Multiple sclerosis 1

P 2080

MHC class II transactivator (CIITA)-driven class II expression by astrocytes promotes autopathogenic peptide presentation but not susceptibility to CNS autoimmune disease

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Introduction We examined the role of the MHC class II transactivator (CIITA) in central nervous system (CNS) class II expression and antigen (Ag) presentation by astrocytes and in experimental autoimmune encephalomyelitis (EAE) susceptibility.
Methods CIITA-transfected astrocytes, newly generated transgenic (Tg) mice that utilized the glial fibrillary acidic protein (GFAP) promoter to target astrocyte expression of (CIITA), and CIITA-deficient mice were utilized for this study.
Results CIITA-transfected astrocytes upregulated class II molecules, whereas IFNγ-activated CIITA-deficient astrocytes did not. CIITA-deficient mice were resistant to EAE by immunization with CNS autoantigen. CIITA-deficient APC were capable of presenting peptide to wild-type $CD4^+$ T cells, indicating the presence of CIITA-independent mechanisms for peripheral T cell priming. Adoptive transfer of wild-type CNS autoantigen-specific $CD4^+$ T cells into CIITA-deficient mice did not induce EAE, indicating that CIITA-dependent class II expression was required for CNS antigen presentation. GFAP-CIITA-Tg mice did not develop spontaneous EAE, or more severe EAE than control mice when immunized with encephalitogenic peptide. Whereas IFNγ-activated astrocytes could present peptide or native antigen, CIITA-transfected astrocytes could present peptide only, indicating that CIITA-transfected astrocytes could not process native antigen. IFNγ-activated astrocytes also upregulated cathepsin (Cat) S, whereas unstimulated, CIITA-transfected astrocytes did not.
Conclusion Our results demonstrate that although CIITA-directed class II expression is required for CNS Ag presentation and EAE induction, CIITA-directed class II expression alone in astrocytes is not sufficient for Ag processing and does not support induction of CNS autoimmune disease.

P 2080a

Two genome-wide linkage disequilibrium screens in Scandinavian multiple sclerosis patients reveal association to chromosome regions 1p34, 6p21, 11q23, 12q23 and 19q13

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Aims and methods In order to identify genomic regions containing susceptibility genes for multiple sclerosis (MS) we performed the first two genome-wide screens for linkage disequilibrium in the genetically homogenous Scandinavian population, using pooled DNA and a dense map of 6000 microsatellite markers provided through the GAMES (Genetic Analysis of Multiple sclerosis in EuropeanS) collaboration. In the first screen, 199 cases were compared with 200 controls; in the second, a further 201 cases were compared with a second set of 200 controls. In each screen, allele image profiles (AIPs) generated from cases and controls were compared statistically in order to identify those markers showing the greatest evidence for association.
Results Data were achieved from 4041 markers in the first screen and from 4228 markers in the second screen. Results for both screens were available in the same 3360 markers. Twenty-three markers showed statistically significant differences between case-control AIPs in both screens. When additional AIPs were generated for these 23 markers, statistical significance was retained for five gene regions, at 1p34 (*MYCL1*), 6p21 (*D6S2447*), 11q23 (*D11S1986*), 12q23 (*D12S377*) and 19q13 (*D19S552*).
Conclusion These genome-wide screens for linkage disequilibrium in Scandinavian MS patients identified novel disease associations with four gene regions, at 1p34 (*MYCL1*), 11q23 (*D11S1986*), 12q23 (*D12S377*) and 19q13 (*D19S552*), in addition to confirming the well known association to the HLA class II region (*D6S2447* at 6p21). Several promising MS susceptibility candidate genes are located within these gene regions.

P 2081

Surrogate markers for disability in multiple sclerosis: the relation of brain-specific proteins to spinal cord degeneration in chronic relapsing experimental allergic encephalomyelitis

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Background Chronic relapsing experimental allergic encephalomyelitis (CREAE) results in spinal cord atrophy. Measurment of brain-specific proteins such as the axonal neurofilaments (Nf), the astrocytic glial fibrillary acidic protein (GFAP)/S100B, and microglial ferritin might allow for quantification of the degenerative process.
Methods CREAE was induced in adult Biozzi AB/H mice (6–8 weeks old) and animals were sacrificed 60–80 days post disease induction (CREAE n=9, control n=6). The spinal cords were homogenised and analysed for Nf, GFAP, S100B, ferritin and total protein using in-house assays. Statistical analysis was performed using Spearman's correlation coefficient and Fischer's exact test.
Results There was marked gliosis and axonal loss in the spinal cord of CREAE animals. The levels of GFAP were 3-fold increased in CREAE (median: 12.5 ug/mg protein, range: 5.0–26.4 ug/mg protein) when compared to controls (4.0 ug/mg protein, 1.4–4.5 ug/mg protein, $p<0.001$). The levels of Nf were about 2-fold decreased in CREAE (27 ug/mg protein, 9–84 ug/mg protein) when compared to controls (61 ug/mg protein, 53–79 ug/mg protein, $p<0.05$). No statistical significant difference was found for levels of S100B and ferritin. However there was a correlation between S100B and Nf ($R=0.88$, $p<0.01$) and between ferritin and Nf ($R=0.99$, $p<0.001$). No such correlation was found with GFAP.
Conclusion Levels of spinal cord neurofilament and GFAP are surrogate markers for axonal degeneration and gliosis, respectively. Because these pathological processes result in clinical disability, these proteins have the potential to be used as secondary outcome measures in neuroprotective treatment studies.

P 2082

Multiple sclerosis: immunological effects of mitoxantrone in vitro reveal antigen-presenting cells as major targets

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Mitoxantrone is an anti-neoplastic anthracenedione derivative successfully used as an immunosuppressive agent in severe forms of multiple sclerosis (MS). Additional immunomodulatory effects have been suggested. In this study, we analysed the immunological effects of mitoxantrone in vitro.
Peripheral blood lymphocytes (PBL) from untreated or interferon-beta-treated MS patients or from healthy donors were stimulated in the presence or absence of mitoxantrone. B cells were isolated from PBL using monoclonal antibody-coated paramagnetic beads. Monocytes were enriched from PBL using their adhesion properties. Dendritic cells were cultured from monocytes. T-cell lines (TCL) reactive against tetanus toxoid (TT) were stimulated with TT on antigen-presenting cells. We analysed proliferation, cytokine production by intracellular immunofluorescence, and surface expression of activation markers, adhesion molecules and chemokine receptors. The mechanisms of cell death were analysed using annexin-V and DNA degradation detection systems.
Irrespective of the source of the PBL, mitoxantrone inhibited proliferation of activated PBL, B cells or TT-reactive TCL in a dose-dependent manner. In T and B-lymphocytes, surface expression of activation markers and cytokine production was not influenced substantially by mitoxantrone. In contrast, in monocytes and dendritic cells, mitoxantrone interfered with the antigen-presenting capabilities. Furthermore, Mitoxantrone induced apoptosis of B cells, monocytes and dendritic cells at low concentrations, whereas higher doses caused cell lysis.
We conclude that the beneficial effects of mitoxantrone in MS result (i) from its immunosuppressive potential based on non-specific cytotoxic effects on lymphocytes, (ii) from predominantly targeting monocytes and dendritic cells as major sources of antigen-presenting cells by inducing programmed cell death.

P 2083

Long-term expression patterns of cell surface bound and soluble adhesion molecules during interferon-ß1b treatment in multiple sclerosis patients

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Introduction Adhesion molecules (AM) have been suggested to regulate the transmigration of leukocytes across the blood-brain-barrier (BBB), which is an essential step in the pathogenesis of multiple sclerosis (MS). In former studies, only the changes of the soluble forms of the adhesion molecules ICAM-1 and VCAM-1 have been serially investigated under treatment with interferon-ß1b (IFN-ß1b) in MS patients.
Methods 68 patients with relapsing-remitting MS were enrolled in this open study. 30 patients were treated with IFN-ß1b, whereas 38 patients decided for themselves against immunomodulatory treatment. Blood was taken and detailed clinical examination was performed every three months, whereas brain MRI was assessed every six months for an observation period of 18 months. The expression levels of cICAM-1 and cICAM-3 on peripheral blood MNC were measured by two colors flow cytometry analysis. ELISA determined the soluble forms of VCAM-1, ICAM-1 and ICAM-3.
Results We found a short-term induction effect on the serum concentration levels of sICAM-1 and sVCAM-1 after three months of IFN-ß1b treatment in MS patients. However, the expression levels of cell surface bound AM on blood MNC remained stable at the levels before treatment in the treated patients, whereas the untreated MS patients showed a continuously decreasing course in the expression of cell surface bound AM expression over 18 months.
Conclusion It can be speculated, that the stabilization of the BBB is one of the beneficial effects of IFN-ß1b therapy in MS patients.

