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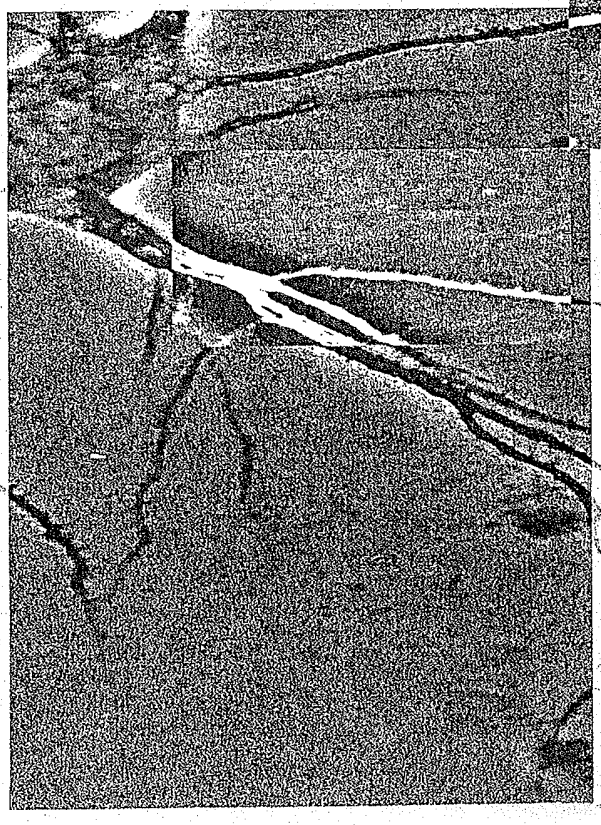

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Abstracts of Symposia, Free Communications and Posters

The abstracts have been reviewed by:
J. Berciano, J. Bogousslavsky, T. Brandt, G. Comi, D. A. S. Compston, S. DiDonato, H.-P. Hartung, J. G. Hildebrand, C. Kennard, C. Krarup, D. Leys, I. Milonas, G. Said, A. Steck, P. Scheltens, F. Van der Meché, J. Van Gijn

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3 timepoints (5 minutes=3.2%, 20 minutes=2.5%, 40 minutes=1.8%, $p < 0.0005$). Such changes were apparent in all MS subgroups. These findings suggest the presence of widespread low-grade and possibly chronic BBB leakage in NAWM and ANEL that may contribute to disease progression in MS.

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THE PATHOGENESIS OF RELAPSING REMITTING MULTIPLE SCLEROSIS [MS]; DESIGN OF A LARGE LONGITUDINAL STUDY. CMB Griffin, DH Miller, AJ Thompson. NMR Research Unit, Institute of Neurology, University College London, UK.

We report the design of a unique serial multi parameter study aimed at examining the temporal relationship between inflammation,demyelination and axonal loss in early MS. At least fifty patients will be recruited with relapsing remitting disease of less than 3 years duration with an EDSS < 3. Follow up will be over at least 3 years as follows; M. R. I. Triple dose gadolinium enhanced images of brain and cord[inflammation]. Magnetisation transfer imaging[demyelination]. Proton spectroscopic imaging[axonal loss]. Hypointense lesion load[axonal loss]. Diffusion tensor imaging[white matter fibre tract integrity] 3D volume imaging of the brain and cord [to quantify atrophy;a marker of axonal loss and demyelination] T1 relaxation measurements [possibly correlating with gliosis]. Clinical: Kurtzke expanded disability status scale, U. S. National M. S. society taskforce composite scale; visual analogue of fatigue, modified fatigue impact scale, short form 36, Queen Square Disease Impact Scale. These will elucidate the relationship between evolving pathology and functional impact. Immunological: Blood; C reactive protein,soluble adhesion molecules,soluble T. N. F. alpha,nitric oxide metabolites. Urine; neopterin and free light chains. This study will elucidate the mechanisms of irreversible tissue damage [especially axonal loss] which is likely to result in clinical progression.

