Literatur-Dauerrecherche Multiple Sklerose

Ausgabe April 2010

Ungefiltert, unredigiert und nach Journals sortiert
Quelle: Public Medline; 196 Abstracts
(= Neuaufnahmen in der Literaturdatenbank)
Inhaltsverzeichnis

Betaferon in the treatment of multiple sclerosis................................................................. 10
Evidence for polygenic susceptibility to multiple sclerosis—the shape of things to come................................................................. 10
Robust replication of genotype-phenotype associations across multiple diseases in an electronic medical record........................................................................................................................................ 11
Fingolimod (FTY720) Enhances Remyelination Following Demyelination of Organotypic Cerebellar Slices................................................................. 11
Evaluating the effects of estradiol on endothelial nitric oxide stimulated by erythrocyte-derived ATP using a microfluidic approach................................................................. 12
Glatiramer acetate: successful desensitization for treatment of multiple sclerosis................................. 12
A 3-year magnetic resonance imaging study of cortical lesions in relapse-onset multiple sclerosis...... 13
Chronic cerebrospinal venous insufficiency and multiple sclerosis................................................................. 13
Paced glottic closure for controlling aspiration pneumonia in patients with neurologic deficits of various causes........................................................................................................................................ 14
Effect of 4-Aminopyridine on Action Potential Parameters in Isolated Dog Purkinje Fibers................................................................. 14
Relationship of cortical atrophy to fatigue in patients with multiple sclerosis................................................................. 15
Interferon neutralizing antibodies in multiple sclerosis: a new perspective................................................................. 15
Overview of the biology of type I interferons........................................................................................................................................ 15
Pathogenic mechanisms and experimental models of multiple sclerosis................................................................. 16
T regulatory cells lacking CD25 are increased in MS during relapse................................................................. 16
Incidental detection of bilateral corectopia by photo screening leads to the diagnosis of multiple sclerosis. A case report........................................................................................................................................ 16
GPR30, but not estrogen receptor-alpha, is crucial in the treatment of experimental autoimmune encephalomyelitis by oral ethinyl estradiol........................................................................................................................................ 17
Custom CGH array profiling of copy number variations (CNVs) on chromosome 6p21.32 (HLA locus) in patients with venous malformations associated with multiple sclerosis........................................................................................................................................ 17
Multiple sclerosis and pregnancy: what does the patient think? a questionnaire study................................................................. 18
Doctor is found guilty of exploiting "desperate" MS patients........................................................................................................................................ 18
Induction of inhibitory central nervous system-derived and stimulatory blood-derived dendritic cells suggests a dual role for granulocyte-macrophage colony-stimulating factor in central nervous system inflammation........................................................................................................................................ 18
Evidence for a two-stage disability progression in multiple sclerosis................................................................. 19
Complement regulator factor H as a serum biomarker of multiple sclerosis disease state................................................................. 19
Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration................................................................. 20
Smad7 in T cells drives T helper 1 responses in multiple sclerosis and experimental autoimmune encephalomyelitis........................................................................................................................................ 21
Resting state networks change in clinically isolated syndrome........................................................................................................................................ 22
Reduced cortisol levels in cerebrospinal fluid and differential distribution of 11beta-hydroxysteroid dehydrogenases in multiple sclerosis: Implications for lesion pathogenesis........................................................................................................................................ 22
Primary central nervous system large B-cell lymphoma with prolific, mixed T-cell and macrophage infiltrates, mimicking multiple sclerosis........................................................................................................................................ 23
microRNAs: critical regulators in Th17 cells and players in diseases........................................................................................................................................ 23
Sphingosine and FTY720 directly bind pro-survival 14-3-3 proteins to regulate their function................................................................. 23
99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: Epstein-Barr virus and multiple sclerosis: epidemiological evidence........................................................................................................................................ 24
99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: triggering of autoimmune diseases by infections................................................................. 24
Role of MRI in diagnosis and treatment of multiple sclerosis. ...................................................... 24
Antiphospholipid syndrome and central nervous system.............................................................. 25
An exploratory study on emotion recognition in patients with a clinically isolated syndrome and multiple sclerosis.................................................................................................................. 25
Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis.......................................................... 25
Therapy of MS................................................................................................................................. 26
Force-pain relationship in functional magnetic and electrical stimulation of subjects with paresis and preserved sensation. .......................................................... 26
A high-density ERP study reveals latency, amplitude, and topographical differences in multiple sclerosis patients versus controls................................................................. 27
Hyperbaric oxygen therapy for multiple sclerosis........................................................................ 27
The influence of pregnancy on development and course of chronic relapsing experimental autoimmune encephalomyelitis in rats: implications for multiple sclerosis. ........................................................................ 28
Epidemiology of multiple sclerosis in western Herzegovina and Herzegovina–Neretva Canton, Bosnia and Herzegovina. .......................................................................................... 28
The pathogenesis of murine coronavirus infection of the central nervous system....................... 29
Laquinimod, a new oral autoimmune modulator for the treatment of relapsing-remitting multiple sclerosis.................................................................................. 29
New drug therapies for multiple sclerosis................................................................................... 29
Stem cell transplantation in multiple sclerosis........................................................................... 30
Multiple Sclerosis-Related Central Pain Disorders. ..................................................................... 30
CNS Penetration for Small Molecule Therapeutics Do Not Increase in Multiple Sclerosis (MS) and Alzheimer’s Disease (AD) Related Animal Models Despite Reported Blood-brain Barrier Disruption. ......................................................... 30
Multiple sclerosis in the elderly patient....................................................................................... 31
[Update on current care guidelines: diagnostics, treatment and rehabilitation of multiple sclerosis]. ................................................................................................................................. 31
Interferon-beta Inhibits Th17 Cell Differentiation in Patients with Multiple Sclerosis............. 31
Relation between Epstein-Barr virus and multiple sclerosis: analytic study of scientific production. ................................................................................................................................. 32
Social consequences of multiple sclerosis: clinical and demographic predictors - a historical prospective cohort study. ................................................................. 32
Epstein-Barr virus neutralizing and early antigen antibodies in multiple sclerosis.................... 32
Appearance of Cxcl10-expressing cell clusters is common for traumatic brain injury and neurodegenerative disorders................................................................. 33
Does hippotherapy improve balance in persons with multiple sclerosis: a systematic review. .... 33
Time-dependent fate of transplanted Neural Precursor Cells in experimental autoimmune encephalomyelitis mice................................................................. 34
The endocannabinoid system in the inflammatory and neurodegenerative processes of multiple sclerosis and of amyotrophic lateral sclerosis................................................................. 34
The endocannabinoid system: A new entry in remote cell death mechanisms............................ 35
Glatiramer acetate and the glatiramoid class of immunomodulator drugs in multiple sclerosis: an update.................................................................................................................... 35
Fingolimod for relapsing multiple sclerosis: an update............................................................... 36
Treating multiple sclerosis with fingolimod or intramuscular interferon.................................... 36
Update on the treatment options for multiple sclerosis ................................................................. 37
Treating multiple sclerosis with monoclonal antibodies: a 2010 update ........................................ 37
Recombinant forms of myelin antigens expressed on Chinese hamster ovary (CHO) cells as a tool for identification of autoantibodies in serum of multiple sclerosis patients .................................................. 38
The effect of textured insoles on gait patterns of people with multiple sclerosis .............................. 38
Mass spectrometry measurement of a therapeutic peptide for use in multiple sclerosis .................. 39
[Multiple sclerosis as a polygenic disease: an update] ..................................................................... 39
Utilization of health promotion and wellness services among middle-aged and older adults with multiple sclerosis in the mid-west US .......................................................... 39
Genome-wide association study of circulating vitamin D levels ......................................................... 40
Peroxisome proliferator-activated receptor delta agonists inhibit T helper type 1 (Th1) and Th17 responses in experimental allergic encephalomyelitis .............................................. 40
Downregulation of IL-17 and IFN-gamma in the optic nerve by beta-elemene in experimental autoimmune encephalomyelitis ......................................................................................... 41
EUROBID-an EU-funded project to study the developing brain barriers ........................................ 41
The osteopontin gene +1239A/C single nucleotide polymorphism is associated with type 1 diabetes mellitus in the Italian population .............................................................................. 42
Soluble CD30: a biomarker for evaluating the clinical risk versus benefit of IFNâ1A treatment in multiple sclerosis patients .................................................................................................. 42
NAD(P)H oxidase and pro-inflammatory response during maximal exercise: role of C242T polymorphism of the P22PHOX subunit ............................................................ 43
Serum and cerebrospinal fluid antioxidant activity and lipid peroxidation in Guillain-Barre syndrome and multiple sclerosis patients .......................................................... 43
Adherence to disease-modifying drugs in patients with multiple sclerosis: a consensus statement from the Middle East MS Advisory Group ............................................................... 44
Prognostic factors of multiple sclerosis in Lebanon ......................................................................... 44
Clinical practice improvement approach in multiple sclerosis rehabilitation: a pilot study .............. 45
Iron Status in Children With Recurrent Episodes of Tumefactive Cerebral Demyelination ................ 47
NRAMP1 (SLC11A1) Variants: Genetic Susceptibility to Multiple Sclerosis ....................................... 47
Non-invasive brain mapping of motor-related areas of four limbs in patients with clinically isolated syndrome compared to healthy normal controls ..................................................... 47
Cutting Edge: critical role for PYCARD/ASC in the development of experimental autoimmune encephalomyelitis .............................................................. 48
An imbalance of two functionally and phenotypically different subsets of plasmacytoid dendritic cells characterizes the dysfunctional immune regulation in multiple sclerosis ................................ 48
TGF-(beta) Enhances Effector Th1 Cell Activation but Promotes Self-Regulation via IL-10 .............. 48
Multiple sclerosis: hyperintense lesions in the brain on T1-weighted MR images assessed by diffusion tensor imaging ................................................................. 49
Imaging biomarkers in multiple sclerosis ...................................................................................... 49
Detection of viral DNA sequences in the cerebrospinal fluid of patients with multiple sclerosis ...... 50
Can psychiatrists and neurologists predict their patients’ participation preferences? ......................... 50
Regionally Distinct White Matter Lesions Do Not Contribute to Regional Gray Matter Atrophy in Patients with Multiple Sclerosis ........................................................... 51
HERVs in Neuropathogenesis ......................................................................................................... 51
Molecular Regulation of JC Virus Tropism: Insights into Potential Therapeutic Targets for Progressive Multifocal Leukoencephalopathy ................................................................. 52
Studies in the Modulation of Experimental Autoimmune Encephalomyelitis ................................ 52
Epstein-Barr Virus Infection and Multiple Sclerosis: A Review ..................................................... 52
Pathogenesis of Murine Coronavirus in the Central Nervous System .......................................................... 53
Genetic association of CASP8 polymorphisms with primary progressive multiple sclerosis .................. 53
What's in a name? Experimental encephalomyelitis: 'Allergic' or 'autoimmune' ........................................ 53
Elevated plasma C4a levels in multiple sclerosis correlate with disease activity ........................................ 54
IL8 and CXCL13 are potent chemokines for the recruitment of human neural precursor cells across brain endothelial cells .......................................................... 54
No evidence for an effect of DNA methylation on multiple sclerosis severity at HLA-DRB1*15 or HLA-DRB5 .......................................................... 55
Anti-myelin antibodies modulate clinical expression of childhood multiple sclerosis .............................. 55
Cyclooxygenase-2 expression in oligodendrocytes increases sensitivity to excitotoxic death .................. 56
Prolyl oligopeptidase is inhibited in relapsing-remitting multiple sclerosis ............................................ 56
Diffusion-weighted imaging in noncompressive myelopathies: a 33-patient prospective study ............... 57
Epstein-Barr virus, 9.4 T MRI and phosphodiesterase inhibitors in multiple sclerosis ............................... 57
Characteristics of multiple sclerosis at onset and delay of diagnosis and treatment in Spain (The Novo Study) ........................................................................................................................................ 57
Pseudobulbar affect: prevalence and quality of life impact in movement disorders ............................... 58
Erratum to: Oligoclonal bands and MRI in clinically isolated syndromes: predicting conversion time to multiple sclerosis .......................................................... 58
Atrophy mainly affects the limbic system and the deep grey matter at the first stage of multiple sclerosis ........................................................................................................................................ 58
Magnetic resonance spectroscopy evaluation in patients with neuromyelitis optica ............................... 59
Impaired information processing speed and attention allocation in multiple sclerosis patients versus controls: A high-density EEG study ........................................................................................................ 59
Factors influencing the health-related quality of life in Hungarian multiple sclerosis patients ............... 60
Midbrain Cleft as a Cause of Chronic Internuclear Ophthalmoplegia, Progressive Ataxia, and Facial Weakness ........................................................................................................................................ 60
Abnormal Anterior Pretectal Nucleus Activity Contributes to Central Pain Syndrome .......................... 60
Activated T-cells inhibit neurogenesis by releasing granzyme B: rescue by Kv1.3 blockers ....................... 61
A Novel Autotaxin Inhibitor Reduces Lysophosphatidic Acid Levels in Plasma and the Site of Inflammation ........................................................................................................................................ 61
Efficacy and Safety of Tadalafil for Erectile Dysfunction in Patients with Multiple Sclerosis ............... 62
Intrathecal baclofen for spasticity management: a comparative analysis of spasticity of spinal vs cortical origin ........................................................................................................................................ 62
The Th17 immune response in renal inflammation .................................................................................... 63
The changing demographic pattern of multiple sclerosis epidemiology ................................................. 63
Venous abnormalities and multiple sclerosis: another breakthrough claim? ........................................... 63
Oral therapies for multiple sclerosis: are we there yet? .......................................................................... 63
Applying functional MRI to the spinal cord and brainstem ................................................................. 64
Specialized support programs increase treatment adherence, reducing relapses for multiple sclerosis patients ........................................................................................................................................ 64
Preclinical testing of strategies for therapeutic targeting of human T-cell trafficking in vivo .................. 64
[Progress of therapy in patients with multiple sclerosis] ........................................................................ 64
Differential ICAM-1 isoform expression regulates the development and progression of experimental autoimmune encephalomyelitis .................................................................................... 65
Heparanase upregulates Th2 cytokines, ameliorating experimental autoimmune encephalitis .......... 65
The estimated benefits of vitamin D for Germany ..................................................................................... 66
Successful Treatment of Metachromatic Leukodystrophy Using Bone Marrow Transplantation of HoxB4 Overexpressing Cells. .................................................................66
A window of opportunity for no treatment in early multiple sclerosis? ................................................66
Analysis of multiple candidate genes in association with phenotypes of multiple sclerosis. .................67
Disease onset in familial and sporadic primary progressive multiple sclerosis. ..................................67
Clinical trial of a formal group fatigue program in multiple sclerosis. ................................................68
Mesenchymal stem cells for multiple sclerosis: can we find the answer? ...........................................68
Interleukin 18 Receptor 1 expression distinguishes patients with multiple sclerosis. ..........................68
Alzheimer drug worsens neurological dysfunction in multiple sclerosis. .............................................68
Behind the paper: saved from the drain. .............................................................................................69
Molecular oracles for multiple sclerosis therapy. ...............................................................................69
Stem cell transplantation in multiple sclerosis: current status and future prospects. ..........................69
Signals to promote myelin formation and repair. .................................................................................69
Genome, epigenome and RNA sequences of monozygotic twins discordant for multiple sclerosis. ....70
Twin study surveys genome for cause of multiple sclerosis. ...............................................................70
[Radiologically isolated syndrome: Multiple sclerosis based solely on MRI findings?] ............................70
["Chronic cerebrospinal venous insufficiency" and multiple sclerosis: Critical analysis and first observation in an unselected cohort of MS patients.] ........................................................71
Subvocal articulatory rehearsal during verbal working memory in multiple sclerosis. .........................71
In vivo multi-slice mapping of myelin water content using T(2)(*) decay. ...........................................72
Disease modeling in multiple sclerosis: Assessment and quantification of sources of variability in brain parenchymal fraction measurements............................................................72
Immunization with pVAXhsp65 Decreases Inflammation and Modulates Immune Response in Experimental Encephalomyelitis. ..........................................................73
Evaluation of postural balance control in patients with multiple sclerosis - effect of different sensory conditions and arithmetic task execution. A pilot study. .............................................73
Clinical and electronystagmographical evaluation of vestibular symptoms in relapsing remitting multiple sclerosis.................................................................74
Multiple sclerosis impairs ability to detect abrupt appearance of a subliminal stimulus. ..................74
A case of neurofibromatosis and multiple sclerosis. ...........................................................................74
Clinical spectrum associated with aquaporin-4 antibodies (NMO-IgG). .............................................75
Cardiotoxicity and other adverse events associated with mitoxantrone treatment for MS. ..................75
A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis. .................................76
Combined effects of smoking, anti-EBNA antibodies, and HLA-DRB1*1501 on multiple sclerosis risk.76
Default-mode network dysfunction and cognitive impairment in progressive MS..................................77
The limits of functional reorganization in multiple sclerosis. ...............................................................77
Role of Cytokines as Mediators and Regulators of Microglial Activity in Inflammatory Demyelination of the CNS..........................................................................................77
Kinetics of IL-17- and interferon-gamma-producing PLPp-specific CD4 T cells in EAE induced by coinjection of PLPP/IFA with pertussis toxin in SJL mice.................................................78
Progesterone attenuates neurological behavioral deficits of experimental autoimmune encephalomyelitis through remyelination with nucleus-sublocalized Olig1 protein..........................................................78
Matrix metalloproteinases and neurotrauma: evolving roles in injury and reparative processes. .......79
Multiple sclerosis: understanding a complex neurological condition.................................................79
Modulation of inflammation by chondroitin sulfate. .........................................................................79
A diminished response to formalin stimulation reveals a role for the glutamate transporters in the altered pain sensitivity of mice with experimental autoimmune encephalomyelitis (EAE). .............80

Economic burden of multiple sclerosis: a systematic review of the literature ........................................... 80
The effect of single nucleotide polymorphisms from genome wide association studies in multiple sclerosis on gene expression ........................................................................................................... 81
Multiple sclerosis susceptibility-associated SNPs do not influence disease severity measures in a cohort of Australian MS patients ........................................................................................................... 81
Imaging evaluation of demyelinating processes of the central nervous system .................................................. 81
Estradiol inhibits ongoing autoimmune neuroinflammation and NF(κ)B-dependent CCL2 expression in reactive astrocytes ........................................................................................................................................ 82
EATING OURSELVES TO DEATH AND DESPAIR: THE CONTRIBUTION OF ADIPOITY AND INFLAMMATION TO DEPRESSION ........................................................................................................... 82
Structural and functional hippocampal changes in multiple sclerosis patients with intact memory function ............................................................................................................................................... 83
[Oral therapy for multiple sclerosis!] ..................................................................................................................................................................................... 83
[Multiple sclerosis. What about treatment with monoclonal antibodies?] ................................................................. 83
A role for VAV1 in experimental autoimmune encephalomyelitis and multiple sclerosis .................................................. 84
Risks vs benefits of glatiramer acetate: a changing perspective as new therapies emerge for multiple sclerosis ............................................................................................................................................... 84
Necrotizing meningoencephalitis of Pug Dogs associates with dog leukocyte antigen class II and resembles acute variant forms of multiple sclerosis ................................................................................................. 85
Characterization of D6S2806 and D6S2879 short tandem repeat loci in HLA-DRB1 region in Iranian population .............................................................................................................................. 85
Infection, inflammation, and chronic diseases: consequences of a modern lifestyle .................................................. 85
A critical role for virus-specific CD8(+) CTLs in protection from Theiler's virus-induced demyelination in disease-susceptible SJL mice ................................................................................................. 86
[A clinical comparative study of multiple sclerosis and neuromyelitis optica.] .................................................................................................................................................................................. 86
[Construction and clinical application of lentivirus-AQP4 expressing vector] .......................................................... 87
**Betaferon in the treatment of multiple sclerosis.**  
Vidović M, Sinanović O, Burina A, Hudić J, Sehanović A.  
University Department of Neurology, Tuzla University Clinical Center, Tuzla, Bosnia and Herzegovina. vidovic_mirjana@hotmail.com  
The aim of the study was to analyze the usefulness and side effects of treatment with interferon beta 1B (Betaferon) in patients with the relapsing-remitting form of multiple sclerosis (RRMS). The study included 32 RRMS patients that had completed two-year therapy with interferon beta 1B or were still receiving this therapy. Every six months, patients were clinically evaluated and scored by the Expanded Disability Status Scale (EDSS). Two-year therapy was completed by 11 (34.3%) of 32 RRMS patients. Relapse was verified in 4 (36.36%) patients. The mean EDSS score was 2.45 +/- 1.03 at the beginning of therapy and 2.54 +/- 0.98 after two-year therapy; the difference was not statistically significant. In 2 (6.25%) patients on therapy for 18 months there was no relapse, and the mean EDSS was 1.75 +/- 0.35 (both at therapy introduction and at 18 months). Five (15.62%) patients were on therapy for one year. The mean EDSS was 1.6 +/- 1.08 at the beginning of therapy and 1.5 +/- 0.70 at one year. One patient experienced relapse. Two patients were on therapy for six months. They had no relapses with the same EDSS at six months as at therapy introduction (2.0). At the beginning of 2008, another 12 patients started therapy with interferon beta 1B. In conclusion, our experience with two-year interferon beta-1B therapy for RRMS is favorable, with a relatively low rate of relapses (36.36%) and without significant worsening on EDSS. The medication side effects were mild and transient.  
PMID: 20405637 [PubMed - in process]

