Multiple sclerosis 1

P1523
PATHOLOGY-IMAGING CORRELATIONS IN NORMAL-APPEARING WHITE MATTER IN MULTIPLE SCLEROSIS

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Objective: To determine the pathologic basis of subtle abnormalities in magnetization transfer ratio (MTR) and diffusion tensor imaging (DTI) parameters observed in normal-appearing white matter (NAWM) in multiple sclerosis (MS) brains.

Methods: Brain tissues were obtained through a rapid post-mortem protocol that included in situ MRI. Four types of MRI-defined regions of interest (ROIs) were analyzed: (1) Regions that were abnormal on all images (“T2T1MTR lesions”); (2) NAWM regions with slightly-abnormal MTR that were close to lesions (“sa-WM Close”); (3) NAWM regions with slightly-abnormal MTR that were far from lesions (“sa-WM Far”); and (4) NAWM regions with normal MTR (“NAWM”).

Immunohistochemical analysis for each ROI comprised immunostaining for myelin, axonal markers, activated microglia/macrophages, astrocytes, serum protein and blood vessels.

Results: 48 ROIs from 4 MS brains were analyzed. Sa-WM Close ROIs were associated with significantly elevated numbers of axonal swellings. There were more enlarged MHCII(+) microglia and macrophages detected in sa-WM Far, sa-WM Close, and T2T1MTR lesions than in NAWM. Across all ROIs, MTR and DTI measures were moderately correlated with myelin density, axonal area and axonal counts. Restricting analysis to NAWM ROIs revealed that MTR and DTI measures were correlated with activated microglia, but not with axons or myelin.

Conclusions: Pathologic substrates for MRI abnormalities in NAWM of MS brains vary based on distance from focal WM lesions. Close to WM lesions, axonal pathology and microglial activation may explain subtle MRI changes. Distant from lesions, profound microglial activation associated with proximity to cortical lesions might underlie MRI abnormalities.

P1524
MULTIPLE SCLEROSIS PATHOLOGY IMPACT THEORY OF MIND: A MULTIMODAL MRI STUDY

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Objectives: Social cognition incorporating Theory of Mind (ToM) is fundamental for successful integration into society. Here, using a multi-modal MRI approach we assessed overall cortical thickness, and lesion load of each major white matter (WM) fibre bundles in multiple sclerosis (MS) to explore their relationship with ToM.

Methods: 49 patients with MS according to McDonald Criteria underwent ToM testing, psychometric assessment, and brain MRI; 24 gender- and age-matched healthy subjects served as controls. Total, and regional lesion load, and cortical thickness were assessed on three-dimensional MPRAGE sequence; fibre tractography was performed on diffusion-weighted echo-planar imaging on 3 Tesla.

Results: MS patients performed significantly poorer in eyes, and irony tests compared to controls (p=0.035, p=0.008, respectively). Eyes test performance significantly correlated with lesion volume of the splenium of corpus callosum (SCC) (p<0.001); and cortical thickness of focal areas in the right premotor cortex, left temporal pole, and left fusiform face area (p<0.01). Fibre tractography traced cortical projection fields of lesions located in SCC. Both focal cortical thinning and regional WM lesion load independently predicted eyes test performance. Lesion volume of SCC independently predicted cortical thickness of left temporal pole area (p<0.003, R2=0.138).

Conclusion: The results suggest that MS brain pathological changes significantly impact ToM by disconnection mechanism and by direct cortical damages including somatotopic-organized mirror neurons. Axonal degeneration in WM lesions associated with declined mentalization mildly relates to focal cortical atrophy correlating with poor ToM, dominant pathologic processes of cortical neurodegeneration are independent from WM lesions.
P1525
THE SOCIOECONOMIC CONSEQUENCES OF OPTIC NEURITIS: A CONTROLLED NATIONAL STUDY

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Optic neuritis (ON) is often a first symptom of multiple sclerosis (MS) which causes serious negative effects on health- and social issues for the patients and society. The burden of ON with and without MS has never been established.

The aim was to determine direct and indirect illness costs in ON patients in a national sample. Using all national records from the Danish National Patient Registry (1998-2006), we identified 1677 patients with ON and compared with 6708 randomly age-, sex- and geography-matched citizens. Direct costs included frequencies and costs of hospitalizations and weighted outpatient use, frequencies of visits and hospitalizations and costs from primary sectors, and the use and costs of drugs. Indirect costs included labour supply; income data. All social transfer payments were also calculated. Patients with ON had significantly higher rates of health-related contact and medication use and very low employment rates which incurred a higher socioeconomic cost. The income level of employed patients was lower than that of control subjects. The annual total excess direct and indirect costs were €3501 for ON pts and €9215 for pts with diagnosis of ON and MS combined. The ON and ON+MS pts received an annual mean excess social transfer income of €1175 and €4619. ON/ON+MS pts presented social and economical consequences up to eight years before diagnosis, and increased after the diagnosis was established.

Conclusion: ON especially if combined with a diagnosis of MS causes significant indirect and direct costs, especially due to reduced employment.

P1526
NEUROPROTECTION AND SYNAPTIC PLASTICITY IS SUPPORTED BY GREY MATTER ASTROCYTES RESPONDING TO REMOTE AXONAL INSULTS

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Grey matter astrocytes become activated (reactive) following axonal insults in direct axonal injuries or in chronic demyelination. The role of this activation in supporting damaged neurones or orchestrating synaptic plasticity is still unclear. In this study we compared neuronal survival and synaptic rearrangements in the facial nucleus in transgenic mice, in which astrocyte reaction was selectively diminished (GFAP-STAT3-CKO), to that seen in wild type animals, following facial nerve axotomy as a model for axonal injuries. We found that 1) there is a decrease in astrocyte response (approx. 44% decrease for GFAP immunoreactive area, 60% reduction in the density of GFAP immunoreactivity, and 43% reduction in the average number of processes) in the knockout mice when compared to that seen for wt mice at day 14 post-axotomy; 2) this decrease correlates well with diminished neuronal survival (from 36% down to 21%) and 3) with the loss in peri-somal synaptic terminals (from 0.19 terminals/mm down to 0.14 terminals/mm); 4) there is less interdigitation between astrocytic and microglial processes around neurones in areas with diminished astrocyte response, being perhaps more exposed to synapse stripping. Our findings suggest that astrocytes with a reactive phenotype are necessary for neuronal protection and for the maintenance of neuronal circuits within the grey matter. A better understanding of the mechanisms may provide new targets for neuroprotective therapies in disease.
P1527

POSTERIOR FOSSA AND CERVICAL LESION SELECTIVITY IN MULTIPLE SCLEROSIS CLINICAL PHENOTYPES

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Objective: To determine the cumulative posterior fossa and cervical lesion distribution in progressive MS (PMS) compared to patients without progression after 20 years of RRMS and among different progressive MS phenotypes.

Background: Disability in MS is associated with increased posterior fossa and spinal cord lesions. Long-term disability is more related to progression regardless of phenotype [primary progressive (PPMS), single-attack progressive (SAPMS) or secondary progressive (SPMS)] than relapses alone. We hypothesize that posterior fossa lesion distribution differs between patients with RRMS and PMS but not as much among different types of progressive MS.