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ERAZIMUS: EARLY AZATHIOPRINE VERSUS BETA-INTERFERON TREATMENT IN MULTIPLE SCLEROSIS. RESULTS OF PILOT SAFETY STUDY. Moreau T, Blanc S, Riche G, Confavreux C (Department of Neurology, Hôpital de l'Antiquaille and Hôpital de la Croix-Rousse, Lyon, France)

As single therapies, both recombinant interferon beta and azathioprine have shown proven efficacy in patients with relapsing-remitting Multiple Sclerosis (MS). The current single-center open pilot study is designed to evaluate the safety and tolerance of interferon beta-1a (AVONEX™) in combination with azathioprine (IMUREL™) for the treatment of relapsing-remitting MS. Thirty patients already receiving azathioprine treatment for at least 6 months for relapsing-remitting MS have been enrolled. Three different dose groups of 10 subjects each have been made up: 50 mg, 100 mg or 150 mg daily. After enrollment, the patients received the first intramuscular injection of interferon beta-1a (6 MIU) followed by a weekly injection for 4 months. The safety profile of the combination was evaluated through hematology and biochemistry laboratory parameters and clinical tolerance performed at specific time points throughout the study. A secondary objective is to produce information on the effects of the combination about residual concentrations of neopterin and 6-thioguanine nucleotide levels. Our results confirm the biological and clinical safety and tolerance of the combination of interferon beta-1a and azathioprine.

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ORAL FUMARIC ACID ESTER (FAE) IN RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS). A SHORT TERM, OPEN, CLINICAL, IMMUNOLOGICAL AND MAGNETIC RESONANCE IMAGING (MRI) CONTROLLED PHASE II TRIAL. Schimrigk S, Meier D, Brune N, Krane M, Hellwig K, Hoffmann V, Rieks M*, Pöhlau D*, Przuntek H. Department of Neurology, St Josef Hospital, 44791 Bochum, Ruhr University Bochum, Germany; * Sauerlandklinik Hachen, Germany

FAE (Fumaderm®) initially proven to be effective in the treatment of psoriasis also showed a semi-selective immuno-modulating influence on T-cells. FAE seem to be very effective in up-regulating TH_2-type cytokines especially IL-4, IL-10 and TGF-. According to the hypothesis that MS is caused by autoreactive T-cells, triggered by the dysbalance of TH_1- and TH_2-type cytokines, we investigated peripheral blood lymphocytes (PBLs) from patients with RRMS under FAE treatment. Methods and subjects: FAE therapy was investigated in regards to effectiveness and safety in a small explorative group of 10 patients over six months. Intracellular TH_1- and TH_2- type cytokines (IL-2, IL-4, IL-10, TNF-α, TGF-β, IFN-γ) of PBLs from patients with RRMS were detected. Serial T1 weighted MRI with triple dose Gd-DTPA during the study phase were performed regulary. Primary outcome parameter of the study was the reduction of active Gd enhancing lesions in T1 weighted MRI. Results: FAE decrease significantly the amount of active lesions and lesion load of Gd-enhancing lesions in T1 weighted MRI. The cytokine balance changed significantly in favor of the TH_2-type cytokines. Clinically 7/10 patients remained stable or improved under FAE therapy during the study. One drop out because of stomach disturbances and two not drug related drop outs. Conclusion: In our small group of patients with RRMS oral FAE therapy was effective most probable due to the selective immunomodulation of TH_2-type cytokines. The influence on serial T1 weighted MRI is striking. The clinical use of oral fumaric acid ester as a possible relevant drug for the treatment of multiple sclerosis is now conceivable.

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EFFECTS OF GLATIRAMER ACETATE ON MRI MEASURED DISEASE ACTIVITY: RESULTS OF A RANDOMISED, DOUBLE BLIND, PLACEBO-CONTROLLED MULTICENTRE STUDY. G. Comi[1], M. Filippi[2] for the Copaxone MRI Study Group. [1]Clinical Trials and [2]Neuroimaging Research Unit, Department of Neuroscience, Scientific Institute Ospedale San Raffaele, University of Milan, Italy.