P 2084

Biochemical changes and cognitive function: Exploring sensitive markers in early stages of multiple sclerosis

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Aim of this study was to investigate cognitive function in relation to biochemical changes in corresponding brain areas of MS patients.
Methods 21 patients with relapsing-remitting MS, all within three year of disease duration and 21 age, sex and education matched controls were investigated. A psychometric assessment consisting of Wechsler Memory Scale (WMS) and the Multiple Sclerosis Functional Composite Score (MSFC) as well as a proton magnetic resonance spectroscopy (^{1}H-MRS) examination of frontal white matter and the frontal part of cingulate gyrus (Area 32) were performed.
Results A significant reduction of the N-acetyl-aspartate (NAA)/Creatine (Cr) ratio in the frontal cingulate gyrus of MS patients was detected in comparison to controls. A significant drop of NAA/Cr ratio also was found in volumes positioned in cerebral white matter of MS patients including normal appearing white matter (NAWM) and plaques. No NAA-changes were found in NAWM. With regard to psychometric results, the WMS general memory score showed significant statistical differences between patients and controls, whereas differences in MSFC results did not reach statistical significance. Regression analysis showed gray matter NAA/Cr ratio of the frontal cingulate gyrus as a significant predictor of distinct memory functions.
Conclusions We conclude that ^{1}H-MRS of gray matter in early stages of relapsing-remitting MS could be more sensitive in detecting early metabolic disturbances than ^{1}H-MRS of white matter, particularly in subjects without or with minor clinical impairment and in the absence of plaques in routine MRI.

P 2085

Comparative study of different brain MTR parameters for the study of multiple sclerosis

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Parameters from magnetic transfer ratio (MTR) have been used to assess multiple sclerosis (MS) disease burdens, predict patients' clinical disability, and study different stages of lesion pathology and pathological evolution in MS patients. This study aims to quantify, in a systematic manner, the behaviours of these different MTR parameters in the context of MS study.
Eight parameters have been calculated. All the MTR parameters consistently showed a smaller value in the MS patients group than in the normal controls group. However, only global MTR, mean MTR, MTR25 and AMTR2/3 presented a significant difference between the MS patients and normal controls groups, with more or less important relative differences. In particular, the parameter AMTR2/3 presented the greatest discriminating ability. When applying the MTR parameters to the two normal controls groups from two different imagers, all the parameters exhibited different values in these two groups cases. But, the variation of the parameter AMTR2/3 was about 5%, and it was not significant; the variation of other MTR parameters was significant, and always more than 20%. In terms of mean, standard deviation and standard deviation to mean ratio, the parameter peak height presented the greatest variability. The other parameters had relatively close variability's. So, the parameter AMTR2/3 was less sensitive to change of imagers than the other MTR parameters while keeping a good ability of discriminating the MS patients and normal controls groups. In conclusion, the MTR histogram parameter AMTR2/3 offers the best compromise between increasing the discriminating ability and reducing variability.

P 2086

A structural, metabolic and functional MRI study in patients at presentation with clinically isolated syndromes suggestive of MS

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Recent MRI and pathologic studies have demonstrated the presence of axonal loss and dysfunction even in the early stages of multiple sclerosis (MS). In this study, we used functional

magnetic resonance imaging (fMRI) to assess the brain pattern of movement-associated cortical activations in patients at presentation with clinically isolated syndromes (CIS) suggestive of MS. To obtain additional information about the role and pathological basis of cortical plasticity in these patients, we also obtained conventional and diffusion tensor (DT) MRI scans of the brain as well as we measured N-acetylaspartate (NAA) concentration of the whole brain and correlated these measures with the extent of brain activations.
From 16 right-handed patients at presentation with CIS and 15 controls, we obtained: a) fMRI (repetitive flexion-extension of the last four fingers of the right hand), b) dual-echo scans, c) pulsed-gradient spin-echo echo-planar sequence to calculate DT-MRI maps, d) 1H-MR spectroscopy sequence to assess whole brain NAA levels.
Compared to controls, patients with CIS had significantly different DT-MRI metrics of the normal-appearing brain tissue and a decreased NAA levels. They also had more significant activation of the contralateral primary somatomotor cortex (SMC), secondary somatosensory cortex, inferior frontal gyrus and cerebellar hemisphere. Relative activation of the contra lateral primary SMC was correlated with T2 lesion volume and whole brain NAA levels.
This study demonstrates that functional cortical changes can be detected in patients at presentation with CIS. These changes might have a favourable role in limiting the impact of sub cortical white matter damage on subsequent disease evolution.

P 2087

Changes of peripheral blood immune phenotypes including interleukin-expressing cells in multiple sclerosis patients, during two-year IFN-b-1a therapy. A flow cytometry analysis.

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Introduction "Peripheral hypothesis" of multiple sclerosis (MS) attributes its origin to an immune-mediated process based on peripheral reactivation of myelin-specific T cells. IFN-beta-1a treatment has shown to be a beneficial in MS but the primary mechanism responsible for its therapeutic influence remains unclear. Possible IFN-beta-1a action might be due to a regulatory effect on the immune system.
Method We have studied 20 outpatients with a relapsing-remitting form of MS treated with IFN-beta-1a for 24 months. Using two-colour flow cytometry we have determined the following immunologic cells phenotypes: CD3+CD19–, CD3–CD19+, CD3+CD8+, CD3+CD4+, CD3–CD16+56+, CD3+CD25+, CD19+CD25+, CD14+CD25+, CD14+CD86+, CD19+CD80+ before treatment, after 6, 9, 12 and 24 months of therapy. Cells producing cytokines: CD3+IL-10, CD14+IL-10, CD3+IL-4, CD3+IFN-gamma, CD14+IL-12 were measured before IFN-beta-1a administration, after 12 and 24 months of treatment.
Results In MS patients an increased percentage of CD3+ CD25+ and CD14+CD86+ cells were noticed after 6, 9 and 12 months of therapy. Among cytokines producing cells, we observed an increased fraction of CD3+IL-4, which persisted to a lower extent (over 24 month-treatment.) In turn, an increased percentage of CD14+IL-10 cells observed after 12 month, decreased after 24 months of IFN-beta-1a administration.
Conclusions The beneficial effect of IFN-beta-1a was well seen during the whole study but was most evident after the first year of treatment.
Activated T cells may represent Th2 subpopulation, which release anti-inflammatory cytokines (e.g. IL-4). They act as antagonists to Th1 pro-inflammatory cytokines, possibly leading to limitation of the myelin sheet damage which results from inflammation ongoing in the brain.

P 2088

Molecular determination of human herpes virus 6 (hhv-6) in serum and CSF of patients with multiple sclerosis (MS)

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Background Different studies found high prevalence of human herpes virus type 6 (HHV-6)-specific IgM antibodies or HHV-6 DNA in serum of patients with multiple sclerosis (MS). No control groups were included in these studies.
Aim of the study Prevalence of HHV-6 DNA in serum and cerebro-spinal fluid (CSF) of both MS-patients and control subjects.
Patients and methods Serum and CSF were obtained from 52 patients with MS and in 52 control subjects with no evidence of neurological disease. HHV-6 DNA was analysed by nested-PCR, amplified region ORF-U31.
Results All CSF and serum samples from controls were negative for HHV-6 DNA. HHV-6 DNA was detected in 9/52 (17%) serum samples and in 22/52 (43%) CSF samples from MS patients.
Conclusion These data support a potential pathogenetic role of HHV-6 in MS.

P 2089

Long-term survey of cytokine production in secondary progressive multiple sclerosis

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Introduction Previous studies found a different cytokine profile in secondary progressive multiple sclerosis (SPMS) in comparison to healthy controls indicating an abnormal T-helper (Th) cell function in SPMS. Most studies are carried out as cross-sectional analyses. Hence, little is known about the evolution of cytokine production in SPMS. Here we report a follow-up of cytokine production in SPMS.
Methods In 34 patients with definite multiple sclerosis (MS) according to the Poser criteria and secondary progressive course of the disease the EDSS was measured before start of treatment and every three months during the 12 months observation period. Additionally, the production of IFG, TNF and IL10 in peripheral blood lymphocytes was measured at study entry and after 12 months of follow-up by flowcytometry.
Results Consistent with previous findings the pro-inflammatory cytokines IFG and TNF were significantly elevated in SPMS compared to healthy controls ($p=0.001$ respectively $p<0.001$, Mann-Whitney-test). Interestingly, IL10 failed to show any differences between both groups. Concurrent with the usual course of SPMS, the EDSS increased significantly from 5.1 to 5.5 within 12 months ($p=0.023$, Wilcoxon test). Additionally, the production of the two pro-inflammatory cytokines IFG ($p=0.039$) and TNF ($p=0.01$) increased significantly

during the follow-up. In contrast, the production of IL10 did not change significantly during the observation period.
Conclusion Confirming previous results, SPMS is accompanied with enhanced production of pro-inflammatory cytokines in comparison to healthy controls. Furthermore, enhanced pro-inflammatory cytokines tend to increase over time as does the disability measure EDSS.