**Evidence for polygenic susceptibility to multiple sclerosis--the shape of things to come.**  
International Multiple Sclerosis Genetics Consortium (IMSGC), Bush WS, Sawcer SJ, de Jager PL, Oksenberg JR, McCauley JL, Pericak-Vance MA, Haines JL.  
Vanderbilt University, USA. wbush@chgr.mc.vanderbilt.edu  
It is well established that the risk of developing multiple sclerosis is substantially increased in the relatives of affected individuals and that most of this increase is genetically determined. The observed pattern of familial recurrence risk has long suggested that multiple variants are involved, but it has proven difficult to identify individual risk variants and little has been established about the genetic architecture underlying susceptibility. By using data from two independent genome-wide association studies (GWAS), we demonstrate that a substantial proportion of the thousands of variants that individually fail to show statistically significant evidence of association have allele frequencies in cases that are skewed away from the null distribution through the effects of multiple as-yet-unidentified risk loci. The collective effect of 12,627 SNPs with Cochran-Mantel-Haenszel test (p < 0.2) in our discovery GWAS set optimally explains approximately 3% of the variance in MS risk in our independent target GWAS set, estimated by Nagelkerke's pseudo-R(2). This model has a highly significant fit (p = 9.90E-19). These results statistically demonstrate a polygenic component to MS susceptibility and suggest that the risk alleles identified to date represent just the tip of an iceberg of risk variants likely to include hundreds of modest effects and possibly thousands of very small effects. (c) 2010 The American Society of Human Genetics. Published by Elsevier Inc. All rights reserved.  
Robust replication of genotype-phenotype associations across multiple diseases in an electronic medical record.
Center for Human Genetics Research, Department of Molecular Physiology and Biophysics, Vanderbilt University School of Medicine, Nashville, TN 37232, USA.
Large-scale DNA databanks linked to electronic medical record (EMR) systems have been proposed as an approach for rapidly generating large, diverse cohorts for discovery and replication of genotype-phenotype associations. However, the extent to which such resources are capable of delivering on this promise is unknown. We studied whether an EMR-linked DNA biorepository can be used to detect known genotype-phenotype associations for five diseases. Twenty-one SNPs previously implicated as common variants predisposing to atrial fibrillation, Crohn disease, multiple sclerosis, rheumatoid arthritis, or type 2 diabetes were successfully genotyped in 9483 samples accrued over 4 mo into BioVU, the Vanderbilt University Medical Center DNA biobank. Previously reported odds ratios (OR(PR)) ranged from 1.14 to 2.36. For each phenotype, natural language processing techniques and billing-code queries were used to identify cases (n = 70-698) and controls (n = 808-3818) from deidentified health records. Each of the 21 tests of association yielded point estimates in the expected direction. Previous genotype-phenotype associations were replicated (p < 0.05) in 8/14 cases when the OR(PR) was > 1.25, and in 0/7 with lower OR(PR). Statistically significant associations were detected in all analyses that were adequately powered. In each of the five diseases studied, at least one previously reported association was replicated. These data demonstrate that phenotypes representing clinical diagnoses can be extracted from EMR systems, and they support the use of DNA resources coupled to EMR systems as tools for rapid generation of large data sets required for replication of associations found in research cohorts and for discovery in genome science. (c) 2010 The American Society of Human Genetics. Published by Elsevier Inc. All rights reserved.

Fingolimod (FTY720) Enhances Remyelination Following Demyelination of Organotypic Cerebellar Slices.
Miron VE, Ludwin SK, Darlington PJ, Jarjour AA, Soliven B, Kennedy TE, Antel JP.
From the Neuroimmunology Unit,* and the Center for Neuronal Survival, McGill University, Montreal Neurological Institute, Montreal, Canada; the Department of Neuropathology, Queen's University, Kingston, Ontario, Canada; the Medical Research Council Centre for Regenerative Medicine, The Queen's Medical Research Institute, University of Edinburgh, Edinburgh, United Kingdom; and the Department of Neurology, University of Chicago, Chicago, Illinois.
Remyelination, which occurs subsequent to demyelination, contributes to functional recovery and is mediated by oligodendrocyte progenitor cells (OPCs) that have differentiated into myelinating cells. Therapeutics that impact remyelination in the CNS could be critical determinants of long-term functional outcome in multiple sclerosis (MS). Fingolimod is a S1P receptor modulator in MS clinical trials due to systemic anti-inflammatory properties, yet may impact cells within the CNS by crossing the blood-brain barrier. Previous studies using isolated dissociated cultures indicate that neural cells express S1P receptors and respond to receptor engagement. Our objective was to assess the effects of fingolimod on myelin-related processes within a multicellular environment that maintains physiological cell-cell interactions, using organotypic cerebellar slice cultures. Fingolimod treatment had no impact on myelin under basal conditions. Fingolimod treatment subsequent to lyssolecithin-induced demyelination enhanced remyelination and process extension by OPCs and mature oligodendrocytes, while increasing microglia numbers and immunoreactivity for the astrocytic marker glial fibrillary acidic protein. The number of phagocytosing microglia was not increased by fingolimod. Using S1P receptor specific agonists and antagonists, we determined that fingolimod-induced effects on remyelination and astrogliosis were mediated primarily through S1P3 and S1P5, whereas enhanced microgliosis was mediated through S1P1 and S1P5. Taken together, these data demonstrate that fingolimod modulates multiple neuroglial cell responses, resulting in enhanced remyelination in organotypic slice cultures that maintain the complex cellular interactions of the mammalian brain.
PMID: 20413685 [PubMed - as supplied by publisher]
5. Anal Bioanal Chem. 2010 Apr 15. [Epub ahead of print]
Evaluating the effects of estradiol on endothelial nitric oxide stimulated by erythrocyte-derived ATP using a microfluidic approach.
Letourneau S, Hernandez L, Faris AN, Spence DM.
Department of Chemistry, Michigan State University, East Lansing, MI, 48824, USA.
Recently, estrogens have been reported to have protective effects against experimental autoimmune encephalomyelitis (EAE), a murine model of multiple sclerosis (MS). Although the molecular mechanism for such a protective effect is currently incomplete, we hypothesized that estradiol may reduce the release of ATP from erythrocytes (ERYs), thereby lowering the production of nitric oxide (NO) by endothelial cells. Here, we report on the use of a microfluidic device to investigate the direct effects of the estrogen estradiol on endothelial cell nitric oxide production. In addition, the incorporation of a thin polycarbonate membrane into the device enabled the passage of ERYs through the device to determine indirect effects of estradiol on NO production that may be mediated by ERYs. When these ERYs were incubated with increasing concentrations of estradiol, the NO production from the endothelial cells was attenuated to a value that was only 59 +/- 7% of ERYs in the absence of estradiol. This decrease in NO production coincides with reductions in ERY-derived ATP release in the presence of estradiol. Estradiol is typically reported to have NO-stimulating effects; however, such reports have employed in vitro experimental designs that include only a single cell type. To demonstrate the potential importance of this attenuation of ATP from ERYs, results from a small-scale study show that the ATP release obtained from healthy controls was 138 +/- 21 nM (n = 18) while the release from the ERYs obtained from people with MS was 375 +/- 51 nM (n = 11). The studies reported here involving multiple cell types (endothelial cells and ERYs) may lead to a reappraisal of the in vivo activities of estradiol.
PMID: 20393839 [PubMed - as supplied by publisher]

Department of Allergy and Immunology, Respiratory Institute, Cleveland Clinic, Cleveland, Ohio 44195, USA.
BACKGROUND: Glatiramer acetate is an immunomodulatory drug that is widely prescribed for the treatment of multiple sclerosis. It is frequently associated with local injection site reactions and generalized urticaria. It is also associated with immediate postinjection systemic reactions in approximately 10% of patients. To our knowledge, no desensitization protocols for glatiramer acetate have been published to date. OBJECTIVES: To evaluate the safety and efficacy of glatiramer acetate desensitization in a series of patients with multiple sclerosis. METHODS: Six patients with multiple sclerosis and glatiramer acetate-associated local or systemic reactions underwent a 4-hour outpatient desensitization procedure at Cleveland Clinic between 2003 and 2008. Beginning with 20 ng, we administered subcutaneous glatiramer acetate suspension in increasing dosages every 15 minutes. Patient outcomes were monitored by return clinic visit and telephone follow-up. RESULTS: No episodes of anaphylaxis or serious adverse reactions occurred during or immediately after desensitization. One patient suspended therapy after 14 months due to persistent local injection site reactions. All other patients successfully continued glatiramer acetate therapy. CONCLUSION: Glatiramer acetate offers significant benefit to patients with multiple sclerosis. Our experience suggests that patients who suspend its use owing to local or systemic reactions can be successfully and safely desensitized and can resume medication use. To our knowledge, this is the first report of successful desensitization to glatiramer acetate in patients with multiple sclerosis.
PMID: 20408342 [PubMed - in process]
**A 3-year magnetic resonance imaging study of cortical lesions in relapse-onset multiple sclerosis.**  
Multiple Sclerosis Center of Veneto Region, First Neurology Clinic, Department of Neurosciences, University Hospital of Padua, Padua, Italy.  
OBJECTIVE: We assessed the occurrence, extent, and frequency of formation of cortical lesions (CLs) in patients with relapsing-remitting (RR) and secondary progressive (SP) multiple sclerosis (MS), and their relationship with cortical atrophy and disability progression. METHODS: One-hundred seven MS patients (76 RRMS and 31 SPMS), enrolled in a prospective, longitudinal magnetic resonance imaging (MRI) study, were assessed clinically and by brain MRI (including a double inversion recovery sequence) 3 years after study initiation. CL number and volume, T2 white matter (WM) lesion volume, gray matter fraction, and expanded disability status scale (EDSS) were measured. RESULTS: At baseline, CLs were detected in 64.4% of RRMS and 74.2% of SPMS patients. During follow-up, 132 new CLs were found in 44 RRMS patients (57.9%; 0.8 new CL/patient/yr) and 61 in 15 SPMS patients (48.4%; 1.0 new CL/patient/yr). Among these patients, only 31 also showed at least 1 new WM lesion. CL number and volume increases were higher in the 52 patients with a clinical worsening compared with those without (p < 0.001). Baseline CL volume correlated with baseline EDSS (r = 0.36, p < 0.001) and EDSS changes over time (r = 0.51, p < 0.001). Baseline CL volume was an independent predictor of EDSS accumulation and GM volume change at follow-up in both patient groups. In SPMS patients, baseline T2 WM lesion volume was another independent predictor of EDSS worsening. INTERPRETATION: In relapse-onset MS, CLs accumulate over time and are associated with disability progression. The quantification of CLs might represent an additional useful paraclinical tool to monitor MS evolution.  
PMID: 20373349 [PubMed - in process]

**Chronic cerebrospinal venous insufficiency and multiple sclerosis.**  
Multiple Sclerosis Center, Department of Neurology, Wayne State University School of Medicine, 4201 St Antoine, Detroit, MI 48323, USA. okhan@med.wayne.edu  
A chronic state of impaired venous drainage from the central nervous system, termed chronic cerebrospinal venous insufficiency (CCSVI), is claimed to be a pathologic phenomenon exclusively seen in multiple sclerosis (MS). This has invigorated the causal debate of MS and generated immense interest in the patient and scientific communities. A potential shift in the treatment paradigm of MS involving endovascular balloon angioplasty or venous stent placement has been proposed as well as conducted in small patient series. In some cases, it may have resulted in serious injury. In this Point of View, we discuss the recent investigations that led to the description of CCSVI as well as the conceptual and technical shortcomings that challenge the potential relationship of this phenomenon to MS. The need for conducting carefully designed and rigorously controlled studies to investigate CCSVI has been recognized by the scientific bodies engaged in MS research. Several scientific endeavors examining the presence of CCSVI in MS are being undertaken. At present, invasive and potentially dangerous endovascular procedures as therapy for patients with MS should be discouraged until such studies have been completed, analyzed, and debated in the scientific arena.  
PMID: 20373339 [PubMed - in process]
**Paced glottic closure for controlling aspiration pneumonia in patients with neurologic deficits of various causes.**
Department of Otolaryngology-Head and Neck Surgery, Case Western Reserve University School of Medicine, Ohio, USA.
OBJECTIVES: We undertook to determine whether paced vocal fold adduction can check aspiration in patients with various neurologic conditions. METHODS: Five patients with fluoroscopically documented aspiration and repeated pneumonias were enrolled. Two previously reported patients with hemispheric stroke were compared to 3 additional subjects with brain stem-basal ganglia and cerebellar stroke, cerebral palsy, and multiple sclerosis. A modified Vocare stimulator was implanted subcutaneously and linked to the ipsilateral recurrent laryngeal nerve via perineural electrodes. Vocal fold adduction and glottic closure were effected with pulse trains (42 Hz; 1.2 mA; 188 to 560 micros) and recorded with Enhanced Image J. Fluoroscopy results with and without stimulation were assessed by 2 independent blinded reviewers. Pneumonia rates were compared before, during, and after the 6- to 12-month enrollment periods. RESULTS: There was statistically significant vocal fold adduction (p < 0.05) for all patients, further verified with bolus arrest (p < 0.05 for thin liquids, thick liquids, and puree depending on the speech-language pathologist). Pneumonia was prevented in 4 of the 5 patients during enrollment. In the fifth patient, who had brain stem-basal ganglia and cerebellar stroke, we were unable to completely seal the glottis and open the cricopharyngeus enough to handle his secretions. CONCLUSIONS: Vocal fold pacing for aspiration pneumonia from a variety of neurologic insults appears to be appropriate as long as the glottis can be sealed. It is not sufficient when the cricopharyngeus must be independently opened.

PMID: 20392026 [PubMed - in process]

**Effect of 4-Aminopyridine on Action Potential Parameters in Isolated Dog Purkinje Fibers.**
Thomas G, Klaft B, Blight A.
INTRODUCTION: 4-Aminopyridine (fampridine), a potassium channel blocker, has demonstrated efficacy in improving lower extremity strength and walking speed in patients with multiple sclerosis. Since in vitro electrophysiologic studies are recommended for evaluating a drug's potential to prolong the QT interval and induce such cardiac arrhythmias as Torsades de Pointes, we examined the electrophysiologic effects of 4-aminopyridine (0.5, 5.0, 50, and 500 microM) on isolated canine Purkinje fibers. METHODS: Microelectrodes monitored the resting membrane potential, overshoot, amplitude of action potential (AP), and maximal rate of depolarization of the AP upstroke in Purkinje fibers stimulated at 0.5 and 1.0 Hz. RESULTS: None of the above variables were altered in the presence of 4-aminopyridine. The AP duration at 30%, 50%, and 90% repolarization was also monitored, with only the 500-microM concentration at the 1.0-Hz frequency significantly increasing these values with respect to baseline (P < 0.05). However, the small sample size (N = 4) was small. The proportional increases, and their 95% confidence intervals, were 90.8% (-36.4%, 218.0%), 25.8% (11.9%, 39.7%), and 22.0% (14.9%, 29.1%) for APD 30%, 50%, and 90% repolarization, respectively. Reverse rate dependence was not observed, suggesting inhibition of ion channels other than those contributing to QT interval prolongation.
PMID: 20428229 [PubMed]
Relationship of cortical atrophy to fatigue in patients with multiple sclerosis.
Pellicano C, Gallo A, Li X, Ikonomidou VN, Evangelou IE, Ohayon JM, Stern SK, Ehrmantraut M, Cantor F, McFarland HF, Bagnato F.
Neuroimmunology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Dr, Bethesda, MD 20892-1400, USA.
BACKGROUND: Fatigue is a common and disabling symptom of multiple sclerosis (MS). Previous studies reported that damage of the corticostriatothalamocortical circuit is critical in its occurrence. OBJECTIVE: To investigate the relationship between fatigue in MS and regional cortical and subcortical gray matter atrophy. DESIGN: Case-control study. SETTING: National Institutes of Health. PARTICIPANTS: Twenty-four patients with MS and 24 matched healthy volunteers who underwent 3.0-T magnetic resonance imaging and evaluations of fatigue (Modified Fatigue Impact Scale) and depression (Center for Epidemiologic Studies Depression Scale). MAIN OUTCOME MEASURES: Relationship between thalamic and basal ganglia volume, cortical thickness of frontal and parietal lobes, and, in patients, T2 lesion volume and normal-appearing white matter volume and the extent of fatigue. RESULTS: Patients were more fatigued than healthy volunteers (P = .04), while controlling for the effect of depression. Modified Fatigue Impact Scale score correlated with cortical thickness of the parietal lobe (r = -0.50, P = .01), explaining 25% of its variance. The posterior parietal cortex was the only parietal area significantly associated with the Modified Fatigue Impact Scale scores. CONCLUSIONS: Cortical atrophy of the parietal lobe had the strongest relationship with fatigue. Given the implications of the posterior parietal cortex in motor planning and integration of information from different sources, our preliminary results suggest that dysfunctions in higher-order aspects of motor control may have a role in determining fatigue in MS.
PMID: 20385911 [PubMed - in process]

Phillips JT.
PMID: 20385901 [PubMed - in process]

Overview of the biology of type I interferons.
Kalliolas GD, Ivashkiv LB.
Arthritis and Tissue Degeneration Program and Department of Medicine, Hospital for Special Surgery, 535 East 70th Street, Research Building 4th floor, New York, NY 10021, USA. ivashkivl@hss.edu.
ABSTRACT: Type I interferons are pleiotropic cytokines with antiviral, antitumor and immunoregulatory functions. An aspect of their complex biology is the paradox that, depending on context, type I interferons can be anti-inflammatory and tissue protective or can be proinflammatory and promote autoimmunity. Along these lines, the activation of type I interferon pathways is effective in suppressing disease activity in patients with multiple sclerosis and in animal models of arthritis and colitis, while there is an expectation that blockade of the same pathways will be beneficial in the treatment of patients with systemic lupus erythematosus.
PMID: 20392288 [PubMed - as supplied by publisher]
Pathogenic mechanisms and experimental models of multiple sclerosis.
Department of Immunology and Inflammation, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, 06887, USA.
Multiple sclerosis (MS) is a devastating autoimmune disease that affects more than 1 million people worldwide and severely compromises motor and sensory function through demyelination and axonal loss. This review covers current therapies, lessons learned from failed clinical trials, genetic susceptibility, key cell types involved, animal models, gene expression, and biomarker information. The current first-line therapies for MS include the type I interferons (IFN-I) and glatiramer acetate (GA) but because of their limited effectiveness new therapeutic modalities are required. Tysabri is an anti very late antigen-4 antibody that antagonizes the migration of multiple cell types and appears more efficacious as compared to the IFNs or GA. Tysabri blocks the transmigration of T cells and monocytes, which indicates that blocking multiple cell types may increase the effectiveness of the therapy. However, this therapy may increase the risk of progressive multifocal leukoencephalopathy. The major cell types hypothesized to be pathogenic include T cells and antigen-presenting cells, including B cells. The correlation of the animal model experimental autoimmune encephalomyelitis (EAE) of MS and its predictive value to determine efficacy in the clinic appears limited. However, all current therapies do demonstrate efficacy in EAE models. There are also examples of mechanisms that have worked in EAE but have failed in the clinic, such as the TNF-alpha antagonists and anti-p40 (a subunit of IL-12 and IL-23). The MS field would benefit if clinical biomarkers were available to monitor clinical efficacy. The etiology of MS remains elusive but additional understanding of mechanisms involved in the pathogenesis of MS may guide us to more effective treatment and management of this autoimmune disease.
PMID: 20380590 [PubMed - as supplied by publisher]

15. Autoimmunity. 2010 Apr 7. [Epub ahead of print]
T regulatory cells lacking CD25 are increased in MS during relapse.
Fransson M, Burman J, Lindqvist C, Atterby C, Fagius J, Loskog A.
Clinical Immunology division, Uppsala University, Uppsala, 751 85, Sweden.
Dysregulation of inflammatory responses is considered to be a key element in autoreactive immune responses. T regulatory cells (Tregs) are important to maintain self-tolerance and the role of CD4(+)CD25(+)FoxP3(+) Tregs in autoimmunity has been extensively investigated. Recently, it was shown that Tregs in systemic lupus erythematosus lacked CD25 but were biologically functional. These data warrants for further investigation of CD25(-) Tregs in human autoimmunity. We analyzed relapsing-remitting multiple sclerosis (MS) patients by multicolor flow cytometry for the expression of CD3, CD4, IL2R (CD25), FoxP3, and the IL7R (CD127). Further, the level of Tregs was compared in remitting and relapsing patients and correlated with disease duration. Patients in relapse exhibited higher levels of FoxP3-positive Tregs lacking CD25 compared to healthy controls (p < 0.05), indicating that Tregs attempt to restrain immune activity during relapse. The proportion of Tregs tended to be decreased with disease duration, while CD25(+)CD4(+) and CD25(+)CD8(+) effector T-cell proportions were elevated and positively correlated with overall disease duration (p < 0.05). In conclusion, while MS patients in remission have normal levels of Tregs of different phenotype, relapsing patients show an increased proportion of systemic CD25(-)FoxP3(+) Tregs. With time, the proportion of Tregs decrease while effector T cells expand.
PMID: 20370571 [PubMed - as supplied by publisher]

Incidental detection of bilateral corectopia by photo screening leads to the diagnosis of multiple sclerosis. A case report.
Braverman RS, Enzenauer RW.
PURPOSE: To describe a case of an incidental finding of bilateral corectopia detected by photo screening which ultimately led to the diagnosis of multiple sclerosis. METHODS: Case presentation and literature review. RESULTS: Corectopia may be congenital or acquired. Midbrain corectopia is commonly caused by infarction and demyelinating disease can cause autonomic pupil abnormalities resulting in corectopia. CONCLUSION: A careful history and ocular examinatin can aid in determining the etiology of corectopia. Additional genetics or neurologic consultation may be necessary to diagnosis systemic disease.
PMID: 20361866 [PubMed - in process]

GPR30, but not estrogen receptor-alpha, is crucial in the treatment of experimental autoimmune encephalomyelitis by oral ethinyl estradiol.

