Multiple sclerosis and related disorders 4

EP4230

Computer assisted cognitive rehabilitation in patients with multiple sclerosis and parenchymal neuro-Behçet’s disease

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Introduction: Cognitive dysfunction is frequent in patients with multiple sclerosis (MS) and parenchymal neuro-Behçet’s disease (pNBD). Cognitive rehabilitation has been proven successful in ameliorating this dysfunction, although its efficacy varies considerably. In this study, we aimed to test home-based computer assisted rehabilitation (HB-CACR) for cognitive rehabilitation in MS and pNBD.

Methods: We recruited 59 MS and 33 pNBD patients. Both groups were randomized to two subgroups. Twenty-nine of MS patients and 16 of pNBD patients were instructed to exercise HB-CACR (MSsoft v.1.0.1) for 2 days per week for 8 weeks. Neuropsychological test scores of symbol digit modalities, Addenbrook’s cognitive examination, digit span, verbal fluency, Burdon attention, 10/36 spatial recall test, selective reminding, and Beck depression inventory at the end of the study period were compared with the scores at baseline.

Results: MS patients who underwent HB-CACR performed better in terms of verbal fluency (p<0.001), and symbol digit modalities tests (p=0.035) at the end of the study, whereas pNBD patients did not benefit from HB-CACR in any of the cognitive domains. Digit span test scores of MS patients were higher than the scores of pNBD patients at baseline (p=0.02). Despite the absence of a change in cognitive domains in pNBD patients, patients who received rehabilitation showed less depression scores at the end of the study period.

Conclusions: HB-CACR seems to be effective in patients with MS. Although our software trained different domains of attention, we could detect some improvements exclusively on tasks of verbal fluency, attention, concentration and inhibition.

Disclosure: This study is partially sponsored by TEVA

EP4231

Cognitive impairment in relapsing-remitting multiple sclerosis (RRMS): psychometric properties of the Brief Repeatable Battery of Neuropsychological tests (BRB-N)

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Introduction: Cognitive impairment in Multiple Sclerosis (MS) patients is difficult to detect in a routine neurological examination. A comprehensive neuropsychological evaluation is necessary to assess patient’s cognitive status and to describe possible cognitive, emotional and behavioral disorders. The aim of the present study was to find out reference values for the Spanish version A of the Brief Repeatable Battery of Neuropsychological Tests (BRB-N) for Relapsing-Remitting Multiple Sclerosis (RRMS) patients according to their degree of disability.

Methods: Observational, cross-sectional and multicenter study. The study group consisted of 293 RRMS patients from 23 Neurology Departments in Spain. The mild disability group (EDSS scale score 0-3) included 148 patients and the moderate disability group (EDSS scale score 3.5-5.5) included 132 patients. A subgroup of 63 patients were evaluated a second time within a week interval (retest visit). Enrollment period finished in October 2013 and final results report will be ready by February 2014.

Results: Psychometric properties of the battery will be analyzed: a) Reliability through the study of the stability of the scores between the first and the second application; b) Convergent validity by studying the relationship between BRB-N and EQ-5D questionnaire scores; c) Construct validity through the association between BRB-N and Beck Depression Inventory (BDI) scores; d) Predictive validity and reference values as well as cut-off points will be estimated from scores obtained in the mild and moderate disability groups.

Conclusions: Results will provide reference values of the BRB-N for RRMS patients in the Spanish population according to the degree of disability.

Disclosure: The study is funded by Novartis Farmacéutica S.A.
EP4232
Relapsing syndrome of an inappropriate antidiuretic hormone secretion in an anti-aquaporin-4 positive pediatric patient with neuromyelitis optica spectrum disorders
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Introduction: Pediatric neuromyelitis optica spectrum disorders (NMOSD) is a rare disease. Although reported in patients with NMOSD, to our best knowledge, syndrome of an inappropriate antidiuretic hormone secretion (SIADH), has not been described repeatedly in single patient.

Case report: A previously healthy girl experienced the first episode of encephalopathy preceeded by intractable vomiting at the age of 14 years. Physical examination revealed no edema, while serum biohemical analyses showed hyponatremia and criteria for SIADH diagnosis were fulfilled. Routine CSF findings were normal. Brain magnetic resonance imaging (MRI) showed nonenhancing T2-weighted hyperintensities in hypothalamus, basal ganglia and right thalamus. High-dose methylprednisolone (HDMP) for 5 days was administrated, intravenously, followed by oral prednisone tapering, and recovered completely. Eight months later, vomiting, hiccup and respiratory failure occurred. CSF analysis revealed normal findings apart from elevated protein level (2.23g/L). Criteria for the diagnosis of SIADH were again fulfilled. She was euthyroid with elevated anti-thyreoglobulin and antithyroid microsomal antibodies, and normal/negative other serological tests for autoimmunity. New MRI lesions were detected. The patient was treated with HDMP for 5 days, with no improvement. Intravenous immunoglobulins (IVIG) were then administered (100g/day, 2 days); patient recovered completely. Afterwards, she was treated, with IVIG, 0.4g/kd/day, monthly, during 5 months. The patient was relapse-free for 17 months. Afterwards, she experienced cerebellar manifestations. Patient was tested for anti-aquaporin 4 antibodies in serum which were positive. Rituximab was introduced with good response.