P 2090

Clinical and laboratory data in 7 cases of acute disseminated encephalomyelitis

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Introduction Acute disseminated encephalomyelitis (ADEM) is reported to be rare in adults and raises diagnostic problems with Multiple Sclerosis and primary infections of the CNS.
Clinical data We report a series of 7 patients (6 males, 1 female, age 17–60) presenting acute neurological disorder within three weeks after an upper respiratory infection (N=4), a flu-like syndrome (N=2), and a gastro-enteritis (N=1). Neurological signs and symptoms were due to transverse myelitis (N=2), cerebellitis (N=2), rhombencephalitis (N=1) and encephalitis (N=2). Seizures and bilateral frontal lobes involvement in the first one, aphasia and coma in the second one characterized the two latter cases. Four patients were treated by high dose of intravenous methylprednisolone. Recovery was complete in three cases and partial in four, but most daily activities were possible. Laboratory and MRI date: CSF was normal in only one case; pleocytosis was detectable in 4 cases and CSF-restricted oligoclonal IgG bands were always absent. EEG was performed in 4 cases and was abnormal in 3. Brain and/or spinal cord MRI was normal in 3 cases and showed lesions corresponding to neurological signs in 4. The infectious causal agent was determined in 5 cases (Parvovirus B19, Epstein Barr virus, Cytomegalovirus, Chlamydia pneumoniae and Mycoplasma pneumoniae).
Conclusion We stress the monophasic course of ADEM, the absence of oligoclonal IgG bands in the CSF, the absence of MRI lesions in three cases and the overall good outcome of these patients.

P 2091

TNF-alpha up regulates chemokines and chemokine receptors in the central nervous system.

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Recent data suggest that the key players in the mechanism of inflammatory cell accumulation in the central nervous system (CNS) during multiple sclerosis (MS) are chemoattractant cytokines – chemokines. The mechanism leading to upregulation of chemokine system in the CNS is still under investigation. Our main goal is to identify factors upregulating chemokines and chemokine receptors in the inflamed CNS. Potential candidates for this role are proinflammatory cytokines, especially tumour necrosis factor -alpha (TNF-alpha).
Methods In this study chemokine and chemokine receptor expression was analysed *in vivo* in mouse brain after stereotaxic injection of TNF-alpha as well as *in vitro* in astrocytic culture stimulated with TNF-alpha. Gene expression was quantitated with RNase Protection Assay (RPA).
Results We detected increased expression of chemokines RANTES, monocyte inflammatory protein-1alpha (MIP-1alpha), MIP-1beta and MIP-2 as well as chemokine receptors CCR1, CCR2 and CCR5 in the brain shortly after intracerebral, stereotaxic injection of TNF-alpha. Cultured astrocytes stimulated *in vivo* with TNF-alpha expressed chemokines RANTES, MIP-1alpha, monocyte chemoattractant protein -1 (MCP-1), gamma-interferon-inducible protein-10 (IP-10) and chemokine receptors CCR1 and CCR5.
Conclusions Our results confirm that proinflammatory cytokine TNF-alpha may upregulate chemokines and chemokine receptors in the brain and may contribute to development of neuroinflammatory disorders like MS.

P 2092

Intrathecal IgG synthesis: indicator of progression in multiple sclerosis patients

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Objectives We studied the power of IgG synthesis value as an indicator of disease activity in multiple sclerosis (MS).
Material and methods Link index (LI) and modifiable Schüller formula (MSF) was used in 100 MS patients. Time between first, second and third attack and progression index (PI) were compared in patient with normal, high and very high Link index and value of intrathecal IgG calculated with modifiable Schiller formula.
Results Secondary progressive (SP) patients had a higher LI and MSF than relapsing-remitting (RR) and primary progressive (PP) courses (1.07 plus minus 0.5 for SP vs. 0.78 plus minus 0.5 for RR and 0.79 plus minus 0.5 for PP, P=0.01 and 0.03, respectively). Having a high index and high level of IgG with MSF in MS RR and SP patients has no time effect in the development of the second and third attack. PI was higher in patients with very high LI and with high level of IgG with MSF vs. patients with normal LI and normal level of IgG with MSF and high LI and high level of intrathecal IgG synthesis.
Conclusions This study confirmed that LI and formulas for determination of intrathecal IgG synthesis is a good marker of subsequent progression of MS.

P 2093

Electrophysiological assessment of cognitive disturbances in patients with multiple sclerosis (study by P300)

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Electrophysiological tests (P300 cognitive potentials) as related to MRI and neuropsychological tests results are rarely studied in MS patients with cognitive dysfunction. Twenty-four patients with clinically defined MS in remission, 18 females and 6 males were examined with neuropsychological and paraclinical tests. The aim of the study was to evaluate the P300 results in MS patients and their relation to the neuropsychological tests and MRI results. The neuropsychological assessment consisted on MMSE examination as a screening test for dementia, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Test (IQ) for verbal intelligence and Wisconsin Card Test for abstract reasoning testing. MS patients were frequently impaired on measures of concentration, sustained attention and immediate memory. P300

cognitive potentials (delay in latency or absence of response) correlated with the degree of MRI abnormalities – brain atrophy on MRI was more frequently found ($p<0.05$) in patients with lower values of IQ. According to our results P300 cognitive potentials abnormalities correlated with cognitive dysfunction and the degree of brain atrophy.

P 2094

Intrathecal IgM synthesis as prognostic factor in multiple sclerosis (MS)

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Introduction We have recently reported that intrathecal IgM synthesis (ITMS) correlates with higher EDSS in MS. In the same study we found that ITMS is more frequent in patients with secondary progressive MS that in those with a relapsing-remitting course. The significance of intrathecal IgM in patients that are in the initial stages of the disease remains uncertain.
Methods We studied 22 laboratory supported MS (LSMS) patients. 21 patients showed a relapsing-remitting (RR) course and one a primary progressive (PP) form. The patients were followed for a variable period of time ranging from 6 to 36 months (mean=18.00±2.83 months). OGC IgM bands were performed by IEF. Samples were diluted in saline to avoid IgM precipitation and incubated with 50 mM DTT at pH 9.5 to reduce IgM. IEF was performed at pH 5–8 and an anti-human IgM labelled with alkaline phosphatase was used in the immunodetection.
Results The probability of remaining without a second relapse was 10% after eight months of follow up for patients with ITMS, and 48.8% after 36 months for patients without ITMS ($p=0.0001$). Patients with ITMS suffered more relapses (2.00±0.50) than those without ITMS (0.58±0.26) ($p=0.022$). At the end of the follow up period, differences were found between EDSS of patients with ITMS (1.70±0.23) and patients without ITMS (0.79±0.22) ($p=0.02$).
Conclusion These data seem to indicate that ITMS is a prognostic factor in the initial stages of MS.

P 2095

Correlations of clinical and immunological data with magnetic resonance imaging (MRI) parameters in patients with multiple sclerosis (MS)

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Introduction MS is an inflammatory, demyelinating and neurodegenerative disease of central nervous system. At the present time the relationship between MRI data, clinical and immune status of MS patients is not clear.
Objective To compare clinical, immunological and MRI parameters in MS patients.
Patients and methods 12 patients with relapsing-remitting and 6 with secondary progressive MS aged 19 to 53 were observed. All patients were in a remissions phase. The duration of the disease was 2–14 years. Patients were assessed using the Kurtzke expanded disability status scale (EDSS) score as well as immunological and MRI examination. Immunological monitoring included the measurement concentration levels of IFN-g and lymphocyte sensitisation to myelin basic protein (MBP) in peripheral blood. 20 healthy volunteers were served as a control group. T2-weighted MRI measured the number and volume of the lesions.
Results Number of lesions correlated with duration of the disease. There are no correlations between lesions volume and EDSS. However, lesions volume correlated positively with the number of exacerbation, concentration levels of IFN-g and lymphocyte sensitisation to MBP.
Conclusion We have demonstrated that degree of inflammatory immunological activities correlated with development of destructive lesions in the brain in MS patients. Our results suggest, that neuro-immunological interactions may play an important role in pathogenesis of disease.

P 2096

MR spectroscopy in Balo's concentric sclerosis

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Introduction Balo's concentric sclerosis (BCS) is one of the rare variants of multiple sclerosis (MS) characterized pathologically by concentric lesions composed of rings of alternating demyelination and relatively spared myelin. BCS which was diagnosed usually post mortem now can be recognized by its characteristic magnetic resonance imaging (MRI) picture consist of irregular, concentric rings of increased signal on T2-weigted and contrast-enhanced on T1-weigted MRI images.
Methods Conventional brain MRI (1.5 T Siemens Magnetom Vision Plus) and MR spectroscopy (H-MRS) was performed in a case of BCS. Spectra were obtained by using stimulated echo acquisition mode (STEAM) [TR=6000 TE=20, 64 average].
Results Two typical concentric ring lesions and also few MS-like lesions were detected on conventional brain MRI. Results of H-MRS obtained from concentric lesion showed the reduction of NAA/Cr and NAA/Chol ratios and increase of Chol/Cr ratio compare to normal white matter with no wide lipid peak located at 0.9–1.5 ppm. There were no differences of metabolites ratios between normal white matter in patient and control group.
Conclusions H-MRS gives additional arguments that BCS is a variant of MS and can be diagnosed ante mortem using MRI techniques.