Methods: We segmented brain (202 PPMS, 55 SAPMS, 231 SPMS, 42 RRMS) and cervical spine MRIs (203 PPMS, 44 SAPMS, 162 SPMS, 19 RRMS) at the last visit into anterior-posterior midbrain, anterior-posterior pons/middle cerebellar peduncle (MCP), anterior-posterior medulla/inferior cerebellar peduncle (ICP), cerebellum, anterior-posterior cervicomedullary (CM) junction and anterior-posterior cervical spinal cord. Two independent reviewers blinded to diagnoses counted T2 hyperintensities ≥2mm manually. Chi-square analysis was used.

Results: Posterior fossa lesions overall were more common (p<0.0001) in PMS (419/457) than RRMS (30/42) matched for MRI age (range 40-89), prominently in the posterior midbrain (p=0.037), posterior pons/MCP (p=0.006), cerebellum (p=0.048), and anterior CM junction (p=0.049). The anterior midbrain lesions (p=0.018) and posterior cervical cord lesions (p=0.004) were less common in PPMS compared to SAPMS and SPMS.

Conclusion: PMS patients have higher posterior fossa lesion load than RRMS patients. PPMS patients differ from SAPMS and SPMS only by the anterior midbrain and posterior cervical cord lesion load.

P1528

DISTINCT PATHOLOGICAL PATTERNS IN RELAPSING-REMITTING AND CHRONIC MODELS OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS AND THE NEOUROPROTECTIVE EFFECT OF GLATIRAMER ACETATE

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The roles of inflammatory versus degenerative processes in the pathology of multiple sclerosis (MS) and in its animal model experimental autoimmune encephalomyelitis (EAE) are controversial. Novel treatment strategies aim to act within the CNS to reduce inflammation and induce neuroprotection and repair processes. In this study we analyzed and compared the in situ pathological manifestations of relapsing-remitting PLP- and chronic MOG-induced EAE models, using transmission electron microscopy (TEM) and immunohistochemistry. The effect of immunomodulatory treatment by glatiramer acetate (GA, Copaxone) on myelin damage/repair and on motor neuron loss/preservation was studied in both models. Ultrastructural spinal cord analysis revealed multiple white matter damages, with different occurrence in the two EAE models. Hence, demyelination and remyelination were characteristic to relapsing-remitting EAE, whereas in the chronic model axonal degeneration and loss of lower motor neurons were mainly manifested. In GA-treated mice, smaller lesions, increased axonal density, higher prevalence of normal appearing axons as well as less demyelination and degeneration were found. Furthermore, quantitative analysis of the relative remyelination extent, compared to demyelination, provides for the first time evidence of significant augmentation of remyelination after GA treatment. The loss of lower motor neuron in GA-treated mice was also reduced in comparison to that of EAE-untreated mice. These effects were obtained even when GA-treatment was applied in a therapeutic schedule, after the appearance of clinical symptoms. The remyelination and neuronal preservation induced by GA support the neuroprotective consequences of this treatment.
P1529

EVALUATION OF A MULTIPLE SCLEROSIS (MS) DISEASE PROGRESSION COMPOSITE [EXPANDED DISABILITY STATUS SCALE [EDSS], MS FUNCTIONAL COMPOSITE [MSFC], AND LOW-CONTRAST LETTER ACUITY [LCA]]

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Objective: To evaluate a composite measure of sustained disability progression in MS patients.

Background: EDSS, widely used to measure disability in MS, may not capture all aspects of disability and requires large studies to detect treatment effects. The MSFC and LCA assess changes in ambulation, upper limb function, cognition, and vision. A composite including EDSS, MSFC, and LCA may provide a more complete measure of disability and require smaller studies.

Methods: Composite progression was defined as 12-week sustained EDSS progression (≥1.0-point increase from baseline EDSS score or ≥1.5-point increase from baseline score of 0.0), MSFC individual component progression (≥15% worsening), or visual function progression (7-letter reduction in LCA [2.5% contrast]). A log-rank test of equality of survival curves was used for sample size calculations.

Results: In AFFIRM, natalizumab reduced the risk of 12-week sustained EDSS progression by 42% (HR=0.58; 95% CI=0.43, 0.77; p<0.001); cumulative 2-year probability of progression was 17% (natalizumab) vs. 29% (placebo). Demonstration of this treatment effect in a 1:1 study (90% power) would require 524 patients. Natalizumab also reduced the risk of 12-week sustained composite progression by 33% (HR=0.67; 95% CI=0.56, 0.79; p<0.0001). Cumulative 2-year probability of composite progression was 55% (natalizumab) vs. 73% (placebo). Accordingly, a 1:1 study using this composite measure (90% power) would require 280 patients.

Conclusions: A composite measure of sustained disability progression (EDSS, MSFC, LCA) continued to demonstrate the effect of natalizumab. This measure may provide a more complete disability assessment and allow for smaller sample sizes in future studies.

P1530

INCIDENCE OF VARIOUS CARDIAC ARRHYTHMIAS AND CONDUCTION DISTURBANCES DUE TO HIGH DOSE INTRAVENOUS METHYLPHREDNISOLONE IN PATIENTS WITH MULTIPLE SCLEROSIS

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Background: High-dose intravenous methylprednisolone is the most common therapeutic modality to treat acute exacerbations in multiple sclerosis (MS). Various cardiac arrhythmias have been reported during corticosteroid pulse therapy. This study was conducted to detect cardiac rhythm changes in patients with MS while receiving high dose methylprednisolone.

Methods: We enrolled 52 consecutive MS patients with acute relapse to perform cardiac monitoring 4 hours before, during and 18 hours after infusion of 1000mg intravenous (IV) methylprednisolone.

Results: Sinus tachycardia was the most common change in cardiac rhythms before, during, and after corticosteroid pulse therapy. Up to 41.9% of the patients, developed sinus bradycardia after pulse infusion. Sinus arrest and sinus exit block were observed in 12 patients. Atrial fibrillation and ventricular tachycardia were observed in 3 and 1 patients, respectively. The most important cardiac arrhythmias including ventricular tachycardia, sinus arrest, and sinus exit block, were correlated with smoking and more commonly observed during 12 hours post infusion. Sinus bradycardia and atrial fibrillation were detected more commonly in patients with history of urinary dysfunction.

Conclusion: High dose intravenous prednisolone might cause different types of arrhythmias in MS patients. Cigarette smokers and patients with autonomic disturbances like sphincter and bowel problems have more chance to develop arrhythmias while receiving high dose steroids.
P1531
EXAMINATION OF CEREBROVASCULAR AUTOREGULATION IN MULTIPLE SCLEROSIS PATIENTS DURING HEAD UP TILT TABLE TEST
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Multiple sclerosis (MS) is a chronic disease of the central nervous system including inflammation and axonal degeneration. Axonal degeneration might cause damage of the vegetative nervous system and secondary impairment of cerebral autoregulation. The aim of our study was to examine the cerebral autoregulation in different phases of the disease assessed from spontaneous and provoked blood pressure fluctuation during head up tilt table test. 30 MS patients (mean age±SD: 35.1±9.6 years, mean EDSS: 2.6±1.24) (20 relapsing-remitting, 7 clinically isolated syndrome, 3 primary-progressive) were enrolled in the study. Registration of blood flow velocity in middle cerebral arteries by transcranial Doppler, continuous blood pressure and heart rate monitoring were done at rest (10 minutes) and during tilt table test (30 minutes rising up). Age matched group of 10 healthy subjects were also examined as controls. Correlations between mean arterial blood pressure (MBP) and cerebral blood flow (CBF) fluctuations were averaged, yielding correlation coefficient index Mx. No significant difference was seen between patients and controls in supine position or during provocation by tilting in Mx indices, but prominent increase in heart rate and more decreased CBF was observed in the patient group after tilting up. Modelling the changes in CBF related to 1mmHg increase in MBP significant difference (p<0.05) was detected in the patient group. These results suggest, that cerebrovascular autoregulation does not seem to be markedly damaged in MS patients with relatively good condition, but slight impairment being detected, indicates damage of the vegetative nervous system.