Conclusion: Patient with pediatric NMOSD may present with SIADH, even repeatedly and as one of the initial manifestations.

Disclosure: Nothing to disclose

EP4233
NMO and NMOSD: clinical presentation, imaging, CSF, laboratory abnormalities and outcome in 50 patients
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Introduction: Little information has been published about the clinical, imaging and laboratory characteristics of NMO specially in the Middle East region. We reviewed on the characteristics of a cohort of 50 Neuromyelitis optica (NMO) patients in our center In Tehran, Iran.

Methods: 50 fulfilled the 2006 criteria, analyzed for the presenting symptoms, number of recurrences, associated disorders, CSF abnormalities, anti NMO and anti MOG antibody, imaging and outcome.

Results: 13% were male, 87% female. Mean age was 36.76 years. Mean disease duration was 71.08 months and the mean follow up time 27.60. 34.8% had optic neuritis as the presenting symptom. 43.5% were not affected by myelitis. 50% had cervical myelitis and 6.5% both cervical and thoracic myelitis. 23.9% had atypical brain symptoms. 80.4% had experienced recurrence from which 62.16% had one time. 24.32% 2 or 3 and 4.3% more than 3. 50.1% had EDSS between 0-2 at presentation. 26.1% 2 to 4. 23.9, 4 to 7 at presentation. 17.4% indicated positive NMO Abs. 30 patients did Anti MOG antibody, positive appeared in 86%. 24.5% had CSF from which 23.9% were OCB positive and 23.9% had elevated IgG index. 54.3% had normal brain in imaging. 37% atypical brain abnormalities in MRI. 37.9% LEMS. We found pain in 69.6%, 28.3% were misdiagnosed as MS.

Conclusions: Despite the relatively high recurrence rate Outcome revealed no significant disability.Inspite of low positivity of NMO antibody, antiMOG antibody was remarkably positive in our patients, however, Further studies seem essential to prove the exact sensitivity of these laboratory tests.

Disclosure: Nothing to disclose
EP4234

Safety and tolerability of teriflunomide in MS patients in clinical practice
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Introduction: Teriflunomide is a novel, once-daily, oral immunomodulator approved by the EMA in August 2013 for use in patients with relapsing multiple sclerosis as a first line therapy. The aim of this study is to assess the short-term safety and tolerability of teriflunomide in clinical practice.

Methods: Observational study in patients with relapsing remitting MS starting treatment with teriflunomide 14 mg in compassionate use. Blood samples were obtained every month and neurological evaluation was performed at baseline and every three months.

Results: Data of the first 20 patients included in our center were analyzed. Mean age was 41 years [28-64], 60% women. Mean time since onset of symptoms of 96 months [12-232]. 65% of patients had a previous first-line treatment and 20% of them had two first-line treatments. 45% of the patients were followed more than six months. The main reason for the switch was adverse events (55%), followed by intolerance to previous treatment. The naive patients have needle phobia. Adverse events were recorded in 35% of patients with the most frequent being very mild lymphopenia (20%), hair thinning (20%), mild liver enzyme elevation (< 2ULN), and diarrhea (5%). There was no case of infection. One patient discontinued the treatment due to withdrawal of consent. Only two patients forgot to take some pills.

Conclusions: The results obtained in this preliminary analysis support that teriflunomide in clinical practice was well tolerated, the adherence of the patients was very good and the short-term safety of teriflunomide was favourable.

Disclosure: Celia Oreja-Guevara received honoraria as consultant on scientific advisory boards or as speaker from Biogen-Idec, Genzyme, Almirall, Merck-Serono, Teva and Novartis

EP4235

Abstract withdrawn

EP4236

The default mode network - the resting-state network most sensitive for cerebral functional changes over short-term in multiple sclerosis
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Introduction: Applying resting state functional MRI (RS-fMRI) in patient cohorts bears great potential to explore functional cerebral reorganization, obviating performance bias associated with task-related fMRI. Given the dynamics of the disease, multiple sclerosis (MS) represents an attractive candidate to test the feasibility of longitudinal RS-fMRI to explore such changes over short-term.

