidis in a 12-month extension (Study Fx-006; all V30M).

**Results:** Tafamidis was generally well-tolerated with no unexpected adverse events. Adverse events possibly related to study medication occurred in 24 (25.8%) patients; most common were headache and fall, each in 2 (2.2%) patients. All patient groups experienced some disease progression (Table). Those with V30M in the tafamidis-tafamidis arm had numerically smaller increases in Neuropathy Impairment Score-Lower Limb (NIS-LL) and Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN) scores than those in the placebo-tafamidis arm at 66 months. Furthermore, once patients in the placebo-tafamidis arm began treatment with tafamidis, their apparent rate of increase in NIS-LL scores was similar to those in the tafamidis-tafamidis arm. NonV30M patients had higher disease burden at baseline and increases in NIS-LL scores at 48 months roughly similar to those seen in the V30M patients at 66 months.

| Table |
|-----------------|-----------------|-----------------|
| **V30M (Fx-005/Fx-006)** | **nonV30M (Fx-001)** |
| **P-T T-T** | **Baseline** | **n=61** | **n=64** | **n=21** |
| NIS-LL total, mean (SD) | 11.45 (3.54) | 8.36 (1.10) | 27.64 (24.67) |
| NIS-LL muscle weakness, mean (SD) | 4.19 (0.28) | 2.87 (0.39) | 14.41 (16.65) |
| NIS-LL reflexes, mean (SD) | 1.09 (0.22) | 1.19 (0.20) | 5.20 (3.67) |
| NIS-LL sensory, mean (SD) | 5.57 (3.00) | 4.31 (3.39) | 8.12 (5.78) |
| QOL-DN, mean (SD) | 30.84 (26.72) | 27.31 (24.71) | 47.81 (35.14) |
| **Change from Baseline** | **at 66 months** | **at 66 months** | **at 48 months** |
| NIS-LL total, LS mean (SE) | 15.48 (2.50) | 9.15 (2.58) | 14.71 (2.87) |
| NIS-LL muscle weakness, LS mean (SE) | 9.50 (0.51) | 4.24 (1.96) | 9.66 (2.35) |
| NIS-LL reflexes, LS mean (SE) | 2.90 (0.50) | 1.78 (0.45) | 1.66 (0.79) |
| NIS-LL sensory, LS mean (SE) | 3.76 (0.54) | 2.20 (0.88) | 2.38 (0.73) |
| QOL-DN, LS mean (SE) | 10.25 (1.87) | 8.20 (3.82) | 23.51 (7.85) |

**Disclosure:** These studies were sponsored by FoldRx Pharmaceuticals, which was acquired by Pfizer Inc in October 2010.
OS3115
Clinical spectrum, causes and evolution of disabling neuropathies in patients with hematopoietic stem cell transplantation on a 20 years period

1Bicêtre Hospital, Univ. Paris Sud, AP-HP, Paris. 2Bicêtre Hospital, Univ. Paris Sud, AP-HP, Kremlin Bicêtre, 3IGR, Villejuif, France

Introduction: Reports concerning neuropathies following hematopoietic stem cell transplantation (HSCT) are scarce in the literature.

Methods: We retrospectively recruited patients who presented disabling neuropathy after HSCT between 1990 and 2012 in our academic hospital.

Results: We report 17 patients, median age 48.5 years [10-66], 12 allografts and 5 autografts. The average delay between HSCT and onset of neuropathy was 10.8 months [pre-existing - 35 months]. We describe different patterns and causes of neuropathy: acute polyradiculoneuropathy or Guillain Barré syndrom (GBS, n=3), chronic inflammatory demyelinating polyradiculo-neuropathy (CIDP, n=3), neuropathy due to graft versus host disease (Np-GVHD, n=4), vasculitis (n=3), toxic neuropathy (n=3), neuropathy revealing hematologic relapse (n=2) and neuropathy of undetermined cause (n=1). Over 50% improved after treatment (n=10). Particular features existed. GBS occurs prematurely after HSCT (average delay m=4.9 months) whereas CIDP or Np-GVHD occur later (respectively m=15.2 and m=14.2 months). Np-GVHD has different characteristics:

i) a polymorphic clinical presentation, non-length-dependent (62.5%), with motor symptoms (87.5%) mimicking CIDP with axonal features;

ii) Neuropathic symptoms often revealing the GVHD, although positive diagnosis was challenging in the absence of other affected organs and

iii) a good response to treatments used in chronic GVHD (steroids and immunosuppressive therapies).

Conclusions: Clinical presentations and causes of disabling neuropathies following HSCT are various. Polyradiculo-neuropathies are not rare and GVHD is often implicated. Systematic and large explorations are necessary in order to introduce appropriate treatment associated in our study with good prognosis.

Disclosure: Nothing to disclose

OS3116
Gene expression changes in chronic inflammatory demyelinating polyneuropathy skin biopsies

S. Puttini1, P.-A. Panaite1, M. Nicolas1, S. Renaud1, A. Steck2, T. Kuntzer1
1Department of Clinical Neurosciences, University Hospital Lausanne, Lausanne, 2University Hospital of Basel, Basel, Switzerland

Introduction: To determine molecular changes occurring in the skin biopsies of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) patients and to identify biomarkers for the disease.

Methods: We performed transcriptional profiling microarray analysis on lower leg skin punch biopsies from 20 CIDP patients and 17 healthy controls to identify disease-associated expression changes. The differential expression of genes with a possible role in the pathogenesis of CIDP from ontological studies was validated by quantitative PCR (qPCR) analysis.

Results: Most of the 190 differentially regulated genes were involved in immune and inflammatory responses, nervous system development, cell adhesion, wound response, angiogenesis and apoptotic processes. The differential expression of 26 genes with a putative role in CIDP pathogenesis was confirmed by qPCR. Four downregulated genes encoded members of the MHC class II family, while 22 upregulated genes were involved in cell proliferation and tissue repair such as PDGF1, VEGFR or KDR, A2M, CAV2 and NOSTRIN. The combined upregulation of KDR/DDR2 was found in 95% of patients.

Conclusions: These findings indicate that gene expression is modified in skin biopsies of CIDP patients, with prominent changes in inflammatory pathway markers. Several repair and protective factors are also activated. The downregulation of HLA II genes may be indirect evidence of activation of dormant multiple sclerosis retrovirus (MSRV) viral particles. Importantly, this study provides a new set of prospective CIDP biomarkers.

Disclosure: Nothing to disclose
**OS3117**

**Antibodies against neurofascin-155 (NF155) in CIDP associated with disabling tremor, distal weakness and poor response to IVIg**

L. Querol1,2, G. Nogales-Gadea1,2, R. Rogas-Garcia1,2, J. Diaz-Manera1,2, J. Pardo1, A. Ortega-Moreno4, M.J. Sedano2,5, E. Gallardo1,2, J. Berciano2,5, R. Blesa1, J. Dalmau6,7, I. Illa1,2

1Neuromuscular Disorders, Hospital de la Santa Creu i de Sant Pau, Barcelona, 2Centro de Investigación Biomédica en Red Enfermedades Neurodegenerativas, Madrid, 3Department of Neurology, Hospital Clínico Universitario, Santiago de Compostela, 4Department of Neurology, Hospital Virgen de las Nieves, Granada, 5Department of Neurology, Hospital Universitario Marqués de Valdecilla, Santander; 6Institució Catalana de Recerca i Estudis Avançats (ICREA), 7Department of Neurology, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

**Introduction:** Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disorder with autoimmune origin. The target antigens of the immune response remain largely unknown. Recent studies found antibodies against node of Ranvier proteins, such as contactin and neurofascin in a subset of CIDP patients. The clinical features associated to neurofascin antibodies have not been described. Our study describes the frequency and clinical features of CIDP patients with antibodies against NF155.

**Methods:** A cell-based assay with NF155-transfected HEK cells was used to screen for the presence of antibodies. Anti-NF155 titers and IgG isotype were determined by ELISA. Serum reactivity against nerve and brain structures was analyzed by teased-nerve fiber and rat brain immunohistochemistry. Clinical features were retrospectively reviewed.

**Results:** Two of 53 CIDP patients from our unit but none of 204 controls had antibodies against NF155 (p=0.041). Both patients shared an aggressive polyneuropathy with predominantly distal weakness and absence of response to IVIg. Eight additional patients classified as refractory for IVIg treatment were obtained from the CIBERNEF national database. Two of these patients were anti-NF155 positive and shared the clinical phenotype with the ones from our unit. Three of the 4 anti-NF155 positive patients presented a prominent, disabling, action tremor with cerebellar features. Anti-NF155 antibodies were predominantly IgG4 in all four patients and their sera bound to paranodal structures and to the neuropil of brainstem, cerebellum and brain.

**Conclusions:** Anti-NF155 antibodies in CIDP associate with a specific phenotype characterized by aggressive onset, distal weakness, disabling tremor and no response to IVIg.

**Disclosure:** Consulting honoraria from Bayer-Shering

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**OS3118**

**Fourteen-year catamnesis of patients with vasculitic neuropathy**

N. Üçeyler, A. Geng, C. Sommer

Department of Neurology, University of Würzburg, Würzburg, Germany

**Introduction:** Vasculitic neuropathies may lead to severe sensory-motor impairment and pain. We retrospectively assessed long-term disease outcome.

**Methods:** We analyzed medical records of 62 patients with vasculitic neuropathy who reported to our Department for diagnostics and treatment between 1999 and 2008. Outcome was followed up until 2013.

**Results:** The cohort consisted of 12 patients with systemic vasculitis and polyneuropathy and 50 patients with non-systemic vasculitic neuropathy. The neuropathy was sensory-motor in 46/62 (74%), pure sensory in 14/62 (23%), pure motor in 2/62 (3%), and painful in 37/62 (60%) cases. No action potential was recordable in the later biopsied sural nerve of 30/62 patients (48%). Although 12/62 (19%) patients had received immunosuppressive treatment before biopsy, histology revealed unequivocal signs of vasculitis in all cases. 56/62 patients (90%) were treated with immunosuppressants after histological confirmation of diagnosis. The major treatment regimes were an initial pulse of i.v. methylprednisolone followed by oral methylprednisolone only (10/56 cases, 18%) or a combination with azathioprine (22/56 cases, 39%). All patients had at least a short term response to steroids. Shorter disease duration and younger age were associated with better long-term outcome. In the majority of patients, however, long-term treatment with immunosuppressants did not lead to further improvement of residual sensory-motor symptoms; several patients remained stable even after treatment cessation. Notably, neurophysiology worsened in some patients with clinically stable disease.