P1532
HIGH FREQUENCY OF THE IL-2-330 T/HLA-DRB1*1501 HAPLOTYPE IN PATIENTS WITH MULTIPLE SCLEROSIS
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Introduction: It is known that activation of the immune system against self myelin antigens is a common process that occurs in the course of this disease. There is also evidence supporting the presence of self-reacting immune components, i.e., the complement system, antibodies and lymphocytes, in MS patients; and there is no doubt that genetic polymorphisms are involved in susceptibility to MS and HLA alleles; and haplotypes might be the most relevant genetic predisposing factors for multiple sclerosis.

Material and methods: We have evaluated the role of the HLA-DRB1*1501 allele and the IL-2-330 T/G polymorphism and their interaction in susceptibility to multiple sclerosis on 360 patients and 426 matched healthy individuals. We used the SSP-PCR method to determine the alleles. Fisher’s exact test was used for analysis.

Result: We observed a significant increase in the T-allele at IL-2-330 position in patients (OR=1.34, p<0.05), and the T/T and T/G genotypes were more frequent among patients than in controls. The HLA-DRB1*1501 allele was overrepresented in patients as compared to the control group (OR=1.7, p=0.0006). The two-locus analysis of the interaction between the IL-2 promoter polymorphism and the HLA-DRB1 allele showed that the HLA-DRB1*1501/T haplotype was more frequent in patients than in controls (OR=16, p<0.0001).

Conclusion: Our study revealed that the T-allele and the G/T and T/T genotypes were associated with a higher risk of developing MS in the studied population. We have provided evidence of an interaction between the T- and HLA-DRB1*1501 alleles in the genetic susceptibility to MS.
P1533
IN VIVO COMPARATIVE METABOLISM OF [14C]-LABELLED TERIFLUNOMIDE IN MICE, RATS, RABBITS, DOGS AND HUMANS
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Introduction: Teriflunomide is a novel oral disease modifier currently being investigated for the treatment of multiple sclerosis.

Objective: To compare the in vivo metabolism of [14C]-teriflunomide in mice, rats, rabbits, dogs and humans.

Method: The metabolism of teriflunomide was examined after a single 7.5mg/kg oral administration of [14C]-teriflunomide in mice, rats, rabbits, and dogs or a single 70mg oral administration of [14C]-teriflunomide in healthy volunteers. Plasma, urine, and faeces samples were analyzed to determine the metabolite radioprofiles and conduct metabolite structure elucidation by radiochromatography and LC-MS/MS.

Results: In plasma, unchanged teriflunomide was the predominant radio-component detected in mice, rats, rabbits, dogs and humans. In urine, TFMA oxanilic acid was the major metabolite (>67% of radioactivity or 5-43% of the dose) in all species except in rabbits where unchanged teriflunomide was the dominant component (>72% of radioactivity or 57% of the dose). In faeces, unchanged teriflunomide was the predominant component (>57% of radioactivity or 20-65% of the dose). Other identified metabolites (each <5% of dose) included Phase I metabolites from oxidation, hydrolysis, or combination of both, and Phase II metabolites from glucuronide and/or sulfate conjugation of the phase I metabolites.

Conclusions: Metabolism of teriflunomide in humans is low. Metabolism was qualitatively similar across all species. Moreover, all detected metabolites in humans were observed in at least one animal species. These findings support the selection of the various animal species (mouse, rat, rabbit, and dog) for safety and pharmacology assessment studies with teriflunomide.

P1534
SEXUAL DYSFUNCTION IN MULTIPLE SCLEROSIS: A 6-YEAR FOLLOW-UP STUDY
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Objective: The objectives of this study were to determine the frequency and nature of sexual dysfunction (SD) in a sample of multiple sclerosis (MS) patients, and to detect the changes in SD after the 6-year follow-up.

Methods: This panel study comprised 109 patients with definite MS (McDonald’s criteria). Exclusion criteria were: exacerbation of the disease in the last month. Any major pre-existing chronic illness, and no sexual experience so far. Information on sexual disturbances have been collected through face to face structured interviews. The sexual dysfunction of the patients was quantified by Szasz sexual functioning scale. Spearman rank correlation coefficient was used to determine the relationship between SD and selected variables. The changes in presence and severity of SD after the 6 years of follow-up were evaluated by Wilcoxon rank test.

Results: In the beginning of the study, the proportion of patients with sexual disturbances was 66.2%. The most commonly reported symptoms of SD were: reduced libido (46.7%), anorgasmia or hyporgasmia (35.7%) and decreased vaginal lubrication (23.4%) in women, and impotence (42.5%), and reduced libido (38.2%) in men. After a 6-year follow-up, the proportion of MS patients with SD was 82.2% and significantly changed over the time (Z=-5.209, p=0.001). Increase in number and extent of SD symptoms has also been observed and directly correlated with disability impairment during the period observed (r=0.482, p=0.001).

Conclusions: Our results have shown that symptoms of SD are very common in MS patients and used to increase in number and significance over the time.
P1535

FOLLOW-UP STUDY ON BIOMARKERS IN MS: CORRELATION BETWEEN IMMUNE, VOLUMETRIC MRI, DIFFUSION TENSOR IMAGING INDICES AND CLINICAL MEASURES

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Objective: To identify inflammatory and degenerative biomarkers in multiple sclerosis (MS), we analyzed the serum profiles of cytokines, chemokines and apoptotic molecules and correlated their levels with clinical, volumetric MRI and diffusion tensor imaging (DTI) measurements.

Methods: The study was a 4-year prospective follow-up study that included 86 subjects: 15 CIS, 33 RRMS, 18 SPMS, 20 PPMS and 10 controls who underwent neurological and MRI examination every year after enrolment. Their serum levels of 14 candidate immune biomarkers were measured and correlated with the clinical parameters, volumetric measures (T1, FLAIR) and novel DTI parameters (ADC and FA) from 10 Normally Appearing White Matter (NAWM) and 3 Normally Appearing Grey Matter (NAGM) regions by region-of-interest (ROI) approach.

Results: According to a one-year follow-up, in clinically definite MS patients the levels of sFas (p=0.019) and MIF (p=0.020) were associated with increasing EDSS. In CIS, the levels of CCL4 correlated negatively with FA (r=-0.720, p=0.002) and positively with ADC (r=0.674, p=0.006) levels in NAWM. In progressive subtypes, increased levels of CCL2 and TNF-α was noticed where TNF-α correlated negatively with FA levels in NAWM (r=-0.422, p=0.008). In RRMS, the levels of sFas were inversely associated with FA levels of NAGM (r=-0.567, p=0.001). Our 4-year follow-up data seem to strengthen these observations.