Yates MA, Li Y, Chlebeck PJ, Offner H.

ABSTRACT: BACKGROUND: Remission of multiple sclerosis during periods of high ovarian hormone secretion (such as pregnancy) has led to a great deal of interest in the potential for estrogens to treat autoimmune disease. Previous work has established that 17beta-estradiol can inhibit onset of experimental autoimmune encephalomyelitis (EAE), while ethinyl estradiol (EE) can reduce the severity of established disease. In the current study, the influence of estrogen receptor-alpha (ERalpha) and the G-protein coupled estrogen receptor (GPR30 or GPER) on EE's ability to treat EAE was explored. RESULTS: EE reduced disease severity in wild-type and ERalpha knockout (ERKO) mice, but did not alter disease in the GPR30KO group. Production of anti-inflammatory IL-10 increased in EE-ERKO mice (which showed reduced disease) but not in EE-GPR30KO mice (who did not have improved disease). CONCLUSIONS: Differential production of IL-10 following EE treatment in ERKO and GPR30KO animals may be responsible for the distinctly different effects on disease severity. Increased IL-10 in ERKO-EE compared to ERKO-Controls is likely to be an important factor in reducing established disease. The inability of EE to reduce disease in GPR30KO mice indicates an important but still undefined role for GPR30 in regulating immune reactivity.

PMID: 20403194 [PubMed - as supplied by publisher]


Custom CGH array profiling of copy number variations (CNVs) on chromosome 6p21.32 (HLA locus) in patients with venous malformations associated with multiple sclerosis.


ABSTRACT: BACKGROUND: Multiple sclerosis (MS) is a complex disorder thought to result from an interaction between environmental and genetic predisposing factors which have not yet been characterised, although it is known to be associated with the HLA region on 6p21.32. Recently, a picture of chronic cerebrospinal venous insufficiency (CCSVI), consequent to stenosing venous malformation of the main extra-cranial outflow routes (VM), has been described in patients affected with MS, introducing an additional phenotype with possible pathogenic significance. METHODS: In order to explore the presence of copy number variations (CNVs) within the HLA locus, a custom CGH array was designed to cover 7 Mb of the HLA locus region (6,899,999bp; chr6:29,900,001-36,800,000). Genomic DNA of the 15 patients with CCSVI/VM and MS was hybridised in duplicate. RESULTS: In total, 322 CNVs, of which 225 were extragenic and 97 intragenic, were identified in 15 patients. 234 known polymorphic CNVs were detected, the majority of these being situated in non-coding or extragenic regions. The overall number of CNVs (both extra- and intragenic) showed a robust and significant correlation with the number of stenosing VMs (Spearman: r=0.6590, p=0.0104; linear regression analysis r=0.6577, p=0.0106). The region we analysed contains 211 known genes. By using pathway analysis focused on angiogenesis and venous development, MS, and immunity, we tentatively highlight several genes as possible susceptibility factor candidates involved in this peculiar phenotype. CONCLUSIONS: The CNVs contained in the HLA locus region in patients with the novel phenotype of CCSVI/VM and MS were mapped in detail, demonstrating a significant correlation between the number of known CNVs found in the HLA region and the number of CCSVI-VMs identified in patients. Pathway analysis revealed common routes of interaction of several of the genes involved in angiogenesis and immunity contained within this region. Despite the small sample size in this pilot study, it does suggest that the number of multiple polymorphic CNVs in the HLA locus deserves further study, owing to their possible involvement in susceptibility to this novel MS/VM plus phenotype, and perhaps even other types of the disease.

PMID: 20426824 [PubMed - as supplied by publisher]
Multiple sclerosis and pregnancy: what does the patient think? a questionnaire study.  
Albrecht P, Fischer D, Moser A.  
Department of Neurology, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany.  
peter.albrecht@neuro.uni-luebeck.de.  
ABSTRACT: BACKGROUND: Multiple Sclerosis (MS) is primarily a disease of women in their childbearing years. Pregnancy and puerperium have opposite effects on the course of the disease. Nevertheless, no studies have been carried out yet on the level of information among female MS-patients regarding the interaction between MS and pregnancy. FINDINGS: Demographic data, clinical features of MS, course of MS during pregnancy and puerperium as well as knowledge concerning MS and pregnancy were evaluated by means of a questionnaire in 154 female MS-patients. The level of information was significantly higher (p < 0.001) in women who had been pregnant in the past with the diagnosis MS known at this point of time. Furthermore patients reported about a lower frequency of relapses during pregnancy and a higher frequency of relapses in the first six months after giving birth. CONCLUSIONS: The findings illustrate a lack of knowledge in female MS-patients concerning the interactions of MS and pregnancy. In order to make their own independent decision based on scientific facts known to date, female MS-patients need to be better informed on issues regarding MS and pregnancy.  
PMCID: PMC2853552 PMID: 20361873 [PubMed - in process]  

Doctor is found guilty of exploiting "desperate" MS patients.  
Dyer C.  
PMID: 20385715 [PubMed - indexed for MEDLINE]  

22. Brain. 2010 Apr 27. [Epub ahead of print]  
Induction of inhibitory central nervous system-derived and stimulatory blood-derived dendritic cells suggests a dual role for granulocyte-macrophage colony-stimulating factor in central nervous system inflammation.  
1 Clinical Immunology, University Hospital of Zurich, Switzerland.  
The mononuclear phagocyte system, particularly dendritic cells, plays several pivotal roles in the development of multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis. Here, we demonstrate that functionally distinct dendritic cell subpopulations are present in the central nervous system during experimental autoimmune encephalomyelitis. At peak experimental autoimmune encephalomyelitis, the majority of dendritic cells consisted of a CD11b(+)F4/80(+) inflammatory dendritic cell subtype. Both granulocyte-macrophage colony-stimulating factor and chemokine (C-C motif) ligand 2 were previously suggested to recruit 'inflammatory' monocyte-derived dendritic cells to the central nervous system during experimental autoimmune encephalomyelitis. We show that intra-cerebral production of granulocyte-macrophage colony-stimulating factor leading to chemokine (C-C motif) ligand 2 induction and attraction of chemokine (C-C motif) receptor 2-positive precursors suffices to recruit dendritic cell populations identical to those observed in experimental autoimmune encephalomyelitis into the central nervous system of healthy mice. This does not occur with fms-like tyrosine kinase-3-ligand treatment. Both during experimental autoimmune encephalomyelitis and upon intra-cerebral granulocyte-macrophage colony-stimulating factor production, all myeloid dendritic cells, lymphoid dendritic cells and periphery-derived inflammatory dendritic cells stimulated T cell proliferation, whereas inflammatory dendritic cells that differentiated from central nervous system precursors inhibited T cell activation and pro-inflammatory cytokine production. Despite the capacity of granulocyte-macrophage colony-stimulating factor to induce central nervous system-derived inhibitory inflammatory dendritic cells, the administration of granulocyte-macrophage colony-stimulating factor into mice with experimental autoimmune encephalomyelitis resulted in exacerbated disease. Granulocyte-macrophage colony-stimulating factor thus has a dual role in the central nervous system: it directs both central nervous system-derived dendritic cells towards an inhibitory phenotype and recruits peripheral dendritic cells exhibiting pro-inflammatory functions.  
PMID: 20424288 [PubMed - as supplied by publisher]
23. Brain. 2010 Apr 27. [Epub ahead of print]
**Evidence for a two-stage disability progression in multiple sclerosis.**
Leray E, Yaouanq J, Le Page E, Coustans M, Laplaud D, Oger J, Edan G.
1 Service d'épidémiologie et santé publique, Centre Hospitalier Universitaire, rue Henri Le Guilloux 35033 Rennes, France.

It is well documented that disability accumulation in multiple sclerosis is correlated with axonal injury and that the extent of axonal injury is correlated with the degree of inflammation. However, the interdependence between focal inflammation, diffuse inflammation and neurodegeneration, and their relative contribution to clinical deficits, remains ambiguous. A hypothesis might be that early focal inflammation could be the pivotal event from which all else follows, suggesting the consideration of multiple sclerosis as a two-stage disease. This prompted us to define two phases in the disease course of multiple sclerosis by using two scores on the Kurtzke Disability Status Scale as benchmarks of disability accumulation: an early phase, 'Phase 1', from multiple sclerosis clinical onset to irreversible Disability Status Scale 3 and a late phase, 'Phase 2', from irreversible Disability Status Scale 3 to irreversible Disability Status Scale 6. Outcome was assessed through five parameters: Phase 1 duration, age at Disability Status Scale 3, time to Disability Status Scale 6 from multiple sclerosis onset, Phase 2 duration and age at Disability Status Scale 6. The first three were calculated among all patients, while the last two were computed only among patients who had reached Disability Status Scale 3. The possible influence of early clinical markers on these outcomes was studied using Kaplan-Meier estimates and Cox models. The analysis was performed in the Rennes multiple sclerosis database (2054 patients, accounting for 26 273 patient-years) as a whole, and according to phenotype at onset (1609 relapsing/445 progressive onset). Our results indicated that the disability progression during Phase 2 was independent of that during Phase 1. Indeed, the median Phase 2 duration was nearly identical (from 6 to 9 years) irrespective of Phase 1 duration (<3, 3 to <6, 6 to <10, 10 to <15, >15 years) in the whole population, and in both phenotypes. In relapsing onset multiple sclerosis, gender, age at onset, residual deficit after the first relapse and relapses during the first 2 years of multiple sclerosis were found to be independent predictive factors of disability progression, but only during Phase 1. Our findings demonstrate that multiple sclerosis disability progression follows a two-stage process, with a first stage probably dependent on focal inflammation and a second stage probably independent of current focal inflammation. This concept has obvious implications for the future therapeutic strategy in multiple sclerosis.

PMID: 20423930 [PubMed - as supplied by publisher]

**Complement regulator factor H as a serum biomarker of multiple sclerosis disease state.**
Ingram G, Hakobyan S, Hirst CL, Harris CL, Pickersgill TP, Cossburn MD, Loveless S, Robertson NP, Morgan BP.
1 Department of Neurosciences, Cardiff University, Cardiff CF14 4XN, UK.

Multiple sclerosis has a variable phenotypic presentation and subsequent disease course that, although unpredictable at disease onset, is of crucial importance in guiding interventions. Effective and accessible biomarkers are required in order to stratify patients and inform treatment. We examined whether the complement regulator factor H and its Tyr402His polymorphism, recently implicated as biomarkers in other chronic inflammatory central nervous system conditions, might identify or predict specific pathological processes and outcomes in multiple sclerosis. Employing novel assays, we measured factor H and its His402 variant in serum from 350 patients with multiple sclerosis classified according to disease course and relapse status. Serum factor H levels were significantly higher in progressive disease (P < 0.001) compared to controls and relapsing patients, after controlling for variables including disease duration, age, gender, disability and treatment. Serum factor H levels were capable of distinguishing secondary progressive from relapsing remitting disease (excluding patients in clinical relapse) with a sensitivity of 89.41%, specificity of 69.47% and a positive predictive value of 72.38%. Acute relapse was also associated with transiently increased factor H levels (P = 0.009) compared to stable relapsing disease. In clinically stable patients, factor H levels remained constant over 1 year (coefficient of variation percentage = 6.8), however, in patients in transition from relapsing to progressive disease, factor H levels significantly increased over a period of 2 years (P = 0.007). Concentration of the His402 variant in heterozygotes was significantly higher in secondary progressive (P < 0.01) and primary progressive (P < 0.05) disease, suggesting altered expression or consumption of variants when factor H is upregulated. Serum factor H may be an effective indicator of progression and a practical and accessible biomarker and stratifying tool in determining disease course, providing objective evidence to help guide therapeutic decisions.

PMID: 20421219 [PubMed - as supplied by publisher]

Bayer Vital GmbH, Specialty Medicine
http://www.bayer-vital.de/
http://www.betaferon.de
http://www.ms-gateway.de
Ocular pathology in multiple sclerosis: retinal atrophy and inflammation irrespective of disease duration.
Green AJ, McQuaid S, Hauser SL, Allen IV, Lyness R.
1 Multiple Sclerosis Center, Department of Neurology, University of California San Francisco, San Francisco, CA 94143, USA.

There has been growing interest in the use of retinal imaging for tracking disease progression in multiple sclerosis. However, systematic and detailed pathological descriptions of retinal tissue in multiple sclerosis are lacking. Graded, histological evaluations on eyes from 82 patients with multiple sclerosis and 10 subjects with other neurological diseases, with immunohistochemistry on a subset, were performed and correlated with clinical and pathological findings. Multiple sclerosis cases demonstrated evidence of retinal atrophy and inflammation even in late-stage disease. Retinal ganglion cell loss was significant and remaining neurons appeared shrunken and were partially engulfed by human leukocyte antigen-DR positive cells with the phenotype of microglia in samples subjected to immunohistochemistry. Neurofilament staining revealed variable but prominent degrees of axonal loss and injury. Neuronal loss was noted in the inner nuclear layer with focal reduction in cell density. Foamy-appearing human leukocyte antigen-DR positive cells were evident near vessels and periphlebitis was found in a small but significant number of multiple sclerosis cases. Glial fibrillary acidic protein staining showed extensive astrocyte hypertrophy and proliferation with prominent gliosis in multiple sclerosis cases. Frequent but previously unreported abnormalities in the iris were documented in the majority of chronic multiple sclerosis cases. The injury to both iris and retina could be seen at all stages of disease. Severity of retinal atrophy was correlated with overall brain weight at time of autopsy (P = 0.04) and a trend for increased atrophy was seen with longer disease duration (P = 0.13). This study provides the first large-scale pathological description of retinas in multiple sclerosis, including patients with different subtypes of disease at all stages, and with variable clinical severity. Changes were seen not only in the retinal nerve fibre layer and ganglion cell layer, but also in the inner nuclear layer, suggesting that retinal injury is more widespread than previously appreciated. Furthermore, the human retina is devoid of myelin, but inflammation was demonstrated to be prominent in multiple sclerosis and to persist in the retina at late stages of disease. The prominent gliosis and inflammation surrounding vessels of the inner retina could potentially impact optical coherence tomography evaluations in multiple sclerosis as standard techniques exploit presumed differences in tissue reflectivity and utilize automated edge detection algorithms to judge axon loss in the nerve fibre layer. Deciphering the relationships between the different types of retinal pathology may aid us in understanding the factors that drive both inflammation and tissue atrophy in multiple sclerosis.

PMID: 20410146 [PubMed - as supplied by publisher]

**Smad7 in T cells drives T helper 1 responses in multiple sclerosis and experimental autoimmune encephalomyelitis.**


Department of Neurology, University Medical Centre Regensburg, Universitätsstrasse 84, 93053 Regensburg, Germany. ingo.kleiter@klinik.uni-regensburg.de

Autoreactive CD4+ T lymphocytes play a vital role in the pathogenesis of multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis. Since the discovery of T helper 17 cells, there is an ongoing debate whether T helper 1, T helper 17 or both subtypes of T lymphocytes are important for the initiation of autoimmune neuroinflammation. We examined peripheral blood CD4+ cells from patients with active and stable relapsing-remitting multiple sclerosis, and used mice with conditional deletion or over-expression of the transforming growth factor-beta inhibitor Smad7, to delineate the role of Smad7 in T cell differentiation and autoimmune neuroinflammation. We found that Smad7 is up-regulated in peripheral CD4+ cells from patients with multiple sclerosis during relapse but not remission, and that expression of Smad7 strongly correlates with T-bet, a transcription factor defining T helper 1 responses. Concordantly, mice with transgenic over-expression of Smad7 in T cells developed an enhanced disease course during experimental autoimmune encephalomyelitis, accompanied by elevated infiltration of inflammatory cells and T helper 1 responses in the central nervous system. On the contrary, mice with a T cell-specific deletion of Smad7 had reduced disease and central nervous system inflammation. Lack of Smad7 in T cells blunted T cell proliferation and T helper 1 responses in the periphery but left helper 17 responses unaltered. Furthermore, frequencies of regulatory T cells were increased in the central nervous system of mice with a T cell-specific deletion and reduced in mice with a T cell-specific over-expression of Smad7. Downstream effects of transforming growth factor-beta on in vitro differentiation of naïve T cells to T helper 1, T helper 17 and regulatory T cell phenotypes were enhanced in T cells lacking Smad7. Finally, Smad7 was induced during T helper 1 differentiation and inhibited during T helper 17 differentiation. Taken together, the level of Smad7 in T cells determines T helper 1 polarization and regulates inflammatory cellular responses. Since a Smad7 deletion in T cells leads to immunosuppression, Smad7 may be a potential new therapeutic target in multiple sclerosis.

PMCID: PMC2850583 PMID: 20354004 [PubMed - indexed for MEDLINE]
27. Brain. 2010 Mar 30. [Epub ahead of print]

**Resting state networks change in clinically isolated syndrome.**

Roosendaal SD, Schoonheim MM, Hulst HE, Sanz-Arigita EJ, Smith SM, Geurts JJ, Barkhof F.

1 MS Centre Amsterdam, Department of Radiology, VU University Medical Centre, 1007 MB, the Netherlands.

Task-functional magnetic resonance imaging studies have shown that early cortical recruitment exists in multiple sclerosis, which can partly explain the discrepancy between conventional magnetic resonance imaging and clinical disability. The study of the brain 'at rest' may provide additional information, because task-induced metabolic changes are relatively small compared to the energy use of the resting brain. We therefore questioned whether functional changes exist at rest in the early phase of multiple sclerosis, and addressed this question by a network analysis of no-task functional magnetic resonance imaging data. Fourteen patients with symptoms suggestive of multiple sclerosis (clinically isolated syndrome), 31 patients with relapsing remitting multiple sclerosis and 41 healthy controls were included. Resting state functional magnetic resonance imaging data were brought to standard space using non-linear registration, and further analysed using multi-subject independent component analysis and individual time-course regression. Eight meaningful resting state networks were identified in our subjects and compared between the three groups with non-parametric permutation testing, using threshold-free cluster enhancement to correct for multiple comparisons. Additionally, quantitative measures of structural damage were obtained. Grey and white matter volumes, normalized for head size, were measured for each subject. White matter integrity was investigated with diffusion tensor measures that were compared between groups voxel-wise using tract-based spatial statistics. Patients with clinically isolated syndrome showed increased synchronization in six of the eight resting state networks, including the default mode network and sensorimotor network, compared to controls or relapsing remitting patients. No significant decreases were found in patients with clinically isolated syndrome. No significant resting state synchronization differences were found between relapsing remitting patients and controls. Normalized grey matter volume was decreased and white matter diffusivity measures were abnormal in relapsing remitting patients compared to controls, whereas no atrophy or diffusivity changes were found for the clinically isolated syndrome group. Thus, early synchronization changes are found in patients with clinically isolated syndrome that are suggestive of cortical reorganization of resting state networks. These changes are lost in patients with relapsing remitting multiple sclerosis with increasing brain damage, indicating that cortical reorganization of resting state networks is an early and finite phenomenon in multiple sclerosis.