**Conclusion:** Early and high dose i.v. steroid treatment was effective in this cohort of patients with vasculitic neuropathy. Remission with residual symptoms was the most frequent outcome.

**Disclosure:** Nothing to disclose
Autonomic nervous system disorders

**OS3201**

**Effect of osteopathic manipulative treatment on variations of HF parameter of HRV in healthy subjects compared to sham therapy and control group: RCT**

N. Ruffini¹, G. D’Alessandro¹, N. Mariani², A. Pollastrelli³, L. Cardinali¹, F. Cerritelli¹,³

¹Research, ²Accademia Italiana Osteopatia Tradizionale, ³Research and Development, European Institute for Evidence Based Osteopathic Medicine, Pescara, Italy

**Introduction:** The effects of osteopathic manipulative treatment (OMT) on autonomic nervous system (ANS) are still under debate. Heart Rate Variability (HRV) is linked to health status and it is an indirect marker of the ANS activity. This randomized placebo controlled within subject cross-over single blinded study investigated the influence of OMT on HRV measures in healthy subjects while at rest. OMT was hypothesised to increase HRV, compared to sham and control, and that the effects would be greatest for a non-linear measure of HRV (the detrended fluctuation scaling exponent).

**Methods:** 66 subjects were randomized into groups OMT, Sham and Control. Subjects allocated into OMT and Sham groups received two weekly treatments. Control group received no intervention. Participants were not on any medications and reported no history of psychiatric illness, neurological disorder, or any other serious medical condition (e.g. diabetes, cardiovascular disease).

**Results:** OMT engenders a statistically significant increase of parasympathetic activity, as shown by HF rate (p<0.001), and decrease of sympathetic activity, as revealed by Low Frequency (LF) rate (p<0.001); results also show a reduction of LF/HF (p<0.001). These effects were largest using the detrended fluctuation scaling exponent, a non-linear measure. Importantly, participants were unable to correctly guess which treatment they had been assigned at either of the two assessments.

**Conclusions:** Findings suggest that OMT can influence ANS activity increasing parasympathetic function and decreasing sympathetic activity, in comparison with sham therapy and control.

**Disclosure:** Nothing to disclose

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**OS3202**

**Composite Autonomic Symptom Scale 31 reveals autonomic pupillary and bladder dysfunction in relapsing remitting multiple sclerosis patients**

T. Intravooth¹, R. Wang¹-², O. Chintakanan³, S. Moeller¹, J. Koehn¹, R. Linker¹, D.-H. Lee¹, M.J. Hilz¹

¹Department of Neurology, University of Erlangen-Nuremberg, Erlangen, Germany, ²Department of Neurology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China, ³Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

**Introduction:** Autonomic nervous dysfunction (AND) is frequent in Multiple Sclerosis (MS). Yet, little is known whether MS severity influences type and degree of ANDs. Therefore, we assessed severity and type of ANDs and compared ANDs with disease severity in patients with relapsing remitting MS patients (RRMS).

**Methods:** In 41 RRMS patients (mean age 35.05±9.88 years, 31 women) and 12 healthy controls (mean age 29.27±9.06 years, 7 women), we determined ANDs using the COMPASS-31, a 31-item questionnaire assigning scores from 0-100 to ANDs in the domains orthostatic intolerance, vasomotor, secretomotor, gastrointestinal, bladder and pupillomotor function. Clinical MS severity was assessed with the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC). The Mann-Whitney-U test compared patient and control values. Spearman signed rank test correlated COMPASS-31 scores with EDSS and MSFC values. Significance was assumed for p<0.05.

**Results:** The COMPASS-31 total score did not differ between MS patients and controls [median 18.78; lower and upper quartile: 7.18-18.79) vs. 12.20; 3.26-21.32; p=0.161]. However, COMPASS-31 subdomain scores were higher in MS patients than in controls for bladder ANDs [1.11; 0.00-3.33 vs. 0.00; 0.00-0.00, p<0.05] and pupillomotor ANDs [1.67; 1.00-2.67 vs. 0.33; 0.00-0.92, p<0.001]. Only COMPASS-31 bladder scores correlated with EDSS values (Spearman-Rho: 0.420; p<0.05). AND scores did not correlate with MSFC values.

**Conclusions:** Total COMPASS-31 scores do not suggest increased AND prevalence in our 41 RRMS patients while subscores unveil prominent pupillomotor and bladder dysfunction. Increasing MS severity bears an increasing risk of bladder dysfunction.

**Disclosure:** Nothing to disclose
Oral Sessions 85

OS3203

Diagnosing PoTS: additional investigations beyond the HUT and standing tests

V. Iodice1,2, D. Low3, C. Mathias1,2
1Imperial College London, 2University College London (UCL) Institute of Neurology, London, 3Liverpool John Moores University, Liverpool, United Kingdom

Introduction: Diagnosing PoTS remains a challenge, and patients are often encountered with orthostatic intolerance and palpitations highly suggestive of PoTS, who do not meet the arbitrary criteria of excessive tachycardia on head-up tilt (HUT) or standing. Additional factors in daily life, such as food ingestion, physical exercise and heat, that cause vasodilatation, are known to exacerbate the postural tachycardia in PoTS. The aim of this study was to objectively evaluate the cardiovascular autonomic responses to food, exercise and heat stimuli in PoTS.

Methods: Patients with a history of orthostatic intolerance and postural tachycardia underwent HUT and standing tests and liquid meal, modified exercise and whole-body heating tests.

Results: We studied 95 patients with PoTS. 39/95 (41%) patients met the criteria for PoTS on HUT whereas 51/95 (54%) patients fulfilled the criteria on standing. There was a significant exacerbation of postural tachycardia on HUT post-meal (p<0.001) and on standing post exercise (p<0.001). There was also an unmasking of postural tachycardia on standing post-heating in 10/20 patients (50%). Food challenge and modified exercise were complementary tests revealing the diagnosis of PoTS in 91% and 84% of patients, respectively, compared with 70% if only the HUT and standing tests were used.

Conclusions: This study emphasises the use of additional and relevant complementary autonomic function tests in confirming diagnosis of PoTS. Furthermore they provide valuable information for patients and their physicians, in the objective evaluation and in tailoring individually targeted management of symptoms exacerbated by key factors in daily life.

Disclosure: Nothing to disclose
**OS3205**

**Autonomic dysfunction is a major feature of the cerebellar ataxia, neuropathy and vestibular areflexia “CANVAS” syndrome which can mimic multiple system atrophy**

T.Y. Wu¹, J. Taylor², D.H. Kilfoyle¹, A. Smith³, B. Mcguinness¹, M. Simpson¹, E. Walker¹, P. Bergin¹, J. Cleland¹, D.O. Hutchinson¹, N.E. Anderson¹, B.J. Snow¹, T.J. Anderson⁴, L. Pamerbier⁴, N.J. Cutfield⁵, A.M. Chancellor¹, S. Mossman², R.H. Roxburgh¹³

¹Neurology, Auckland City Hospital, Auckland, ²Wellington Hospital, Wellington, ³Radiology, Auckland City Hospital, Auckland, ⁴New Zealand Brain Research Institute, ⁵Department of Medicine, University of Otago, Christchurch, ⁶Department of Medicine, Brain Health Research Centre, Dunedin, ⁷Neurology Department, Tauranga Hospital, Tauranga, ⁸Centre for Brain Research, University of Auckland, Auckland, New Zealand

**Introduction:** Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a recently recognised neuro-degenerative disorder. Prompted by the presence of symptomatic postural hypotension in two patients previously diagnosed with CANVAS, we hypothesised that autonomic dysfunction may be a common feature of other CANVAS patients.

**Methods:** In a cohort of 27 patients from New Zealand with CANVAS, we performed autonomic nervous system testing based on Ewing and Clarke’s battery of autonomic tests and assessed symptoms of autonomic dysfunction using the Survey of Autonomic Symptoms and Total Impact Score questionnaires.

**Results:** 42% of patients had definite parasympathetic dysfunction and 79% of patients had definite sympathetic dysfunction according to the pre-specified criteria. In total, 83% of our patients had evidence of sympathetic or parasympathetic dysfunction. Two had previously, incorrectly, been diagnosed with multiple system atrophy. All patients had at least one symptom of autonomic disease and 92% had more than two symptoms.

**Conclusions:** Our results support the hypothesis that autonomic dysfunction is a major feature of CANVAS. This has implications for the management of patients diagnosed with CANVAS as they are likely to have treatable autonomic symptoms. The findings also provide an important differential diagnosis from multiple system atrophy (MSA) for patients who present with ataxia and autonomic failure. Autonomic failure in MSA is preganglionic whereas evidence points to the autonomic failure of CANVAS as being “post ganglionic”. We suspect that, in keeping with the postmortem proven sensory and vestibular ganglionopathies, it is the autonomic ganglia themselves that are affected by the condition.

**Disclosure:** Nothing to disclose

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**OS3206**

**The usefulness of 24 hour ambulatory blood pressure and heart rate monitoring (24hr-ABPM) in diagnosing orthostatic hypotension (OH) in patients with parkinsonian disorders**

E. Vichayanrat¹², D.A. Low¹³, E. Stuebner⁴, V. Iodice¹², C.J. Mathias¹²

¹St. Mary’s Hospital, Imperial College Neurovascular Medicine Unit, ²UCL, Institute of Neurology, London, ³Liverpool John Moores University, Liverpool, United Kingdom, ⁴Neurology and Clinical Neurophysiology, University of Witten/Herdecke, Wuppertal, Germany

**Introduction:** Orthostatic hypotension (OH) is a common non-motor feature in Parkinson’s disease (PD) and a diagnostic criteria of MSA patients. 24 hour ambulatory blood pressure monitoring (24hr-ABPM) can be used to assess circadian BP pattern and OH during daily activities. The aim of this study was to determine the effectiveness of 24hr-ABPM compared to a standard Head-up Tilting (HUT) in diagnosing OH in patients with parkinsonian disorders.