Conclusion: An association between increased levels of blood immune molecules and MRI/DTI abnormalities reflects involvement of these molecules in development of tissue integrity loss that is consistent with neurological worsening in MS indicating their role as biomarkers of disease process.

P1536

UNMET NEEDS OF IRISH MS PATIENTS

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Background: Over 30% of MS patients respond suboptimally to disease modifying therapy (DMT), and accumulate disability. There is no evidence that DMTs modify progressive MS. However, these patients may benefit from multidisciplinary interventions, and require financial and community support. Non-pharmacological needs may be overlooked during fund allocation; and identification of unmet needs is important to optimise care and resource allocation.

Aim: To identify unmet needs of MS patients in 3 areas in Ireland.

Patients and methods: Observational study in 3 regions in Ireland: South Dublin SCD (urban), Donegal DGL and Wexford WEX (rural counties). Patients completed a validated Needs Assessment Questionnaire (NAQ). MS subtype, EDSS and DMT details were recorded.

Results: We identified 632 patients: 23% in SCD (urban), 30.8% in WEX, 46.2% in DGL. MS subtype: RR in 51.1%, SP in 39.7%, PP in 9.2%. EDSS in 86% was ≤6 and >6.5 in 14%. NAQ completed by 325 (49.9%), and 52.3% (170) reported unmet needs relating to MS: ≥2 needs in 73% and ≥5 in 24%. Unmet needs correlated with EDSS >6.5 (p<0.001), MS subtype: RR 36.9%, SP 76.3%, PP 62.5% (p<0.001), increased age (p 0.003), MS duration (p=0.003), rural residence (p<0.05).

Discussion: Over 50% reported unmet needs relating to MS, suggesting that non-pharmacological needs are suboptimally addressed, particularly in older, disabled patients with progressive MS. This highlights need for increased fund allocation, especially to develop community supports and multidisciplinary services. Identifying unmet needs may help guiding health service planning.
P1537
IS ALEMTUZUMAB A SAFE, EFFECTIVE TREATMENT CHOICE FOR PATIENTS WHO FAIL NATALIZUMAB?
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Introduction: Alemtuzumab is undergoing phase 3 evaluation as a treatment for highly active relapsing-remitting multiple sclerosis (RRMS). We assessed a small cohort of patients who had received alemtuzumab, on a named patient basis, after failed treatment with natalizumab.

Methods: Patients who stopped natalizumab and received alemtuzumab from July 2009 to January 2011 were reviewed. We examined the efficacy of the drug on clinical and MRI markers of disease-activity and expanded disability status scale (EDSS) and evaluated its safety after failed natalizumab therapy.

Results: 11 patients received alemtuzumab having received natalizumab for highly-active RRMS. 3/11 had an allergic reaction to natalizumab and 8/11 failed treatment. Lymphopaenia developed 1 month after alemtuzumab in all patients. 4/11 developed leukopaenia without neutropaenia within 3 months. There were no serious infections. 1/11 developed thyroid peroxidase antibodies at 3 months and biochemical hypothyroidism at 9 months. The average annualised relapse rate on natalizumab was 2.5. This fell to 0.1 in the first year of alemtuzumab therapy. Prior to alemtuzumab 8/11 exhibited an increasing lesion load, of whom, 4/11 had gadolinium-enhancing lesions. MRI one year after alemtuzumab therapy demonstrated no gadolinium-enhancement or new lesions in all patients. EDSS improved in 6/11 (55%) and stabilised in 4/11. 1 patient relapsed with deterioration in EDSS and received an alternative treatment.

Conclusions: Alemtuzumab therapy after failed treatment with natalizumab is well-tolerated and results in a substantial reduction in clinical and MRI disease-activity. It is important to monitor patients closely due to the unknown risks of sequential use of biological therapies.

P1538
NEURONAL SURVIVAL AND DENDRITIC PROTRUSION/SPINE LENGTH ARE PROMOTED BY ASTROCYTES VIA A STAT3 DEPENDENT PATHWAY
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Following axonal insults, such as axotomy or demyelination, increased synaptic plasticity distant to the axotomy site can be observed. At present the role that the glial environment plays in orchestrating this plasticity is unclear. In order to better understand how reactive astrocytes affect neurons and their synapses, we used various astrocyte-neuron co-culture systems for analysis. In particular we compared the effects of wild type (wt) astrocytes to those with a reduced ability to react to in vitro insults (GFAP-STAT3 conditional knockout mice) on neuronal survival, dendritic spine morphology and synapse formation.

In this study we show that 1) neuronal survival increases with the addition of wt astrocytes in a dose-dependent manner, 2) the length of dendritic protrusions of neurons increases upon addition of wt astrocytes, but this is not observed with the addition of astrocytes with impaired reactivity, 3) the proportion of filopodial protrusions is increased with the addition of wt astrocytes, but not with the addition of astrocytes with impaired reactivity.

This highlights the possibility that grey matter astrocytes with reactive phenotypes are necessary to support neuronal survival and synapse formation, and reveals a beneficial aspect of astrogliosis in the CNS.
P1539
EFFECTS OF A 24-WEEK NATALIZUMAB TREATMENT INTERRUPTION ON VARIOUS IMMUNE PARAMETERS AND MULTIPLE SCLEROSIS (MS) DISEASE ACTIVITY: THE RESTORE STUDY
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Objective: RESTORE is an ongoing, randomized, placebo-controlled, parallel-group study to evaluate the effect of a 24-week interruption in natalizumab treatment on various immune parameters and MS disease activity compared with continuing natalizumab or switching to alternative immunomodulatory therapies (AIT).

Background: In post-marketing experience, progressive multifocal leukoencephalopathy (PML) risk increases with increasing natalizumab treatment duration. It has been hypothesized that treatment interruption might decrease PML risk; however, underlying MS may also return. Because PML is rare, a study to evaluate the potential impact of treatment interruption on PML risk would be prohibitively large.

Methods: Eligible patients received natalizumab for at least the preceding 12 months without relapse and did not have gadolinium-enhancing lesions on screening brain MRI. Patients were randomized to continue natalizumab or discontinue and switch to either placebo or open-label AIT. Following the 24-week treatment interruption, open-label natalizumab may be reintroduced for 24 weeks.

Results: As of December 2010, 175 patients (female, 77%) aged 20 to 61 years (mean 41.2) were randomized. Disease duration at baseline was between 2 and 41 years (median 11.0) and patients had received a median of 29 prior natalizumab doses (min, max: 12, 51). In the year prior to initial natalizumab therapy, 39% of patients had ≥2 relapses. At baseline, the mean Expanded Disability Status Scale score was 3.2±1.72. Anti-JC virus antibody at baseline was detected in 55% of patients.

Conclusions: RESTORE will provide longitudinal data to evaluate pharmacodynamic markers, immune function, and disease activity during and after a 24-week interruption of natalizumab.