P 2097

Cellular immunity in patients with multiple sclerosis

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Introduction There are two types of multiple sclerosis (MS) courses remitting and progressing ones. The object of the study was to investigate cellular immunity typical for both MS types.
Methods A total of 28 MS patients were observed, 13 progressing type (PT), 15 remitting type (RT), 10 remissions, and 5 exacerbations. Lymphocyte CD+ subpopulations were studied using immunophenotyping method as well as their phagocytic function and natural toxicity (as compared with healthy donors).

Results In 2/3 of RT patients, CD3+ and CD8+ values decreased 1.5–2 times along with CD4/CD8 index increase by 10–30%; the values of CD25+, CD69+, and CD95+ increased 1.5, 2, and 3–5 times, correspondingly. In 11 of 13 PT patients, the values of CD3+, CD4+ and CD8+ decreased 1.5–2 times. The values of CD16+, CD20+, CD25+ and CD95+ didn't significantly differ from the control. None of the patients had any difference in CD5+, CD7+ and CD22+ values. CD95+ rise in RT patients correlate with amounts of CD16+, CD56+, CD19+, CD20+ and CD25+, bearing Fas (CD95)-ligand on their surface. Such a correlation wasn't noted in PT patients with decreased CD95+ value. The levels of CD16+ and CD56+ increased 8–12 times that correlated with natural cytotoxicity growth by 25–60%.
Conclusion Increased CD95+ level in the RT patients apparently reflects an activation of apoptosis having a defending function of both eliminating autoreactive T-killers and limiting the process of demyelination. Decrease of the general level of T-cells, T-helpers and T-killers/suppressors is characteristic for RT-type of MS.

P 2098

Cerebrospinal fluid and serum interleukin-6 and its receptors levels in relapsing-remitting multiple sclerosis patients

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Introduction Inteleukin-6 (IL-6) has recently been implicated in the pathogenesis of multiple sclerosis (MS), as it was found localized in MS lesions. The functional receptor for IL-6 is a complex of signal transducing subunit glycoprotein 130 (sgp130) and the ligand binding subunit gp80 (sIL-6R). They interact to mediate intracellular signalling.
The aim of this study was to measure IL-6 and its soluble receptors (sIL-6R and sgp130) in the cerebrospinal fluid (CSF) and serum from relapsing-remitting MS patients (RRMS).
Patients and methods We analysed CSF and serum samples of 21 RRMS patients during acute exacerbation of the disease, and 19 patients with noninflammatory neurological diseases (NIND), as controls. IL-6, sIL-6R and sgp130 levels were measured using enzymeimmuno test (ELISA). One-way ANOVA was applied for statistical analysis of the data.
Results Our preliminary results (mean±S.D. in pg/mL) showed statistically different serum IL-6 level in RRMS (27.79±61.33) and NIND (106.04±125.93) patients. However, there was no statistical difference between CSF IL-6 level in RRMS (2.90±2.68) and NIND (2.97±2.59) patients. Serum sIL-6R level was not statistically different between RRMS (25 795.55±8511.27) and NIND (21840.12±6379.43) patients, but CSF level were statistically different between RRMS (630.26±522.19) and NIND (159.84±273.41) group. Serum sgp130 levels were statistically different in RRMS (333750±88070) and NIND (415590±124160) patients. The CSF sgp130 level between RRMS (46710±26280) and NIND (54250±22560) group was not statistically different.
Conclusion Our preliminary results suggest that IL-6 and its soluble receptors (sIL-6R and sgp130) regulation may be altered in RRMS during acute exacerbation of the disease.

P 2099

Relapsing optic neuritis: neurosyphilis, multiple sclerosis or both

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Introduction Optic neuritis (ON) may be idiopathic or secondary too much different aetiology, the most common of which is multiple sclerosis (MS). Neurosyphilis can also cause ON due to vasculitic demyelination. Both disorders may have similar aspects in brain imaging and CSF studies play an important role in the differential diagnosis, although oligoclonal bands may be present both in MS and neurosyphilis. We present a case of bilateral relapsing-remitting ON in which the aetiology remains controversial.
Case report A Female, 44 years old; in 1999, she had several episodes of blurred vision in the right eye with progressive decrease in visual acuity. One year later, she had a transient episode of visual deficit on the left eye. Brain MRI (01/2001): several white matter lesions suggestive of inflammatory/demyelinating disorder. In June 2001 there was worsening of the visual acuity on the left, which improved only slightly with corticosteroids. Neurological examination: bilateral papilitis; low visual acuity; no other deficits. Positive VDRL, reactive TPHA; CSF: 124 cells, 70% lymphocytes; proteins: 0.6 g/dl; normal glucose; positive VDRL, reactive TPHA; oligoclonal bands positive in CSF, absent in serum. She was treated with penicillin, with slight improvement of the visual acuity. Brain spectroscopic MRI (three months later): demyelinating lesions highly suggestive of MS. She will repeat CSF studies.
Conclusions Although CSF tests are in favour of neurosyphilis, imaging tests still raise some doubt about the definitive diagnosis. This case exemplifies the difficulties in making the differential diagnosis between MS and MS-like conditions such as neurosyphilis, in monosymptomatic ON.

P 2100

Quantitation of the specific and polyspecific intrathecal immune response in herpes simplex encephalitis, subacute sclerosing panencephalitis and multiple sclerosis

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Introduction In acute diseases intrathecally synthesized antibodies against the causal antigen and in multiple sclerosis (MS) an intrathecal synthesis of measles, rubella and varicella-zoster virus (VZV) antibodies, the MRZ-antibody-reaction, as a part of the oligoclonal polyspecific immune response, can be measured.
Methods We measured the concentration of herpes simplex virus (HSV) antibodies in HSV encephalitis (n=4), measles antibodies in subacute sclerosing panencephalitis (SSPE) (n=5), of the MRZ-antibody-reaction in MS (n=65) and of measles, rubella, VZV and HSV antibodies in controls (n=25; except HSV antibodies, n=7) with an ELISA in cerebrospinal fluid and serum.
Results The concentration of intrathecally synthesized measles antibodies in SSPE is around 300-fold higher (median: 27.2 mg/l, range: 19.5–42.4 mg/l) than in MS-patients, who synthesize these antibodies intrathecally (median: 0.09 mg/l, range: 0.002–2.1 mg/l). The fraction of intrathecally synthesized virus specific antibodies as part of the total intrathecally synthesized IgG is 18.8% (range 11.8–27.5%) in SSPE (measles antibodies)

and 8.8% (range: 3.5–12.5%) in HSV encephalitis (HSV antibodies). These results show that there is also a large polyspecific immune response in acute diseases.
The fraction of measles, rubella and VZV antibodies in MS is 0.52%, 0.53% and 0.23% (for all three median of 1.4%, maximum 7%).
Conclusion In conclusion, the concentration of intrathecally synthesized antibodies against the causal antigen has higher amounts (titers) and leads to a higher fraction of intrathecally synthesized specific antibodies than the polyspecific immune response in multiple sclerosis, but seems just to be a small part of the total intrathecal immune response.

P 2101

Cerebrospinal fluid/serum nitrite and nitrate ratio correlates with blood brain barrier disruption in relapsing-remitting multiple sclerosis patients

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Introduction An increase of interest has been witnessed in the role that nitric oxide plays in inflammation, demyelination and axonal injury, and also in the role that nitric oxide plays in multiple sclerosis (MS).
Methods We compared levels of cerebrospinal fluid (CSF) and serum nitric oxide metabolites in 63 patients with relapsing-remitting MS to those in 15 patients with other inflammatory neurological diseases (OINDs) and those in 10 patients with non-inflammatory neurological diseases (NINDs). Nitric oxide metabolites (nitrites and nitrates) were measured by the nitrate reductase and Griess reaction methods.
Results The MS patients were found to have significantly higher CSF and serum nitrite and nitrate levels compared with OIND and NIND patients (mean±SD; CSF=10.04±1.68 μM vs. 9.56±1.33 μM vs. 8.7±1.57 μM, $p<0.001$, and serum= 57.86±7.17 μM vs. 52.05±3.11 μM vs. 45.51±6.06 μM, $p<0.001$, respectively). The CSF/serum nitrate and nitrite ratio was significantly elevated in MS patients ($p<0.01$). The CSF/serum nitrate and nitrite ratio correlates with blood brain barrier disruption ($p=0.002$) and has a trend to correlate with clinical activity of MS ($p=0.057$).
Conclusion These results support the evidence that nitric oxide has been implicated in inflammatory processes and suggest that nitric oxide might be potential mediator of blood brain barrier break down in inflammatory disease of the central nervous system, such as MS.