**Methods:** 44 patients (17 MSA, 27 PD) underwent cardiovascular autonomic screening tests and 24hr-ABPM. Patients were classified into 2 groups: patients with OH (OH+ group; N=28) and without OH (OH-; N=16). The number of patients with abnormal circadian BP rhythms were compared between groups. Standing tests were included during 24hr-ABPM. The sensitivity and specificity in detecting OH from the 24hr-ABPM standing test was compared with HUT.

**Results:** During HUT, BP was significantly lower in OH+ group compared to OH- and the degree of BP fall during HUT was significantly greater in OH+ group (both p<0.01). With 24hr-ABPM, OH+ patients had a higher proportion of patients with abnormal BP and reversed circadian rhythms than OH- groups (both p<0.01). Using 24hr-ABPM with the diary, a fall of 20mmHg or more in SBP showed a sensitivity and specificity of 82% and 100% (AUC 0.91, 95% CI 0.84-0.98) in differentiating OH+ from OH-, respectively.

**Conclusions:** This study demonstrates that 24hr-ABPM with the diary has reasonably high sensitivity and specificity in detecting OH compared to a standard HUT tests in patients with parkinsonian disorders.

**Disclosure:** Nothing to disclose
Epilepsy 2

OS3207

Long-term follow-up of genetic generalized epilepsy with typical absence seizures and generalized paroxysmal fast activity in adulthood

Z. Aydın Özemir¹,², Z. Matur³, N. Bebek¹, C. Gürses¹, A. Gökyiğit¹, B. Baykan¹
¹Department of Neurology, Clinical Neurophysiology Unit, Istanbul University, Epilepsy Center (EPIMER) and Istanbul Faculty of Medicine, ²Department of Neurology, Memorial Atasehir Hospital, ³Department of Neurology, Istanbul Bilim University, Istanbul, Turkey

Introduction: Generalized paroxysmal fast activity (GPFA), a rhythmic EEG pattern of unknown significance was reported in a few patients with genetic generalized epilepsy (GGE) presenting with typical absence seizures (TAS). Our aim was to report the long-term follow-up and genetic findings in GGE patients with TAS having GPFA in their EEG.

Methods: We had investigated all EEGs of the adult GGE patients with TAS between the years of 1997 and 2002 for another study and eventually recorded GPFA in 12 of them. Afterwards these patients were followed up for their clinical and electroencephalographic course and their genetic features were also investigated. The control group was composed of 24 adult GGE patients who also had TAS without GPFA with similar follow-up duration in the same epilepsy center.

Results: Durations of epilepsy and TAS were significantly longer in the GPFA group. There is no significant difference between the groups in comparison of the electroclinical characteristics except EEG photosensitivity, which was significantly common in GPFA Group. The age at detection of GPFA was 33±16.6 (16-71) and 80% still have GPFA in their last EEG. 60% of the GPFA group had consanguineous parents whereas only 4.17% had consanguinity in the Control Group. Five relatives with epilepsy from GPFA Group were also evaluated but GPFA could not be seen in their 30 evaluated EEGs. We could not show the responsible mutations.

Conclusions: GPFA is an ignored EEG pattern of adult GGE patients with TAS, indicating life-long course for epilepsy and TAS.

Disclosure: Nothing to disclose
OS3209

Is serotonin transporter implicated in mesial temporal lobe epilepsy development?

B. Leal¹, J. Chaves³, A.C. Barreira¹, C. Carvalho¹, A. Bettencourt¹, J. Lopes², J. Ramalheira², A. Martins da Silva², P.P. Costa², B. Martins da Silva¹
¹UMIB-ICBAS, University Porto, ²Hospital Santo António-Centro Hospitalar do Porto, ³Instituto Nacional de Saúde Dr. Ricardo Jorge, Delegação do Porto, Porto, Portugal

Background: Human and animal studies demonstrated that deregulation of serotonergic neurotransmission can be involved in the pathophysiology of epilepsy. Serotonin transporter (5-HTT) plays a key role in the regulation of serotonin levels. It has been described that expression of the 5-HTT gene could be modulated by a 17bp variable number of tandem repeats (VNTR) in the second intron (5-HTTVNTR). This VNTR can have 9, 10 or 12 repeats. The 12-repeat allele has been associated with higher transcriptional activity. Investigation of the association between 5-HTTVNTR and the development of Temporal Lobe Epilepsy (TLE) has been inconclusive. Our aim was to analyse the association between 5-HTTVNTR and Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis (MTLE-HS) in a Portuguese population.

Methods: A cohort of 119 MTLE patients (65F, 54M, mean age= 44±11 years, age of onset= 13±9 years, 62 with Febrile Seizures antecedents) was compared with a cohort of 236 healthy individuals (HI). HTTVNTR genotyping was performed by PCR fragment sizing.

Results: The genotype 12/9 was overrepresented in MTLE-HS patients compared to controls (2.5% in MTLE vs 0.0% in HI, p=0.037 OR=1.026 (0.997 - 1.056). MTLE-HS subgroups (with and without febrile seizures antecedents) showed no differences in 5-HTTVNTR allelic or genotypic frequencies.

Conclusion: These results suggest that serotonin transporter gene may play a role in MTLE-HS susceptibility. Variations in the 5-HTT gene expression may lead to changes in serotonergic neurotransmission and consequently in brain homeostasis, lowering the threshold for seizure development. Supported by a BICE Tecnifar Grant 2012

Disclosure: Nothing to disclose

OS3210

Family impact and parental perception of childhood epilepsy

P.C.C. Mbonda¹, Y. Fogang², D. Toffa², M. Ndiaye², A.G. Diop², M.M. Ndiaye²
¹Catholic University of Louvain, Brussels, Belgium, ²Fann Teaching Hospital, Dakar, Senegal

Introduction: Epilepsy is a real public health problem; patients living with epilepsy suffer from psychological and socio-cultural problems which are barriers to their development and social integration. Our objective was to assess the impact of epilepsy on quality of life of parents and their perception of the disease.

Methods: For 1 year, 146 children (2-16 years) with epilepsy were recruited, and their parents were interviewed, the parent interviewed lived with the patient for at least 1 year. The presence of major life changes during the previous 3 months on the social or economic conditions of the family unrelated to epilepsy, significant comorbidities and mental retardation was an exclusion criteria.

Results: Epilepsy has an impact on the health of mothers, 73% of mothers had sleep disorders, and 33% had headaches. More than half of mothers had seen a considerable impact on their work, 85% of mothers felt that family economy was affected by the disease. If 18% of parents believe that their child’s epilepsy brought them together, 68% believe it has not led to conflicts in their married life, and 14% thought the opposite. According to 9.5% of the mothers, their child’s epilepsy removed any desire to conceive again.

Conclusions: Epilepsy is a major neurological problem in developing countries and is associated with significant psychosocial maladjustment among both children involved and family members.

Disclosure: Nothing to disclose
OS3211

**Reflex seizures induced by reading, rub, music and startle: a video-EEG analysis**

J. Fulton¹, R. Mohanraj¹,²
¹University of Manchester, Manchester; ²Greater Manchester Neurosciences Centre, Salford, United Kingdom

**Introduction:** Reflex epilepsies are a group of disorders in which seizures are habitually provoked by a specific sensory stimulus or cognitive process. The nosological status of reflex epilepsies remains unclear. Analysis of reflex seizures can help identify the cortical networks underlying each specific type of seizure.

**Methods:** We undertook a clinical and video electroencephalographic (EEG) analysis of 2 cases each of primary reading epilepsy and rub epilepsy, and 1 case each of epilepsy relating to music and startle.

**Results:** Two cases of reading epilepsy exhibited myoclonic jerks of the jaw and tongue during silent reading. EEG was normal in one, and in the other showed 3-4 Hz rhythmic spike wave in the central region suggesting involvement of the left precentral cortex. Both patients with rub epilepsy showed asymmetric tonic posturing of the limbs with stimulation of the susceptible area. EEG showed spikes and rhythmic slow activity frontocentrally, suggesting involvement of the supplementary motor area. The patient with musicogenic epilepsy, on being played a specific song during EEG recording exhibited jerking of the right arm and jaw, followed by loss of awareness, and secondary generalisation. EEG showed rhythmic spike wave discharges in the left fronto-temporal region. The patient with startle epilepsy exhibited asymmetric tonic spasm of the limbs with a gelastic component in response to unexpected auditory stimulation. EEG showed right frontocentral rhythmic activity.

**Conclusions:** Our results help confirm the location of epileptogenic networks in patients with reflex seizures provoked by various stimuli. Video and EEG data will be presented.

**Disclosure:** Nothing to disclose

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OS3212

**Psychiatric disease, social aspects and life events in young men with epilepsy**

S.F. Reiter¹, G. Veiby¹,², M.H. Bjørk¹,², A.K. Daltveit³,⁴, B.A. Engelsen¹,², N.E. Gilhus¹,²
¹Department of Clinical Medicine, University of Bergen, Bergen; ²Department of Neurology, Haukeland University Hospital, ³Department of Global Health and Primary Care, University of Bergen, ⁴Medical Birth Registry of Norway, Division of Epidemiology, Norwegian Institute of Public Health, Bergen, Norway

**Introduction:** We investigated psychiatric disease, adverse social aspects and life events in men with epilepsy.

**Methods:** This study was based on the Norwegian Mother and Child Cohort Study (MoBa). Data included information on diagnoses, symptoms from validated diagnostic instruments and adverse social aspects from 71,700 men, registered as fathers of children in MoBa around week 18 of pregnancy.