Glatiramer acetate is a mixture of synthetic polypeptides which suppresses both acute and chronic experimental allergic encephalomyelitis. Two double-blind, placebo-controlled trials demonstrated that glatiramer acetate reduces relapse rate in patients with relapsing-remitting multiple sclerosis (RRMS). The aim of this study was to determine the effects of daily s. c. injection of 20 mg glatiramer acetate on MRI-measured disease activity in RRMS, during a 9-month double blind placebo-controlled phase, followed by a 9-month open label phase. One or more relapses in the two years prior to study entry and at least one enhancing lesion on the screening MRI scans were required for enrollment. Brain MRI was performed monthly during the double blind phase. The primary end-point was the total number of enhancing lesions. Two hundred thirty-nine patients were enrolled (119 received glatiramer acetate and 120 placebo). There was a significant reduction in the total number of enhancing lesions in the treated group (29% reduction in LOCF adjusted mean, p=0.003, 35% reduction on data as is p=0.0007). Differences in favor of glatiramer acetate were also found for: mean number of new enhancing lesions (30% reduction, p=0.0029), number of new T2 lesions (35% reduction, p= 0.001), median change from baseline in volume of enhancing lesions (p=0.0098), median change from baseline of T2 lesion load (p=0.0245). The relapse rate was also reduced in glatiramer acetate compared to placebo group (-33%, p=0.0117). In RRMS glatiramer acetate significantly reduced the MRI disease activity and burden. This effect mirrored the reduction of clinical activity.

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T-CELL DEPLETED AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR MULTIPLE SCLEROSIS; TRANSPLANTATION RELATED TOXICITY AND EARLY RESULTS IN THREE PATIENTS. J. P. A. Samijn, M. R. Schipperus, P. A. van Doorn, J. J. Cornelissen, J. W. B. Moll, C. A. M. Huisman, B. Löwenberg and F. G. A. van der Meché. Department of Neurologyand hematology, Erasmus Medical Center Rotterdam.

Based on animal models and clinical observations autologous stem cell transplantation and bone marrow transplantation (BMT) may be effective therapies for several autoimmune diseases. Phase II studies with different conditioning regimens have been initiated worldwide to evaluate if BMT can halt disease progression in patients with malignant multiple sclerosis (MS). We selected patients by predefined criteria: definite MS according to Poser's criteria, an expanded disability status score (EDSS) ≥ 3 within two years and progression of disability in the years prior to inclusion. Current EDSS had to be between 5 and 7. The patients received total body irradiation (2x5Gy) and cyclophosphamide (120 mg/kg). Anti-thymocytic immunoglobulins were administered for in vivo T-cell depletion. This was followed by CD34 selected autologous BMT. Supportive care and isolation methods were according to standard procedure. In three patients (m, 30 yr; m, 39 yr; f, 48 yr) the transplantation procedure has been completed. All patients suffered from general malaise. Liver function disturbances and moderately severe toxicodermia were observed in two patients. Two

measurement of CNS atrophy has been proposed as a surrogate marker for disease progression. We evaluated the enlargement of the ventricular system as a marker for brain atrophy with magnetic resonace imaging (MRI) and transcranial sonography (TCS) to look for an association between ventricular system diameter and disability, cognitive performance and mood in a group of MS patients. Methods: 74 MS patients (48 f, 26 m, mean age 42 y) were included. Disability was assesed by the expanded disability status scale (EDSS). Neuropsychlogical test batteries and routine depression scales were administered. All patients were submitted to a standardized TCS and MRI-protocol. For TCS we applied a color-coded- phased array ultrasound system with a 2.5 MHz transducer (Siemens Sonoline Ellegra). Ventricular width of the third ventricles and the frontal horns were measured by two independent investigators. Results: Interobserver reliability was high for the measurement of ventricle size (MRI r = 0.9, TCS r = 0.8 III. for ventricle). Comparison of the data for the diameter of the ventricular system obtained by TCS and MRI yielded a significant correlation (r = 0.9 III. for ventricle). There was a significant correlation between the diameter of the third ventricle and disability measured by EDSS. In addition TCS and MRI data correlated significantly with the neuropychological tests. Correlation with the with of the frontal horns was substantially lower for both imaging techniques. No correlation was found between diameter of the ventricles and depression scales. Conclusion: The study demonstrates a correlation between ventricular size, disability and neuropsychological performance and suggests that the ventricular size in MS is a robust parameter for the purpose of such correlative studies. Moreover it was shown that TCS is a valuable method for the assessment of the ventricluar system in MS patients. Therefore this easy applicable technique will be further evaluated in serial studies to elucidate the relation between inflammation and tissue destruction and for the evaluation of putative treatments.