PMID: 20356855 [PubMed - as supplied by publisher]


**Reduced cortisol levels in cerebrospinal fluid and differential distribution of 11beta-hydroxysteroid dehydrogenases in multiple sclerosis: Implications for lesion pathogenesis.**


Department for Obstetrics and Gynecology, University of Würzburg, Josef-Schneider-Str. 4, 97080 Würzburg, Germany; Interdisciplinary Center for Clinical Research (IZKF), University of Würzburg, Josef-Schneider-Str. 2, 97080 Würzburg, Germany.

Relapses during multiple sclerosis (MS) are treated by administration of exogenous corticosteroids. However, little is known about the bioavailability of endogenous steroids in the central nervous system (CNS) of MS patients. We thus determined cortisol and dehydroepiandrosterone (DHEA) levels in serum and cerebrospinal fluid (CSF) samples from 34 MS patients, 28 patients with non-inflammatory neurological diseases (NIND) and 16 patients with other inflammatory neurological diseases (OIND). This revealed that MS patients - in sharp contrast to patients with OIND - show normal cortisol concentrations in serum and lowered cortisol levels in the CSF during acute relapses. This local cortisol deficit may relate to poor local activation of cortisone via 11beta-hydroxysteroid dehydrogenase type 1 (11bHSD1) or to inactivation via 11bHSD2. Accordingly, 11bHSD2 was found to be expressed within active plaques, whereas 11bHSD1 was predominantly detected in surrounding "foamy" macrophages. Our study thus provides new insights into the impaired endogenous CNS cortisol regulation in MS patients and its possible relation to MS lesion pathogenesis. Moreover, an observed upregulation of 11bHSD1 in myelin-loaded macrophages in vitro suggests an intriguing hypothesis for the self-limiting nature of MS lesion development. Finally, our findings provide an attractive explanation for the effectivity of high- vs. low-dose exogenous corticosteroids in the therapy of acute relapses. Copyright © 2010 Elsevier Inc. All rights reserved.

PMID: 20385225 [PubMed - as supplied by publisher]
**Primary central nervous system large B-cell lymphoma with prolific, mixed T-cell and macrophage infiltrates, mimicking multiple sclerosis.**  
Department of Neurosurgery, Kitasato University School of Medicine, 1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555, Japan. utsuki@med.kitasato-u.ac.jp  
Although tissue confirmation is essential for a diagnosis of primary central nervous system large B-cell lymphoma (PCNSBL), accurate assessment may still be difficult, even when tissue is obtained. We report a 59-year-old man, first diagnosed as multiple sclerosis by open biopsy at another institution, who was then correctly diagnosed as PCNSBL after stereotactic biopsy at our hospital. The initial biopsy showed heavy lymphoid and macrophage influx with visible demyelination. On rebiopsy, a diffuse infiltrate of small to medium-sized lymphocytes was prominent and largely stained as T cells (CD3) by immunohistochemistry. There was also an admixture of macrophages, but this time, relatively low numbers of large malignant cells were also identified. The latter stained as B cells (CD20), enabling a diagnosis of B-cell lymphoma, and the condition responded fully to high-dose methotrexate. It is thus possible for PCNSBL to be histologically misinterpreted as a result of ancillary inflammation, characterized here as a profusion of T cells and macrophages.  
PMID: 20425050 [PubMed - in process]  
**microRNAs: critical regulators in Th17 cells and players in diseases.**  
Wei B, Pei G.  
microRNAs are a novel group of small, conserved, non-coding RNA molecules that are present in all species. These molecules post-transcriptionally regulate gene expression by targeting mRNAs for degradation or by repressing the translation of the mRNAs. A good understanding of miRNA-mediated gene regulation is critical to gain a comprehensive view of many physiological processes and disease states. Emerging evidence demonstrates that miRNAs play an important role in the differentiation and function of the adaptive immune system. This review provides an overview of the diverse functions of miRNAs in modulating immune responses and in immune cell development, particularly the development of Th17 cells, and explores the involvement of miRNAs in several autoimmune diseases including multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and diabetes.  
PMID: 20364159 [PubMed - as supplied by publisher]  
**Sphingosine and FTY720 directly bind pro-survival 14-3-3 proteins to regulate their function.**  
Woodcock JM, Ma Y, Coolen C, Pham D, Jones C, Lopez AF, Pitson SM.  
Cell Regulation Networks Laboratory, Division of Human Immunology, Centre for Cancer Biology, SA Pathology, Adelaide, SA 5000, Australia.  
The dimeric 14-3-3 protein family protects cells from apoptosis by regulating pro-apoptotic molecules. Conversely, the cationic lipid sphingosine is associated with physiological apoptosis and induces apoptosis in its own right by a largely undefined mechanism. We show here that sphingosine and 14-3-3 interact directly in the control of cell death. The binding of sphingosine to 14-3-3 proteins renders them phosphorylatable at the dimer interface, an event that abolishes the pro-survival signalling of 14-3-3. Sphingosine kinase 1 reduces availability of sphingosine for interaction with 14-3-3, thus inhibiting cell death and providing a new mechanistic insight into the role of this enzyme in cell survival and oncogenesis. Importantly, FTY720, a sphingosine analogue with apoptotic activity that is currently in phase III clinical trials for multiple sclerosis, acts in a similar manner to sphingosine in potentiating 14-3-3 phosphorylation. The biological significance of 14-3-3 phosphorylation was demonstrated with a non-phosphorylatable 14-3-3zeta mutant which retarded apoptosis induced by sphingosine and FTY720. These results demonstrate that direct association of sphingosine with 14-3-3 is required for 14-3-3 phosphorylation, and that this axis can control cell fate. Furthermore, these results suggest a new therapeutic activity for FTY720 as an anti-cancer agent based on this mechanism. Copyright © 2010. Published by Elsevier Inc.  
PMID: 20403428 [PubMed - as supplied by publisher]
99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: Epstein-Barr virus and multiple sclerosis: epidemiological evidence.
Ascherio A, Munger KL.
Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115, USA.
aascheri@hsph.harvard.edu
While the causes of multiple sclerosis (MS) are unknown, there is strong evidence that infection with Epstein-Barr virus (EBV) is an important factor. In this review, we discuss the epidemiological evidence and argue for a causal role of EBV in MS aetiology. One of the most striking and consistent observations is that MS is extremely rare among EBV-negative individuals. Further, the timing of EBV infection appears to be critical, with individuals who are infected during adolescence and young adulthood, when the infection is more likely to manifest as mononucleosis, having a two- to threefold greater risk of MS compared to individuals infected in early life. These observations challenge the hygiene hypothesis which states that being in a high hygiene environment in early life increases future risk of MS - if this general formulation were true, EBV-negative individuals would be expected to have an increased risk of MS. Additional support for the causal role of EBV comes from longitudinal, prospective studies which show remarkable consistency, in that antibodies against EBV are elevated prior to MS onset. However, while infection with EBV is consistent with many observations of MS epidemiology, there are some that remain unexplained, suggesting that other factors are also involved in determining risk.

99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: triggering of autoimmune diseases by infections.
Getts MT, Miller SD.
Department of Microbiology-Immunology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.
Human autoimmune diseases, such as multiple sclerosis, type 1 diabetes, rheumatoid arthritis and systemic lupus erythematosus (SLE), are linked genetically to distinct major histocompatibility complex (MHC) class II molecules and other immune modulators. However, genetic predisposition is only one risk factor for the development of these diseases, and low concordance rates in monozygotic twins as well as geographical distribution of disease risk suggest a critical role for environmental factors in the triggering of these autoimmune diseases. Among potential environmental factors, infections have been implicated in the onset and/or promotion of autoimmunity. This review will discuss human autoimmune diseases with a potential viral cause, and outline potential mechanisms by which pathogens can trigger autoimmune disease as discerned from various animal models of infection-induced autoimmune disease.

Role of MRI in diagnosis and treatment of multiple sclerosis.
Sahraian MA, Eshaghi A.
Department of Neurology, Sina Hospital, Tehran University of Medical Sciences, Iran.
Magnetic resonance imaging (MRI) has played a unique role in the diagnosis and management of patients with multiple sclerosis (MS). In the recent years, there have been considerable changes in the diagnostic criteria for MS as MR-based studies demonstrated its power in earlier and more accurate diagnosis of the disease. Moreover, MRI metrics have become key supportive outcome measures to evaluate the efficacy of experimental treatments in randomized, controlled trials. MRI can also be used as a prognostic tool in patients with clinically isolated syndrome. Although advanced quantitative MRI measures such as magnetization transfer, spectroscopy, and diffusion imaging have added much more to our knowledge about pathogenesis and natural history of the disease but their cost, availability, complexity and lack of validation have limited their use in routine clinical practice. Conventional MR techniques including proton density, T1/T2-weighted images and fluid-attenuated inversion recovery sequences are now accepted in standard protocols for diagnosis and treatment outcome measures in clinical trials for MS. The present review will focus on the type, morphology and evolution of MS lesions in conventional MRI and discusses their use for the monitoring of the disease both in daily clinical practice and experimental trials. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20417027 [PubMed - as supplied by publisher]
**Antiphospholipid syndrome and central nervous system.**
Mayer M, Cerovec M, Radoš M, Cikeš N.
University Hospital Center Zagreb, University of Zagreb, School of Medicine, Department of Medicine, Division of Clinical Immunology and Rheumatology, Kispaticeva ulica 12, 10000 Zagreb, Croatia.
Classification criteria, etiology, pathogenesis, major central nervous system (CNS) manifestations of the antiphospholipid syndrome (APS), as well as diagnostic and therapeutic approach are discussed in the article, supported by several MRI findings to illustrate differential complexity of selected topics. Close interplay of inflammation, autoimmunity, coagulation cascade, vasculature bed, neuron physiology and demyelination in APS is elaborated. Cerebrovascular disease, multiple sclerosis-like syndrome, seizures, cognitive dysfunction, headache and migraine, chorea and catastrophic antiphospholipid syndrome (CAPS) are discussed as the most prominent CNS manifestations of the APS. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20417026 [PubMed - as supplied by publisher]

**An exploratory study on emotion recognition in patients with a clinically isolated syndrome and multiple sclerosis.**
Institute for Psychology, Karl Franzens University Graz, Austria; Department of Neurology, Medical University of Graz, Auenbruggerplatz 22, A-8036 Graz, Austria.
OBJECTIVES: Multiple sclerosis (MS) is a chronic multifocal CNS disorder which can affect higher order cognitive processes. Whereas cognitive disturbances in MS are increasingly better characterised, emotional facial expression (EFE) has rarely been tested, despite its importance for adequate social behaviour.
PATIENTS AND METHODS: We tested 20 patients with a clinically isolated syndrome suggestive of MS (CIS) or MS and 23 healthy controls (HC) for the ability to differ between emotional facial stimuli, controlling for the influence of depressive mood (ADS-L). We screened for cognitive dysfunction using The Faces Symbol Test (FST). RESULTS: The patients demonstrated significant decreased reaction-times regarding emotion recognition tests compared to HC. However, the results also suggested worse cognitive abilities in the patients. Emotional and cognitive test results were correlated. CONCLUSION: This exploratory pilot study suggests that emotion recognition deficits might be prevalent in MS. However, future studies will be needed to overcome the limitations of this study. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20399006 [PubMed - as supplied by publisher]

**Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis.**
Velikonja O, Cerić K, Ožura A, Jazbec SS.
University of Ljubljana, Medical Faculty, Vrazov trg 2, 1104 Ljubljana, Slovenia.
OBJECTIVES: Spasticity, cognitive impairment, depression and fatigue significantly reduce the quality of life in multiple sclerosis (MS) patients. To find out whether nonpharmalogical treatment approaches can reduce these symptoms we investigated effects of sports climbing (SC) and yoga on spasticity, cognitive impairment, mood change and fatigue in MS patients. Sports climbing (SC) and yoga are aerobic physical activities comprised a series of stretching techniques, implementation of which demands body control and planning of complex movements. MATERIALS AND METHODS: 20 subjects with relapsing-remitting or progressive MS, 26-50 years of age, with EDSS<=6 and EDSS pyramidal functions score (EDSSpyr)>2 were enrolled in a randomized prospective study. The participants were randomly divided into SC and yoga group. We evaluated spasticity, cognitive function, mood and fatigue before and after both programs, that lasted 10 weeks, with standardized assessment methods. RESULTS: There were no significant improvements in spasticity after SC and yoga. In the SC group we found a 25% reduction (p=0.046) in EDSSpyr. There were no differences in executive function after the completion of both programs. There was a 17% increase in selective attention performance after yoga (p=0.005). SC reduced fatigue for 32.5% (p=0.015), while yoga had no effect. We found no significant impact of SC and yoga on mood.
CONCLUSIONS: Yoga and SC might improve some of the MS symptoms and should be considered in the future as possible complementary treatments. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20371148 [PubMed - as supplied by publisher]

**Therapy of MS.**

Vosoughi R, Freedman MS.
The Ottawa Hospital, General Campus, Ottawa, Ont., Canada.
The era of disease-modifying drugs (DMDs) in multiple sclerosis (MS) treatment began in the 1990s, first with interferon-beta (IFNbeta), and the number of agents has increased steadily since then. Currently, there are six different parenteral formulations approved for MS treatment and many other oral and parenteral ones are in different stages of investigation or awaiting approval by federal agencies. All of these medications have demonstrated partial efficacy along with different side effect profiles. Increasing our understanding about the natural behaviour of MS and its different types and stages, diversity of different therapies, their strength and weaknesses, and their serious and sometimes life-threatening side effects have created challenges for treating physicians; making the choice of individualized optimal treatment increasingly more complicated. In this review, we will summarize present and future treatment options and also address clinical challenges we are regularly facing in arriving at treatment choices for our patients. Copyright © 2010 Elsevier B.V. All rights reserved.

PMID: 20362388 [PubMed - as supplied by publisher]


**Force-pain relationship in functional magnetic and electrical stimulation of subjects with paresis and preserved sensation.**

Szecsi J, Götz S, Pöllmann W, Straube A.
Center for Sensorimotor Research, Department of Neurology, Ludwig-Maximilians University, Munich, Germany.

OBJECTIVE: Using "painless" magnetic stimulation (FMS) to support the cycling of paretic subjects with preserved sensation is possible and potentially superior to electrical stimulation (FES). We investigated the dependence of the torque and the pain evoked by FMS and FES on stimulation conditions in order to optimize magnetic stimulation. METHODS: Torque and pain induced by quadriceps stimulation in 13 subjects with paresis and preserved sensation (due to multiple sclerosis) were compared under the conditions: (1) small vs large stimulated surfaces of the thigh, (2) varying contraction velocities of the muscle (isometric vs 15 and 30rpm isokinetic speed), (3) FMS vs FES modalities, and (4) varying magnetic coil locations. RESULTS: Torque and pain significantly depended on the amount of surface and location of stimulation during FMS, on the stimulation modality, and on the muscle contraction velocity during FES and FMS. FMS with a saddle-shaped coil produced more torque (p<0.05) than any other stimulation modality, even at 30rpm velocity. CONCLUSIONS: To support leg cycling of subjects with preserved sensation, the application of FMS stimulation with a large-surface saddle-shaped coil and the focusing of stimulation on the lateral-frontal surface of the thigh produces greater torque and less pain than FES. SIGNIFICANCE: Optimized magnetic stimulation is a superior alternative to electrical stimulation in the rehabilitation of subjects with preserved sensation. Copyright © 2010 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.

PMID: 20382558 [PubMed - as supplied by publisher]
A high-density ERP study reveals latency, amplitude, and topographical differences in multiple sclerosis patients versus controls.
Department of Neurology, St. Vincent's University Hospital/University College Dublin, Ireland; Trinity Center for Bioengineering, Trinity College Dublin, Ireland.
OBJECTIVE: To quantify latency, amplitude and topographical differences in event-related potential (ERP) components between multiple sclerosis (MS) patients and controls and to compare ERP findings with results from the paced auditory serial addition test (PASAT). METHODS: Fifty-four subjects (17 relapsing remitting (RRMS) patients, 16 secondary progressive (SPMS) patients, and 21 controls) completed visual and auditory oddball tasks while data were recorded from 134 EEG channels. Latency and amplitude differences, calculated using composite mean amplitude measures, were tested using an ANOVA. Topographical differences were tested using statistical parametric mapping (SPM). RESULTS: In the visual modality, P2, P3 amplitudes and N2 latency were significantly different across groups. In the auditory modality, P2, N2, and P3 latencies and N1 amplitude were significantly different across groups. There were no significant differences between RRMS and SPMS patients on any ERP component. There were no topographical differences between MS patients and controls for both early and late components for the visual modality, but only in the early components for the auditory modality. PASAT score correlated significantly with auditory P3 latency for MS patients. CONCLUSIONS: There were significant ERP differences between MS patients and controls. SIGNIFICANCE: The present study indicated that both early sensory and later cognitive ERP components are impaired in MS patients relative to controls. Copyright © 2010 International Federation of Clinical Neurophysiology. Published by Elsevier Ireland Ltd. All rights reserved.
PMID: 20381418 [PubMed - as supplied by publisher]

42. CNS Neurosci Ther. 2010 Apr;16(2):115-24.
Hyperbaric oxygen therapy for multiple sclerosis.
Bennett M, Heard R.
Conjoint Associate Professor, Department of Diving and Hyperbaric Medicine, Prince of Wales Hospital and the University of New South Wales, Barker St., Randwick, NSW 2031, Australia. m.bennett@unsw.edu.au
Multiple sclerosis (MS) is a chronic, inflammatory, and degenerative neurological illness with no cure. It has been suggested that Hyperbaric Oxygen Therapy (HBO(2)T) may slow or reverse the progress of the disease. This article summarizes the clinical evidence for the use of HBO(2)T in the treatment of MS. We conducted a literature review focused on the interaction of hyperbaric oxygenation and MS. In particular, we appraised the clinical data regarding treatment and performed a meta-analysis of the randomized evidence using the methodology of the Cochrane Collaboration. We found 12 randomized studies in the area, all of which were performed between 1983 and 1987. A meta-analysis of this evidence suggests there is no clinically significant benefit from the administration of HBO(2)T. The great majority of randomized trials investigated a course of 20 treatments at pressures between 1.75ATA and 2.5ATA daily for 60-120 min over 4 weeks against a placebo regimen. None have tested the efficacy of HBO(2)T against alternative current best practice. No plausible benefit of HBO(2)T on the clinical course of MS was identified in this review. It remains possible that HBO(2)T is effective in a subgroup of individuals not clearly identified in the trials to date, but any benefit is unlikely to be of great clinical significance. There is some case for further human trials in selected subgroups and for prolonged courses of HBO(2)T at modest pressures, but the case is not strong. At this time, the routine treatment of MS with HBO(2)T is not recommended.
PMID: 20415839 [PubMed - in process]
The influence of pregnancy on development and course of chronic relapsing experimental autoimmune encephalomyelitis in rats: implications for multiple sclerosis.
Barac-Latas V, Muhvić D, Radosević-Stabić B.
Department of Physiology and Immunology, School of Medicine, University of Rijeka, Rijeka, Croatia.
Vesna.Barac-Latas@medri.hr
Multiple sclerosis is a chronic, autoimmune disease of the central nervous system, which mainly affects young women during a reproductive period of life. Since, its symptoms might be significantly affected by pregnancy, in this study we investigated the development and kinetics of disease in the model of chronic relapsing experimental autoimmune encephalomyelitis (CR-EAE), induced in genetically susceptible Dark Agouti (DA) strain of rats. They were sensitized with bovine brain white matter homogenate (BBH) in complete Freund's adjuvant during the first, second or third week of pregnancy, and the disease scores were compared between treatment groups, and identically treated nongravid females. Additionally, the susceptibility to the induction of EAE was tested in offspring of mothers that during the pregnancy were sensitized with BBH. The data have shown that pregnancy does not block the induction of EAE, but that it significantly changes the course of diseases, depending on time of immunization. In rats sensitized during the first week of gestation the onset of the clinical signs was delayed, but after the delivery the intensity of disease significantly increased. Similar aggravation, with appearance of monophasic form of disease was observed in the group of rats sensitized during the third week of gestation. On the contrary, in rats sensitized during the second week of gestation the beneficial effects were observed, with later onset of attacks, and lower disease score. Furthermore, offspring of these rats after immunization with BBH developed a monophasic form of EAE of lower intensity, suggesting that some protective factors might be transferred across the placenta.
PMID: 20402331 [PubMed - in process]