**Results:** 658 men (mean age 31.8 years) reported epilepsy, 36.9% using antiepileptic drugs (AEDs). Men with epilepsy more often screened positive for present depression (3.9% vs. 2.5%, p=0.023) compared to the references without epilepsy. Symptoms of anxiety was linked to untreated epilepsy (7.0% vs. 4.6%, p=0.004), as was self-reported ADHD (3.4% vs. 0.4%, p<0.001), bipolar disorder (2.2% vs. 0.3%, p=0.003), unspecified psychiatric disorders (5.6% vs. 2.3%, p=0.008), low self-esteem (2.5% vs. 1.3%, p=0.011) and episodes of physical violence (3.3% vs. 1.5%, p=0.021). Low satisfaction with life (1.7% vs. 0.7%, p=0.010) and serious somatic illness (10.7% vs. 4.3%, p<0.001) was more often reported among AED treated men compared to the references. Unemployment due to disability was linked to both AED treated (9.1% vs. 1.4%, p<0.001) and untreated epilepsy (2.9% vs. 1.4%, p=0.009), as were low income (10.3% vs. 5.4%, p=0.031 and 9.7% vs. 5.4%, p=0.011).

**Conclusions:** Epilepsy in young men was associated with a higher frequency of psychiatric disorders, adverse socioeconomic aspects, and lower satisfaction with life. Men with untreated epilepsy appear to be the most vulnerable group concerning psychiatric comorbidity, and this may be relevant for their children's development.

**Disclosure:** Nothing to disclose
Infection and AIDS

OS3213
Which viral encephalitis do we treat?
A review of four-year data
B. Ciftci Kavaklioglu, E. Coban, A. Sen, E. Soylemezoglu, M.A. Aldan, D. Atakli, A. Soysal
Neurology, Bakirkoy Prof Dr Mazhar Osman Education and Research Hospital for Psychiatric and Neurological Diseases, Istanbul, Turkey

Introduction: To determine the prevalence of herpes encephalitis, known as the most common, potentially mortal and treatable cause of sporadic encephalitis, in a sample Turkish population.

Methods: Demographic, clinical, laboratory, imaging, electrophysiology and PCR-DNA results of patients examined with a pre-diagnosis of encephalitis, i.e. ICD-10 of A81-86, G04, G05, B00, in our clinic between June 2010 - December 2013 were examined retrospectively.

Results: A total of 68 patients were included. The most common presenting symptom was altered behavior (67.6%), followed by headache and seizures. Neurological examination was mainly normal in 14.7%, whereas isolated findings of altered consciousness was determined in %66.2. Temporal T2 hyperintensity was determined in the MRI of 27.9%, and EEG abnormalities were determined in 35.3% of patients. Lymphocytic pleocytosis was determined in the CSF of 35 patients, whereas increased leukocyte count was determined in 20 patients; and CSF protein count was increased overall in 27 patients. In the end, 57 patients had been diagnosed with viral encephalitis, 3 bacterial meningitis, 3 tuberculous meningitis, 2 sporadic Creutzfeld-Jacobs disease, 2 acute disseminating encephalomyelitis, and 1 Brucella encephalitis. Seven (10.2%) cases of viral encephalitis were HSV DNA PCR positive.

Conclusions: Viral encephalitis is the most common cause of infectious encephalitis; however, other atypical causes and tuberculous and Brucella encephalitis should be noted, particularly in the Turkish population. Negative HSV DNA PCR results do not always exclude the need for antiviral therapy in patients with a strong pre-diagnosis of herpes encephalitis since several microbiological factors might result in false negativity.

Disclosure: Nothing to disclose

OS3214
Stroke in HIV infected patients: a case series reviewing etiologic mechanisms
A. Costa1,2, A. Silva-Pinto3, P. Abreu1,2
1Neurology, Centro Hospitalar São João, 2Faculty of Medicine, University of Porto, 3Infectious Diseases, Centro Hospitalar São João, Porto, Portugal

Introduction: A high incidence of stroke is observed in younger patients with uncontrolled human immunodeficiency virus (HIV) infection and severe immunosuppression. In previous studies, opportunistic infections and HIV coagulopathy/vasculopathy explained more than 60% of the strokes.

Methods: We made a retrospective transversal study of patients with stroke between 2006 and 2013 and who had a previous or concomitant diagnosis of HIV infection. The Stroke mechanism was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. The aim of this study was to characterize this population and categorize the possible etiologic mechanisms of stroke.

Results: Nineteen (17 men) HIV (18 HIV-1, 1 HIV-2) patients were included. The mean age at the stroke diagnosis was 49.5 (SD 11.6) and stroke occurred at a median of 9.5 years (0-22) after HIV infection diagnosis. The median of CD4 cells was 225.5/µL (0-853) and the median viral load was 0.0 copies/mL (0-1220000). There were 16 ischemic strokes and 3 transient ischemic attacks. The mean admission NIHSS was 7.3 (SD 6.5). The stroke aetiology according to the TOAST criteria was: 3 large-artery atherosclerosis (15.8%), 4 cardioembolism (21.0%), 7 small-vessel occlusion (36.8%), 1 other determined aetiology (5.2%) (cocaine) and 4 undetermined aetiology (21.0%) (incomplete evaluation). Central nervous system opportunistic infections or HIV vasculopathy/coagulopathy were not diagnosed.

Conclusions: Many mechanisms may concur to the aetiology of stroke in HIV infected patients. In this HIV patients’ cohort, and contradicting previous studies, vascular factors and cardiac mechanisms were highly recognized mechanisms of stroke.

Disclosure: Nothing to disclose
OS3215
Tuberculomas of brain: an unpredictable entity
A. Haldar\textsuperscript{1}, G. Gupta\textsuperscript{2}, D. Chakraborty\textsuperscript{1}
\textsuperscript{1}Neurology, \textsuperscript{2}Radiology, Fortis Hospital, Kolkata, India

Introduction: Mycobacterium tuberculosis is one of the commonest causes of central nervous system (CNS) infections. They cause tuberculous meningitis, vasculitis, encephalopathy, abscesses tuberculomas and caries spine. The nature of the lesion depends on the host immunity and virulence of the bacteria. Of the CNS lesions, the tuberculomas are the most unpredictable. Keeping this in mind, we decided to retrospectively study the cases of tuberculomas of brain and their response to anti-tubercular drugs in order to formulate a standard treatment plan.

Methods: This was a retrospective study conducted in our hospital. The patients who had a MRI diagnosis of CNS tuberculoma with minimum 6 month follow-up were included. The diagnosis of tuberculomas was either confirmed by brain biopsy or was supported by evidence of tuberculosis in the cerebrospinal fluid or in other organs like the lungs.

Results: 6 patients met the selection criteria. Their age ranged from 11–70 years. Duration of receiving anti-tubercular treatment varied from 6 months to 2 years. 1 patient, aged 70 years died of septicaemia. Of the remaining five, 1 patient had complete resolution of the lesion. 2 patients had incomplete resolution, in spite of more than 1 year ATD (anti-tubercular drug) treatment. Remaining 2 patients had significant decrease in size of the lesions after 1 year of treatment.

Conclusions: The results show that the response to treatment is mixed. However presence of multiple tuberculomas and larger lesions heralded worse prognosis. A more elaborate study with larger patient number is needed to formulate a standardized treatment plan.

Disclosure: Nothing to disclose
OS3216

Serum glucose adjusted cut-off values for normal cerebrospinal fluid/serum glucose ratio

H. Hegen, M. Auer, F. Deisenhammer
Department of Neurology, Innsbruck Medical University, Innsbruck, Austria

Introduction: Calculation of the cerebrospinal fluid/serum glucose (CSF/S-Glu) ratio is part of the routine CSF work-up, however, different cut-off values ranging from 0.3 to 0.5 have been suggested so far to distinguish physiological from pathological conditions.

Objective: To determine normal cut-off values of the CSF/S-Glu ratio.

Methods: As an Austrian reference laboratory we screened our database for paired CSF and serum samples, which have been collected by lumbar puncture, were processed within one hour after withdrawal, showed cell count <5/µl, erythrocyte count <500/µl and age-related normal CSF total protein resulting in 1036 sample pairs. Glucose concentrations in CSF and serum were measured by enzymatic spectrophotometry.

Results: Glucose concentrations in CSF were approximately 60% of those in serum. CSF/S-Glu ratios negatively correlated with serum glucose levels (R=-0.586, p<0.001) and cut-off values for normal CSF/S-Glu ratio defined as the 5th percentile were 0.5 for patients with a serum glucose concentration <100mg/dl, 0.4 for those with a glucose level of 100-149mg/dl and 0.3 for serum glucose concentrations ≥150mg/dl.

Conclusions: CSF/S-Glu ratio inversely correlates with serum glucose concentrations in a non-linear manner. These findings suggest that cut-off values for normal CSF/S-Glu ratio must be adjusted to serum glucose levels, probably explaining the considerably varying cut-offs that have been reported so far.

Disclosure: Nothing to disclose

OS3217

Migration of toxocara canis into the spinal cord in poorly treated patients

R.A. Jabbour¹, L.A. Atweh², M.H. Hourani³, S.F. Atweh³
¹St George Hospital University Medical Center-UOB, Beirut, Lebanon, ²Texas Children’s Hospital, Houston, TX, United States, ³American University of Beirut and Medical Center, Beirut, Lebanon

Introduction: Although Toxocara myelitis is a rare entity, 17 cases were recently diagnosed in Lebanon and published. Radiological features of the Visceral Larva Migrants (VLM) infection of the spinal cord seem to be specific. Lesions on the magnetic resonance imaging (MRI) showed fusiform enlargement with focal nodular enhancement after Gadolinium injection. Two of these patients were initially poorly treated and had multiple MRIs.

Methods: Serial MRI pictures of two patients with prolonged Toxocara myelitis were reviewed and compared.

Results: One patient was followed up for a period of 4 months with an unknown myelitis. The lesion was noticed in this patient to migrate upward from C8 to C2-C3 level with time. The patient was eventually diagnosed to have Toxocara infection and treated with anti-helminthic agents with complete resolution. The second patient had a C2-C3 myelopathy that was diagnosed to be a Toxocara infection and treated for a 2 week period. He relapsed 2 months later with a new lesion at C4 level. Treatment for 2 more months cleared the lesion permanently.

Conclusion: In untreated or poorly treated Toxocara canis myelitis, the lesion in the spinal cord seems to migrate from one area to another as seen on MRI. This worm which can migrate in blood and solid organs seems also to migrate within the spinal cord if poorly treated. In this particular condition, treatment with anti-helminthic agents should be continued until complete resolution of the clinical symptoms and normalization of the MRI.