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ORAL FUMARIC-ACID ESTER THERAPY (FAE) INFLUENCE T-HELPER CELL APOPTOSIS IN PERIPHERAL BLOOD LYMPHOCYTES (PBLS) AND SOLUBLE INTERCELLULAR ADHESION MOLECULE-I (SICAM-1) IN SERUM OF PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS (RRMS). Brune N, Schimrigk S, Meier D, Krane M, Rieks M*, Hoffmann V, Hellwig K, Pöhlau D*, Przuntek H. Department of Neurology, St. Josef Hospital, 44791 Bochum, Ruhr University Bochum, Germany, * Sauerlandklinik Hachen, Germany

Relapses in RRMS are assumed to be induced by autoreactive TH_1-type lymphocytes whereas remissions are associated with TH_2-type cytokine pattern, a deletion of autoreactive T-cells and decline of inflammation. Th_2-type cytokines are able to induce apoptosis in autoreactive T-cells and down regulate inflammatory processes mediated by adhesion molecules like sICAM-1. FAE (Fumaderm®) a potent immunomodulator known to alter TH_1- towards a TH_2-type cytokine pattern in vitro and in vivo. We investigated the influence of oral FAE therapy, as a possible treatment for patients with RRMS during an open phase II prospective study. Materials and Methods: We examined 10 patients with definitive RRMS. The investigation over 28 weeks was divided into a baseline section (6 weeks), a treatment period (18 weeks) and a post-study section (4 weeks). During the investigation, we detected T-cell apoptosis of PBLs using the annexin-V-binding-method by flowcytometry. Additionally we measured serum levels of sICAM1 by enzyme linked immunosorbent assay (ELISA). Results: Operating with those techniques, we were able to correlate the alteration in T-helper cell apoptosis with the observed TH_2 -type cytokine shift under drug therapy. We found an increased (50%) rate of apoptosis in T-helper cells after 6 weeks of treatment which declined to baseline levels afterwards in accordance to the IL-10 producing lymphocytes. Serum concentrations of sICAM-1 remained stable throughout the entire investigation. Conclusion: FAE (Fumaderm®) seem to have beneficial effects on the disease course during the study. Soluble ICAM-1 as a proposed long-term marker of the disease activity remains stable. The rate of T-helper cell apoptosis correlates directly with the observed IL-10 induction.

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IN VITRO STIMULATION OF PERIPHERAL BLOOD LYMPHOCYTES WITH CALCIUM MONOMETHYLFUMARATE (CAMF) INFLUENCE PRODUCTION OF INTRACELLULAR TH_1- AND TH_2-TYPE CYTOKINES IN A SPECIFIC MANNER.Schimrigk S, Krane M, Hellwig K, Hoffmann V, Rieks M*, Pöhlau D*, Przuntek H. Department of Neurology, St Josef Hospital, 44791 Bochum, Ruhr University Bochum, Germany; * Sauerlandklinik Hachen, Germany