Epidemiology of multiple sclerosis in western Herzegovina and Herzegovina–Neretva Canton, Bosnia and Herzegovina.
Klupka-Sarić I, Galić M.
Department of Neurology, University Hospital Mostar, Mostar, Bosnia and Herzegovina. ingeks@tel.net.ba
The aim of this study was to investigate the selected indicators of multiple sclerosis (MS) in Herzegovina (Western Herzegovina Canton and Herzegovina-Neretva Canton). By using all available health and medical sources in the studied area and using McDonald's criteria, a total of 96 patients were identified in the period from 1996 to 2006. Results of the study show that the crude prevalence of MS was 30.99/100,000 (95% confidence interval [CIC 24.8-37.2), the highest one in the municipality of Posusje (49.6/100,000) and the lowest one in the municipalities of Neum and Ravno (no recorded cases); the female/male ratio was 1.5; the mean age of the patients on the prevalence day was 41.4 +/- 10.2 years and the mean age at the disease onset was 30.7 +/- 6.4 years; the most often clinical course of the disease was relapsing-remitting (58%); secondary progressive course was present in 28% patients, primary progressive in 9% and progressive relapsing in 1% of patients; the most frequent initial signs of the disease were motor (33%) and sensory ones (24%). According to the results of the study, the south-western part of Bosnia and Herzegovina is an area on the crossing from moderate risk to high risk zone for MS. The distribution of MS is heterogeneous. MS was more prevalent in the municipalities with colder climate and more winter precipitation and it is not present in the coastal region with warmer climate and almost without winter precipitation.
PMID: 20402317 [PubMed - in process]
The pathogenesis of murine coronavirus infection of the central nervous system.
Lane TE, Hosking MP.
Department of Molecular Biology and Biochemistry, University of California, Irvine, California 92697-3900, USA.
Mouse hepatitis virus (MHV) is a positive-strand RNA virus that causes an acute encephalomyelitis that later resolves into a chronic fulminating demyelinating disease. Cytokine production, chemokine secretion, and immune cell infiltration into the central nervous system are critical to control viral replication during acute infection. Despite potent antiviral T-lymphocyte activity, sterile immunity is not achieved, and MHV chronically persists within oligodendrocytes. Continued infiltration and activation of the immune system, a result of the lingering viral antigen and RNA within oligodendrocytes, leads directly to the development of an immune-mediated demyelination that bears remarkable similarities, both clinically and histologically, to the human demyelinating disease multiple sclerosis. MHV offers a unique model system for studying host defense during acute viral infection and immune-mediated demyelination during chronic infection.
PMCID: PMC2852265 PMID: 20370625 [PubMed - in process]

Laquinimod, a new oral autoimmune modulator for the treatment of relapsing-remitting multiple sclerosis.
Tselis A.
Wayne State University, Department of Neurology, 4201 St Antoine Street, Detroit, MI 48201, USA.
atelis@med.wayne.edu
Laquinimod, a second-generation quinoline-3-carboxamide, is being developed by Active Biotech AB and Teva Pharmaceutical Industries Ltd for the treatment of relapsing-remitting multiple sclerosis (RRMS). Laquinimod has demonstrated significant activity in suppressing experimental autoimmune encephalomyelitis, an animal model of RRMS. In phase I and II clinical trials, the drug was well tolerated, with some hints of efficacy in small numbers of patients with RRMS. While the mechanism of action of the drug is unknown, it likely involves Th1 to Th2/Th3 immune deviation, promotion of the synthesis and release of neurotrophic factors, and other possible neuroprotective effects. Two phase III clinical trials are ongoing and, if successful, will lead to the approval of the first oral immunomodulatory drug for suppressing multiple sclerosis disease activity.
PMID: 20419604 [PubMed - in process]

47. Curr Opin Neurol. 2010 Apr 21. [Epub ahead of print]
New drug therapies for multiple sclerosis.
Mangas A, Coveñas R, Geffard M.
aInstitute of Neurosciences of Castilla y León (INCYL), Laboratory 14, Salamanca, Spain bIMS Laboratory, ENSCPB-E.PHE, Pessac, France.
PURPOSE OF REVIEW: Multiple sclerosis (MS) is an autoimmune and inflammatory disease of the central nervous system (CNS) that causes neurological disability in young adults and that to date has no cure. Until now, expensive and only partially efficacious therapies have become available. For this reason, researchers, clinicians and pharmaceutical companies are currently investigating new drugs for the treatment of MS. Here, we review the most recent data on drug candidates for MS. RECENT FINDINGS: In the preclinical phase, such drug candidates have shown a beneficial effect on the onset of experimental autoimmune encephalomyelitis (microtubule-stabilizing drugs, MS14, Lithium, GEMSP...), a decrease in CNS cell infiltrates (recombinant T cell receptor ligand, lovastatin-rolipram, ribavirin, GEMSP...), prevention of demyelination (lovastatin-rolipram, calpain inhibitor, lithium...); and a reduction of axonal loss (phenytoin, lovastatin-rolipram, calpain inhibitor). In clinical trials, drug candidates against MS have shown safety (rituximab, ustekinumab, intravenous immunoglobulin, laquinimod, BHT-3009, fumarate, chaperonin 10, GEMSP...), an improvement of gadolinium-enhanced lesions (protiramer, fingolimod, laquinimod, BHT-3009, fumarate, daclizumab...), and an improvement of the relapse rate (fingolimod, fumarate...). SUMMARY: Future research into MS should focus on a combination of therapies and on the development of drugs directed against the remitting and progressive phases of the disease. In this sense, MS is a very complex multifactorial disease that requires treatment able to cover all the aspects of MS and not only the anti-inflammatory aspect.
PMID: 20414110 [PubMed - as supplied by publisher]
48. Curr Opin Neurol. 2010 Apr 5. [Epub ahead of print]

**Stem cell transplantation in multiple sclerosis.**

Uccelli A, Mancardi G.
aDepartment of Neurosciences, Ophthalmology and Genetics, Italy bCenter of Excellence for Biomedical Research, University of Genoa, Genoa, Italy cAdvanced Biotechnology Center (ABC), Genoa, Italy.

**PURPOSE OF REVIEW:** The recent advances in our understanding of stem cell biology, the availability of innovative techniques that allow large-scale acquisition of stem cells, and the increasing pressure from the multiple sclerosis (MS) patient community seeking tissue repair strategies have launched stem cell treatments as one of the most exciting and difficult challenges in the MS field. Here, we provide an overview of the current status of stem cell research in MS focusing on secured actuality, reasonable hopes and unrealistic myths. **RECENT FINDINGS:** Results obtained from small clinical studies with transplantation of autologous hematopoietic stem cells have demonstrated that this procedure is feasible and possibly effective in severe forms of MS but tackles exclusively inflammation without affecting tissue regeneration. Results from preclinical studies with other adult stem cells such as mesenchymal stem cells and neural precursor cells have shown that they may be a powerful tool to regulate pathogenic immune response and foster tissue repair through bystander mechanisms with limited cell replacement. However, the clinical translation of these results still requires careful evaluation. **CONCLUSION:** Current experimental evidence suggests that the sound clinical exploitation of stem cells for MS may lead to novel strategies aimed at blocking uncontrolled inflammation, protecting neurons and promoting remyelination but not at restoring the chronically deranged neural network responsible for irreversible disability typical of the late phase of MS.

PMID: 20375893 [PubMed - as supplied by publisher]


**Multiple Sclerosis-Related Central Pain Disorders.**

Nurmikko TJ, Gupta S, Maclver K.
Neuroscience Research Unit, Clinical Sciences Centre, Lower Lane, Liverpool, L9 7AL, UK, tjn@liverpool.ac.uk.

Central neuropathic pain is common in multiple sclerosis (MS), and its prevalence increases with physical disability. Sufficient evidence links dysesthetic pain, trigeminal neuralgia, Lhermitte's sign, and painful tonic spasms to plaque formation in the spinal cord and brain, whereas the association with headache and back pain remains unclear. Management varies according to the pain in question. For dysesthetic pain, drugs in use for neuropathic pain in general are recommended as first-line treatment, and emerging evidence suggests some benefit from cannabinoids and levetiracetam. Because of unique characteristics of MS-related trigeminal neuralgia, ganglion and root level neuroablative procedures are worth considering before microvascular decompression. Overall, the lack of controlled clinical trials, together with our limited understanding of the pathophysiological mechanisms involved, form a hindrance to a systematic and rational management of MS-related pain.

PMID: 20425191 [PubMed - as supplied by publisher]

50. Drug Metab Dispos. 2010 Apr 28. [Epub ahead of print]

**CNS Penetration for Small Molecule Therapeutics Do Not Increase in Multiple Sclerosis (MS) and Alzheimer's Disease (AD) Related Animal Models Despite Reported Blood-brain Barrier Disruption.**

GlaxoSmithKline (GSK) R&D China.

Therapy for central nervous system (CNS) diseases requires drugs that can cross blood-brain barrier (BBB). BBB disruption has been reported in multiple sclerosis (MS) and Alzheimer's disease (AD) patients and the related animal models as evidenced by increased infiltration of inflammatory cells or increased staining of immunoglobins in central nervous system. Although CNS penetration of therapeutic agents under pathological conditions has rarely been investigated, it's commonly assumed that BBB disruption may lead to enhanced CNS penetration and also provide "window of opportunity" through which drugs that do not normally cross BBB are able to do so. In this paper, we have compared brain penetration of eight small molecules in naive animals and experimental autoimmune encephalomyelitis (EAE) mice, streptozotocin (STZ) induced mice and TASTPM transgenic mice. The tool compounds include lipophilic transcellular drugs (GSK-A, GSK-B, GSK-C and naproxen), lipophilic P-glycoprotein (Pgp) substrates (amprenavir and loperamide), hydrophilic paracellular compounds (sodium fluorescein (NaF) and atenolol). Our data showed that rate and extent of CNS penetration for lipophilic transcellular drugs and Pgp substrates are similar in naive and all tested animal models. The brain penetration for paracellular drugs in EAE mice is transiently increased but similar to naive mice at steady state. Our data suggests that, despite reported BBB disruption, CNS penetration for small molecule therapeutics do not increase in MS and AD related animal models.

PMID: 20427691 [PubMed - as supplied by publisher]

**Multiple sclerosis in the elderly patient.**

Awad A, Stüve O.

Department of Neurology, University of Texas Southwestern Medical Center at Dallas, Dallas, Texas, USA.

Multiple sclerosis (MS) is an acquired inflammatory demyelinating disease of the CNS that is typically diagnosed in the second or third decade of life. It is generally believed that over the last few decades the life expectancy of patients with adult onset MS (AOMS) has approached that of the general population as a result of better medical and nursing care. Thus, an increasing number of MS patients are entering or have reached senescence. A second group of elderly patients with MS that may be very different in terms of disease pathogenesis are patients with late onset MS (LOMS). The diagnosis in LOMS patients can be challenging because of a large number of age-associated MS differential diagnoses, atypical presentations, a low index of suspicion and the lack of diagnostic criteria specific to this age group. Also, specific problems these patients encounter have only recently become a focus of attention. Changes in renal and hepatic function with age, in addition to the coexistence of medical co-morbidities, require special attention in the management of elderly patients with MS. In this review we outline the characteristics of senescent AOMS and LOMS patients. In addition, we discuss therapeutic strategies in elderly patients with MS based on our knowledge of immunosenescence and age-associated characteristics of this disorder. Given the overall aging of the population, focusing on these two patient groups appears highly relevant.

PMID: 20359260 [PubMed - in process]


**[Update on current care guidelines: diagnostics, treatment and rehabilitation of multiple sclerosis]**

[Article in Finnish]


Treatment is initiated when the McDonald criteria for relapsing-remitting multiple sclerosis (RRMS) are fulfilled. High-risk patients with clinically isolated syndrome are followed using magnetic resonance imaging for one year after the first imaging. Interferon-beta or glatiramer acetate are the first-line immunomodulating drugs (IMD) for RRMS. MxA protein is measured 12 and 24 months after initiation of Interferon-beta to evaluate possible development of neutralizing antibodies. If MxA protein may not be detected repeatedly interferon-beta treatment is discontinued. If the disease is active in spite of treatment with first-line IMD, natalizumab may be considered as a second-line therapy. IMD is stopped when the transition to secondary progressive phase has occurred (or upon transition to secondary progressive phase).

PMID: 20405605 [PubMed - in process]


**Interferon-beta Inhibits Th17 Cell Differentiation in Patients with Multiple Sclerosis.**

Ramgolam VS, Markovic-Plese S.

6109 Neuroscience Research Building, 103 Mason Farm Road, Chapel Hill, NC 27599, USA.
markovics@neurology.unc.edu.

Interferon-beta (IFNb) has been used over the past 15 years as a first-line therapy for relapsing remitting multiple sclerosis (RR MS), however its mechanisms of action are still not completely elucidated. Recently discovered Th17 cells have been hypothesized to play a crucial role in the development of autoimmune diseases, including MS. Studies from our laboratory and others have demonstrated that IFNb treatment suppresses Th17 cells' differentiation, mediated by its effects on dendritic cells (DCs), B-cells and T-cells. IFNb induces the production of the Th17-suppressive cytokines interleukin (IL)-27 and IL-12 in DCs and B-cells through the phosphorylation of signal transducers and activators of the transcription protein (STAT)1. Its inhibition of the Th17-promoting cytokines IL-1b and IL-23 is mediated via induction of suppressor of cytokine signaling (SOCS)3 expression. In naïve CD45RA+ T-cells, IFNb directly suppresses Th17 cells’ differentiation, as evidenced by the suppression of this cell subset's specific transcription factor retinoic acid-related orphan receptor (ROR)γ, cytokine IL-17A and the surface markers chemokine receptor (CCR)6 and IL-23R. The IFNb-mediated induction of IL-10 in T-cells and B-cells represents an important additional immunoregulatory mechanism. Described IFNb's mechanisms of action selectively target Th17 cell-mediated autoimmune responses in patients with RR MS.

PMID: 20384573 [PubMed - as supplied by publisher]
Relation between Epstein-Barr virus and multiple sclerosis: analytic study of scientific production.
Santiago O, Gutierrez J, Sorlozano A, de Dios Luna J, Villegas E, Fernandez O.
Department of Microbiology, School of Medicine, University of Granada, Avenida de Madrid, 11, 18012, Granada, Spain.
Numerous studies have been carried out to determine whether infection by the Epstein-Barr virus (EBV) can be considered as a risk factor for multiple sclerosis (MS). This work is a meta-analysis of case-control observational studies published before January 2009 aimed at assessing the degree of association between EBV and MS infections. A Medline electronic database search was carried out using "Epstein-Barr virus" and "multiple sclerosis" as keywords, from which we selected 30 published studies that met our methodology criteria. We found an association between MS and an exposure to EBV, studied by determining the anti-VCA IgG antibodies (odds ratio [OR] = 5.5; 95% confidence interval [CI] = 3.37-8.81; p < 0.0001), anti-complex EBNA IgG (OR = 5.4; 95% CI = 2.94-9.76; p < 0.0001) and anti-EBNA-1 IgG (OR = 12.1; 95% CI = 3.13-46.89; p < 0.0001). No significant association could be found when studying anti-EA IgG (OR = 1.3; 95% CI = 0.68-2.35; p = 0.457), EBV DNA in serum (OR = 1.8; 95% CI = 0.99-3.36; p = 0.051) and DNA in brain tissues and in cerebrospinal fluid (CSF) (OR = 0.9; 95% CI = 0.38-2.01; p = 0.768). This meta-analysis detected an association between infection by EBV and MS through the investigation of antibodies, mainly anti-EBNA-1, anti-complex EBNA and anti-VCA IgG.
PMID: 20428908 [PubMed - as supplied by publisher]

Pfleger CC, Flachs EM, Koch-Henriksen N.
Department of Neurology, Aarhus University Hospital in Aalborg, Aalborg.
Background: Time to disability pension is one of the endpoints to be used to determine the prognosis of multiple sclerosis (MS) in prospective studies. Objective: To assess the time to cessation of work and receiving disability pension in MS, and how it may depend on gender, type of work and age and symptom at onset. Method: A total of 2240 Danes with onset of definite/probable MS 1980-1989, identified from the Danish MS-Registry, were included. Information on social endpoints was retrieved from Statistics Denmark. Cox regression analyses were used with onset as starting point. Results: Afferent onset symptoms [hazard ratio (HR 0.57)] and non-physical type of work (HR 0.70) were favourable prognostic factors compared with high age at onset, physical work and efferent symptoms at onset. The mean time to disability pension was 13 years for patients with afferent/brainstem onset symptom but 8.7 years for those with efferent onset symptoms (P < 0.0001). The effect of onset symptom was reduced and the effect of sex became significant when all covariates and age at onset were included in multivariate Cox regression. Conclusions: Onset age, type of onset symptom and work are robust predictors of disability pension in MS. Disability pension proves to be a reliable milestone in estimation of the prognosis of MS.
PMID: 20402759 [PubMed - as supplied by publisher]

56. Eur J Neurol. 2010 Apr 8. [Epub ahead of print]
Epstein-Barr virus neutralizing and early antigen antibodies in multiple sclerosis.
Lindsey JW, Hatfield LM, Vu T.
University of Texas Health Science Center at Houston, Houston, TX, USA.
Background: Our objective was to determine whether antibodies against the Epstein-Barr virus (EBV) nuclear antigen-1 (EBNA-1), early antigen (EA), and EBV neutralizing antibodies (NeutAb) are altered in multiple sclerosis (MS). Methods: We measured EBNA-1 IgG, EA IgG, and EA IgA using quantitative ELISA. We measured NeutAb using a quantitative competitive ELISA. We studied 80 patients with MS, 80 matched controls, and 19 patients with MS with samples collected both whilst stable and in relapse. Results: Epstein-Barr virus nuclear antigen-1 IgG and EA IgA were increased in MS compared to controls. The EBNA-1 index value was 23.3 +/- 18.3 in the patients with MS (mean +/- SD) and 16.3 +/- 17.4 in the controls (P = 0.007, paired t-test). EA IgA had a median value of 1.964 in the patients with MS and 1.248 in the controls (P = 0.029, Wilcoxon signed rank test). EA IgG and NeutAb were not significantly different. None of the antibody levels were altered in relapse. The correlation between concentrations of different antibodies was minimal. Conclusions: IgG antibodies to EBNA-1 are significantly increased in MS. IgA antibodies against EBV EA are also increased. The EBV neutralizing antibody response is similar in MS and controls.
PMID: 20402753 [PubMed - as supplied by publisher]
Appearance of Cxcl10-expressing cell clusters is common for traumatic brain injury and neurodegenerative disorders.  
Department of Neuroscience, Developmental Neuroscience, Biomedical Center, Uppsala University, PO Box 593, SE-751 24 Uppsala, Sweden.  
Traumatic brain injury (TBI) in the mouse results in the rapid appearance of scattered clusters of cells expressing the chemokine Cxcl10 in cortical and subcortical areas. To extend the observation of this unique pattern, we used neuropathological mouse models using quantitative reverse transcriptase-polymerase chain reaction, gene array analysis, in-situ hybridization and flow cytometry. As for TBI, cell clusters of 150-200 mum expressing Cxcl10 characterize the cerebral cortex of mice carrying a transgene encoding the Swedish mutation of amyloid precursor protein, a model of amyloid Alzheimer pathology. The same pattern was found in experimental autoimmune encephalomyelitis in mice modelling multiple sclerosis. In contrast, mice carrying a SOD1(G93A) mutant mimicking amyotrophic lateral sclerosis pathology lacked such cell clusters in the cerebral cortex, whereas clusters appeared in the brainstem and spinal cord. Mice homozygous for a null mutation of the Cxcl10 gene did not show detectable levels of Cxcl10 transcript after TBI, confirming the quantitative reverse transcriptase-polymerase chain reaction and in-situ hybridization signals. Moreover, unbiased microarray expression analysis showed that Cxcl10 was among 112 transcripts in the neocortex upregulated at least threefold in both TBI and ageing TgSwe mice, many of them involved in inflammation. The identity of the Cxcl10(+) cells remains unclear but flow cytometry showed increased numbers of activated microglia/macrophages as well as myeloid dendritic cells in the TBI and experimental autoimmune encephalomyelitis models. It is concluded that the Cxcl10(+) cells appear in the inflamed central nervous system and may represent a novel population of cells that it may be possible to target pharmacologically in a broad range of neurodegenerative conditions.  
PMID: 20374285 [PubMed - in process]