Disclosure: Nothing to disclose
OS3218

Assessment of HIV-infected patients with neurological complications in a multidisciplinary platform

S. Simioni1, M. Cavassini2, D. Alves2, R. Meuli3, G.E. Maccaferri4, A. Berney4, R.A. Du Pasquier1

1Neurology, 2Infectious Diseases, 3Radiology, 4Psychiatry, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Introduction: Despite combination antiretroviral therapy (cART), neurological complications, in particular the cognitive ones, remain a challenge in HIV-infected patients. Frequently, co-morbidities are intermingled with HIV infection, rendering the management of these patients difficult.

Methods: We set up a multi-disciplinary Neuro-HIV Platform composed of infectiologists, neurologists, neuropsychologists, psychiatrists, and neuroradiologists. During a day-hospitalization, the patient benefits from a clinical evaluation by all these specialists, together with blood work-up, brain MRI and lumbar puncture.

Results: From March 2011 to November 2013, we evaluated 80 consecutive patients (52 men, 49.6±9.1 y, nadir CD4+ T-cells 172.2±142.7 cells/mm3, current CD4+ 568.8±257 cells/mm3, 76% with undetectable plasma HIV RNA, 89% with undetectable CSF viral load, 99% on cART). Main referral cause was cognitive complaints (90%), which were confirmed in 78% of those. Main causes of cognitive disorders were psychiatric conditions (41%) and HIV-associated neurocognitive disorders (HAND) (30%). Neurological deficits were evidenced in 46% of the cohort. Brain MRI was abnormal in 54%, mostly due to slight to moderate cortical/subcortical atrophy. The presence of HAND was correlated with a lower nadir CD4+ T-cells (p=0.02). No other correlation was found between HIV disease status and neurological deficits.

Conclusions: Neurological/neuropsychological complications are frequent in well-treated HIV+ patients. The latter are more often ascribed to a psychiatric condition than to HIV infection itself. A multi-disciplinary approach is a real asset to take care of these complex patients.

Disclosure: We are indebted to AbbVie, Gilead, and Bristo-Myers Squibb who made this Neuro-HIV platform possible.
Neurogenetics

OS3219

Autosomal-dominant proximal spinal muscular atrophy caused by mutations in a novel gene-motor adaptor BICD2

K. Peeters1,2, I. Litvinenko3, T. Chamova4, B. Asselbergh2,5, L. Almeida-Souza2,6, T. Geuens2,5, E. Ydens2,3, M. Zimon1,2, J. Irobi1,2, E. De Vriendt1,2, V. De Winter1,6, T. Ooms1,2, V. Timmerman2,6, I. Tournev3,7, A. Jordanova2,8

1Department of Molecular Genetics, VIB, Molecular Neurogenomics Group, 2Neurogenetics Laboratory, Institute Born-Bunge, University of Antwerp, Antwerp, Belgium, 3Department of Pediatrics, Clinic of Child Neurology, Medical University, 4Department of Neurology, University Hospital ‘Alexandrovska’, Medical Faculty, Medical University, Sofia, Bulgaria, 5Department of Molecular Genetics, VIB, Centralized Service Facility, 6Department of Molecular Genetics, VIB, Peripheral Neuropathy Group, Antwerp, Belgium, 7Department of Cognitive Science and Psychology, New Bulgarian University, 8Department of Medical Chemistry and Biochemistry, Molecular Medicine Center, Medical University, Sofia, Bulgaria

Introduction: Spinal muscular atrophy (SMA) refers to a group of genetic disorders characterized by degeneration of anterior horn cells of the spinal cord. Although the most common SMA cases are inherited in autosomal-recessive trait and caused by homozygous deletion or mutation of the survival of motor neuron 1 (SMN1), rare families with dominant inheritance have been reported.

Materials and methods: A four-generation Bulgarian family with 11 affected members and one sporadic patient afflicted with autosomal dominant proximal SMA were involved in the study. The evaluation included detailed neurological examination and testing of muscle strength. Evaluation of serum creatine phosphokinase (CPK) levels and electromyography (EMG) were performed of 6 patients. The molecular-genetic analysis encompassed genome-wide linkage analysis and whole-exome sequencing.

Results: The clinical onset age varied between 1 and 6 years (mean 3.17±1.70 years), and individuals presented with delayed motor milestones, such as walking, difficulties in getting upright from a squatting position and in climbing stairs, a waddling gait, and slow running. The weakness was limited to the lower limbs and did not progress significantly over time, given that affected individuals still remained ambulatory into the fifth decade. The genome-wide linkage analysis and whole-exome sequencing found a heterozygous de novo c.320C>T (p.Ser107Leu) mutation in bicaudal D homolog 2 (Drosophila) (BICD2) in the 11 affected from the four-generation family and c.2321A>G (p.Glu774Gly) in the sporadic case.

Conclusion: Our study identifies BICD2 gene mutations as a novel cause of non-5q linked SMA and highlights its importance in the motor neuron function in humans.

Disclosure: Nothing to disclose

OS3220

Molecular diagnosis and disease gene identification in neurological disorders using exome sequencing

T.B. Haack1, P. Freisinger2, H. Mayr3, W. Sperl1, C. Kornblum4, T. Klopstock5, T.M. Strom1, T. Meitinger1, H. Prokisch1

1Technische Universität München, Institute of Human Genetics, 2Community Hospital Reutlingen, Munich, Germany, 3Paracelsus Medical University, Salzburg, Austria, 4University of Bonn, Bonn, 5Ludwig-Maximilians University, Munich, Germany

Introduction: Genetic and clinical heterogeneity make the molecular diagnosis of various neurological disorders challenging. One example are disorders arising from faulty oxidative phosphorylation. Despite good progress in the field, most disease causing mutations still have to be identified.

Methods: We applied exome sequencing to 300 unrelated individuals with suspected mitochondrial disease. Variant filtering was performed to prioritize likely pathogenic mutations. Cellular studies were conducted to establish the disease-causing role of mutations in new disease genes and to gain insights into the physiological role of encoded proteins.

Results: In one quarter of patients, we identified mutations in known disease genes (e.g. POLG1, TWINKLE). In another quarter, we detected defects in genes previously not associated with mitochondrial disease. Clear candidate mutations were rare, predicted a loss-of-function, and affected evolutionary conserved genes such as MGME1, the first exonuclease to be involved in mitochondrial replication. The pathogenicity of other defects is supported by statistical evidence with one example being mutant ACAD9 detected in 15 cases. More difficult is the interpretation of mutations in genes coding orphan proteins such as FBXL4 associated with reduced mitochondrial content. Evolving issues are factors involved in mitochondrial protein translation (tRNA synthetases, ELAC2, MTO1, and a new tRNA modifying enzyme) as well as perturbations of cofactor metabolism. The latter offer therapeutic perspectives such as riboflavin supplementation in hRFT2/3 defects.

Conclusion: Genome wide sequencing comprehensively detects causal mutations and enables identification of novel disease genes. Technological advances hold promise for improvement of the diagnostic yield and implementation in routine clinical testing.

Disclosure: Nothing to disclose
OS3221
ATM mutations are not exclusively associated with ataxia-telangiectasia but may also cause focal or generalized dystonia
C. Kuhn1, C. Gallemmüller1, S. Biskup2, T. Klopstock1
1Universitätsklinik München, Campus Innenstadt, Friedrich Baur Institut, Munich, 2CeGaT GmbH, Center for Genomics and Transcriptomics, Tübingen, Germany

Introduction: Ataxia-telangiectasia (A-T) is an autosomal recessive inherited disease characterized by progressive childhood-onset cerebellar ataxia, oculomotor apraxia, telangiectasias of the conjunctivae, and immunodeficiency caused by homozygous mutations in the ATM gene. Besides this classic manifestation several other non-classic forms exist including milder or incomplete A-T phenotypes. Recently, ATM mutations were found in 13 Canadian Mennonites with primary-appearing dystonia, a French family with generalized dystonia and in a Muslim Indian family with dopa-responsive cervical dystonia.

Methods: A 45-year-old German female patient reported delayed motor development, speech and swallowing difficulties, impaired trunk and head control, and abnormal posturing since childhood. Physical examination revealed generalized dystonia including torticollis and dystonic head tremor. Ataxia of stance and gait and telangiectasias were absent. There was no family history of neurological disease. The further diagnostic workup including brain MRI, neuronal electrophysiology, cerebrospinal fluid, and neuropsychological testing was unremarkable.

Results: Alpha fetoprotein was highly increased to 208 kIU/l (normal <5.8). Genetic testing revealed compound heterozygous mutations in the ATM gene. The c.8147T>C, p.V2716A variant is a known causative A-T mutation, and the novel variant c.8578_8580delTCT is predicted to be pathogenic. Previous treatment with botulinum toxin, L-Dopa (300mg/day), benzodiazepines and deep brain stimulation had no benefit.

Conclusions: This patient adds to the recent literature that ATM mutations are not exclusively associated with A-T but may also cause focal or generalized dystonia.

Disclosure: Nothing to disclose

OS3222
Influence of MTHFR, eNOS, ACE and ApoE haplotypes in modulating serum vitamin profiles among ischaemic stroke patients
K.W. Loo1,2, L. Griffiths3, S.H. Gan1
1Human Genome Centre, University Sains Malaysia, Kubang Kerian, Malaysia, 2Genomics Research Centre, Griffith Health Institute, Griffith University, Gold Coast, 3Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, Australia

Introduction: Hyperhomocysteinemia, endothelial dysfunction, deregulation of blood pressure and impaired cholesterol metabolism may increase the risk of individuals towards ischaemic stroke. The aims of this study are to (i) investigate the association of methylenetetrahydrofolate reductase (MTHFR), endothelial nitric oxide synthase (eNOS), angiotensin converting enzyme (ACE) and apolipoprotein E (ApoE) gene polymorphisms and/or haplotypes with ischaemic stroke susceptibility and (ii) to compare serum vitamin profiles with MTHFR, eNOS, ACE and APOE gene polymorphisms and/or haplotypes.