P1540
DEMYELINATION PROCESSES AFFECT TEMPORAL ASPECTS OF PERCEPTION: A LONGITUDINAL OPTIC NEURITIS STUDY
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Objective: Visual Evoked Potentials (VEP) following acute optic neuritis (ON) remains chronically prolonged, although standard visual tests indicate full recovery. No behavioural correlate for this prolongation, which is considered the gold standard test for ON, was previously identified.

Methods: 21 patients with acute unilateral, first-ever ON were studied over the course of one year. Static and dynamic visual functions, VEPs and optical coherence tomography (OCT), were assessed repeatedly.

Results: Visual and electrophysiological measurements reached maximal performance 4 months following the acute phase, with no subsequent improvement. While VEP latency and static visual functions recovered, VEP latency remained significantly prolonged and motion perception remained impaired throughout the 12-month period. A strong correlation was found between VEP latencies and motion perception. Visual performance one month following the acute phase was found to be strongly predictive of visual outcome. The magnitude of improvement in motion perception was constant across patients, independent of the initial deficit level.

Conclusions: Our findings demonstrate that dynamic visual functions remain chronically impaired following optic neuritis. Motion perception deficit was closely correlated to prolongation of VEP latencies, implicating the need for rapid transmission of visual input in order to perceive motion. Our results can be evaluated in the light of currently developing neuro-protective and regenerative therapeutic strategies, targeting myelination in the CNS. Dynamic visual functions may be used as a quantifiable tool to demonstrate the process of myelin preservation and remyelination in the visual pathways.
P1541
DO WE NEED BROAD IMMUNOLOGICAL WORK-UP IN ALL PATIENTS WITH CIS?
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Background: The aim of this study was to determine the prevalence of altered immunological tests and their clinical significance in patients with clinically isolated syndrome (CIS) suggestive of multiple sclerosis (MS).

Patients and methods: The information was gathered from medical records of patients hospitalized in the Department of Neurology in the 2008-2010 period. All patients had ANA, ENA profile, ANCA, aCl IgG and IgM, lupus anticoagulant, C3, C4, CH50, anti-TPO antibodies tested.

Results: From 210 patients with CIS that were reviewed, the immunological tests were performed in 178 of them, representing our cohort. Altered tests were found in 95 patients (53%). 34 patients (19%) had positive antinuclear antibodies (4 patients had homogeneous pattern, 28 dot-like, 2 nucleolar). ENA was positive in 8 patients (4.5%); ENA profile was: U1- RNP in 1 patient, SS-A in 2 patients, DNA-topo 1 in 3 patients, Jo-1 in 1 patients and NuMa one patient. Furthermore, 18 patients (10%) had positive aCl- IgG, while aCl- IgM was positive in 32 patients (18%). Anti TPO antibodies were found in 11 patients (6.2%). None of the patients had any clinical manifestations other than MS symptoms.

Conclusion: These results indicate that a significant number of patients with CIS have altered immunological tests but nevertheless none of them had clinical expression of any other autoimmune disease. In conclusion there is no need to perform expensive immunological work-up in all patients with CIS, unless signs or symptoms indicate other autoimmune diseases.

P1542
MINI-AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT) +/- CONSOLIDATION THERAPY IN THE POSTTRANSPLANT PERIOD FOR MULTIPLE SCLEROSIS (MS)
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High dose immunosuppressive therapy (HDIT) with AHSCT has been used with increasing frequency as a therapeutic option for MS. We aimed to study the safety and efficacy of mini-AHSCT with or without Mitoxantrone consolidation therapy in the post-transplant period. 187 patients (secondary progressive - 65, primary progressive - 27, progressive-relapsing - 4, relapsing-remitting - 91) were included in this study (mean age - 33.0; male/female - 74/113). Among them 55 patients had consolidation therapy with Mitoxantrone in the total dose of 60-72mg/m\textsuperscript{2} within the first year after transplantation. Median EDSS at baseline was 4.0. Neurological evaluation was performed at baseline, at discharge, at 3, 6, 9, 12, and every 6 months thereafter. The median follow-up duration was 27 months (range 9-52). There were no transplant-related deaths throughout the follow-up period. The mobilization and transplantation procedures were well tolerated. At 6 months after transplantation in the group without consolidation all the patients, except one, responded to treatment. At long-term follow-up overall clinical response was registered in 87% of patients: 38% experienced neurological improvement; 49% remained stable. Proportion of relapse-free patients was 94%. In Mitoxantrone group all the patients responded to treatment: 56% of patients had improvement, 44% showed stabilization. At long-term follow-up all the patients were either stable or had improved. Proportion of relapse-free patients was 100%. Mini-AHSCST appears to be a safe and effective treatment for MS patients. Long-term follow-up is worthwhile to determine the feasibility of consolidation therapy in the post-transplant period.
P1543

MORTALITY AND SURVIVAL TRENDS IN MULTIPLE SCLEROSIS: PARTICIPANTS OF A LARGE INJURED COHORT AND A MULTIPLE SCLEROSIS REGISTRY

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Objective: To estimate survival and cause-specific mortality in multiple sclerosis (MS) subjects compared with matched controls.

Methods: A longitudinal, population-based study was conducted using data from a large, i3-affiliated health plan and a US-based MS registry (North American Committee on MS [NARCOMS]) covering 1993-2008. An algorithm combining International Classification of Diseases (ICD)-9 and disease-modifying treatment (DMT) codes was used to identify the health plan MS patients, who were then matched with non-MS subjects 3:1 on gender, age, geographic residence and the year MS was first identified in the database. The NARCOMS population was analysed and compared separately. Individuals were followed through 2008 by linking their data to the National Death Index (NDI) and Social Security Administration Data Master File (SS-ADMF) to obtain vital status and cause of death by calendar year to assess mortality rates, risks, and survival patterns.

Results: 29,126 individuals from the healthcare database satisfied the MS selection criteria and were compared with 86,129 non-MS matching individuals. Most MS patients were women (76.9%) and 63% of the population was 35-54 years old. Information on all 112,255 participants, as well as 20,255 from NARCOMS, is being linked with NDI and SS-ADMF data to obtain vital status. Interim analysis of a sub-sample of NARCOMS indicated that 78.4% were women and 42.4% were 35-54 years old. Additional demographic, socioeconomic and survival information will be presented.

Conclusion: Results of this study will enhance understanding of survival patterns and mortality risk in US MS populations as compared to non-MS counterparts.

P1544

TGF-β1 INDUCES MATRIX METALLOPROTEINASE-9 AND CELL MIGRATION VIA ROS-DEPENDENT ERK-AND JNK-NF-κB PATHWAYS IN ASTROCYTES

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Background: Transforming growth factor-β (TGF-β) and matrix metalloproteinases (MMPs) are the multifunctional factors during diverse physiological and pathological processes including development, wound healing, proliferation, and cancer metastasis. Both TGF-β and MMPs have been shown to play crucial roles in brain pathological changes. Thus, we investigate the molecular mechanisms underlying TGF-β1-induced MMP-9 expression in brain astrocytes.

Methods: Rat brain astrocytes (RBA-1) were used. The MMP-9 expression was analyzed by gelatin zymography and RT-PCR. The involvement of signalling molecules including MAPKs and NF-κB in the responses was investigated using pharmacological inhibitors and dominant negative mutants, determined by Western blot and gene promoter assay. The functional activity of MMP-9 was evaluated by cell migration assay.