Bronson C, Brewerton K, Ong J, Palanca C, Sullivan SJ.  
School of Physiotherapy, Centre for Physiotherapy Research, University of Otago, Dunedin, New Zealand.  
AIM: Multiple sclerosis (MS) leads to changes in balance due to the breakdown of a number of neurological processes. Hippotherapy utilizes the movement of the horse to provide sensory feedback and has been used as a therapeutic intervention for different neurological conditions. Little is known about the effects of hippotherapy in MS. The purpose of this study is to systematically review and examine the evidence for hippotherapy as an intervention to improve balance in persons with MS. METHODS: Major electronic databases were searched for articles relating to hippotherapy, MS and balance. Only full length articles published in peer reviewed journals that were written in English or translated into English were included. Articles were assessed using a modified quality index that was used for descriptive purposes only and did not exclude any study from the review. RESULTS: All studies examined in this review were either case-control or case-series. Collectively all three studies reported improvements in balance. Pre-test and post-test Berg Balance Scale scores in two studies revealed that primary progressive MS demonstrated the greatest amount of change after hippotherapy compared to other subtypes of MS. CONCLUSION: Hippotherapy has a positive effect on balance in persons with MS and has an added benefit of enhancing quality of life. The data is limited and further research will lead to a greater knowledge base and has the potential to increase accessibility for hippotherapy to be used as a rehabilitation modality.  
PMID: 20386517 [PubMed - as supplied by publisher]
59. Exp Neurol. 2010 Apr 23. [Epub ahead of print]
**Time-dependent fate of transplanted Neural Precursor Cells in experimental autoimmune encephalomyelitis mice.**
Second Department of Neurology, AHEPA University Hospital, Aristotle University of Thessaloniki, Macedonia, Greece; Laboratory of Anatomy, Histology and Embryology, Veterinary School, Aristotle University of Thessaloniki, Macedonia, Greece.
Transplanted Neural Precursor Cells (NPCs) are capable of long-distance migration inside the inflamed CNS, but exhibit limited myelinating capacities in animal models of Multiple Sclerosis (MS). Inflammation seems to be both beneficial for the recruitment and migration of NPCs and restrictive for their terminal differentiation. In the present study, a set of transplantation experiments was applied in order to investigate the migratory potential, the differentiation pattern and long term survival of NPCs in Experimental Autoimmune Encephalomyelitis (EAE) mice, the animal model of MS. The in vitro differentiation potential of NPCs in the presence of either pro- (TNFa, INFgamma) or anti- (TGFb) inflammatory cytokines was also analyzed. According to the in vivo results obtained, at the acute phase of EAE only a small fraction of transplanted NPCs succeed to differentiate, whereas at chronic phase most of them followed a differentiation process to glial cell lineage along white matter tracts. However, this differentiation was not fully completed, since 8months after their transplantation a number of NPCs remained as pre-oligodendrocytes. Glial differentiation of NPCs was also found to be inhibited or promoted following their treatment with TNFa or TGFb respectively, in vitro. Our findings suggest that inflammation triggers migration whereas the anti-inflammatory component is a prerequisite for NPCs to follow glial differentiation thereby providing myelinating oligodendrocytes. It is speculated that the fine balance between the pro- and anti-inflammatory determinants in the CNS may be a key factor for transplanted NPCs to exhibit a better therapeutic effect in EAE and MS. Copyright © 2010. Published by Elsevier Inc.
PMID: 20420833 [PubMed - as supplied by publisher]

**The endocannabinoid system in the inflammatory and neurodegenerative processes of multiple sclerosis and of amyotrophic lateral sclerosis.**
Rossi S, Bernardi G, Centonze D.
Clinica Neurologica, Dipartimento di Neuroscienze, Università Tor Vergata, Rome, Italy; Centro Europeo per la Ricerca sul Cervello (CERC)/Fondazione Santa Lucia, Rome, Italy.
Multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) are chronic diseases of the central nervous system (CNS), featured by a complex interplay between inflammation and neurodegeneration. Increasing evidence supports the involvement of the endocannabinoid system (ECS) in both inflammatory and neurodegenerative processes typical of these pathological conditions. Exogenous or endogenous cannabinoids regulate the function of immune system by limiting immune response. On the other hand, by preventing excitotoxic damage, cannabinoids protect neuronal integrity and function. Of note, the ECS not only plays a role as modulator of disease processes, but it can also be disrupted by the same diseases. Agents modulating cannabinoid receptors or endocannabinoid tone provide promising therapeutic opportunities in the treatment of inflammatory neurodegenerative disorders of the CNS. Copyright © 2010 Elsevier Inc. All rights reserved.
PMID: 20353778 [PubMed - as supplied by publisher]

**The endocannabinoid system: A new entry in remote cell death mechanisms.**

Viscomi MT, Oddi S, Latini L, Biscicchia E, Maccarrone M, Molinari M.  
Santa Lucia Foundation I.R.C.C.S., Via del Fosso di Fiorano 65, 00143 Rome, Italy.  
Functional impairment after development of focal CNS lesions depends highly on damage that occurs in regions that are remote but functionally connected to the primary lesion site. These remote effects include cell death and structural changes, and they are important predictors of outcome in several pathologies, such as stroke, multiple sclerosis, and brain trauma. A greater understanding of the neuropathological mechanisms that exist in regions that are remote from focal primary lesions is therefore essential for the development of neuroprotective strategies. Endocannabinoids constitute a novel class of lipids that regulate mammalian cell apoptosis and the pathogenesis of neuroinflammatory and neurodegenerative diseases. In addition to well-described pharmacological actions in the brain, such as analgesia, hypokinesia, and hypothermia, endocannabinoids have been recently reported to control neuronal cell fate in various neuropathological conditions. Following brain injury, endocannabinoids are released, causing both protective and degenerative effects. Several hypotheses have been proposed to explain their role, but the mechanisms by which they act are largely unknown. New evidence indicates that the endocannabinoid system is a key participant in the determination of cell fate in remote cell death and its associated mechanisms. This review addresses recent findings on endocannabinoid function, focusing particularly on the relationships between the nitrergic, purinergic, and endocannabinoid systems. Copyright © 2010 Elsevier Inc. All rights reserved.  
PMID: 20353775 [PubMed - as supplied by publisher]


**Glatiramer acetate and the glatiramoid class of immunomodulator drugs in multiple sclerosis: an update.**

Johnson KP.  
University of Maryland Baltimore, Baltimore, Maryland 21201, USA. kjohnson@som.umaryland.edu  
IMPORTANCE OF THE FIELD: MS is a chronic progressive inflammatory and neurodegenerative disease associated with autoimmune dysregulation. Glatiramer acetate (GA), a complex polypeptides mixture and first member of the glatiramoid class, is a first-line therapy for relapsing MS. New glatiramoids are under development. AREAS COVERED IN THIS REVIEW: Studies from a PubMed search with terms ‘glatiramer’ and ‘glatiramoid’ were evaluated, focussing on studies conducted between 2007 and 2010. WHAT THE READER WILL GAIN: We review newly discovered GA effects on innate and acquired immunity and results of recent clinical studies. GA delays conversion from a clinically isolated syndrome to definite MS and has clinical benefits comparable to those of IFN-beta drugs, but is more cost-effective and improves quality of life. Preclinical studies of protiramer, a higher molecular mass glatiramoid, showed unexpected toxicity in animals, resulting in discontinuation of drug development. TAKE HOME MESSAGES: GA is a cost-effective, safe and efficacious MS treatment with pleiotropic immunomodulation activity, is best prescribed early and may safely enhance outcomes when used with other immunomodulators. Protiramer experience indicates the potential for unexpected toxicity associated with new glatiramoids. The safety, efficacy and immunogenicity of new glatiramoids must be evaluated thoroughly.  
PMID: 20397968 [PubMed - in process]
64. Expert Opin Pharmacother. 2010 May;11(7):1183-96.  
**Fingolimod for relapsing multiple sclerosis: an update.**  
Horga A, Castilló J, Montalban X.  
Multiple Sclerosis Centre of Catalonia (CEM-Cat), Vall d'Hebron University Hospital, Passeig Vall d'Hebron, 119-129, 08035 Barcelona, Spain. ahorga@cem-cat.org  
**IMPORTANCE OF THE FIELD:** Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the CNS. There is a large unmet need for new disease-modifying therapies with improved convenience, safety and efficacy. Fingolimod is an oral sphingosine-1-phosphate (S1P) receptor modulator under clinical investigation for the treatment of relapsing-remitting and primary progressive MS.  
**AREAS COVERED IN THIS REVIEW:** This review provides an update on the mechanism of action, pharmacological properties and efficacy and safety of fingolimod in patients with relapsing MS, with a particular emphasis on clinical trials.  
**WHAT THE READER WILL GAIN:** The reader will gain a comprehensive overview of the mechanism of action of fingolimod, particularly how the drug inhibits lymphocyte egress from secondary lymphoid organs by modulation of S1P receptors, and its pharmacokinetic and pharmacodynamic properties. Results from Phase II studies and pivotal Phase III trials of fingolimod for relapsing MS are discussed in depth.  
**TAKE HOME MESSAGE:** Randomized clinical trials have demonstrated the superior efficacy of fingolimod in reducing relapse rates and MRI measures of disease activity, as compared with placebo and intramuscular IFN-beta-1a. Fingolimod also lowered the risk of disability progression compared with placebo. Adverse events included bradycardia and atrioventricular block, respiratory and herpesvirus infections, increased liver enzyme levels, hypertension and macular edema. Fingolimod 0.5 mg seems to provide the best risk-benefit ratio.  
PMID: 20367536 [PubMed - in process]

**Treating multiple sclerosis with fingolimod or intramuscular interferon.**  
Pozzilli C, Prosperini L, Borriello G.  
"La Sapienza" University, S. Andrea Hospital, Multiple Sclerosis Centre, Department of Neurological Sciences, Viale dell'Università, 30, 00185 Rome, Italy +39 06 4991 4708 ; +39 06 3377 5900 ; carlo.pozzilli@uniroma1.it.  
The 12-month, double-blind TRANSFORMS study compared two dose regimens of oral fingolimod (0.5 and 1.25 mg/day) with intramuscular (i.m.) interferon beta-1a (IFN-beta-1a) administered once weekly at dosage of 30 mug in a study population of 1292 patients with relapsing remitting multiple sclerosis. Both doses of fingolimod were shown to be superior to i.m. IFN-beta-1a in reducing relapse rate and disease activity as detected by magnetic resonance imaging, while no significant effect on disability progression was observed. Although about 90% of patients completed the study, a greater proportion receiving a higher dose of fingolimod discontinued treatment because of adverse events, such as herpes virus infections (fatal in two patients assigned to higher dose), dose-dependent bradyarrhythmias and lymphopenia, transient macular edema, skin cancer and liver enzyme increase. Because of these safety concerns, a long-term evaluation is required to define the risk-benefit ratio. The TRANSFORMS study clearly showed a superior efficacy of oral fingolimod over i.m. IFN-beta-1a, but it is still uncertain whether oral fingolimod could be used as first-line treatment, or as an alternative treatment for patients who have failed immunomodulating therapy.  
PMID: 20426705 [PubMed - as supplied by publisher]
Doggrell SA.
Queensland University of Technology, Faculty of Science and Technology, GPO 2343, QLD 4001, Brisbane, Australia +61 7 3138 2015 ; +61 7 3138 1534 ; sheila.doggrell@qut.edu.au.
Most people with multiple sclerosis (MS) have the relapsing-remitting type. The objective was to evaluate two clinical trials of fingolimod in relapsing MS. FREEDOMS (FTY720 Research Evaluation Effects of Daily Oral therapy in Multiple Sclerosis), a Phase III placebo-controlled trial, showed that fingolimod (0.5 or 1.25 mg) reduced the relapse rate and disability in MS, compared with placebo. Fingolimod (0.5 or 1.25 mg) has been compared to interferon-beta-1a in a Phase III clinical trial (TRANSFORMS; Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis) and shown to be more efficacious than interferon-beta-1a in reducing relapse rates. However, fingolimod did increase the risk of infections and skin cancers. Only the lower dose of fingolimod (0.5 mg), which possibly has less toxicity, should be considered for prevention of relapses in relapsing-remitting MS.
PMID: 20408749 [PubMed - as supplied by publisher]

Update on the treatment options for multiple sclerosis.
Niino M, Sasaki H.
Department of Neurology, Hokkaido University Graduate School of Medicine, Kita-15 Nishi-7, Kita-ku, Sapporo 060-8638, Japan. niino@med.hokudai.ac.jp
Recent progress in the treatment of multiple sclerosis (MS) is remarkable, and the introduction of new therapies is yielding improvements in the management of MS. Furthermore, clinical trials with many different types of agents, especially selected monoclonal antibodies, have been undertaken or are ongoing, and some of the agents involved will probably be available as treatments for MS in the near future. Although these new and promising agents include targeted immunotherapies, some of them have limitations such as associated severe adverse events and the development of neutralizing antibodies. With regard to risk-benefit ratios, pharmacogenetics could shed light on inherited differences in drug metabolism and response, which would make individualized therapy possible in MS. Here, we review the recent progress in current therapeutic strategies for MS, and the potential options for future MS treatment.
PMID: 20383893 [PubMed - indexed for MEDLINE]

Buttmann M.
Department of Neurology, Julius Maximilian University, Josef-Schneider-Str. 11, Würzburg, Germany. m.buttmann@uni-wuerzburg.de
Treating multiple sclerosis (MS) with monoclonal antibodies (mAbs) has been marked by both progress and setbacks in the past 2 years, which are reviewed here. The natalizumab section of the article centers around progressive multifocal leukoencephalopathy (PML), and discusses PML risk in relation to treatment duration, bioassays for individual risk prediction, the concept of drug holidays, clinical course and treatment of PML, as well as safety-related regulatory actions. The rituximab section critically analyzes recent clinical trial results, discusses the clinical relevance of anti-idiotypic mAbs and makes a short excursion to neuromyelitis optica. Following this, the newer anti-CD20 mAbs ocrelizumab and ofatumumab, which are currently being tested in Phase II for MS, are reviewed and compared. The alemtuzumab section highlights novel data on mechanisms of action, potentially allowing individual risk prediction, and new results from the CAMMS223 trial, as well as the current status of the pivotal MS studies. The daclizumab section summarizes new open-label data, shedding more light on the adverse-effect profile of the drug in MS patients, and reports on its Phase III status. Subsequently, a failed ustekinumab trial and LY2127399 are reviewed. Taking into account late Phase II and III data on novel oral agents, the final section attempts to provide a detailed perspective on disease-modifying MS therapy in the medium term.
PMID: 20420497 [PubMed - in process]
Recombinant forms of myelin antigens expressed on Chinese hamster ovary (CHO) cells as a tool for identification of autoantibodies in serum of multiple sclerosis patients.
Jaśkiewicz E, Michalowska-Wender G, Pyszczek A, Wender M.
Laboratory of Neurogenetics, University of Medical Sciences, Poznań, Poland. grazynawender@wp.pl
A contribution of B cells and autoantibodies has been demonstrated in MS leading to interest in the use of such autoantibodies as diagnostic or prognostic markers and as a basis for immunomodulatory therapy. ELISA and Western fail to detect reactivity against epitopes displayed by native antigens expressed on myelin sheaths. We describe a cell-based assay that specifically identifies serum antibodies directed against three major myelin autoantigens: MBP, PLP and MOG. The method detects antibody binding to recombinant antigens in their native conformation on MBP, PLP and MOG transfected mammalian (hamster ovary) cells. 36 patients with relapsing-remitting MS diagnosed according to criteria of McDonald were recruited. Age 38.2 and duration of the disease 7.1. Serum anti-MBP, anti-PLP and anti-MOG IgG autoantibodies were detected in MS patients and 35 healthy donors by FACS analysis. Compared with healthy controls the titres of IgG autoantibodies directed against membrane-bound recombinant myelin antigens were most significantly increased for PLP, no quite significant for MBP and not significant for MOG. The titres of anti-MBP antibodies were low in contrast to high titre of anti-MOG antibodies in both groups suggesting a nonspecific binding. The cell-based assay detection of autoantibodies directed against recombinant myelin antigens could be a useful tool providing the serological markers in diagnosis and progression of MS. Indeed, it could allow obtaining molecular characteristics of disease in each patient in term of an antibody response against certain myelin and non-myelin antigens. We have shown that in RRMS patients elevated level of serum antibodies against PLP is significant, what should be considered in search for specific immunomodulatory therapy in MS.
PMID: 20383810 [PubMed - in process]

70. Gait Posture. 2010 Apr 16. [Epub ahead of print]
The effect of textured insoles on gait patterns of people with multiple sclerosis.
Kelleher KJ, Spence WD, Solomonidis S, Apatidis D.
Department of Mechanical and Biomedical Engineering, Nun's Island, National University of Ireland, Galway, Ireland; Bioengineering Unit, 106 Rottenrow East, University of Strathclyde, Glasgow G4 0NW, UK.
BACKGROUND: Somatosensory deficit is a common feature of MS. One method serving to combat impaired plantar sensation may be to provide enhanced sensory feedback from the sole of the foot by changing the characteristics of a shoe sole or surface. This study aimed to inspect the effect of textured insoles on gait patterns in a group of MS patients. METHODS: 14 patients with MS and 10 healthy control subjects were recruited for this study. Plantar sensation was evaluated using Semmes-Weinstein monofilaments. Kinematic, kinetic and EMG gait data were collected for MS patients walking with flat shoes only and again with shoes and a textured insole in contact with the sole of patients' feet. RESULTS: A reduction in plantar sensation was identified in the MS patient group compared to the control group. Wearing the textured insoles there was a significant increase in hip and knee sagittal plane excursion, maximum ankle dorsiflexion, knee flexion and in peak acceleration ground reaction force. Throughout the stance phase, EMG activity of shank muscles was typically found to increase whilst wearing the textured insoles. DISCUSSION AND CONCLUSION: Despite some positive changes in gait patterns when wearing textured insoles, an increased foot-shank angle in terminal stance suggests that patients did not propel their swing limb through increased contribution of ankle plantarflexor muscles, perhaps favouring more proximal muscle groups. Whilst the textured insoles may alter gait patterns in MS patients, their contribution to achieving a more regular gait pattern with sufficient propulsion from ankle plantarflexors remains uncertain. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20400312 [PubMed - as supplied by publisher]
71. Gene Ther. 2010 Apr 29. [Epub ahead of print]

**Mass spectrometry measurement of a therapeutic peptide for use in multiple sclerosis.**
Dadgari JM, Moore RE, Louie KA, Lee TD, McMillan M.

[1] Department of Neurology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA
[2] Department of Microbiology, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA.

Multiple sclerosis is an autoimmune disease of the central nervous system believed to be mediated by pathogenic T lymphocytes. We have developed a next-generation therapy in which cells secrete specific therapeutic molecules to silence these aberrant T cells. We have shown that fibroblasts, transduced to secrete a myelin basic protein-derived peptide, abrogate disease in the murine experimental autoimmune encephalomyelitis model of multiple sclerosis, which we hypothesized using a low-zone tolerance mechanism. To determine the efficacy (or not) of this therapy in humans, we must ensure that patients receive comparable doses of therapeutic peptide. To this end, we have used liquid chromatography coupled to tandem mass spectrometry to detect a tryptic peptide, derived from the secreted therapeutic product, at nanomolar concentrations. Success depended on growing the transduced fibroblasts in defined PC-1 medium in the presence of a cocktail of protease inhibitors. Gene Therapy advance online publication, 29 April 2010; doi:10.1038/gt.2010.19.

PMID: 20428213 [PubMed - as supplied by publisher]


**[Multiple sclerosis as a polygenic disease: an update]**
[Article in Russian]
[No authors listed]

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system. The observed type of heredity associated with MS is characteristic of polygenic diseases, which is produced by a joint contribution of a number of autonomously acting or interacting polymorphic genes. Recently to identify the genes responsible for genetic predisposition to MS two main approaches have been applied: (1) analysis of association of individual "candidate genes" with the disease and (2) analysis of the wide spectrum of chromosomal loci (complete genomic search) linkage with the disease in families with several MS patients. In the last two years, a new method, which borrowed the best approaches of the previous studies, genome-wide association screening (GWAS), which is based on the modern high-throughput DNA analysis, has been developed. This review describes reproduced (validated) results for individual genes and DNA loci located on the majority of chromosomes obtained using these three strategies as well as data on association of MS with allelic combinations of various genes.

PMID: 20391774 [PubMed - in process]

73. Health Promot Int. 2010 Apr 28. [Epub ahead of print]

**Utilization of health promotion and wellness services among middle-aged and older adults with multiple sclerosis in the mid-west US.**
Plow M, Cho C, Finlayson M.

Department of Occupational Therapy, University of Illinois at Chicago, 1919 W. Taylor Street (MC 811), Chicago, IL 60612, USA.

Routine engagement in healthy behaviors may improve quality of life in older adults with chronic disabling conditions, such as multiple sclerosis (MS). However, older adults with chronic conditions may face many barriers to engaging in healthy behaviors. Health promotion and wellness services may help older adults with chronic conditions engage in healthy behaviors. Thus, the purpose of this study was to identify factors associated with the use of and unmet needs for health promotion services among middle-aged and older adults with MS. Data from a cross-sectional telephone survey of individuals aging with MS in the mid-west USA were used for this study (n = 1282). A multinomial regression model was used to identify variables associated with the utilization of health promotion services. A logistic regression model was used to identify variables associated with unmet needs for these services. Females (OR = 1.51; CI: 1.13, 2.00), high school graduates (OR = 1.77; CI: 1.34, 2.34) and people who reported no problems with mobility or balance (OR = 1.68; CI: 1.12, 2.51) were more likely to utilize health promotion and wellness services. Factors that increased the likelihood of reporting an unmet need for these services were being female (OR = 2.34; CI: 1.56, 3.51), greater than a high school education (OR = 1.58; CI: 1.14, 2.20), not being married (OR = 1.79; CI: 1.31, 2.43), having inadequate income (OR = 1.83; CI: 1.31, 2.56), experiencing pain (OR = 1.96; CI: 1.34, 2.87) and reporting less ability to do everyday activities now compared with 1 year ago (OR = 2.13; CI: 1.16, 3.92). To avoid widening the health-disparities gap, future research needs to explore strategies that promote utilization of health promotion services among all middle-aged and older adults with MS.