P 2102

Activated protein C resistance in multiple sclerosis

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Introduction Prothrombotic states may be heritable, acquired or mixed. Although factor V Leiden is the most common cause of inherited activated protein C (APC) resistance, other changes in haemostasis cause acquired APC resistance, e.g. increased plasma levels of factor VIII or the presence of antiphospholipid antibodies. Prevalence of inherited APC resistance is reported to be between 2 and 15%. There is no report concerning acquired APC resistance in MS patients.
Methods 65 patients (14 men) with definite relapsing-remitting MS (RRMS), without a history of thromboembolism in their families, were examined for a prothrombotic state. Serum samples were investigated for APC resistance, antithrombin III, protein C and S.
Results We found a prevalence of 9.23% (n=6) of pathologic APC resistance, whereas 11 patients were at the lowest normal limit. One female patient experienced deep vein thrombosis. Anticoagulation was initiated.
Conclusion Although there are no prevalence data for acquired pathologic APC resistance, the prevalence in our group of patients seems to be surprisingly high. This preliminary study should be the trigger for further investigations on APC resistance in MS patients.

P 2103

Humoral immunity in patients with multiple sclerosis

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P 2104

Relations between the membrane-mediated lipid and immune disturbances in multiple sclerosis

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Carnitine is a cellular component exerting a key-role in the energy metabolism control.
Aim of this study was to determine the efficacy of acetyl L-carnitine in MS patients complaining fatigue when compared with amantadine, a drug commonly used to treat fatigue in MS. Thirty-six MS patients with fatigue (21 relapsing-remitting, 15 secondary-progressive) were enrolled into a crossover double-blind treatment program with acetyl L-carnitine (2 gr/die) and amantadine (200 mg/die). Each drug was given for 3 months, with a 3-month washout period. Alternate patients were assigned to be treated with acetyl L-carnitine or amantadine first. All patients were assessed before and after each 3 month-treatment program by using fatigue severity scale (FSS), fatigue impact scale, Beck depression inventory, social experience checklist, and Coop Wonca tables. Changes respects to previous measurements were calculated. Five patients on amantadine and one on acetyl L-carnitine discontinued the treatment due to side effects. In those patients who completed the treatment program, there was a significant improvement in FSS score during the acetyl L-carnitine administration when compared to amantadine intake ($p=0.039$). No significant difference was found in the other clinical scales. Acetyl L-carnitine is better tolerated than amantadine and it results more effective in treating MS-related fatigue. As in chronic fatigue syndrome (CFS), an abnormal carnitine metabolism may be involved in the altered peripheral exercise response observed in MS patients complaining fatigue.

Multiple sclerosis 2

P 3198

Enhancement of motor rehabilitation in multiple sclerosis (MS) patients after Dopamine treatment

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Background It is well established that the metabolism of dopamine in the brain enhances the motor recovery. Besides, no side effects were observed, in mini doses of administration. Because of that, for the period of 3 months we tried the action and the effectiveness of dopamine in patients with MS.
Methods and material We studied the action of levodopa-carbidopa providing with 100mg/d for 3 months vs. placebo 120 patients with definite MS according to MacAlpine criteria. The patients were evaluated according to Kurtzke EDSS and MRI at the beginning and at the end of the treatment. We compared the results of two groups.
Results The group of patients who received dopamine appeared a net improvement of the motor recovery contrary to those who did not receive it.
Conclusion The experience of this study shows a remarkable action of dopamine in the improvement of the motor functions due to MS. This leads to the fact that dopamine, taking into account that it has no side effects, can be administrated as additional medical treatment in MS.

P 3199

Acetyl L-carnitine treatment of fatigue in multiple sclerosis

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Fatigue is a common and disabling symptom of multiple sclerosis (MS). The cause of fatigue is partially known; both peripheral and central mechanisms have been hypothesized.

P 3200

IVIg-treatment of experimental autoimmune encephalomyelitis

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Objective Clinical trials have shown that intravenous administration of immunoglobulin (IVIg) has the potential to reduce disease activity in multiple sclerosis (MS). However, the mechanisms by which IVIg interferes with the pathophysiology of MS are not yet fully understood. In the present study, we evaluated IVIg treatment of experimental autoimmune encephalomyelitis (EAE). The objectives of the study were to assess the effects of IVIg on the incidence and severity of active EAE and the EAE pathology in the CNS.
Methods EAE was induced in rats by immunization with spinal cord homogenate. After immunization, animals were treated with infusions of IVIg (1 g/kg) or placebo (10% maltose). The animals were weighed and observed daily, and the clinical disease severity graded on a scale 0–6. At the end of the experiment the animals were sacrificed and the brain and spinal cord dissected and cut for histological examinations.
Results and conclusion Treatment with IVIg significantly suppressed the development of EAE as measured by incidence (placebo 92%, IVIg 50%), day of onset, weight loss and maximal average EAE score (placebo 2.6, IVIg 0.7). In the placebo group, the development of active disease was associated with severe inflammation and demyelination in the CNS. When animals were treated with IVIg, these pathological changes were significantly reduced as measured by the average histological score (placebo 8.8, IVIg 5.3). In conclusion, IVIg treatment of EAE did not simply ameliorate the clinical symptoms of experimental autoimmune disease but had a protective effect against the pathological changes in the CNS.

P 3201

Potential mechanism of action (MOA) of Natalizumab (Antegren™) for multiple sclerosis and other chronic inflammatory diseases

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Introduction Inflammatory foci and demyelination within the central nervous system (CNS) are the hallmark presentation of multiple sclerosis (MS). Integral to this process, leukocyte migration, activation and survival are modulated by the α4 integrins. α4β1 integrin, expressed by circulating leukocytes, mediates their adhesion to VCAM-1, a ligand expressed by vascular endothelial cells at chronic sites of inflammation. Transendothelial migration of leukocytes allows α4 integrin interaction with additional inflammation-associated ligands supporting leukocyte activation. Thus, α4 integrin is an attractive target for treatment of inflammatory diseases; its antagonists represent a new class of agents called selective adhesion molecule (SAM) inhibitors. Natalizumab, a humanized monoclonal antibody against a4 integrin is the first of this class.
Methods In vitro and in vivo studies with natalizumab and its murine antibody precursor (mNat).
Results mNat inhibited human lymphocytes adhesion to VCAM-1 with half maximal inhibition at a concentration of 0.3μg/mL (2nM); complete inhibition at 1μg/mL. Consistent with the known expression pattern of α4 integrin, cytometric analysis documented mNat binding to human lymphocytes and monocytes, and weakly labelled human neutrophils. The affinity of natalizumab and mNat was comparable for guinea pig, primate, and human lymphocytes, with half maximal binding at 0.2μg/mL (K_d=1.3nM). Studies in a guinea pig model of experimental allergic encephalomyelitis demonstrated dose-dependent reversal of disease, including reversal of CNS leukocyte infiltration, hind limb paralysis, cerebral oedema, and blood-brain barrier disruption (measured by MRI).
Conclusion Natalizumab inhibits and reverses inflammation, offering a potential new approach in the treatment of MS and other immune diseases.

P 3202

Differential antigen-specific prevention of experimental autoimmune encephalomyelitis, with naked DNA.

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Introduction Vaccination with naked DNA, by activation of cell-mediated and humoral immune responses, can generate protective immunity against autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE). We have evaluated the effect of DNA vaccination with plasmids encoding different myelin proteins.
Methods Plasmid vectors, containing proteolipid protein (pvaxPLP) and myelin oligodendrocyte glycoprotein (pvaxMOG) genes, were constructed. We assessed DNA immunization effects on EAE course in SJL/J mice, evoked with PLP (peptide 139–151) and in B6 mice, evoked with MOG (peptide 35–55).
Results The EAE course, in mice immunized with pvaxMOG 4 and 12 weeks prior to EAE induction, was significantly ameliorated. However, in mice immunized with pvaxPLP 4 weeks prior EAE induction, more severe disease was observed and only 12 weeks after DNA vaccination, the EAE course was ameliorated. Prevention of EAE was connected with a decrease in Th1-type cytokine response and in T cell proliferation in both groups of EAE animals.
Conclusion These results indicate that tolerance of EAE with DNA vaccination depends on antigen and/or mouse genetic background.