Methods: Cases (n=297) and controls (n=297) originating from three generations of Kelantan’s Malays were recruited. The rs1801133 and rs1801131 in MTHFR; rs2070744, variable number tandem repeat (VNTR) and rs1799983 in eNOS; rs4646994 in ACE and rs429358-rs7412 in ApoE were genotyped and the haplotypes were inferred. Serum vitamin profiles (homocysteine, folate, vitamin B12) were determined.

Results: Both rs1801133 [adjusted OR=5.67; 95%±CI:2.27-14.19; p=0.001] and eNOS VNTR [adjusted OR=16.77; 95%±CI:8.71-32.29; p<0.001] were significantly associated with ischaemic stroke susceptibility due to their effects on serum homocysteine and vitamin B12 levels. Amongst the haplotypes, MTHFR Trs1801133Ars1801131 [adjusted OR=1.98; 95%±CI:1.41-2.78; p<0.001] and eNOS Trs2070744aVNTRTrs1799983 [adjusted OR=3.51; 95%±CI:2.51-4.89; p<0.001] showed higher risk towards ischaemic stroke by increasing serum homocysteine [adjusted β=0.04, p=0.002 and adjusted β=0.04, p<0.001 respectively] and vitamin B12 levels [adjusted β=0.04, p=0.031 and adjusted β=0.05, p<0.001 respectively] when compared to controls.

Conclusions: Trs1801133 and aVNTR are potential biomarkers for ischaemic stroke susceptibilities by influencing serum homocysteine and vitamin B12 levels leading to endothelial dysfunction and predisposition to ischaemic stroke.

Disclosure: The authors declare that there are no conflicts of interests.
OS3223
Genotype and phenotype heterogeneity of transthyretin-associated amyloidosis – A report from the German amyloidosis referral center

J. Purrucker¹, E. Hund¹, A. Brauer², K. Hinderhofer³, U. Hegenbart⁴, S. Schönland⁴, A. Kristen²
¹Neurology, ²Cardiology, ³Institute of Human Genetics, ⁴Medical Department V, Amyloidosis Center, University of Heidelberg, Heidelberg, Germany

Introduction: Transthyretin(TTR)-associated amyloidosis is a rare, fatal protein-deposition disease characterized by a wide spectrum of genotypes and heterogeneous phenotypes. The aim of the present study is to describe genotypes and phenotypes of patients with TTR-amyloidosis evaluated at the Heidelberg Amyloidosis Center between 2001 and 2013.

Methods: Records of 220 patients with mutations within the TTR gene and/or histologically confirmed TTR amyloidosis were reviewed regarding cardiac and neurologic parameters to define different phenotypes, i.e. polyneuropathy (TTR-FAP), cardiomyopathy (TTR-FAC), mixed phenotype, wild-type amyloidosis (senile systemic amyloidosis, SSA), and asymptomatic gene carriers. TTR-FAC was diagnosed in patients with heart failure, diastolic dysfunction, LV-hypertrophy, pseudoinfarction pattern and/or bundle branch block. TTR-FAP was defined as neurologic symptoms consistent with sensorimotor polyneuropathy. The mixed phenotype was diagnosed if criteria for both, TTR-FAP and TTR-FAC, were present.

Results: Cardiac phenotype was present in 13%, neurologic phenotype in 4%, and mixed phenotype in 30% of patients. SSA was diagnosed in 54 pts. Sixty patients were asymptomatic gene carriers. There were 29 different TTR-mutations, the most common being Val30Met and Val20Ile. Patients with SSA were almost exclusively male (93%) and had cardiac involvement, whereas 72% of mixed phenotype and 59% of cardiac phenotype were male.

Conclusions: Mixed-type hereditary and wild-type amyloidosis were the two largest groups in our national referral center. A pure neurologic phenotype is rare. In patients with polyneuropathy of unknown etiology, cardiac involvement may provide an important clue towards the diagnosis of TTR-amyloidosis.

Disclosure: JP received travel support from Pfizer.

OS3224
Adult-onset leukoencephalopathies with predominant involvement of brainstem and cerebellum can be related to histiocytosis

Fondazione Istituto Neuroligico ‘Carlo Besta’, Milano, Italy

Introduction: Histiocytoses are disorders resulting from abnormal histiocyte proliferation, and – in children – they can determine neurological dysfunctions associated with a characteristic pattern of white matter abnormalities, predominantly involving cerebellum and brainstem (henceforth “infratentorial leukoencephalopathy” [ITL]). We aim to report the clinical and paraclinical features of nine adults admitted to our Institute with a diagnosis of ITL.

Methods: We reviewed the clinical and laboratory information of 7 males, and 2 females (all isolated cases) with prominent T2- and FLAIR-weighted signal abnormalities in the posterior fossa structures, unremarkable CSF examination, and no evidence of autoimmune or hereditary diseases.

Results: Mean age at presentation was 49 years (range 38–59); clinical features were a variable combination of ataxia, spasticity, cranial nerve dysfunction, cognitive decline, neurogenic bladder, and diabetes insipidus. Supratentorial white matter abnormalities and spinal cord lesions were present in three and four individuals, respectively. Tc99m bone scintigraphy was consistent with histiocytosis in five individuals, and one had histiocytic (hairy-cell) leukemia. Retroperitoneal or bone biopsies confirmed the diagnosis in the four investigated cases.

Conclusions: Adult-onset ITL can be related to histiocytoses, and therefore the search for bone lesions is mandatory. There are substantial clinical and MRI similarities among the individuals with histologically proven histiocytosis and those with no evidence of systemic manifestations compatible with histiocytosis. Consequently, our cases support the hypothesis that the brain involvement – supposed to be paraneoplastic – may appear years before the onset of systemic manifestations, thus making a definite diagnosis impossible without a long-term follow-up.

Disclosure: Nothing to disclose
Tuesday, 3 June 2014

Cerebrovascular diseases 2

OS4101

Continue or stop pre-stroke antihypertensive therapy in acute stroke: main results from the efficacy of nitric oxide in stroke (ENOS) trial

P.M.W. Bath, L. Woodhouse, S. Utton, N. Sprigg
Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, United Kingdom

Background: A majority of patients are taking antihypertensive medication before their stroke. However, management of such treatment(s) remains unclear and is the subject of the ENOS trial.

Methods: ENOS is an international multicentre prospective randomised open-label blinded-endpoint trial. Patients with acute ischaemic stroke (IS) or intracerebral haemorrhage (ICH), systolic BP 140-220 mmHg, and taking antihypertensive therapy immediately before their stroke were randomised to continue or stop this for 7 days; all patients were also randomised to transdermal glyceryl trinitrate (GTN) or no GTN (single-blind, results reported separately). The primary outcome is shift in modified Rankin Scale at 3 months. Patients or relatives gave written informed consent and all sites had research ethics approval. Analysis is by intention-to-treat.

Results: 2,097 patients were enrolled from 152 sites in 23 countries across 5 continents between July 2001 and October 2013 (with 82% patients recruited from start of 2007). At baseline: age 73 (SD 11); male 51%; recruitment from Asia 10%, Europe 19%, UK 65%; number of BP drugs before stroke, 1: 44%, 2: 35%, 3: 16%, 4: 4%, >4: 1% (median 2); angiotensin modifier 64%, beta-blocker 39%, calcium channel blocker 35%, diuretic 35%, alpha-blocker 7%; prior stroke 20%; diabetes 23%; atrial fibrillation 22%; mean BP 167 (19)/88 (13) mmHg; severity (Scandinavian Stroke Scale) 33 (13)/58; total anterior circulation syndrome 33%; IS 85%, ICH 12%; median time to recruitment 26 (IQR 20) hours.

Summary: The main results will be available for presentation in quarter 2 2014. ENOS is large enough to influence clinical practice.

Disclosure: Nothing to disclose

OS4102

Exosomes reduce brain injury in a rodent stroke model via immunomodulatory actions and stimulation of post-ischemic neuroregeneration

T.R. Doepner1, J. Herz1,2, A. Görgens1, J. Schlechter1, A.-K. Ludwig1, K. de Mirochedji3, B. Giebel1, D.M. Hermann4
1Neurology, 2Pediatrics, 3Transfusion Medicine, University of Duisburg-Essen, Essen, Germany

Introduction: Mesenchymal stem cells (MSCs) induce neuroprotection against cerebral ischemia without being integrated into residing neural networks. Rather, MSCs seem to modulate post-ischemic immune responses in a paracrine way. Recent findings suggest that immunomodulatory properties of MSCs are mediated by exosomes. Accordingly, these small extracellular vesicles (70-140 nm) might provide a powerful, alternative therapeutic tool in experimental stroke research.

Methods: Male C57BL6 mice were exposed to cerebral ischemia for 30 min. MSC-derived exosomes or PBS were intravenously administered on days 1, 3 and 5 post-stroke. To compare exosome efficacy, MSCs were injected on day 1 followed by PBS injections on days 3 and 5. Brain injury, functional outcome, neurogenesis and peripheral/cerebral immune states were analyzed for up to 28 days post-stroke.

Results: In comparison to PBS controls, application of MSC-derived exosomes reduced the extent of brain injury and enhanced functional recovery during the four week lasting observation period in a similar manner as did injected MSCs. Ongoing experiments revealed that MSC-derived exosomes promote neuroregeneration by fostering endogenous neurogenesis and – as revealed via flow cytometric analysis – by affecting the immune state in the peripheral blood and within the affected brain hemispheres.

Conclusions: Intravenous delivery of MSC-derived exosomes is neuroprotective. It enhances neuroregeneration and modulates post-ischemic immune responses. Thus, MSC-derived exosomes provide a non-cellular tool for stroke treatment, which might prove qualified for clinical treatment of stroke patients in the future.