T-helper lymphocytes classified as TH_1- and TH_2-type lymphocytes, depending on their different cytokine pattern, have different functions in the immune system. TH_1-type cytokines like IFN-γ and TNF-α are predominantly pro-inflammatory and TH_2-type cytokines like IL-4 and IL-10 can down regulate inflammation. We investigated the influence of CaMF on the TH_1- and TH_2- type cytokine pattern of peripheral blood lymphocytes in vitro. Methods: PBLs from healthy donors were stimulated in vitro with CaMF in different concentrations (50, 100 and 200µM) and with different incubation times (24, 48 and 72h). Controls without stimulation were included. Cytokines were measured after single stimulation in culture plates. TH_1-type cytokines (IL-2, IFN-γ, TNF-α) and TH_2-type cytokines (IL-4, IL-10, TGF-) were detected intracellular by flowcytometry. Results: We found a dose dependent influence on intracellular TH_1- and TH_2-type cytokine production. There is a marked decrease in the production of TH_1-type cytokines and a significant increase of TH_2-type cytokines after a 24h incubation time. The substance affected primarily CD4 positive cells. Discussion: The changes in the intracellular cytokine pattern after stimulation of PBLs in vitro with CaMF are reproducible and suggest a possible protective role of this substance in inflammatory diseases.

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INTERFERON BETA-1B IN THE TREATMENT OF RELAPSING-REMITTING MULTIPLE SCLEROSIS: CLINICAL AND MRI RESULTS. Ozakbas S, Idiman E, Cakmakci H, Yener GG, Kovanlikaya I.Dokuz Eylul University, School of Medicine, Departments of Neurology and Radiology.Izmir Turkey

Several evidences suggest that immunopathological factors are critically involved in the pathogenesis of multiple sclerosis (MS). Some clinical trials demonstrated that interferon beta-1b reduces the frequency and severity of exacerbations, slow the accumulation of disability and supressed magnetic resonance imaging (MRI) activity and lesion accrual. In this study, seventeen relapsing-remitting MS patients (2 male and 15 female), who has short disease period and 2 relapse in the last two years, have received 8 million unit interferon beta-1b every other day subcutaneously for nine months. They are evaluated clinically and on the base of MRI in the second, forth, sixth and ninth months. Clinical evaluation was performed with expanded disability status scale (EDSS). Mean age was 32.29 ± 5.45, mean disease duration was 2.44 ± 0.61 years, mean EDSS score was 2.20 ± 0.41 and mean relapse rate was 2.06 ± 0.90 in the last two years. Mean MRI score (which was assigned depending on the volume and number of lesions) was 44.12. EDSS scores were significantly decreased in the forth (p=0.0277), sixth (p=0.0015) and ninth (0.0015) months of the treatment. MRI scores were significantly decreased in the forth (p=0.0409), sixth (p=0.0019) and ninth (p=0.0007) months. No serious side effect was seen during the therapy. We concluded that interferon beta-1b might decrease both clinical disability and MRI lesions.

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CORTICOSTEROID INDUCED GENE EXPRESSION IN PERIPHERAL BLOOD MONONUCLEAR CELLS OF MULTIPLE SCLEROSIS PATIENTS DETECTED BY cDNA MICROARRAYS. Weilbach F.X., Gold, R. and Toyka K.V.Department of Neurology, Julius-Maximilians-Universität, Würzburg, Germany.

The cDNA microarray technique is a recently introduced method to simultaneously survey the expression of multiple genes synchronously. This method has been applied to cell cultures and tissue specimens to detect transformation- or differentiation-induced gene expression. Using Clontech microarrays we have monitored the change of gene expression patterns induced by standard intravenous steroid pulse therapy for treatment of MS relapses in human PBMCs ex vivo. Total RNA was isolated from density gradient purified lymphocytes of freshly accessed blood samples. $dCTP^{32}$ labeled cDNA was then hybridized to human cDNA expression array membranes. Simultaneous autoradiographic analysis of 588 genes indicated an increase in the expression of several transcription, differentiation and proliferation factors in 5 patients. Upregulated genes included granulocyte colony stimulating factor receptor-1, LFA-1, interferon gamma induced protein, PDGF, IL-2, Interleukin-1 Receptor Type II, whereas prothymosin alpha, calgranulin B, thymosin-beta and connective tissue growth factor were downregulated. Amongst these are genes hitherto not described as steroid-responsive in lymphocytes or PBMCs. This technique may be applied to PBMCs ex vivo and allow to detect and monitor disease specific or treatment induced gene expression patterns in a easily accessible material. *Funding: University Research Funds*