Results: Here we reported that TGF-β1 induced MMP-9 expression and enzymatic activity via a TGF-β receptor-activated reactive oxygen species (ROS)-dependent signalling pathway. ROS production led to activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and c-Jun-N-terminal kinase (JNK) and then activated the NF-κB transcription factor. The activated NF-κB turned on transcription of MMP-9 gene. The rat MMP-9 promoter containing an NF-κB cis-binding site was identified as a crucial domain linking to TGF-β1 action.

Conclusions: Collectively, in RBA-1 cells, activation of ERK1/2- and JNK-NF-κB cascades by a ROS-dependent manner is essential for MMP-9 up-regulation/activation and cell migration induced by TGF-β1. These findings indicate a new regulatory pathway of TGF-β1 in regulating expression of MMP-9 in brain astrocytes, which is involved in physiological and pathological tissue remodelling of central nervous system (CNS).
P1545
METABOLISM COMPARISON BETWEEN LEFLUNOMIDE AND TERIFLUNOMIDE IN HUMANS
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Introduction: Leflunomide (Arava), a prodrug of teriflunomide, is used for the treatment of rheumatoid arthritis. Teriflunomide is a novel oral disease modifier currently being investigated for the treatment of multiple sclerosis.

Objective: To compare metabolism between leflunomide and teriflunomide in humans.

Method: The metabolism of leflunomide and teriflunomide was examined after a single oral administration of 100mg [14C]-leflunomide or 70mg [14C]-teriflunomide to healthy volunteers. Plasma and excreta samples were analyzed to determine the metabolite radioprofiles and conduct metabolite structure elucidation by radiochromatography and LC-MS/MS.

Results: Leflunomide was extensively metabolized into teriflunomide through a ring opening process involving both oxidation (multiple liver CYP450 enzymes) and hydrolysis (possibly non-specific esterases). Metabolism of teriflunomide in human was less extensive and mainly involved non-CYP enzymes. In human plasma, teriflunomide was the only drug related component detected for either drug. In faeces, teriflunomide was the predominant component accounting for 11% (up to 72-h collection period) and 36% (21-day) of the radioactive dose for leflunomide and teriflunomide, respectively. In urine, hydroxylated metabolites and further glucuronidated metabolites of leflunomide were the major components accounting for 12% of dose (96-h), in addition to trifluoromethyl aniline (TFMA) oxanilic acid (10% of dose). After teriflunomide administration, TFMA oxanilic acid was the major metabolite accounting for 18% of dose (21-day) in urine.

Conclusions: Compared to leflunomide, teriflunomide metabolism is low and CYP450 enzymes involvement is limited. It is unlikely that interaction with other drugs would significantly alter the pharmacokinetics of teriflunomide.

P1546
THE NQO1 C609T INBORN POLYMORPHISM IS ASSOCIATED WITH SUSCEPTIBILITY TO MULTIPLE SCLEROSIS (MS) AND AFFECTS THE RISK OF DEVELOPMENT OF PRIMARY PROGRESSIVE MS
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Accumulating data indicate the importance of oxidative stress in the pathogenesis of MS and suggest that genes mediating the cellular antioxidant response are candidates for MS development and progression. Inactivating polymorphism of genes encoding detoxification enzymes, such as NAD(P)H:quinone oxidoreductase 1 (NQO1), could influence susceptibility to MS.

Purpose: The investigation of the potential role of NQO1 inborn polymorphism in MS susceptibility.

Methods: We performed a case-control study in which we compared the distribution of NQO1 genotypes between 231 MS patients and 380 controls, using both PCR-RFLPs and real-time PCR assays. Correlations with disability status (EDSS grade), clinical subtypes and gender, were also evaluated.

Results: A significantly higher frequency of the homozygous (T/T) and heterozygous (C/T), variant genotypes was observed among MS patients, as compared to controls (p=0.01), with MS patients showing a 1.5-fold increased risk of carrying at least one variant T-allele (p=0.009). Interestingly, patients belonging to the primary progressive subgroup (PPMS) exhibited a significantly higher incidence of heterozygotes C/T variant genotype, as compared to the other forms of MS (p=0.019). There was no impact of the NQO1 polymorphism on disease severity after 10 years of onset or gender.

Conclusions: The results provide the first molecular epidemiological evidence of a pathogenetic role of the NQO1 C609T polymorphism on MS susceptibility. Our study also suggests that interindividual differences in the capacity to counteract ROS-induced cellular damage, due to the genetic background, may modify the individual’s risk of developing the primary progressive form of MS.
P1547

LONG-TERM FOLLOW-UP OF BENIGN MULTIPLE SCLEROSIS IN BELGRADE, SERBIA: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

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Objective: We analyzed demographic and clinical characteristics of relapsing-remitting (RR) multiple sclerosis (MS) patients after 25 years of disease duration.

Patients and methods: 119 immunomodulatory treatment-naive patients were followed at the Clinic of Neurology, Belgrade, from their MS onset (January 1, 1941-December 31, 1970) to the cut-off date (January 31, 2008). Out of 119 patients, 82 initially had RRMS. Median follow-up time was 39 years (range, 26-48 years). After ≥25 years of the disease duration, 12 patients (10.1% of the total) had RRMS.

Results: Female/male ratio was 5:1 and mean age at onset was 28.9±10.8 years (95% CI, 22.1-35.8). Disease onset was monosymptomatic in about 30% of patients with pyramidal, sensory and brainstem symptoms/signs being most frequent. First remission lasted 1-84 months (median, 19.5 months) and was complete in 75% of patients. Median EDSS score after 5 years was 2.0 and remained the same after 25 years. In 6 patients who were alive by the cut-off date, median EDSS was 3.5 (range, 3.0-4.0). In 5 patients who reached EDSS 4.0, median time to reach this score was 16 years (range, 7-45). Based on the comparison with patients who converted to secondary-progressive disease (data not shown), variables associated with non-conversion were: female gender (p=0.002), unilateral sensory impairment (p=0.003) and absence of optic neuritis (p=0.026) at onset, and lower EDSS score after 5 years (p=0.033).

Conclusion: Our results further support a potentially favourable prognosis of MS in female patients with sensory symptoms at onset and lower EDSS score after 5 years.

P1548

CLINICAL, LABORATORY, MRI, AND ELECTROPHYSIOLOGIC FINDINGS IN LONGITUDINALLY SHORT TRANSVERSE MYELITIS: COMPARISON WITH LONGITUDINALLY EXTENSIVE TRANSVERSE MYELITIS

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Background: Longitudinally extensive transverse myelitis (LETM) is a syndrome showing extensive spinal cord lesions on MRI, involving three or more vertebral segments. It is rare in patients with typical MS in Western countries and is also regarded as a characteristic feature of NMO in Western countries or recurrent myelitis in Korea. On the contrary, longitudinally short transverse myelitis (LSTM), a syndrome showing short spinal cord lesions on MRI, involving less than three vertebral segments is not fully understood for clinical features, laboratory findings, and MR findings in Korea.

Method: We retrospectively analyzed the patient demographics, clinical impairment at the last clinical visit, ancillary tests including CSF, MRI, evoked potentials of Korean patients with LSTM or LETM.