PMID: 20427373 [PubMed - as supplied by publisher]
**Genome-wide association study of circulating D levels.**
Division of Epidemiology, Department of Environmental Medicine, New York University School of Medicine, New York, NY, 10016, USA.
The primary circulating form of vitamin D, 25-hydroxy-vitamin D (25(OH)D), is associated with multiple medical outcomes, including rickets, osteoporosis, multiple sclerosis, and cancer. In a genome-wide association study (GWAS) of 4,501 persons of European ancestry drawn from five cohorts, we identified single nucleotide polymorphisms (SNPs) in the gene encoding group-specific component (vitamin D binding) protein, GC, on chromosome 4q12-13 that were associated with 25(OH)D concentrations: rs2282679 (P=2.0 x 10(-30)), in LD with rs7041, a nonsynonymous SNP (D432E; P=4.1 x 10(-22)), and rs1155563 (P = 3.8 x 10(-25)). Suggestive signals for association with 25(OH)D were also observed for SNPs in or near three other genes involved in vitamin D synthesis or activation: rs3829251 on chromosome 11q13.4 in NADSYN1 (encoding nicotinamide adenine dinucleotide (NAD) synthetase; P=8.8 x 10(-7)), which was in high LD with rs1790349, located in DHCR7, the gene encoding 7-dehydrocholesterol reductase which synthesizes cholesterol from 7-dehydrocholesterol; rs8599638 in the region harboring the open reading frame 88 (C10orf88) on chromosome 10q26.13 in the vicinity of ACADS (acyl-coenzyme A dehydrogenase), involved in cholesterol and vitamin D synthesis (P=3.3 x 10(-7)); and, rs2060793 on chromosome 11p15.2 in CYP2R1 (encoding a key C-25-hydroxylase that converts vitamin D(3) to an active vitamin D receptor ligand; P=1.4 x 10(-5)). We genotyped SNPs in these four regions in 2,221 additional samples and confirmed strong genome-wide significant associations with 25(OH)D through meta-analysis with the GWAS data for GC (P=1.8 x 10(-49)), NADSYN1/DHCR7 (P=3.4 x 10(-9)), and CYP2R1 (P=2.9 x 10(-17)), but not C10orf88 (P=2.4 x 10(-5)).
PMID: 20418485 [PubMed - as supplied by publisher]

76. Immunology. 2010 Apr 6. [Epub ahead of print]
**Peroxisome proliferator-activated receptor delta agonists inhibit T helper type 1 (Th1) and Th17 responses in experimental allergic encephalomyelitis.**
Kanakasabai S, Chearwae W, Walline CC, Iams W, Adams SM, Bright JJ.
Neuroscience Research Laboratory, Methodist Research Institute, Indianapolis, IN.
Summary Multiple sclerosis (MS) is a neurological disorder that affects more than a million people worldwide. The aetiology of MS is not known and there is no medical treatment available that can cure MS. Experimental autoimmune encephalomyelitis (EAE) is a T-cell-mediated autoimmune disease model of MS. The pathogenesis of EAE/MS is a complex process involving activation of immune cells, secretion of inflammatory cytokines and destruction of myelin sheath in the central nervous system (CNS). Peroxisome proliferator-activated receptors (PPARs) are nuclear hormone receptor transcription factors that regulate cell growth, differentiation and homeostasis. PPAR agonists have been used in the treatment of obesity, diabetes, cancer and inflammation. We and others have shown that PPARgamma, alpha and delta agonists inhibit CNS inflammation and demyelination in the EAE model of MS. In this study we show that the PPARdelta agonists GW501516 and L165041 ameliorate MOGp35-55-induced EAE in C57BL/6 mice by blocking interferon (IFN)-gamma and interleukin (IL)-17 production by T helper type 1 (Th1) and Th17 cells. The inhibition of EAE by PPARdelta agonists was also associated with a decrease in IL-12 and IL-23 and an increase in IL-4 and IL-10 expression in the CNS and lymphoid organs. These findings indicate that PPARdelta agonists modulate Th1 and Th17 responses in EAE and suggest their use in the treatment of MS and other autoimmune diseases.
PMID: 20406305 [PubMed - as supplied by publisher]
77. Int Immunopharmacol. 2010 Apr 21. [Epub ahead of print]
Downregulation of IL-17 and IFN-gamma in the optic nerve by beta-elemene in experimental autoimmune encephalomyelitis.
Zhang R, Tian A, Shi X, Yu H, Chen L.
Department of Geriatrics, the First Affiliated Hospital of China Medical University, No.155 Nanjing Bei Street, Heping, 110001 Shenyang, Liaoning, People's Republic of China.
BACKGROUND: beta-elemene is a natural antitumor plant drug. Beneficial effects of beta-elemene therapy have been demonstrated in some kinds of tumor clinically. Especially, it has been found to pass through the blood brain barrier easily. Other reports have indicated that immune disorder that appeared in some tumors usually can be seen in demyelinating diseases including multiple sclerosis and experimental autoimmune encephalomyelitis. However, no information regarding the effects of beta-elemene therapy on the T helper cell subsets, Th1 or Th17 cells in experimental autoimmune encephalomyelitis has been found.
METHODS AND FINDINGS: We first determined morphologically that beta-elemene therapy markedly suppressed the inflammation in experimental autoimmune encephalomyelitis optic nerve. We then determined the effect in vivo of beta-elemene on Treg cells and Th17 and Th1 cells. We found that beta-elemene treatment modulated immune balance in both the periphery and the inflamed optic nerve by promoting less downregulation in Treg cells, inhibiting Th17 and Th1 polarization.
CONCLUSIONS: Taken together, our finding reveals an important new locus where beta-elemene induces substantial protection in experimental autoimmune encephalomyelitis optic nerve through signaling to several critical subsets of immune cells that reside in the peripheral and central nervous system. Copyright © 2010. Published by Elsevier B.V. PMID: 20399285 [PubMed - as supplied by publisher]

78. Int J Dev Neurosci. 2010 Apr 20. [Epub ahead of print]
NEUROBID-an EU-funded project to study the developing brain barriers.
Bueter W, Saunders NR, Mallard C, Bauer HC, Stolp HB, Kavelaars A, Dammann O; for the NEUROBID consortium.
Hannover Medical School, Hannover, Germany.
Brain diseases are one of the most prevalent groups of diseases in Europe with estimated annual costs amounting to euro386 billion. Data collected by the WHO suggest that brain diseases are responsible for 35% of Europe's total disease burden. In the treatment of neurological disease, the blood brain barrier (BBB) still represents an obstacle for the delivery of drugs to the brain and thus a major challenge for the development of therapeutic regimens. Understanding the molecular basis and functioning of the BBB in health and disease, including transport mechanisms across the BBB, therefore holds significant potential for future strategies to prevent and ameliorate neurological disease. Recent research indicates that some neurological disorders have a developmental etiologic component. The major goal of the NEUROBID project is thus to understand the molecular mechanisms and function of the BBB in health and disease both in the developing brain and the adult central nervous system. With an interdisciplinary consortium from the fields of developmental neurobiology and BBB research, NEUROBID aims to (i) understand the involvement of normal and disturbed BBB function in normal and abnormal brain development and (ii) to develop novel strategies for drug delivery to the brain. Unique transport mechanisms across the BBB will be used to target potential therapeutic macromolecular and cellular agents specifically to the brain barriers and transport them into the brain. The main target disorders of NEUROBID are non-inherited neurodevelopmental disorders arising from perinatal adverse exposure, such as cerebral palsy, and classic adult neurological disorders such as multiple sclerosis and stroke. In the long term, NEUROBID hopes to pave the way for new treatment strategies and thus reduce the economic and social burden of neurological disease. Copyright © 2010. Published by Elsevier Ltd. PMID: 20412847 [PubMed - as supplied by publisher]

**The osteopontin gene +1239A/C single nucleotide polymorphism is associated with type 1 diabetes mellitus in the Italian population.**


Interdisciplinary Research Center of Autoimmune Diseases and Department of Medical Sciences, A. Avogadro University of Eastern Piedmont, Novara, Italy.

Secreted phosphoprotein 1, also known as Osteopontin (Opn), is a proinflammatory cytokine involved in the TH1 response and is highly expressed in the islets and pancreatic lymph nodes of non-obese diabetic mice before the onset of diabetes. In humans, typing of the +1239A/C single nucleotide polymorphism (SNP) in the 3UTR of the Opn gene (SPP1) showed that +1239C carriers displayed higher Opn serum levels than +1239A homozygotes and a higher risk of developing autoimmune/lymphoproliferative syndrome, multiple sclerosis, and systemic lupus erythematosus. The aim of this work is to evaluate whether +1239A/C is also associated with type 1 diabetes mellitus (T1DM). We typed +1239A/C in an initial cohort of 184 T1DM patients and 361 controls, and confirmed our data in a second cohort of 513 patients and 857 controls. In both cohorts, +1239C carriers displayed a significantly higher risk of T1DM than +1239A homozygotes (combined cohorts: OR=1.63, 95 percent CI: 1.34-1.97). Clinical analysis did not detect any differences between patients carrying or not +1239C in terms of gender distribution and age at T1DM diagnosis. These data suggest that SPP1 variants marked by +1239C are associated with T1DM development in the Italian population. The predisposing effect may depend on its effect on Opn levels.

PMID: 20378012 [PubMed - in process]


**Soluble CD30: a biomarker for evaluating the clinical risk versus benefit of IFNα1A treatment in multiple sclerosis patients.**

Contasta I, Totaro R, Berghella AM, Pellegrini P, Del Beato T, Carolei A, Adorno D.

Istituto CNR per i Trapianti di Organo e Immunocitologia, LAquila, Italy.

Aberrant redox regulation occurs in immune and neurological pathologies, hence targeting the pathways involved in the regulation of the redox system could provide further insights into these diseases and open up new avenues for therapy. Soluble (s) CD30 is of key clinical importance in this respect, as its levels reflect the functionality of the CD30 receptor (CD30R), the specific lymphocyte receptor for thiol disulfide/oxidoreductase thioredoxin 1 (Trx1) which is known to regulate important immune and neurological processes. Increased levels of sCD30 appear to be a common element of oxidative stress, immunological alterations and neurological deficit, therefore these increases could be used as a clinical biomarker and target for therapy. We targeted sCD30 in our study of dendritic cell (DC) regulation of the T helper (Th) cell network in multiple sclerosis (MS) patients, as abnormalities in T regulatory (Treg)/Th1/Th17 pathways contribute to the pathogenesis of this immunological/neurological disease. DC profiles in Treg/Th1/Th2/Th17-types of cytokine production in culture supernatants were used as they determine the type of Th differentiation. Our results show that sCD30 levels increase significantly in MS patients, reflecting the disruption in the regulation of the Treg/Th1/Th17 cell network. A fall in the level of soluble CD30, induced by IFNbeta1a therapy, opposed the increase of neurologival deficit through increasing IL10 and TGFbeta levels, thus re-establishing network homeostasis but only when this was accompanied by an increase in IL12p70 levels. Since IL12p70 cytokine production is regulated by Trx1, our results indicate that redox system alterations may be the cause of IFNbeta1a therapeutic inefficacy. We conclude that an increase in the level of IL10, TGFbeta and IL12p70 and a fall in the level of sCD30 represent a means of evaluating the clinical risk/benefit of IFNbeta1a treatment.

PMID: 20378007 [PubMed - in process]
NAD(P)H oxidase and pro-inflammatory response during maximal exercise: role of C242T polymorphism of the P22PHOX subunit.
Department of Biomorphology, University of Chieti, Italy.
Aberrant redox regulation occurs in immune and neurological pathologies, hence targeting the pathways involved in the regulation of the redox system could provide further insights into these diseases and open up new avenues for therapy. Soluble (s) CD30 is of key clinical importance in this respect, as its levels reflect the functionality of the CD30 receptor (CD30R), the specific lymphocyte receptor for thioldisulfide/oxidoreductase thioredoxin 1 (Trx1) which is known to regulate important immune and neurological processes. Increased levels of sCD30 appear to be a common element of oxidative stress, immunological alterations and neurological deficit, therefore these increases could be used as a clinical biomarker and target for therapy. We targeted sCD30 in our study of dendritic cell (DC) regulation of the T helper (Th) cell network in multiple sclerosis (MS) patients, as abnormalities in T regulatory (Treg)/Th1/Th17 pathways contribute to the pathogenesis of this immunological/neurological disease. DC profiles in Treg/Th1/Th2/Th17-types of cytokine production in culture supernatants were used as they determine the type of Th differentiation. Our results show that sCD30 levels increase significantly in MS patients, reflecting the disruption in the regulation of the Treg/Th1/Th17 cell network. A fall in the level of soluble CD30, induced by IFNbeta1a therapy, opposed the increase of neurological deficit through increasing IL10 and TGFbeta levels, thus re-establishing network homeostasis but only when this was accompanied by an increase in IL12p70 levels. Since IL12p70 cytokine production is regulated by Trx1, our results indicate that redox system alterations may be the cause of IFNbeta1a therapeutic inefficacy. We conclude that an increase in the level of IL10, TGFbeta and IL12p70 and a fall in the level of sCD30 represent a means of evaluating the clinical risk/benefit of IFNbeta1a treatment.
PMID: 20378006 [PubMed - in process]

Serum and cerebrospinal fluid antioxidant activity and lipid peroxidation in Guillain-Barre syndrome and multiple sclerosis patients.
Ghabaei M, Jabedari B, Al-E-Eshagh N, Ghaffarpour M, Asadi F.
Iranian Center of Neurological Research, Tehran University of Medical Sciences, Tehran, Iran.
Oxidative stress through the changes in the levels of reactive oxygen species and antioxidative parameters can cause various neurological disorders. The aim of the present study was to show antioxidant activity (AOA) and malondialdehyde (MDA) levels in affected people with Guillain-Barre syndrome (GBS) and multiple sclerosis (MS). A total of 15 GBS patients, 13 MS patients, and 15 age and sex matched controls were included in this study. MDA and AOA values were determined in both cerebrospinal fluid (CSF) and serum, spectrophotometrically. We have shown an increase in the values of MDA in the CSF of both GBS and MS patients (0.32 +/- 0.073 and 0.22 +/- 0.06 micromol/L) compared to the control (undetectable levels). Furthermore, a significant decrease in the serum MDA levels was shown in both GBS and MS patients (0.81 +/- 0.18 and 0.73 +/- 0.18 micromol/L) when compared to the control (1.7 +/- 0.46 micromol/L). A decrease was shown for serum AOA in both GBS (1.7 +/- 0.21 mmol/L) and MS patients (2.6 +/- 0.62 mmol/L) when compared to the control (3.2 +/- 0.17 mmol/L). However, a significant increase in the values of CSF AOA was shown in both MS and GBS patients (1.47 +/- 0.19 and 1.42 +/- 0.26 mmol/L) compared to the control (0.71 +/- 0.19 mmol/L). An imbalance between the levels of AOA and MDA in both CSF and serum can be followed in both MS and GBS patients.
PMID: 20374079 [PubMed - in process]

**Adherence to disease-modifying drugs in patients with multiple sclerosis: a consensus statement from the Middle East MS Advisory Group.**

Yamout BI, Dahdaleh M, Al Jumah MA, Al-Shammri S, Al Sharoqi I, Al-Tahan AR, Bohlega S, Deleu D, Inshasi J, Khalifa A, Szólics M.

Internal Medicine, American University of Beirut, Beirut, Lebanon. yamoutba@idm.net.lb

Adherence to therapy is a key issue in chronic illnesses. In addition, several features of multiple sclerosis (MS) and its treatment may increase the likelihood of patient nonadherence and discontinuation of treatment. Nonadherence will obviously compromise the efficacy of disease-modifying drugs in patients with MS. This subject was discussed by a group of local MS specialists from the Middle East. The group debated several key questions about the features and causes of patient nonadherence and its management. Further, they made recommendations for optimizing treatment adherence in this area.

PMID: 20374075 [PubMed - in process]


**Prognostic factors of multiple sclerosis in Lebanon.**

Yamout B, Itani S, Arabi A, Hamzeh D, Yaghi S.

Department of Neurology, American University of Beirut Medical Center, Beirut, Lebanon. yamoutba@idm.net.lb

BACKGROUND: Multiple sclerosis (MS) has a variable disease course. Identifying early predictive prognostic factors is of paramount importance. Most of the data on these factors however comes from studies performed in western countries. Such data is lacking in the Arab World. The objective of this study is to identify early predictors of disability among MS patients in Lebanon. METHODS: 75 relapsing-remitting MS patients with 5 year follow-up from disease onset were selected from Project MS Lebanon database. The following parameters were studied as potential causes of early disability as defined by an EDSS > or = 3, after five years from disease onset: age at onset of MS, gender, interval between first and second attack, residual deficit after first attack, initial symptoms, treatment for at least 1 year in the first 5 years, and the number of relapses in the first 2 and 5 years. RESULTS: Patients with incomplete recovery from the first relapse were 11.66 times more likely to have a higher EDSS after 5 years (CI = 2.02-67.31, p = .001). Furthermore, the number of relapses during the first 5 years was also an independent predictor of EDSS > or = 3 at 5 years (p = .024). Other factors were not shown to predict a worse outcome. CONCLUSION: Overall, early predictors of disability in MS among the Lebanese population were not very different from similar predictors in western countries.

PMID: 20374088 [PubMed - in process]
Khan F, Pallant JF, Zhang N, Turner-Stokes L.

Objective The objective of this study was to explore methods examining patient complexity and therapy interventions in relation to functional outcomes from an inpatient multiple sclerosis (MS) rehabilitation program.

Methods Retrospective and prospective data for 24 consecutive inpatients at a tertiary rehabilitation facility assessed discharged to community. Over one-half had 'moderate-severe' scores for fatigue, and deficits in motor function and mood that resulted in significant functional limitation. Rehabilitation Complexity Scale scores showed substantial complexity with two-thirds requiring specialized nursing. The NPTDA score (median 22 interquartile range 20-23) showed moderate dependency on admission in the following domains: physical, cognitive and psychosocial programs and preparing for discharge. The mean physiotherapy and occupational therapy received was 45.76 and 24.04 min/day, respectively. Functional gains from admission to discharge for FIM and BI were significant (P<0.001). There were strong correlations between the total NPTDA and FIM motor scores (Spearman's rho -0.80) and BI (rho -0.83), but only weak correlations with the FIM cognitive score (rho -0.33). In conclusion, this pilot study provided information about the complex interplay of patient and process factors, and their interrelationships that impact functional outcomes in MS rehabilitation. A prospective study is now planned using appropriate tools to understand the 'black box' of rehabilitation.

Khan F, Pallant JF, Zhang N, Turner-Stokes L.

Objective: The objective of this study was to explore methods examining patient complexity and therapy interventions in relation to functional outcomes from an inpatient multiple sclerosis (MS) rehabilitation program.

Methods: Retrospective and prospective data for 24 consecutive inpatients at a tertiary rehabilitation facility assessed discharged to community. Over one-half had 'moderate-severe' scores for fatigue, and deficits in motor function and mood that resulted in significant functional limitation. Rehabilitation Complexity Scale scores showed substantial complexity with two-thirds requiring specialized nursing. The NPTDA score (median 22 interquartile range 20-23) showed moderate dependency on admission in the following domains: physical, cognitive, and psychosocial programs and preparing for discharge. The mean physiotherapy and occupational therapy received was 45.76 and 24.04 min/day, respectively. Functional gains from admission to discharge for FIM and BI were significant (P<0.001). There were strong correlations between the total NPTDA and FIM motor scores (Spearman's rho -0.80) and BI (rho -0.83), but only weak correlations with the FIM cognitive score (rho -0.33). In conclusion, this pilot study provided information about the complex interplay of patient and process factors, and their interrelationships that impact functional outcomes in MS rehabilitation. A prospective study is now planned using appropriate tools to understand the 'black box' of rehabilitation.

http://www.bayer-vital.de/
http://www.betaferon.de/
http://www.ms-gateway.de
mediante el Índice de Barthel (IB) y la medida de la independencia funcional (MIF); 4) duración de la estancia hospitalaria y el lugar de destino del paciente después del alta. El valor medio de la duración del estancia hospitalaria fue de 20 días (DE=15.7); la proporción varones : mujeres fue de 10 : 14; en 11 (46%) de estos pacientes los valores de la Escala Expandida para la Valoración del Grado de Discapacidad fue mayor que 6.5, y después del alta todos regresaron a su hogar. En más de la mitad de los pacientes el grado de astenia fue de entre moderado e intenso, y presentaron alteraciones de las funciones motoras y del estado de ánimo que causaron importantes limitaciones funcionales. Los puntajes de la Escala de Complejidad del Tratamiento de Rehabilitación mostraron que el grado de complejidad suele ser alto, pues dos tercios de los pacientes necesitan atención especializada de enfermería. Los puntajes la NPTDA (la mediana del intervalo entre cuartillas, de entre 20 y 23) mostró un grado de dependencia moderado al ingreso en los siguientes dominios: físico, cognitivo, y psicológico, y durante la preparación para el alta. La media de la duración del tratamiento de fisioterapia y de terapia ocupacional fueron de 45.76 y 24.04 min/día, respectivamente. Se logró una gran mejora en la esfera funcional desde el momento del ingreso hasta el alta, según los puntajes de la MIF y del IB (P<0.001). Se hallaron importantes correlaciones entre los puntajes totales de la NPTDA y de la MIF de la esfera motora (coeficiente de correlación de Spearman, rho -0.80) y el IB (rho -0.83), pero las correlaciones entre la NPTDA y de la MIF de la esfera cognitiva (rho -0.33). En conclusión, este estudio preliminar aportó información importante sobre la compleja interacción entre los pacientes y los factores del proceso a rehabilitación, y las interrelaciones entre estos que influyen en los resultados funcionales de la rehabilitación de pacientes con EM. Se realizará un estudio prospectivo utilizando las herramientas adecuadas para lograr descifrar la <<caja negra>> de la rehabilitación.