Disclosure: Nothing to disclose
OS4103

B-type natriuretic peptide predicts stroke of presumable cardioembolic origin in addition to coronary artery calcification

K. Kara1, J. Gronewold2, U.K. Seidel1, T. Neumann1, A.A. Mahabadi3, C. Weimar2, N. Lehmann1, K. Berger2, H. Kälsch1, M. Bauer1, M. Broecker-Preuss3, S. Möhlenkamp1, S. Moebus3, K.-H. Jöckel5, R. Erbel1, D.M. Hermann2, Heinz Nixdorf Recall Study Investigative Group

1Cardiology, 2Neurology, University Hospital Essen, 3Institute of Medical Informatics, Biometry and Epidemiology, University of Duisburg-Essen, Essen, 4Institute of Epidemiology and Social Medicine, University of Münster, Münster, 5Clinical Chemistry, University Hospital Essen, Essen, 6Cardiology, Hospital Bethanien, Moers, Germany

Introduction: B-type natriuretic peptide (BNP) is a marker of cardiac dysfunction that is released from myocytes in response to ventricular wall stress. Previous studies suggested that BNP predicts stroke events in addition to classical risk factors. It was suggested that the BNP-associated risk results from coronary atherosclerosis, atrial fibrillation or heart failure.

Methods: 3675 subjects from the population-based Heinz Nixdorf Recall study (45-75 years, 47.6% men) without previous stroke, coronary heart disease, myocardial infarcts, open cardiac valve surgery, pacemakers and defibrillators were followed up over 9.2±1.9 years. Cox proportional hazards regressions were used to examine BNP as stroke predictor in addition to vascular risk factors (age, gender, systolic blood pressure, LDL, HDL, diabetes, smoking), renal insufficiency, atrial fibrillation/heart failure and coronary artery calcification.

Results: 89 incident strokes occurred (80 ischemic, 9 hemorrhagic). Subjects suffering stroke had significantly higher BNP values at baseline than the remaining subjects (26.3[Q1;Q3=12.9;51.0] vs. 17.4[9.4;31.4]; p<0.001). In a multivariable regression, log10BNP was an independent stroke predictor (hazard ratio=1.96[95%-confidence interval=1.13-3.41]; p=0.017) in addition to age (1.24 per 5 years[1.04-1.49]; p=0.016), systolic blood pressure (1.25 per 10 mmHg[1.14-1.38]; p<0.001), smoking (2.05[1.24-3.39]; p=0.005), atrial fibrillation/heart failure (2.25[1.05-4.83]; p=0.037) and computed tomography-based log10 (coronary artery calcification+1) (1.47[1.15-1.88]; p=0.002). Log10BNP predicted stroke in men, but not women, both in subjects ≤65 and >65 years. In subsequent analyses, BNP discriminated the incidence of cardioembolic stroke (p for trends=0.001), but not stroke of macroangiopathic (p=0.555), microangiopathic (p=0.809) or unknown (p=0.367) origin.

Conclusion: BNP predicts presumable cardioembolic stroke independent of coronary calcification.

Disclosure: Nothing to disclose

OS4104

HMG-CoA reductase inhibition promotes stroke recovery and perilesional tissue remodeling and contralesional pyramidal tract plasticity

E. Kilic1, R. Reitmeir2, U. Kilic3, A.B. Çağlayan1, M.C. Beker1, S. Ethemoglu1, D.M. Hermann4

1Physiology, Istanbul Medipol University, Istanbul, Turkey, 2Neurology, University of Essen, Essen, Germany, 3Medical Biology, Bezmialem Foundation University, Istanbul, Turkey, 4University of Essen, Essen, Germany

Introduction: 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are widely used for secondary stroke prevention. Besides their lipid-lowering effects, pleiotropic effects on neuronal survival, angiogenesis and neurogenesis have been described. In view of these promising actions, we were interested whether post-acute HMG-CoA reductase inhibition promotes functional neurological recovery, perilesional and contralesional neuronal plasticity.

Methods: We examined effects of rosuvastatin (0.2-2mg/kg/day i.c.v.), administered starting 3 days after 30 min of middle cerebral artery occlusion, on motor-coordination, perilesional tissue remodeling and contralesional axonal plasticity.

Results: Rosuvastatin, administered at a dose of 2 but not 0.2 mg/day, significantly increased the motor grip strength and coordination of ischemic mice, promoted exploration behavior and reduced anxiety. Neurological recovery was associated with structural remodeling of peri-lesional brain tissue, reflected by increased neuronal survival, enhanced angiogenesis, and reduced corpus callosum and striatal atrophy. Increased sprouting of contralesional pyramidal tract fibers crossing the midline in order to innervate the ipsilesional red nucleus was noticed in rosuvastatin injected in the motor cortex.

Conclusion: Our data support the idea that HMG-CoA reductase inhibition promotes brain plasticity far beyond the acute stroke phase.

Disclosure: Nothing to disclose
OS4105

Motor recovery after ischemic stroke in mice is age-dependent and correlates with brain BDNF levels

S. Ress1,2, E. Göb1, F. Fluri1,2, F. Langhauser1, U. Malzahn1, R. Blum2, M. Sendtner1, C. Kleinschnitz1
1Department of Neurology, 2Institute for Clinical Neurobiology, 3Institute for Clinical Epidemiology and Biometry, University Hospital of Würzburg, Würzburg, Germany

Objective: Ischemic stroke frequently affects motor function. This is of particular relevance in elderly patients who have a lower ability to recover from ischemic brain injury. Brain derived neurotrophic factor (BDNF) modulates activity-dependent synaptic plasticity in the motor cortex and improves motor symptoms after cerebral ischemia in young and otherwise healthy rodents. To uncover a potential age-dependent effect of BDNF on motor recovery after stroke, we investigated whether BDNF-expression after stroke correlates with age and whether different BDNF levels in young and aged mice may influence motor function.

Methods: 8-week- and 1-year-old wild-type (WT) as well as 8-week-old bdnf±mice were subjected to 30 or 60 min transient middle cerebral artery occlusion (tMCAO). 24 h after 60 min tMCAO BDNF protein levels and subcellular localization were determined. Motor recovery was assessed in mice undergoing 30 min tMCAO from day 1 to day 24 using a foot fault score (FFS).

Results: At day 1 after 60 min tMCAO, BDNF protein levels were significantly increased in young (8-week) versus aged (1-year) WT mice. Motor function analysis up to day 24 post stroke revealed an age-dependent correlation between BDNF content and motor recovery as young WT mice showed a significant improvement in the FFS compared to bdnf±mice and 1-year-old WT mice, respectively.

Conclusion: Motor recovery after stroke is age-dependent and depends on the expression of BDNF. Modulation of BDNF levels might become a promising strategy to improve stroke outcome especially in older patients.

Disclosure: Nothing to disclose

OS4106

Cooperative hand movements in stroke patients: impaired neural coupling

M. Schrafl, V. Dietz
Spinal Cord Injury Center, Balgrist University Hospital, Zurich, Switzerland

Introduction: Recent research indicates that task-specific, interhemispheric neural coupling is involved in the control of the cooperative hand movements required for activities of daily living. This neural coupling is reflected in bilateral electromyographic (EMG) reflex responses in the arm muscles to unilateral nerve stimulation and an exclusive activation of secondary somatosensory (S2) cortical areas during functional magnetic resonance imaging. The aim of this study was to investigate these reflex responses in the forearm muscles in chronic post-stroke patients.

Methods: EMG responses in forearm muscles were reorded in 15 stroke patients and 12 healthy volunteers following unilateral electrical stimulations of the ulnar nerve during a dynamic-cooperative (dyn-coop) task and two control tasks.

Results: When the nerve of the unaffected arm was stimulated during dyn-coop, bilateral EMG responses were generated, similar to those seen in healthy subjects. Stimulation of the affected arm only evoked ipsilateral responses. The presence of contralateral EMG responses correlated with the clinical motor impairment as measured using the Fugl-Meyer test. Only ipsilateral EMG responses were recorded during the control tasks.

Conclusions: These observations suggest impaired processing of afferent input leading to defective neural coupling during cooperative hand movements after stroke. In severely affected patients, movement execution seems to rely on the involvement of the ipsilateral tract arising in the non-damaged hemisphere. The rehabilitation of stroke patients, currently focused on reach and grasp movements of the affected arm/hand, should be supplemented with the training of the cooperative hand movements required during activities of daily living.

Disclosure: Nothing to disclose
Multiple sclerosis and related disorders

OS4201

Active-controlled study to investigate the ability of the HAP score to predict responders to Octagam 5% in patients with early relapsing multiple sclerosis (PREDICT study)

T. Berger¹, A. Boyko², G. Comi³, I. Elovaara⁴, H.-P. Hartung⁵, L. Kappos⁶, X. Montalban⁷, S. Wietek⁸, S. Meuer⁹, T. Giese³

¹Clinical Department of Neurology, Innsbruck Medical University, Head Neuroimmunology and Multiple Sclerosis Clinic & Research Unit, Innsbruck, Austria, ²City Hospital, Moscow, Moscow, Russian Federation, ³Department of Neurology, Scientific Institute H.S. Raffaele, Milan, Italy, ⁴Department of Neurology, University of Tampere, Medical School, Tampere, Finland, ⁵Heinrich-Heine-Universität, Neurological Clinic, Düsseldorf, Germany, ⁶Universitätsklinik, Basel, Neurologische Universitätsklinik, Basel, Switzerland, ⁷Hospital Universitari Vall d’Hebron, Multiple Sclerosis Center of Catalonia, Barcelona, Spain, ⁸Octapharma Pharmazeutika Produktionsges.m.b.H., Vienna, Austria, ⁹University of Heidelberg, Institute for Immunology, Heidelberg, Germany

Introduction: Since three decades treatment of multiple sclerosis (MS) patients with intravenous immunoglobulin (IVIG) has been employed. However, after somewhat contradicting study results, it seems possible that only a subgroup of patients benefits from IVIG therapy. We hypothesise, based on results from open-label, exploratory predecessor study GAM-25 in 33 patients with relapsing-remitting multiple sclerosis (RR-MS) that responsiveness to IVIG therapy might be individually predictable by combination of immunologic and genomic parameters.

Methods and results: Patients on glatiramer acetate or IFN-beta will be randomised to IVIG treatment (0.6g/kg Octagam® 5% at 4-week intervals) or alternate first-line therapy. Before enrolment, nine predictive genotypes will be combined with quartile based scores of 66 immune parameters - including leukocyte phenotypes, plasma cytokine levels as well as basic and induced gene expression. In a stepwise approach for each genotype 0 to 4 biomarkers will be added using linear discriminant analysis. Non-responders are defined as being positive for 5 or more out of 9 individually calculated scores. Clinical response is defined after 2 years treatment if a) no relapses, b) Expanded Disability Status Scale (EDSS) not increasing by ≥1.0 step, and c) no MRI activity. Confirmatory, active-controlled, rater-blinded PREDICT study (GAM-27) started enrolling 216 adult patients with early relapsing MS and EDSS ≤3.5 in December 2013.