Results: We identified 63 patients with a first-ever transverse myelitis admitted to our institution from January 2005 to December 2009. The follow-up time ranged from 8 to 126 months (mean 30 months). LSTM (n=41) showed less severe disability than LETM (n=22) (lower EDSS on the last clinical visit, 2.4 vs. 4.9, p<0.05). There were different distribution of clinical course such as more MS cases (36.6%) in LSTM and less MS cases (13.6%) in LETM. On the MR features, LSTM showed more limited lateral or posterior patterns (68.3% vs. 9.1%), less contrast enhanced lesions (58.5% vs. 95.4%), no low signal in T1 weighted images (0% vs. 13.6%) than those of LETM (p<0.05).

Conclusion: Our study showed LSTM is different from LETM clinically and radiologically.
ABERRANT EXPRESSION OF APOPTOSIS-RELATED GENES IN EARLY MS: A NEW PROGNOSTIC MARKER?

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**Background:** In multiple sclerosis (MS), dysregulation of apoptotic events may cause persistence of immune responses followed by the development of tissue damage in the CNS. The purpose of the present study was to define prognostic markers for disease activity and conversion to MS.

**Methods:** The expression of 93 apoptosis-related genes was analyzed from PBMC obtained from patients with CIS, RRMS and healthy controls. All patients underwent neurological and MRI examinations at baseline and thereafter were followed up for two years.

**Results:** At baseline, 7 of the 93 genes of the death receptor pathway that can activate (APAF, PYCARD, IFT57) or inhibit (XIAP, BIRC6) caspases or mediate NF-κB activation (REL, CARD6) were found to be upregulated in those CIS patients who over the two-year follow-up converted to definite MS. In patients with RRMS, 12 genes included in the proapoptotic Bcl-2 family (BAD, BBC3, BCL2L14, BIK, BOK), death receptor pathway (CASP1, FADD, PYCARD, TNFRSF25) and the NF-kB family (IKBKE, NFKBID, NFKBIE) were found to be upregulated initially. High clinical disease activity was associated especially with proapoptotic Bcl-2 family genes (BAD, BAX, BIK, BOK).

**Conclusions:** These data show that the early phases of MS are associated with an enhanced potential for apoptosis in mononuclear cells directed at controlling MS disease activity. We suggest that genes of the Bcl-2 family might serve as candidate immunological markers for disease activity in RRMS, while death receptor pathway molecules could be used as prognostic biomarkers for conversion to definite MS.

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SERUM IL-17A TITER IN MS PATIENTS TREATED WITH IFN-β

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**Background:** Only two thirds of IFN-β treated MS patients respond to treatment. The IFN-β mechanism of action is among others, suppressing the newly described Th17 cells that secrete proinflammatory IL-17A. In healthy subject IL-17A serum levels are undetectable.

**Objectives:** To determine the serum level of IL-17A in IFN-β treated MS patients and to find correlations between these titres and patients’ MS characteristics. If trials have studied plasma IL-17A in untreated patients, this is the first study within this approach.

**Methods:** 158 patients with MS (mean age: 42.1±9.8, mean EDSS: 2.7±1.95, 70.2% RRMS and 29.7% SPMS, mean relapses in the past 12 months: 0.43±0.6) who had at least 18 months of IFN-β treatment as unique DMT, underwent a serological IL-17A test. IL-17A was tested using ELISA-indirect method and values over 1.6pg were significant. All patients had at least 30 days without steroids. For each patient, were recorded: epidemiological, clinical and treatment feature (early vs. late treatment, responder vs. non-responder, duration of treatment). Spearman correlation was used and p-values of <0.05 were significant.

**Results:** 28 (17.7%) patients had significant IL-17A. We found correlations between the IL-17A titre, higher number of MS relapses (p<0.009) and higher EDSS (p<0.05). A trend toward significance was found at IL-17 titre in late versus early start of therapy. No other parameters correlated.

**Conclusions:** High IL-17 concentration in the serum of MS treated patients plays a role in non-responsiveness to IFN-β therapy. A correlation with NABs and other MS biomarkers is required in the future.

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P1551

GLYCOSPHINGOLIPIDS AND THEIR ANTIBODIES IN HEALTHY SIBLINGS OF MS PATIENTS: EXPANDING THE CONCEPT OF THE "MS TRAIT" ENDOPHENOTYPE

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An “MS immunopathic trait” defined as CSF enriched oligoclonal bands was found in 18% of healthy siblings to MS patients and in healthy members of two multiplex families (Haghighi et al 2000, 2006). We also reported that MS patients have increased CSF levels of sulfatide, and serum IgM antibodies against two myelin glycosphingolipids, sulfatide and galactosylceramide (GalCer).

Material: 46 pairs of one MS patient and one healthy sibling, and 50 unrelated healthy controls were included. The median age of the siblings was 43 years and of the unrelated controls 33 years.

Results: There was a higher concentration of sulfatide in the CSF in the healthy siblings than in the healthy unrelated controls (p<0.001 with age as a covariate). Using a cut-off level deriving from the controls, 15 healthy siblings and 10 MS patients had increased CSF sulfatide levels. Titres of anti-GalCer (p=0.01) and anti-sulfatide antibodies (p=0.048) were higher in the healthy siblings group than in the healthy volunteers. There was an individual correlation between detectable sulfatide in the CSF and detectable serum anti-sulfatide (p=0.007). Only one of the healthy siblings with increased CSF sulfatide and none with increased GalCer had “immunopathic trait”.

Discussion: This “myelin fragility” endophenotype in siblings to MS patients is probably a genetic trait indicating subclinical myelin inflammation or lesion in relatives. It seems essentially independent of the endophenotype termed the “immunopathic trait”, while the individual combination of both phenotypes occurs in manifest MS.

P1552

PREVALENCE OF MULTIPLE SCLEROSIS IN DEBRECEN, HUNGARY

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Objective: The aim of this study was to examine the prevalence of multiple sclerosis (MS) in the population of Debrecen, the second largest city in Hungary and to determine the functional status of the patients according to the clinical course of their disease.

Methods: The diagnosis was based on Poser criteria, and the degree of physical disability was evaluated using Kurtzke’s EDSS.

Results: In Debrecen city, the prevalence of MS was 68/100,000 in 2008, whereas it was retrospectively calculated only 38/100,000 for 1998. 70% of the patients came at regular check-ups. The mean age was 45±11 years (16-74 years), female:male ratio 2:1, mean EDSS: 3.0. The distribution of MS according to the clinical course: 24% had benign, 50% relapsing-remitting, 10% primary progressive, 16% secondary progressive form in 2008, 36% of the patients had been treated by immunomodulatory drugs. 2% of the patients were wheelchair dependent and 4% of them were bedridden. 18 MS patients died during this 10-year duration. The incidence of MS fluctuated between 5-13/year from 1999-2008. 51 patients who did not fulfil the criteria for definitive MS either by Poser or McDonald during 12 years follow-up remained on observation. 25 new patients were diagnosed according to the McDonald criteria in 2009-2010.