P 3203

Prospective, randomised, multicentre, assessor-blinded, parallel-group, comparison of the two licensed interferon beta-1a treatment regimens in relapsing-remitting multiple sclerosis

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Introduction/methods The EVIDENCE trial directly compared the efficacy of subcutaneous interferon (IFN) beta-1a (Rebif®), 44mcg three times weekly, with intramuscular IFN beta-1a (Avonex®), 30mcg once weekly, in 677 patients with relapsing-remitting multiple sclerosis.
Results Rebif® demonstrated significant advantages over Avonex® on clinical and magnetic resonance imaging (MRI) endpoints. After 24 weeks, 74.9% of Rebif® patients remained relapse-free versus 63.3% of Avonex® patients (a 32% relative reduction in the proportion of relapsing patients, $p<0.001$). The hazard ratio (HR) for the probability of a relapse on Rebif® compared with Avonex® was 0.63. Rebif® patients had fewer combined unique active lesions (mean 0.7 versus 1.3 with Avonex®, $p<0.001$). At week 48, 96% of patients remained on study, and the treatment effect at week 24 was maintained: the odds ratio was 1.5 ($p=0.009$) and the HR was 0.70 ($p=0.003$). T2 scan results demonstrated that the mean T2 active lesion count per patient per scan was 0.9 (Rebif® group) versus 1.4 (Avonex® group; $p<0.001$) – a 37% relative reduction. The proportion of active scans was reduced in the Rebif® group and 63% (versus 45% in the Avonex® group) demonstrated no MRI activity over 48 weeks. Injection-site reactions (83% vs. 24%), liver (18% vs. 9%) and haematological (11% vs. 5%) adverse events (AEs) were significantly more common in the Rebif® group (but usually mild). There were 17 AE dropouts on Rebif® and 15 on Avonex®.
Conclusions The EVIDENCE trial demonstrated the superiority of Rebif® over Avonex® on MRI lesion activity and the proportion of relapse-free patients.

P 3204

Does the pulsed methylprednisolone therapy influence cognitive functions in patients with multiple sclerosis?

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Introduction Treatment with high-dose glucocorticoids is a well established therapy in multiple sclerosis (MS), but only little is known about the side effects on cognitive functions.
Methods We studied sixteen patients (11 females, 5 males; mean age 33+/–9.34 years) with relapsing-remitting MS in early disease stage treated for a relapse and eight healthy controls matched for age, gender and IQ clinically and neuropsychologically. To detect dose-dependent effects, one half of the patients were treated with 500-mg/d methylprednisolone (MP) over five days, the other half received 2000 mg/d MP. Neuropsychological investigations were made before (day 0) and at day 6 and day 60 after starting the therapy.

Results Results show significant deficits of free and cued retrieval of declarative memory in the patients at day 6 compared to day 0. These cognitive deficits recovered completely at day 60. All other functions were unaffected. In contrast, the untreated controls showed a slightly improvement in their declarative memory at day 6. No differences were found between the profile and severity of the cognitive impairment of the two dose groups.
Conclusion The findings suggest that high-dose treatment with MP may be associated with selective, but reversible impairment of the declarative memory-recall in MS patients. There may be no association to the administered MP dose.

P 3205

Impairment and driving performance in relapsing remitting multiple sclerosis

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Introduction Different deficits may influence driving capacity in relapsing-remitting multiple sclerosis (RRMS). Our study compared driving simulator performance with fatigue, physical and cognitive functions in RRMS.
Methods 31 RRMS patients (18 women, 13 men, mean age 35.6±8.3 years) and 19 healthy controls (9 men, 1 woman, age: 55.1+7.8 years) were assessed by:
– Extended Disability Status Scale (EDSS)
– MS Functional Composite (MSFC) based on arm function, ambulation and cognition (paced auditory serial addition test, PASAT).
– Fatigue Severity Scale (FSS)
– Driving simulator: Driving on a highway for 60 minutes (mean speed 100 km/h). Presentation of a monotonous condition with different weather and daytime conditions. Obstacles occurred infrequently.
Results FSS - Score was raised with intra-individual variability (38.5±15.5). FSS correlated with arm function ($r=0.465$) and ambulation ($r=0.436$) in the MSFC ($p<0.05$). Compared to controls accident rate (5.3±3.8 vs. 1.3±1.5, $p<0.001$) and concentration faults (21.1±15.5 vs. 7.1±2.6, $p<0.01$) of RRMS patients in the driving simulator were increased. MSFC correlated with accident rate ($r:-0.5$, $p<0.05$). Correlation depended on cognitive function measured by the PASAT($r:-0.33$, $p<0.05$).
Conclusion Impaired driving skills in RRMS could be demonstrated. In the MSFC, most patients showed cognitive deficits. Correlation of PASAT and driving simulator accidents indicated that accidents are more influenced by cognitive decline than by physical impairment. The driving simulator seems to be the best instrument for judging driving ability.

P 3206

Multiple sclerosis patients with autoimmune thyroiditis have a worse disease course

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Introduction There is no report concerning the course of multiple sclerosis (MS) in patients with co-existing autoimmune thyroiditis (AIT). Thyroid hormones are essential for normal brain development and myelination and therefore might influence remyelination in MS. Moreover, thyroid hormones influence the differentiation of oligodendrocyte precursor cells.
Methods We included 92 patients (68 women and 24 men) with definite relapsing-remitting MS and examined the thyroid gland and the disability status via the expanded disability status scale (EDSS) every three months during a prospective three-year surveillance. Thyroid examination included: clinical and ultrasound investigation, detection of thyroid hormones and antithyroid antibodies. The EDSS-examiner was blinded with regard to thyroid disease. All patients lived about 100 km around the hospital and therefore had a comparable iodine intake.
Results The patients with AIT showed a clearly worse disease course as shown by EDSS. No severe thyroid dysfunction could be observed.
Conclusion The co-existence of another organ-specific autoimmune disease with MS obviously accelerates the progression of disability.

P 3207

Epidemiological and clinical aspects of multiple sclerosis (MS) in Tunisia

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Background Prevalence of MS was considered to be low in Tunisia. The use of MRI criteria allows earlier diagnosis and the use of Kurtzke scale for disability allows a better management.
Patients and Methods Among 1058 records of patients classified MS and followed in our department between 1974 and 2000, we selected two groups of patients belonging to two periods differing in the diagnosis tools and the type of management: group I (1974–1978, 125 patients classified according to Mac Alpine criteria) and group II (1996–2000, 247 patients classified according to Poser's criteria). The two groups of patients were compared for clinical and paraclinical parameters and outcome.
Results The prevalence of the disease was similar over the 2 periods and higher than expected for a low prevalence zone. Age of onset was 32.4±10.1 years, delay between the onset of the disease and diagnosis was 3.8±4.4 years and mean disease duration was 6.2±6.7 years. Most patients (72.6%) had relapsing-remitting MS. Most frequent symptoms of onset were motor (53.5%), sensory (42.7%) and visual (32.8%). MRI allowed earlier diagnosis in group II as compared to group I. Systematic treatment with methylprednisolone in patients of the group II shortened the duration of relapses but did not influence the final disability.
Conclusion Tunisia is a medium prevalence zone for MS. The use of MRI allowed earlier diagnosis of paucisymptomatic forms of MS but did not increase the overall proportion of definite MS.

P 3208

Co-incidence of multiple sclerosis and immune thrombocytopenic purpura (a case report)

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Background Multiple sclerosis (MS) and immune thrombocytopenic purpura (ITP) are immunologic diseases of which the aetiologies are unknown.
Report of case A 17-year-old girl was referred to neurology clinic because of diplopia since 4 days. She had a history of ITP from 5 years ago. In examination, we find right side inter-

neuclear ophthalmoplegia. Other examinations were normal. Brain MRI showed multiple hyperintense lesions around lateral ventricles and one in pons. Right side VEP was abnormal. Brain stem and somatosensory evoked potentials were normal. Cerebrospinal fluid was normal. Blood count was normal except thrombocytopenia.
This patient had been treated by methyl prednisolone 1000 mg/day for 5 days and then 50 mg prednisolone orally for 10 days. After 3 days, she felt better and her diplopia had disappeared. About 4 months later, she noticed ataxia and right side weakness. Platelet counts were lower than normal again. MRI revealed new plaques in her cerebellum and brain stem. After repeated pulse therapy, Beta Interferron 1b (betaseron) was started. Now she has been okay and under control for 22 months but her neurological problem and thrombocytopenia are bothering her every now and then.
Conclusion Neurological autoimmune disorder such as MS, Myasthenia Gravis, etc, may accompany some other diseases. This may be due to genetic susceptibility or any unknown aetiologies, but accompanying MS and ITP is a rare condition. In our investigation, we could not find any other cases like this in her family. Good response to immunomodulator treatments suggest autoimmune basis for the aetiology.