Conclusions: Combining genomic and functional immune parameters into a biomarker panel could be the first step to support personalised medicine by prospectively allowing the discrimination of individual immunotypes into responders and non-responders to IVIG therapy in patients with relapsing MS.

Disclosure: The study is sponsored by Octapharma AG, Seidenstrasse 2, 8853 Lachen, Switzerland.

OS4202

Patients who switch to natalizumab have better outcomes than those who continue on the same platform therapy after a relapse

H. Butzkueven¹, T. Spelman¹, T. Kalincik¹, F. Pellegrini², A. Zhang³, M. Trojano³, H. Wiendl⁴, L. Kappos⁶, R. Hyde³, S. Belachew³, F. Verheul⁵, F. Grand-Maison⁸, G. Izquierdo⁶, MSCOMET (an MSBase Substudy) and TOP Investigators

¹Department of Medicine and Melbourne Brain Centre, Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia, ²Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Chiari, Italy, ³Biogen Idec, Cambridge, MA, United States, ⁴Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy, ⁵Neurology, University of Muenster, Münster, Germany, ⁶Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland, ⁷Groene Hart Ziekenhuis, Gouda, Netherlands, ⁸Neuro Rive-Sud, Hopital Charles LeMoyne, Quebec, QC, Canada, ⁹Hospital Universitario Virgen Macarena, Seville, Spain

Introduction: Randomized clinical trials comparing treatment options for patients who relapse on a platform therapy (interferon-beta [IFN-β]) or glatiramer acetate [GA]) are not available. Propensity-matching patients from observational cohorts can approximate randomization by comparing patients with similar baseline characteristics. Clinical outcomes and treatment discontinuation were compared between propensity-matched patients who either switched to natalizumab or who continued on the same platform therapy after an on-treatment relapse.

Methods: 759 patients from the MSCOMET study who remained on IFN-beta or GA after relapse were propensity-matched patients who either switched to natalizumab or who continued on the same platform therapy after a relapse. Clinical outcomes and treatment discontinuation were compared between propensity-matched patients who either switched to natalizumab or who continued on the same platform therapy after an on-treatment relapse.

Results: Switching to natalizumab decreased the risk of future relapse by 57% (HR=0.43; 95%CI=0.35-0.52; p<0.0001) (figure 1) and decreased the risk of treatment discontinuation by 52% (HR=0.48; 95%CI=0.40-0.58; p<0.0001) (figure 2) compared to remaining on the same platform therapy after relapse (follow-up, years, mean[SD]: TOP, 1.80[1.24]; MSCOMET, 0.91[0.82]).

Conclusions: Switching to natalizumab after a relapse on IFN-β or GA may improve clinical outcomes and reduce the risk of treatment discontinuation in MS patients. In the absence of relevant randomized clinical trials, comparisons of propensity-matched patients from large, observational cohorts are useful to estimate the relative risks associated...
with various treatment decisions in a clinical practice setting.

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**OS4203**  
**After a relapse, patients who switch to natalizumab have better outcomes than those who switch between platform therapies**  

1 Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy, 2Department of Medicine and Melbourne Brain Centre, Royal Melbourne Hospital, University of Melbourne, Melbourne, VIC, Australia, 3Biogen Idec, Cambridge, MA, United States, 4Neurology, University of Münster, Münster, Germany, 5Neurology and Biomedicine, University Hospital Basel, Basel, Switzerland, 6Groene Hart Ziekenhuis, Gouda, Netherlands, 7Neuro Rive-Sud, Hospital Charles LeMoyne, Quebec, QC, Canada, 8Hospital Universitario Virgen Macarena, Sevilla, Spain

**Introduction:** Randomized clinical trials comparing treatment options after patients relapse on platform therapies (interferon-beta [IFN-β] or glatiramer acetate [GA]) are not available. Propensity-matching techniques approximate randomization by comparing patients with similar baseline characteristics. Using propensity-matched groups, clinical outcomes and treatment discontinuation were compared between patients who switched to natalizumab and those who switched between IFN-β and GA after an on-treatment relapse.

**Methods:** From MSBase and TOP observational studies, 578 patients switching from IFN-β to GA and 165 patients switching from GA to IFN-β were propensity-matched (based on age, sex, disease duration, EDSS score, prior number of treatments and relapse history) to equivalent numbers who switched to natalizumab (table 1); treatment switches occurred ≤12 months after relapse. Times to next relapse on treatment and to treatment discontinuation were compared using Cox time-to-event analysis with propensity-matched patients jointly censored (mean follow-up=1.69-2.24 years).

**Results:** Switching to natalizumab reduced relapse risk by 63% (figure 1) and discontinuation risk by 62% (figure 2) compared to switching from IFN-β to GA. Switching to natalizumab reduced relapse risk by 53% (HR=0.47; 95%CI=0.30-0.74; p<0.001) and discontinuation risk by 48% (HR=0.52; 95%CI=0.36-0.75; p<0.001) compared to switching from GA to IFN-beta.

**Conclusions:** When considering treatment sequence for MS patients who relapse on platform therapies, switching to natalizumab rather than switching between IFN-beta and GA may improve clinical outcomes and reduce the risk of treatment discontinuation. In the absence of randomized clinical trials, propensity-matching techniques can compare the risks associated with various treatment decisions in a clinical practice setting.

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OS4204
Clinical efficacy and safety of peginterferon beta-1a in patients with relapsing-remitting multiple sclerosis: 2-year data from the pivotal phase 3 ADVANCE study
B.C. Kieseier¹, L. Balcer², A. Boyko³, J. Pelletier¹, S. Liu¹, Y. Zhu¹, A. Seddighzadeh³, S. Hung³, A. Deykin³, D. Arnold²
¹Department of Neurology, Heinrich-Heine University, Düsseldorf, Germany, ²Department of Neurology, New York University, New York, NY, United States, ³Moscow MS Center at RSMU, Moscow, Russian Federation

Objectives: At Year 1 of the ADVANCE study, in patients with relapsing-remitting multiple sclerosis (RRMS), subcutaneous peginterferon beta-1a (PEG-IFN; 125µg administered every 2 [Q2W] or 4 [Q4W] weeks) provided benefits versus placebo. Here, we evaluate the interim 2-year efficacy and safety of PEG-IFN in ADVANCE.

Methods: During Year 2 all patients received dose-regimen blinded PEG-IFN (at the end of Year 1 patients on placebo were re-randomised to PEG-IFN 125µg Q2W or Q4W). Interim analyses were conducted for patients with 2 years of data at cut-off. Post-hoc analyses compared the efficacy of Q2W versus Q4W.

Results: For patients continuing PEG-IFN in Year 2, annualised relapse rate (ARR) was maintained (for Q4W) or further numerically reduced (for Q2W) versus Year 1, and new or newly-enlarging T2 lesions were numerically lower for both regimens. Versus those originally assigned to placebo, reductions in ARR, risk of relapse and disability progression were seen for patients on PEG-IFN over 2 years. Q2W provided numerically larger treatment effects over 2 years versus Q4W for the majority of efficacy measures. Over 2 years, adverse events (AEs) were reported in 96% of patients on both Q2W and Q4W; the majority were mild or moderate in severity. Incidences of serious AEs were 16% on Q2W and 21% on Q4W.

Conclusions: Interim 2-year results support the maintained benefits of PEG-IFN beyond 1 year in RRMS, with numerically greater efficacy for Q2W versus Q4W, and a safety profile consistent with Year 1 of ADVANCE and other beta interferons.

OS4206
Effect of teriflunomide on MRI activity in patients with early MS: outcomes from the phase 3 TOPIC study

J.S. Wolinsky1, G. Comi2, L. Kappos3, D. Bauer4, P. Truffinet5, A.E. Miller6
1University of Texas Health Science Center at Houston, Houston, TX, United States, 2University Vita-Salute San Raffaele, Milan, Italy, 3University of Basel, Basel, Switzerland, 4Sanofi, Bridgewater, NJ, United States, 5Genzyme, a Sanofi Company, Chilly-Mazarin, France, 6Icahn School of Medicine at Mount Sinai, New York, NY, United States

Introduction: Teriflunomide is a once-daily oral immunomodulator for relapsing-remitting multiple sclerosis (RRMS). The phase 3 TOPIC study (NCT00622700) assessed use of teriflunomide in patients with a first clinical episode consistent with MS plus ≥2 lesions. This analysis evaluated treatment effect on magnetic resonance imagining (MRI) activity.

Methods: Randomised patients received once-daily teriflunomide 14mg, teriflunomide 7mg, or placebo. When reaching the primary endpoint (risk of relapse determining clinically definite MS), patients could enter an open-label extension. MRI was performed at screening, 12, 24, 48, 72, and 108 weeks (pre-defined main timepoint for analysis), and processed at a centralised analysis centre.

Results: Baseline characteristics were generally balanced (n=618). At baseline, 31.4% had ≥1 gadolinium (Gd)-enhancing lesion and mean total lesion volume (TLV) was 8.66mL. Teriflunomide 14mg significantly reduced TLV increase from baseline at 108 weeks (p=0.04 vs placebo), at all other timepoints and as early as 12 weeks (p≤0.04 vs placebo). Teriflunomide 14mg reduced number of Gd-enhancing T1 lesions per scan vs placebo (0.40 vs 0.95); relative risk reduction 58.5% (p<0.001); total enhanced volume per scan 0.03 vs 0.08 (p<0.0001 vs placebo). Teriflunomide 14mg significantly reduced the volume of T2-lesion component at every visit (p<0.05 vs placebo), except 12 and 108 weeks (p=0.0503). Apart from Week 24 (p=0.0524), teriflunomide 14mg significantly decreased T1-hypointense lesion volume from baseline (p<0.05 vs placebo) at all visits.

Conclusions: In patients with early MS, teriflunomide 14mg had a significant, positive impact on MRI activity supporting the observed beneficial clinical effects.

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