Conclusion: Our result is very similar to those published from another region of Hungary suggesting that about 8000 patients in Hungary suffer from MS.
P1553
PRESERVED IN VIVO RESPONSE TO INTERFERON-α IN MULTIPLE SCLEROSIS PATIENTS WITH NEUTRALISING ANTIBODIES AGAINST INTERFERON-β: AN ONGOING CLINICAL TRIAL
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A major problem in the treatment of multiple sclerosis (MS) patients with interferon-beta (IFN)-β is the development of neutralising antibodies (NAbs) directed against IFN-β. High levels of NAbs block the induction of Myxovirus Resistance Protein A (encoded by the MX1 gene) and other IFN-β-inducible markers, meaning loss of bioactivity and therapeutic benefit. In this open-label phase II study we used in vivo MX1 mRNA induction as measure of biological response to interferon-alpha (IFN-α) in patients with NAbs and abolished mRNA MxA response to IFN-β. We included 8 patients with relapsing remitting MS, who had sustained presence of high-level NAbs against IFN-β and no in vivo MX1 mRNA response. The primary endpoint was the in vivo MX1 mRNA response after an injection of IFN-α compared with the response after an injection of IFN-β. We also studied the in vivo response to IFN-α of four other well-known IFN-β inducible molecules: interleukin-10, tumour necrosis factor-related apoptosis-inducing ligand, IFN-α-inducible protein 27, and the chemokine CXCL10. All patients had previously been treated with IFN-β for 1 year or more and had persisting NAbs and no MX1 response. In all 8 patients we found high mRNA MxA expression after subcutaneous injection of IFN-α (Multiferon®) 6 MIU, indicating a preserved in vivo response to IFN-α. The complete immunological analyses will be presented. Based on the preliminary data we suggest that IFN-β could be a therapeutic option in patients, who have developed NAbs against IFN-α and therefore have lost the biological response to IFN-β.

P1554
POTENTIAL BENEFITS OF PEGYLATION IN THE TREATMENT OF MULTIPLE SCLEROSIS: A SYSTEMATIC REVIEW OF THE PHARMACOECONOMIC LITERATURE
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Objective: To understand the potential economic impact of pegylation on the treatment of relapsing-remitting multiple sclerosis (RRMS).

Background: Pegylated interferon-beta 1a is being developed for the treatment of RRMS. The goal of this study is to better understand the economic benefits of pegylated analogues currently available in other disease areas.

Methods: A comprehensive search of medical literature published between 1985 and 2010 was conducted using PubMed/MEDLINE, article links, and supplemental searches, to compare costs and cost-effectiveness of approved pegylated versus non-pegylated drugs. Reviewed references were prospective or retrospective studies examining medical costs, cost offsets, cost drivers, and cost-effectiveness associated with pegylated drugs. All costs in this study are adjusted to 2010 US dollars.

Results: 25 articles were reviewed. Most pegylated drugs required less frequent administration than non-pegylated versions. This resource utilization reduction translated into cost savings ranging from $235 per treatment course for pegfilgrastim to $10,146 per treatment course for pegaspargase. Lower adverse event rates for pegylated drugs (e.g., pegfilgrastim) also produced cost savings in multiple studies conducted in Germany, the UK and the US. 13 of 15 cost-effectiveness studies yielded incremental cost-effectiveness ratios below $50,000 per quality-adjusted life-year, or showed cost savings ranging up to $7743 per treatment course, or were less costly and more effective compared to non-pegylated drugs.

Conclusions: Pegylated drugs frequently reduce resource utilization and costs, including costs associated with drug administration and adverse events. Multiple studies have demonstrated that pegylated drugs are cost-effective versus non-pegylated drugs across various therapies and indications.
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CLINICAL AND SYMPTOM PROFILE IN MULTIPLE SCLEROSIS PATIENTS AFTER AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION (AHSCT)
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High-dose immunosuppressive therapy (HDIT) with AHSCT is a new therapeutic option for MS patients. We aimed to evaluate clinical and symptom profile in MS patients after AHSCT. 52 patients (secondary progressive - 15, primary progressive - 8 and relapsing-remitting - 29) were included in this study. Mean age - 32.4, male/female - 20/32; median EDSS at base-line 3.0. Symptom assessment and neurological examination were performed at baseline, at discharge, at 3, 6, 9, 12 months, and every 6 months thereafter. All the patients have filled out the Comprehensive Symptom Profile in MS Patients (Novik A. et al, 2010). The median follow-up duration was 18 months. Clinical response in terms of EDSS changes at 6 months post-transplant was achieved in all patients. At long-term follow-up 40% of patients improved, 56% stabilized, and 4% worsened. Before transplantation all the patients experienced at least one symptom; 56% of patients had more than 20 symptoms, among them 79% with moderate-to-severe symptoms. After AHSCT, a reduction in the severity in the vast majority of symptoms was observed. At 3 and 6 months post-transplant there was a significant decrease in the severity of 30 and 22 symptoms, respectively (p<0.05). At long-term follow-up 18 symptoms were significantly less severe compared with base-line and the number of patients with moderate-to-severe symptoms was significantly lower (p<0.05). HDIT+AHSCT is an effective MS treatment modality from both the physician’s and patient’s perspective. Comprehensive symptom monitoring along with traditional clinical evaluation is recommended to determine treatment outcomes.

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INDUCTION OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS BY ACTIVE IMMUNIZATION
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Efficacy of different approaches to induce CNS demyelination in animal experiments differs a lot. We compared methods that utilize immunisation with spinal cord homogenate in Freund’s adjuvant supplemented with Mycobacterium tuberculosis (HFA). Wistar rats were treated with HFA plus octreotide (group I, n=10) or HFA alone (group II, n=15). C57Bl/6 mice were treated either with HFA plus octreotide (group III, n=7) or HFA plus Pertussis toxin (group IV, n=7). Neurological symptoms were recorded for 2 months using a 5-degree scale evaluation scheme. In group I, 60% of rats showed neurological symptoms of demyelination (2 animals with paralysis; 4 lost tail tonus) while in group II, 47% of rats were affected (4 rats with limb paralysis; 3 with unsteady gait). After reaching the peak in symptoms, all animals in both groups recovered spontaneously. In group III 100% of mice showed symptoms of experimental autoimmune encephalomyelitis (EAE: 2 mice suffered from paralysis; 5 mice showed symptoms of unsteady gait). In group IV neurological symptoms appeared in 100% of mice (5 mice were paralytic; 2 with unsteady gait). In groups III and IV, all animals showed signs of EAE for more than 40 days. Histological examination of the spinal cord of affected animals showed areas of demyelination, cell infiltrates and axonal damage. Augmentation of immune response with octreotide was found to be less effective than sensitisation with Pertussis toxin. Demyelination induced in C57BL6 mice (group IV) followed by Pertussis toxin administration represents a reliable model of EAE.

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THE EFFECT OF INTERFERON β1A AND INTERFERON β1B LONG-TIME THERAPY ON THE SERUM CONCENTRATION OF THE PROINFLAMMATORY AND ANTI-INFLAMMATORY FACTORS IN PATIENTS WITH MULTIPLE SCLEROSIS
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THE EFFECT OF INF-β1A AND INF-β1B TREATMENT ON iNOS EXPRESSION AND INFLAMMATORY FACTORS IN BRAIN CORTEX OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS
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AN EXACERBATION OF MULTIPLE SCLEROSIS MIMICKING BACTERIAL MENINGITIS
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COGNITIVE IMPAIRMENT IN MULTIPLE SCLEROSIS PATIENTS
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