P 3209

Reduced functional and respiratory parameters in multiple sclerosis and the relation to fatigue

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We have monitored functional and respiratory parameters in multiple sclerosis (MS) and tried to find their relation to fatigue. 54 MS outpatients were studied. Disability was evaluated according to expanded disability status scale. Fatigue, according to modified fatigue impact scale. Respiratory parameters on Spiro meter, by flow/volume method. Functional parameters were evaluated on bicycle spiroergometer using the anaerobic threshold method. Obtained values were compared with the norm, and statistical analyses were carried out using Statistical Analysis System.
14 of the subjects were men, mean age of subjects was 37.03±10.1 years, disability 2.8±1.53, and illness duration 8.33±6.62. Maximal functional parameters W/kg, HR, VE/kg, MET, VO2/kg/ml, BF, VTex ($p<0.001$), O2HR ($p<0.05$) and respiratory parameters PEF ($p<0.001$), MEF75, 50, 25 ($p<0.05$) were significantly lower. RQ, EqO2, EqCO2 VCin, VCex, ERV, FVC, FEV1 corresponded to the norm. Fatigue increases significantly with increasing degree of disability ($p<0.05$), further with age and duration of the illness ($p<0.1$). However, it decreases significantly with relative weight ($p<0.1$). We found an important correlation between fatigue and respiratory parameters METS ($p<0.001$), VTex, HR, VO2/kg/ml, O2HR ($p<0.05$), W/kg, VE/kg ($p<0.1$). We did not find any correlation between fatigue and respiratory parameters, even though a larger percentage of the patients (78%) complained of dyspnoea.
Even in people with relatively low degree of disability cardiovascular fitness is reduced. It decreases with disability and the duration of the illness as well, and participates in the genesis of fatigue. Significantly, decreased values of the expiratory flow, which may reflect muscle weakness, do not participate in the genesis of fatigue.

P 3210

Lower urinary tract dysfunction in patients with multiple sclerosis.

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Objective The lower urinary tract (LUT) symptoms are common in multiple sclerosis (MS) patients and may be main cause of social disability.
The **aim** of the study was assessment frequency and nature of LUT dysfunction in MS population and their impact on quality of life.
Materials and method 60 consecutive MS patients were included (mean age 42.2; mean duration of disease 13.1; mean age of MS onset 28). 65% of patients were female.
The symptoms were assessed with multiplane questionnaire: A list of symptoms and signs, "obstructive" and "irritative" scores (International Prostate Symptom Score (IPSS), Boyarsky, Madsen), and patient self-assessment of the quality of life (QOL). Functional bladder capacity and the post-void residual urine volume (PVR) were measured ultrasonographycally.
Results In 5% of patients, LUT symptoms were the first manifestation of the disease. LUT dysfunction occurred in 93.3% of patients: frequency 63.3%, nocturia 61.6%, urgency 43.3%, hesitancy 48.3%, interrupted urinary flow 41.6%, sensation of incomplete emptying 48.3%, incontinence 48.3%, in 28% PVR was over 100ml. The intensity of LUT symptoms correlate well with EDDS, lower limbs paraparesis, results of QOL and scores ($r=0.65-0.78$; $p<0.05$). Before study inclusion, only 15% of patients were pharmacologically treated and few were treated with physiotherapy
Conclusions Urological disturbances occur in most patients with MS, careful diagnostic procedure should be performed for each patient. Appropriate management strategies are needed to improve the function and quality of the patient's life.

P 3211

Injuries in the pathogenesis of multiple sclerosis

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Background and purpose An injury might derange the protective function of the blood-brain barrier, and thus it represents one of the possible pathogenetic factors in the demyelination of the neural axis. However, the effect of injury on the occurrence or deterioration of multiple sclerosis (MS) is still controversial.
Methods In this research, for every MS patient there was a randomly chosen control patient/subject of same gender, same birthplace and place of residence.
These control study subjects could have been diagnosed with any other illness except MS, other illnesses of known immunocauses or mental illness.
In this research, we used the statistical methods "case-control" studies.
Results In three patients following multi-traumatic injuries or serious head injuries, which followed after being diagnosed with MS, there was a worsened state.
Conclusion According to most authors, the importance of injury in individual cases of MS is undeniable, as well as the fact that injuries are factors of progression and deterioration of the disease, but never its cause. Consequently, injuries can cause only temporary disability, and not permanent. Nevertheless, the

incidence of MS increases proportionally to the severity of injury. The length of the period from the occurrence of injury to possible demyelination is still not established. Studies and clinical reports point to the fact that in the evaluation of injury as a precipitating factor for the vulnerability of the blood-brain barrier, the severity of the injury is of greater importance than its site.

P 3212

Fatigue in patients with multiple sclerosis: relationship to disease pattern, disability, and depression

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The symptom of fatigue is a frequent complaint in multiple sclerosis (MS) patients.
The **aim** of this study was to determine the link between fatigue and clinical features of MS and evaluate the specificity of three fatigue scales in this condition.
109 individuals with clinically definite MS: relapsing-remitting 79 (72.5%), secondary progressive MS 17 (15.6%), and primary progressive 13 (11.9%). Mean disease duration was 8.3 years. Mean EDSS score was 4.2 (range 1.0–8.0). Fatigue was measured using the Fatigue Descriptive Scale (FDS), Fatigue Severity Scale (FSS), and Visual Analogue Scale (VAS).
Fatigue was present in 92% of MS patients. The global FDS score was 5.0+2.6 (range 1–13), FSS was 5.2+1.5 (range 1.5–10) and VAS was 58.8+22.4 (range 10–100). FDS and FSS were highly correlated ($r=0.61$, $p<0.0001$). Patients with progressive MS had higher fatigue score than relapsing remitting MS patients, but the difference was not significant ($p=0.247$). FSS and FDS scores no longer correlate with EDSS ($r=0.27$, $p=0.09$). Patients with MS experienced significant fatigue not related to depression ($r=-0.087$, $p=0.385$).
Our **results** supports the notions that fatigue is very frequently present in MS and suggest that it is not related to affective disturbance and neurological impairment in these patients.

P 3213

Schilder's myelinoclastic diffuse sclerosis – a case report

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Introduction Schilder's myelinoclastic diffuse sclerosis, a variant of multiple sclerosis, is a very rare disease that occurs in children and adults. It is usually presenting as an intracranial mass lesion.
Case report The 49-year female patient was referred to our hospital with progressive right-sided hemi paresis, motor dysphasia and frontal lobe syndrome. Symptoms started 14 days earlier with acute headache. Febrile state was not examined. MRI of the head revealed two oval lesions with hyper intensity in T2 weighted images of left frontal and parietal lobe. The first diagnostic impression was of glioblastoma multiform. Analysis of CSF revealed increased immunoglobulins, 3 OCB and increased intrathecal synthesis of IgG. The biopsy after neurosurgical stereotactic treatment yielded five needle cores of greyish tissue. Haematoxylin and eosin stained sections of paraffin embedded tissue showed cerebral white mater infiltrated by large numbers of Luxol fast blue negative, lipid containing macrophage which were CD 68 immuno-positive. Enlarged number of astrocytes was also present. Some of them contained granulated nucleus like sign of mitosis. Proliferating cell nuclear antigen (PCNA) and Ki67 indicated that these cells proliferated. Fragmenting myelin sheaths were present at the relatively sharp edge of inflammatory lesion. Perivascular cuffing by CD3 and CD 20 lymphocytes were scant. Silver impregnation and immunocytochemical reaction with monoclonal antibodies to neurofilaments indicated that in demyelinating lesions network of axons was preserved.
Conclusion Pathohistological findings are consistent with the diagnosis of Schilder's myelinoclastic diffuse sclerosis.

P 3214

First demyelinating syndrome and risk of progression to multiple sclerosis in Chinese patients

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Objectives To study the clinical, cerebrospinal fluid (CSF), and radiological findings in Chinese patients with first demyelinating syndrome and the risk of progression to multiple sclerosis.
Methods All patients presenting with first demyelinating syndrome to our unit over the period 1993 to 2001 were included. The hospital records were retrospectively reviewed and data on clinical features, CSF findings and MRI of the brain and/or spinal cord were systemically analysed. The progression to multiple sclerosis and the associated risk factors were also studied.
Results Twenty-seven patients with first demyelinating syndrome were identified over the study period of 105 months: eighteen were females and mean age 43.2 years. The syndromes were: transverse myelitis (66.7%), optic neuritis (25.9%) and brainstem syndrome (7.4%). Eleven percent (3/27) of patients with transverse myelitis had concomitant optic neuritis on evoked potential study. Oligoclonal bands were positive in 25% (3/12) of patients. MRI showed the corresponding lesion in 76% (19/25) and 36% (9/25) had additional lesion in other sites. One patient died, four had recovery with significant deficit, and twenty-two had good recovery. The treatment with pulse methylprednisolone was associated with good outcomes (complete recovery) in 16/19 versus 3/8 patients. After a mean follow up of 29 months (range 5 to 84 months), 8 patients (25.5%) progressed to multiple sclerosis. The associated factor identified was high lesion load on MRI.
Conclusion In Chinese transverse myelitis is the most common presentation for demyelinating disease. The prevalence and risk of progression to MS is lower than that of Caucasians.