Methods: For this purpose, we selected two patient groups, 9 MS patients on conventional disease-modifying treatment (DMT; glatirameracetate or β-interferons) and 11 MS patients with active disease in whom Natalizumab treatment had been initiated recently (NAT). Participants underwent structural, functional MRI, neurological and neuropsychological examinations at baseline (BL) and at 3 months of follow-up (FU).

Results: At BL, we succeeded in identifying nine networks in both groups, without any differences between groups. At FU, significant changes had occurred in only one out the nine networks, i.e. the default mode network (DMN). Functional increases were greater in the DMT group than in the NAT group, comprising the anterior and posterior cingulate, the middle frontal gyrus, the supramarginal gyrus, the occipital pole, and the cerebellum.

Conclusions: This study demonstrates that changes in RS activation in MS may already be captured over short-term. The stability (and thus reproducibility) of all but one RS networks attests to the validity of the analytical approach used. Consistent with the notion of the DMN as a critical functional hub sensitive to changes in brain integrity, the only changes observed affected the DMN changes, suggesting its potential relevance for sensitive monitoring of disease evolution in MS.

Disclosure: Nothing to disclose
EP4237

Long-term safety of fingolimod: interim evaluation of data from the LONGTERMS trial

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Introduction: Multiple sclerosis patients participating in the fingolimod phase 2/3 core and extension studies were eligible to transfer to LONGTERMS, an open-label, multicentre, single-arm, long-term safety and tolerability study. We compared the long-term fingolimod (0.5 mg dose) safety data in the LONGTERMS study (up to data cut-off), with shorter-term (1-2 years) safety data pooled from the randomised controlled trials.

Design and methods: In this study, patients from two cohorts (Core Cohort, CC; LONGTERMS cohort, LC) were compared. Patients in CC [n=1212; median (range) exposure: 1.6 (0.0-2.4) years] were pooled from the fingolimod 0.5 mg arms of the core phase 2/3 trials. Patients in LC [n=1655; median (range) exposure: 3.7 (0.0-7.4)] included CC and phase 2/3 core comparator patients transitioned to fingolimod 0.5mg in their extensions. Incidence rates (number of patients experiencing ≥1 event/100 patient-years) were determined for adverse events (AEs) of special interest.

Results: The Incidence rates for AEs of special interest were similar or lower in LC compared with CC, for: infections (LC, 68.3; CC, 91.0), skin cancer and other malignant neoplasms (LC, 0.7 and 0.4; CC, 1.3 and 0.4), thromboembolic events (LC, 0.9; CC, 1.0), hypertension (LC, 3.6; CC, 5.5), respiratory conditions (LC, 1.2; CC, 1.5) and reactivation of viral infections (LC, 5.3; CC, 5.9).

Conclusions: With long-term use of fingolimod (median: 3.7 years), incidence rates for AEs of special interest were comparable with those in controlled studies. There were no new safety signals detected with the long-term use of fingolimod.

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EP4238

Cognitive and neural correlates of TNFRSF1A gene polymorphism (rs1800693) in multiple sclerosis

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Introduction: TNFRSF1A encodes a major receptor for the tumor necrosis factor-alpha. Its functional genome-wide supported multiple sclerosis (MS) risk variant (rs1800693) has recently been the focus of intense research. However, these studies have not demonstrated any associations between clinical disability and global radiological indices with the rs1800693 genotype in MS. Here we investigated the impact of this polymorphism on regional neuroanatomical measures and cognitive performance in MS patients.

Methods: Eighty-nine individuals with relapse-onset MS underwent structural brain MRI, clinical examination and cognitive assessment with SDMT, PASAT and CVLT. Association between test scores and genotypes were assessed using general linear models, with age and gender as covariates. Vertex-wise analysis of cortical thickness and surface area were carried out using the CIVET pipeline (Lerch and Evans, 2005).

Results: Results from the MANOVA with three cognitive measures as the dependent variables revealed a significant main effect for rs1800693 genotype status [Wilks’ λ F(3,72)=3.485, p=0.05], G-allele carriers performed significantly worse in SDMT [F1,85=7.2, p=0.009] and PASAT [F1,78=4.2, p=0.04] and significantly worse on CVLT scores. Vertex-wise analysis - while covarying for EDSS, age and gender- demonstrated bilateral decreased surface area in medial temporal area (parahippocampal gyrus) and the left occipital pole, with increasing G-allele dosage. Only left-sided surface area changes remained significant after correction for multiple comparisons (at false discovery rate <10%).

Conclusions: Our findings demonstrate how a genome-wide supported MS-risk variant could regionally impact brain structure and result in specific pattern of cognitive deterioration in the course of the disease.

Disclosure: Nothing to disclose
EP4239

Acute disseminated encephalomyelitis in a natalizumab treated patient

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Introduction: Natalizumab is a highly effective treatment for relapsing-remitting multiple sclerosis (RRMS) patients. It implies close follow-up, mainly regarding PML-risk.

Clinical case: A 26-year-old male with RRMS treated with Natalizumab for 28 months and JC virus seronegative (at 12th month of treatment) started rapid progressive headache, vomiting, fever and consciousness impairment. Cerebral CT angiogram was normal and CSF was hemorrhagic with pleocytosis and increased proteinorrachia. Empiric antibiotics were initiated. His alertness was fluctuating, he had frontal and left pyramidal syndromes. EEG suggested encephalopathy. Brain MRI showed generalized white matter T2-hyperintense lesions, including corpus callosum, not suggesting PML. Microbiological and serological studies were negative but showed JC virus seroconversion; blood, urine and CSF samples were JC-negative, even with high sensitivity techniques. On day 24, patient became comatose and MRI showed aggravation, including thalamic lesions and extensive spinal cord involvement. Aquaporin-4 antibodies were negative. Intravenous high dose corticosteroids were ineffective. Brain biopsy showed active demyelinating process without infection (including JC virus) or neoplasm. He was submitted to plasmapheresis, with progressive clinical/imaging improvement and CSF normalization. After 9 months without disease modifying treatment, he suffered another relapse (motor), starting Copaxone®. Five months later, another motor relapse, with new active lesions on MRI, starting Fingolimod. Actually, after seventeen months, his EDSS is 5 and he has recovered autonomy.

Conclusion: As far as we know, this is the only reported case of ADEM in a Natalizumab treated patient. It was a severe life-threatening condition which etiology remained unknown after extensive investigation, but plasmapheresis was effective.

Disclosure: Nothing to disclose

EP4240

Language performance in patients with multiple sclerosis: a linguistic approach

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Introduction: Language is frequently impaired in Multiple Sclerosis (MS). No comprehensive study has yet been done investigating MS abilities in all the major language domains. The aim of this research was to investigate whether different levels of language production were altered in patients with MS, and to compare those results with a control group.

Methods: 50 MS patients and 50 healthy control subjects matched by age and education were studied. First of all participants were instructed to talk about their life for 15-20 minutes and then one receptive and one expressive test was used for each of syntax, semantics, phonology, and written language to assess patterns in MS language skills. The patients were then divided according to MS subtype.

Results: The results of the group analysis indicate that MS patients are significantly impaired in receptive syntax, word-finding, spelling and non-word repetition. Syntax was impaired in exactly half of each subset, and double dissociations were seen between syntax and semantics. An individual analysis showed that subsets of individuals are significantly impaired all the major language domains in patients with MS.

Conclusions: MS patients should be investigated for language difficulties clinically, as they may well benefit from speech and language therapy. Furthermore, evidence of language impairment following from subcortical damage is of interest to the field of linguistics and neurology, and might prove fruitful for investigators interested in the neural substrates of language. Language impairment could be an early warning sign of MS, and this possibility is worthy of further investigation.

Disclosure: Nothing to disclose
EP4241
Effects of different natalizumab treatment modalities on pharmacokinetics and -dynamics
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Introduction: Natalizumab inhibits leukocytes migration into CNS blocking VLA-4. In long-term treatment natalizumab exerts significant effects on central immunosurveillance leading to substantial risk for PML. Little is known about effects of long-term treatment compared to infusion intervals or treatment holidays on immune cell VLA-4-expression, cell-bound and free natalizumab.

Methods: Measures of free and cell-bound natalizumab concentrations in addition to VLA-4-expression was done by FACS-based-assay. Blood samples from 10 natalizumab treated MS-patients were drawn including baseline, month 1, 2, 3, 6, 9, 12, 24 and 36. Infusion intervals of 4, 5 and 8 weeks and treatment holidays versus restart were analyzed.

Results: After initiating natalizumab, VLA-4-expression significantly decreased whereas cell-bound natalizumab and saturation increased. During long-term treatment stable values of cell-bound natalizumab and saturation were presented while VLA-4-expression demonstrated constant decrease. A high inter-individual variability was detected. Free natalizumab concentration remained stable during 3 years follow up. Extension of treatment intervals caused significant lower concentrations of free and cell-bound natalizumab in periphery and CSF. After natalizumab cessation, free and cell-bound natalizumab and saturation constantly reduced, VLA-4-expression ran opposed. Three to five months after last infusion, 4/5 patients developed severe relapses. At relapse, only low amounts of free natalizumab could be detected in serum and CSF. After restart, parameters proceeded as seen in long-term treatment.