P 3215

Management of co-ordination disorders in multiple sclerosis patients.

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Co-ordination and vestibular disorders lead to malfunction problems in 60–70% multiple sclerosis (MS) patients. There is still no specific pharmaceutical management of such conditions. The **aim** of this research has been to develop a vestibular-training programme to counteract various types of ataxia in patients with MS. The vestibular-training programme has been introduced to a group of 19 patients (18–42 years old, 12 female, 7 male). Average duration of the disease was 8.2±1.4 years. All patients displayed moderate symptoms of dynamic and static ataxia. A control group included ten patients with no

vestibular training form. Three principle VT schemes, combined with biofeedback method, were used for managing the following symptoms: 1) dynamic ataxia 2) static ataxia 3) vestibular-sensor disturbances. Vestibular-sensor, vegetal reactions and coordination tests were conducted. The rehabilitation indices in the MS patients receiving VT were significantly better. It is believed that the VT method serves to engage new interneuronal links and thus reduce coordination disorders.

P 3216

An erythromelalgia case occurred during interferon beta treatment for multiple sclerosis

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Introduction Common side effects of the interferon beta (IFNB) therapy include flu-like symptoms, skin reactions at the injection sites, leukopenia and raised concentrations of liver enzymes. In addition, of these well-known side effects, vascular complications associated with IFNB have also been, although rare, reported. Nevertheless, erythromelalgia related to the IFNB beta treatment has not yet been encountered. We report the first erythromelalgia case occurred during the interferon beta-1a (IFNB-1a) treatment for multiple sclerosis.
Case reports A 38-year-old woman who had been treated with IFNB-1a for relapsing remitting multiple sclerosis for 20 months was evaluated with the complaints of burning pain, elevated temperature and dermal erythema in feet. She described relieving of the pain with elevation of the lower extremities and cold exposure. She was diagnosed as having erythromelalgia and secondary causes were investigated. After excluding all possible causes, erythromelalgia in this case was thought to be associated with IFNB-1a treatment and the drug was discontinued. Following the withdrawal of the IFNB-1a, the symptoms and signs recovered gradually and disappeared completely at the end of 15th day.
Conclusions Erythromelalgia as a result of IFNB has not been reported in literature. The present case is believed to be the first report about the association of erythromelalgia with IFNB.

P 3217

Effect of glatiramer acetate(Copaxone) on the level of IL-10 and IL-12 in multiple sclerosis

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Introduction Proinflammatory cytokines produced by Th-1 cells and cytokines with immunosuppressive properties play on important role in the pathogenesis of multiple sclerosis (MS). Glatiramer acetate (GA) is one of the most important immunomodulatory agent used in the therapy of MS. The mechanism of action of GA in MS is not yet fully explained. The purpose of this study was to evaluate the effect of GA in a dose 20 mg daily in a period of 6 months on interleukins IL-10 and IL-12.
Methods Thirty-one patients with definite MS and 30 control subjects were the subjects of our study. The ELISA measured the interleukin levels in sera.
Results A significant increase was found of IL-12 and also of IL-10 levels in MS patients in comparison with control groups. We have also established a significant decrease of IL-12 after 3 and 6 months of GA therapy and some insignificant differences in the level of IL-10.
Conclusion IL-12 seems to contribute to the pathogenesis of MS. The established down regulation of IL-12 suggest down regulatory action of GA on IL-12.
The insignificant change of IL-10 level observed in course of GA therapy seems to indicate that this cytokine is not connected with the immunomodulatory effect of GA in MS.

P 3218

4-year clinical experience with interferon beta 1b in relapsing-remitting multiple sclerosis patients

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Introduction The benefit of interferon beta was shown to decrease the clinical and MR activities of multiple sclerosis (MS) in several large studies. We wanted to obtain a feedback from the everyday practice with interferon beta in our MS Centre.
Methods In the retrospective study, we selected 55 patients with relapse-remitting multiple sclerosis started on the first interferon beta available in the Czech Republic since 1996.
Results The relapse rate tremendously declined from 1.87 in 2-year pre-treatment period to 0.43 in the first year of treatment. Thereafter it remained relatively stable for the following 3 years (0.4, 0.2, 0.3, respectively). Clinical disability preserved unchanged ranging from 2.4 to 2.7 through the period analysed. 25% of patients, 20% of patients were relapse-free after 2, 3 years, respectively. Five patients failed to respond. 21% of patients exhibited necrosis.
Discussion The overall clinical efficiency in our group was found to be higher than in classical Betaferon studies due to several reasons. The study design was obviously different. The candidates eligible for interferon therapy were strictly selected, especially according to the high activity of the disease before interferon treatment. Moreover, we usually combine disease-modifying therapy with corticosteroids or immunosuppressive drug that may reduce further a CNS inflammation. Higher frequency of necrosis was probably caused by the inappropriate injection procedure, since this adverse event has been reduced by auto injectors' introduction nowadays.
Conclusion Combination therapy is more effective than isolated interferon treatment only.

P 3219

Effects of a cooling suit in multiple sclerosis

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Introduction Personal cooling systems are used to alleviate symptoms of multiple sclerosis (MS) with great success. Recently a portable cooling suit and a cooling helmet were constructed to cool head and neck regions of patients with MS, but little scientific work has been done on these types of suits.
Methods As part of a retrospective study, 30 females and 20 males aged 18–65 years were interviewed by telephone. All of the subjects were asked the following: Where there any subjective changes in the movement of legs or arms, in eyesight, in

feeling of energy, in pain, mood, fitness or cognitive ability after the treatment with the cooling suit and helmet, how long did they feel better and was the cooling system pleasant.
Most of the subjects had a progressive course of MS and stated that they were heat sensitive.
Results In 94 percent of patients the cooling therapy was pleasant, no one took a turn for the worse. An unexpected result was found in 12%. These subjects could see better and one third of all subjects had more control over their muscular movements after 30 minutes of the cooling period.
Regarding the mobility and nicotine-consumption only 27% of smokers but 40% of non-smokers indicated improvement.
In our spot check, more subjects with normal cholesterol levels felt better, than patients with pathologic cholesterol levels.
Conclusions These results show that the cooling suit seems to be an effective method for improving the eyesight and mobility of MS patients.

P 3220

Clinical and immunological monitoring in secondary progressive multiple sclerosis (SPMS) patients during transcranial magnetic stimulation (TMS).

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P 3221

Therapeutic aspects of multiple sclerosis at the neurology clinic of clinical centre of Sarajevo University

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P 3222

The epidemiology of multiple sclerosis in Devon: A comparison of the new and old classification criteria

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Multiple sclerosis (MS) is the most common cause of neurological disability in young adults in the United Kingdom (UK). There is significant variation in the worldwide distribution of MS and it remains debatable as to whether a latitudinal gradient exists across the UK. We present the first epidemiological study of MS to be conducted in Devon. With its low latitude and relatively low migration rates it is an ideal region to be studied and compared with the north of the UK.
A population-based survey was carried out using seven sources (neurology department, hospital episode statistics, MS specialist nurse, MS society, regional residential/nursing homes and general practitioners). Hospital notes were inspected to ensure accurate diagnosis and cases were classified according to both the Poser criteria and the new McDonald criteria. We report a crude prevalence of 118 per 100,000 (Poser criteria) in a population of 341,796, on prevalence day 1st June 2001.
This study provides the first prevalence figure for this part of the UK, as well as being the first to use the new diagnostic guidelines and compare them with the Poser criteria. Age-sex standardisation was used to allow for the demographic structure of the population. This figure is one of the highest reported in the south of the UK and provides further support for a north-south divide, indicating that this is a step effect rather than a direct latitudinal gradient.

P 3223

The effect of oral cannabis oil on tremor in patients with multiple sclerosis

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Introduction Tremor is a common symptom in patients with multiple sclerosis. Anecdotal evidence suggests that some such patients find relief by using cannabis. However, no previous randomised controlled trials of cannabis as a treatment for tremor have been performed.
Methods We carried out a randomised double blind placebo controlled crossover trial of oral cannador (cannabis oil) in 14 patients with multiple sclerosis and significant tremor. Patients received each treatment for a period of two weeks before assessment of effect. The primary outcome measure was improvement on a 0 to 10 clinical rating scale of tremor, with secondary outcome measures including accelerometry, spiral drawing, finger tapping and nine-hole peg board.
Results There was no significant improvement in any of the objective outcome measures. Despite this, more patients reported subjective improvement in their tremor when given cannador (5 out of 14) than when given placebo (1 out of 14).
Discussion The trial was powered to detect an improvement in tremor of 50%, which was felt to be the minimum which would be clinically significant. The absence of any significant result suggests that, despite anecdotal reports, cannabis cannot be considered an effective treatment for tremor secondary to multiple sclerosis.