Conclusions: We present different pharmacokinetics and -dynamics of cell-bound and free natalizumab and VLA-4-expression during several natalizumab treatment-modalities. Evaluation of these parameters could be potential monitoring and dosing tool for effectiveness and safety in natalizumab therapy.

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EP4242
Effect of aspirin pretreatment or slow dose titration on number and duration of flushing and gastrointestinal (GI) events associated with delayed-release dimethyl fumarate
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Introduction: A study in healthy volunteers evaluated the effect of aspirin (ASA) pretreatment and slow dose titration (SDT) on the incidence and severity of flushing and GI events with delayed-release dimethyl fumarate (DMF). Here we report number and duration of these events.

Methods: Subjects were randomized to four groups: PBO/PBO received placebo ASA 30 minutes before placebo delayed-release DMF (weeks 1–8). PBO/DMF received placebo ASA 30 minutes before delayed-release DMF (weeks 1–4), then delayed-release DMF alone (weeks 5–8). ASA/DMF received ASA 30 minutes before delayed-release DMF (weeks 1–4), then delayed-release DMF alone (weeks 5–8). In both groups, delayed-release DMF was dosed at 120mg BID (week 1) and 240mg BID (weeks 2–8). PBO/SDT received placebo ASA 30 minutes before delayed-release DMF (weeks 1–4), then delayed-release DMF alone (weeks 5–8). ASA/SDT received ASA 30 minutes before delayed-release DMF (weeks 1–4), then delayed-release DMF alone (weeks 5–8); delayed-release DMF was administered with SDT (120mg QD [week 1], 120mg BID [week 2], 240mg morning/120mg night [week 3], 240mg BID [weeks 4–8]). Flushing and GI events were rated in an eDiary.

Results: In PBO/PBO, PBO/DMF, ASA/DMF, and PBO/SDT, respectively, mean (median) number of overall flushing events in weeks 1–4 was 5.1 (0), 25.8 (23.0), 11.7 (2.0), and 24.5 (18.0), and in weeks 5–8 was 3.7 (0), 28.0 (22.0), 15.9 (6.5), and 21.6 (15.0); median duration (minutes) of flushing in weeks 1–4 was 57.3, 61.8, 53.8, and 62.5, and in weeks 5–8 was 60.0, 54.6, 68.7, and 53.7. GI results will be presented.

Conclusions: ASA reduced number but not duration of flushing events. SDT had no effect on the flushing event profile.

Disclosure: Study supported by: Biogen Idec, Inc.
EP4243

Safety and tolerability of delayed-release dimethyl fumarate administered as add-on therapy to beta interferons or glatiramer acetate in relapsing-remitting multiple sclerosis (RRMS) patients

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Introduction: Here we describe the safety and tolerability of delayed-release dimethyl fumarate (DMF) as add-on therapy to beta-interferons (IFNβ) or glatiramer acetate (GA) in the Phase 2, open-label EXPLORE study.

Methods: Eligibility criteria included age 18-55 years, RRMS diagnosis (McDonald criteria), EDSS score 0-5.0, established therapy with the same dose of IFNβ or GA for ≥12 months, and ≥1 relapse within 12 months or gadolinium-enhancing lesion(s) on MRI within 6 weeks prior to enrolment. Patients continued on their prescribed MS therapy for 2 months (monotherapy period), then received delayed-release DMF 240mg three times daily (TID) in addition to their prescribed MS therapy for 6 months (add-on therapy period).

Results: During the add-on therapy period, in the delayed-release DMF/IFNβ (n=57) and delayed-release DMF/GA (n=47) groups, the overall incidence of adverse events (AEs) was 95% and 100%; the most common AEs were flushing (42% and 53%), diarrhea (32% and 15%), and abdominal pain (21% and 6%). Most AEs were reported as mild or moderate in severity. There was no overall increased risk of infection. No malignancies were reported. At Week 24, mean percentage decrease of lymphocyte counts from baseline was 22% (delayed-release DMF/IFNβ) and 7% (delayed-release DMF/GA). There was a transient increase in liver transaminases; no case fulfilled Hy’s law. There were no deaths.

Conclusions: The safety profile of delayed-release DMF in combination with IFNβ or GA was similar to the known safety profile of delayed-release DMF monotherapy.

Disclosure: Study supported by: Biogen Idec, Inc.