Cette étude avait pour objet d’explorer des méthodes qui examinent la complexité des patients et les interventions de thérapie par rapport aux résultats fonctionnels d'un programme de rééducation de patients hospitalisés souffrant de sclérose en plaques. Les données rétrospectives et prospectives pour 24 patients consécutifs hospitalisés dans un établissement de rééducation tertiaire évaluaient (i) la déficience ou l'invalidité - échelle de statut d'incapacité augmenté, jeu d'affections neurologiques, (ii) la complexité de l'intervention - échelle de complexité de la rééducation, évaluation NPTDA (Northwick Park Therapy Dependency Assessment), le type et la durée du traitement, (iii) les fonctions - indice de Barthel (BI), la mesure d'indépendance fonctionnelle (FIM), (iv) la durée du séjour hospitalier, la destination à la sortie de l'hôpital. La durée moyenne du séjour était de 20 jours (écart type = 15.7); le ratio homme : femmes était de 10 : 14; 11 sujets (46) présentaient des scores supérieurs à 6.5, sur l’échelle de statut d’incapacité augmenté et tous ont été replacés dans la collectivité à la sortie de l'hôpital. Plus de la moitié présentaient des scores modérés à sévères pour la fatigue, et des déficits de la fonction motrice et de l'humeur qui provoquaient de significatives limitations fonctionnelles. Les scores sur l’échelle de complexité de la rééducation indiquaient une complexité considérable, les deux tiers nécessitant des soins spécialisés. Le score NPTDA (médiane de 22, écart interquartile 20-23) faisaient apparaître une dépendance modérée à l'admission dans les domaines suivants:programmes physiques, cognitifs et psychosociaux et préparation au départ de l'hôpital. La moyenne reçue par la physiothérapie et l’ergothérapie était de 45.76 et 24.04 min/jour, respectivement. Les gains fonctionnels de l'admission au départ pour le FIM et le BI étaient significatifs (P<0.001). On a constaté de fortes corrélations entre les scores moteurs NPTDA et FIM totaux (rho de Spearman 0.80) et BI (rho -0.83), mais seulement des corrélations faibles avec le score cognitif FIM (rho -0.33). En conclusion, cette étude pilote a apporté des informations sur l'interaction complexe des patients et des facteurs du processus et leurs interrelations qui influent sur les résultats de la rééducation fonctionnelle de la sclérose en plaques. Une étude prospective est maintenant planifiée en utilisant les outils appropriés pour comprendre la <<boîte noire>> de la rééducation.

PMID: 20410826 [PubMed - as supplied by publisher]
88. J Child Neurol. 2010 Apr 15. [Epub ahead of print]

Iron Status in Children With Recurrent Episodes of Tumefactive Cerebral Demyelination.
van Toorn R, Schoeman JF, Solomons R, Rensburg MA, van Rensburg SJ.
Department of Pediatrics and Child Health, Tygerberg Children's Hospital Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa.
Iron is a vital element in the multifactorial initiation of myelination. It is required for cholesterol and lipid biosynthesis, both key components of myelin. Iron also plays an important role in energy production by mitochondrial oxidative metabolism which occurs in myelin-producing oligodendrocytes at a higher rate than in any other cell. Iron deficiency can, therefore, result in decreased oligodendrocyte survival and defective myelination. This led us to investigate iron status in 2 consecutive children with multiple sclerosis who presented with recurrent episodes of tumefactive demyelination. Testing revealed nonanemic iron deficiency in both patients. Discontinuation of iron supplementation in both children resulted in recurrent decreased iron parameters which can indicate mutations in proteins responsible for regulation of iron uptake. Further studies are warranted to explore the association of low iron in children presenting with recurrent episodes of tumefactive demyelination.

PMID: 20395637 [PubMed - as supplied by publisher]


NRAMP1 (SLC11A1) Variants: Genetic Susceptibility to Multiple Sclerosis.
Ates O, Kurt S, Bozkurt N, Karaer H.
Department of Medical Biology, Medical Faculty, Gaziosmanpasa University, 60100, Tokat, Turkey, omerates27@yahoo.com.
OBJECTIVES: Multiple sclerosis (MS) is an inflammatory, autoimmune demyelinating disease of the central nervous system. Human Natural Resistance Associated Macrophage Protein 1 (NRAMP1) gene polymorphisms have been implicated in the immune mediated diseases susceptibility. This study aimed to investigate the plausible association between NRAMP1 gene and MS susceptibility. METHODS: We analyzed (GT)(n,) INT4, 3'UTR and D543N polymorphisms of NRAMP1 gene in 100 MS patients and 104 healthy subjects by using amplification refractory mutation system-polymerase chain reaction and sequence analysis. RESULTS: No significant association was found between (GT)(n,) INT4, 3'UTR and D543N polymorphisms and MS. There was also no correlation between NRAMP1 polymorphisms and MS clinical forms. CONCLUSIONS: Our findings suggest that NRAMP1 polymorphisms do not play a role in MS susceptibility and clinical finding of MS in Turkish patients.

PMID: 20405176 [PubMed - as supplied by publisher]


Non-invasive brain mapping of motor-related areas of four limbs in patients with clinically isolated syndrome compared to healthy normal controls.
Iranian Center of Neurological Research, Imam Khomeini Hospital, Tehran, Iran.
Functional MRI studies on patients with multiple sclerosis (MS) have demonstrated widespread cortical reorganization of the motor network. However, few functional studies have addressed cortical plasticity in patients with clinically isolated syndrome (CIS). The activity of the lower limb motor system, despite its highlighted involvement in patients with CIS and MS, has been little studied. Thus, brain activation was compared in CIS patients with clinically intact motor systems with that in healthy control participants while they were performing motor tasks with four limbs. A total of 26 right-handed patients with CIS with clinically intact motor systems and 28 right-handed age and sex-matched controls participated in the functional MRI (fMRI) motor task. Patients with CIS showed greater activation in the ipsilateral secondary somatosensory cortex, cingulate gyrus and precuneus cortex while performing the ankle movement task compared to healthy controls. In the finger-tapping task, patients with CIS showed greater activity in the contralateral thalamus, ipsilateral premotor and superior temporal gyrus. In addition, the left inferior frontal gyrus was activated more in patients with CIS, regardless of the hand used. Therefore, despite having clinically intact motor systems, patients with CIS had different motor networks. All novel recruited regions were adjacent to the somatotopy of the primary motor areas of the limbs. Our finding confirm that brain reorganization precedes clinical manifestation, as no patient had any clinical manifestation that suggested involvement of the motor system. Copyright © 2009 Elsevier Ltd. All rights reserved.

PMID: 20382535 [PubMed - as supplied by publisher]
Cutting Edge: critical role for PYCARD/ASC in the development of experimental autoimmune encephalomyelitis.
Shaw PJ, Lukens JR, Burns S, Chi H, McGargill MA, Kanneganti TD.
Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN 38104, USA.
Multiple sclerosis is an autoimmune disease in which self-reactive T cells attack oligodendrocytes that myelinate axons in the CNS. Experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, is dependent on caspase-1; however, the role of Nod-like receptors upstream of caspase-1 is unknown. Danger- and pathogen-associated molecular patterns activate Nod-like receptor 3, which activates caspase-1 through the adaptor protein, apoptosis-associated speck-like protein containing CARD (ASC). We report that the progression of EAE is dependent on ASC and caspase-1 but not Nod-like receptor 3. ASC(-/-) mice were even more protected from the progression of EAE than were caspase-1(-/-) mice, suggesting that an inflammasome-independent function of ASC contributes to the progression of EAE. We found that CD4(+) T cells deficient in ASC exhibited impaired survival; accordingly, ASC(-/-) mice had fewer myelin oligodendrocyte glycoprotein-specific T cells in the draining lymph nodes and CNS.
PMID: 20368281 [PubMed - in process]

An imbalance of two functionally and phenotypically different subsets of plasmacytoid dendritic cells characterizes the dysfunctional immune regulation in multiple sclerosis.
Schwab N, Zozulya AL, Kieseier BC, Toyka KV, Wiendl H.
Department of Neurology, Clinical Research Group for Multiple Sclerosis and Neuroimmunology, University of Wuerzburg, Wuerzburg, Germany.
Plasmacytoid dendritic cells (pDCs) are instrumental in peripheral T cell tolerance and innate immunity. How pDCs control peripheral immunetolerance and local parenchymal immune response and contribute to the altered immunoregulation in autoimmune disorders in humans is poorly understood. Based on their surface markers, cytokine production, and ability to prime naive allogenic T cells, we found that purified BDCA-2(+)BDCA-4(+) pDCs consist of at least two separate populations, which differed in their response to oligodeoxynucleotides and IFNs (IFN-beta), and differently induced IL-17- or IL-10-producing T cells. To evaluate the potential immunoregulatory role of these two types of pDCs in multiple sclerosis (MS) and other human autoimmune disorders (myasthenia gravis), we studied the phenotype and regulatory function of pDCs isolated from clinically stable, untreated patients with MS (n = 16). Patients with MS showed a reversed ratio of pDC1/pDC2 in peripheral blood (4.4:1 in healthy controls, 0.69:1 in MS), a phenomenon not observed in the other autoimmune disorders. As a consequence, MS pDCs had an overall propensity to prime IL-17-secreting cells over IL-10-secreting CD4+ T cells. Immunomodulatory therapy with IFN-beta induced an increase of the pDC1 population in vivo (n = 5). Our data offer a plausible explanation for the disturbed immune tolerance in MS patients and provide evidence that immunomodulatory therapy acts at the level of reconstituting homeostasis of pDC, thus reconstituting the disturbed balance.
PMID: 20357264 [PubMed - in process]

TGF-{beta} Enhances Effector Th1 Cell Activation but Promotes Self-Regulation via IL-10.
Department of Molecular Virology, Immunology, and Medical Genetics.
Myelin-specific effector Th1 cells are able to perpetuate CNS inflammation in experimental autoimmune encephalomyelitis, an animal model representative of multiple sclerosis. Although the effects of cytokines in the CNS microenvironment on naive CD4(+) T cells have been well described, much less is known about their ability to influence Ag-experienced effector cells. TGF-beta is a multifunctioning cytokine present in the healthy and inflamed CNS with well-characterized suppressive effects on naive T cell functions. However, the effects of TGF-beta on effector Th1 cells are not well defined. Using myelin-specific TCR transgenic mice, we demonstrate that TGF-beta elicits differential effects on naive versus effector Th1 cells. TGF-beta enhances cellular activation, proliferation, and cytokine production of effector Th1 cells; however, adoptive transfer of these cells into naive mice showed a reduction in encephalitogenicity. We subsequently demonstrate that the reduced encephalitogenic capacity is due to the ability of TGF-beta to promote the self-regulation of Th1 effector cells via IL-10 production. These data demonstrate a mechanism by which TGF-beta is able to suppress the encephalitogenicity of myelin-specific Th1 effector cells that is unique from its suppression of naive T cells.
PMID: 20393141 [PubMed - as supplied by publisher]
Multiple sclerosis: hyperintense lesions in the brain on T1-weighted MR images assessed by diffusion tensor imaging.
Zhou F, Shiroishi M, Gong H, Zee CS.
Department of Radiology, The First Affiliated Hospital, NanChang University, NanChang, JiangXi, China.
PURPOSE: To evaluate retrospectively quantitative diffusion tensor imaging (DTI) values of hyperintense lesions on nonenhanced T1-weighted magnetic resonance (MR) images in patients with multiple sclerosis (MS) to elucidate the degree of demyelination or remyelination associated with T1 hyperintense lesions and study their relationship to MR markers of tissue damage (brain atrophy). MATERIALS AND METHODS: Institutional review board approval was obtained; informed consent was waived for this HIPAA-compliant study, including 76 patients with MS and 20 healthy control subjects without evidence of MS clinically or on imaging. T1 lesions were compared with normal white matter on nonenhanced images and judged to be hyperintense. Quantitative DTI metrics of T1 hyperintense lesions were examined, and the relationship between DTI parameters and brain atrophy were investigated in this study. RESULTS: At least one T1 hyperintense lesion was found in 16 patients (total, 28 lesions). Hyperintense lesions on T1-weighted imaging (T1WI) had lower mean diffusion (MD) than others signal intensity lesions on T1WI but higher MD than normal white matter (F = 3.931; P < 0.001); Fractional anisotropy (FA; F = 3.24; P < 0.001) and volume ratio (VR; F = 1.864; P < 0.001) were higher in hyperintense lesions on T1WI than hypointense/isointense lesions on T1WI, but were lower than normal-appearing white matter (NAWM) and normal white matter in controls. There was correlation between FA and VR (r = 0.678; P < 0.001) and inverse correlation between FA and MD (r = -0.437; P = 0.02), MD and VR (r = -0.423; P = 0.025) for T1 hyperintense lesion. The MD values of T1 hyperintense lesions (r = -0.304; P < 0.001) and the VR values of T1 hyperintense lesions (r = 0.096; P = 0.042) were significantly (negative) correlated with Brain parenchymal fraction (BPF; higher BPF score); the FA values of T1 hyperintense lesions (r = -0.111; P = 0.018), the MD values of T1 hyperintense lesions (r = 0.379; P < 0.001) and the VR values of T1 hyperintense lesions (r = -0.142; P = 0.003) were significantly correlated with third ventricular width (lower width). However, the FA value of T1 hyperintense lesions was not significantly associated with BPF(r = 0.083; P = 0.08). CONCLUSION: The quantitative DTI values of T1 hyperintense MS plaques were between hypo-/isointense lesions and NAWM or normal white matter, and correlated with BPF and third ventricular width. Our results supports the notion that axonal remyelination may be the reason for T1 hyperintense lesions. (c) 2010 Wiley-Liss, Inc.
PMID: 20373421 [PubMed - in process]

Imaging biomarkers in multiple sclerosis.
Filippi M, Agosta F.
Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University Hospital San Raffaele, Milan, Italy. m.filippi@hsr.it
Recent years have witnessed impressive advances in the use of magnetic resonance imaging (MRI) for the assessment of patients with multiple sclerosis (MS). Complementary to the clinical evaluation, conventional MRI provides crucial pieces of information for the diagnosis of MS. However, the correlation between the burden of lesions observed on conventional MRI scans and the clinical manifestations of the disease remains weak. The discrepancy between clinical and conventional MRI findings in MS is explained, at least partially, by the limited ability of conventional MRI to characterize and quantify the heterogeneous features of MS pathology. Other quantitative MR-based techniques, however, have the potential to overcome such a limitation of conventional MRI. Indeed, magnetization transfer MRI, diffusion tensor MRI, proton MR spectroscopy, and functional MRI are contributing to elucidate the mechanisms that underlie injury, repair, and functional adaptation in patients with MS. Such techniques are likely to benefit from the use of high-field MR systems and thus allow in the near future providing additional insight into all these aspects of the disease. This review summarizes how MRI is dramatically changing our understanding of the factors associated with the accumulation of irreversible disability in MS and highlights the reasons why they should be used more extensively in studies of disease evolution and clinical trials. (c) 2010 Wiley-Liss, Inc.
PMID: 20373420 [PubMed - in process]
Detection of viral DNA sequences in the cerebrospinal fluid of patients with multiple sclerosis.
Laboratory of Molecular Medicine and Biotechnology, Don C Gnocchi Foundation, IRCCS S Maria Nascente, Milan, Italy. rmancuso@dongnocchi.it
The role of viruses in the pathogenesis of multiple sclerosis (MS) is a subject of heated debate. The presence of six different neurotropic viruses was sought, including JC virus (JCV), varicella zoster virus (VZV), human herpesvirus 6 (HHV-6), and Epstein-Barr virus (EBV), in cerebrospinal fluid (CSF) samples collected from 51 patients with MS and 30 patients with other neurological diseases. Cell-free or cell-associated viral DNA in CSF samples was detected by real-time PCR, and viral loads were determined. Magnetic resonance imaging (MRI) examinations were also performed to look for active lesions. Cell-associated JCV DNA was detected in 3 of the 51 patients with MS and in 2 of the 30 patients with other neurological disease. Cell-free JCV DNA was detected in one additional patient with MS. Cell-free VZV DNA was detected in one patient without MS, cell-free HHV-6 was detected in one patient with MS, and cell-free EBV was detected in one patient with MS. All other study patients had no detectable viral DNA in CSF samples and no double infections were found. The small percentage of patients with detectable viral DNA in CSF samples was comparable between patients with MS and those with other neurological disease, and presence of viral DNA was not a predictor of brain lesions. Additional observations suggest that cell trafficking from the periphery, rather than leakage through the blood-brain barrier, results in the transport of viruses to the CNS, where local immunosurveillance can control viral replication in immunocompetent individuals. (c) 2010 Wiley-Liss, Inc.
PMID: 20419821 [PubMed - in process]

Can psychiatrists and neurologists predict their patients' participation preferences?
Klinik und Poliklinik für Psychiatrie und Psychotherapie, Technische Universität München, München, Germany. j.hamann@lrz.tum.de
There is evidence that an optimal match of patients' participation preferences improves health outcomes. Since it is unknown whether psychiatrists and neurologists can predict their patients' participation preferences we performed a cross-sectional survey involving N = 101 inpatients with schizophrenia/schizoaffective disorder and N = 102 inpatients with multiple sclerosis. Both patients and their physicians in charge were surveyed with respect to the patients' participation preferences, using the Autonomy Preference Index and a global estimate. Most patients wished to participate in medical decision making. Doctors performed poorly when predicting their individual patients' participation preferences and tended to overestimate their patients' participation preferences. A longer duration of the hospital stay did not improve the accuracy of doctors' estimates. Thus, neurologists and psychiatrists fail at predicting their patients' participation preferences accurately, which might challenge patients' treatment satisfaction. More attention in the consultation should be paid to patients' preferences.
PMID: 20386262 [PubMed - indexed for MEDLINE]
Regionally Distinct White Matter Lesions Do Not Contribute to Regional Gray Matter Atrophy in Patients with Multiple Sclerosis.
Antulov R, Carone DA, Bruce J, Yella V, Dwyer MG, Tjoa CW, Benedict RH, Zivadinov R.
From the Department of Neurology, Buffalo Neuroimaging Analysis Center, State University of New York at Buffalo, Buffalo, New York, NY (RA, VY, MGD, CWT, RZ); Department of Radiology, Clinical Hospital Centre Rijeka, Rijeka, Croatia (RA); State University of New York, Upstate Medical University, Syracuse, NY (DAC); Brown University, Providence, RI (JB); The Jacobs Neurological Institute, Department of Neurology, State University of New York at Buffalo, Buffalo, NY (RHBB, RZ).
ABSTRACT
PURPOSE To determine to what extent T1- and T2-regional lesion volumes (RLVs) contribute to total and/or regional gray matter (GM) atrophy in multiple sclerosis (MS).
METHODS We studied 110 (67 relapsing-remitting and 43 secondary-progressive) MS patients. SABRE program was used to parcel the brain into 13 regions per hemisphere. Total and regional GM fractions (GMFs) were determined in each region to correct for intraregional size variability. Partial correlations were used to determine associations (holding the converse constant) between RLVs, GMF, and regional GMFs (P < .001 to avoid Type 1 error).
RESULTS Partial correlations between RLVs and regional GMFs (controlling for total GMF) for the total MS group were not significant for any of the 26 regions for T2, whereas they were significant for two of the 26 regions for T1. Partial correlations between RLVs and total GMF (controlling for regional GMF) for the total MS group were significant in 9 of 26 regions for T2 (largest r = right lateral inferior frontal, -.45) and 5 of 26 regions for T1 (largest r = right inferior parietal, -.45). CONCLUSIONS Results suggest a model whereby a distinct generalized disease process accounts for GM atrophy better than regionally distinct Wallerian degeneration.
PMID: 20412395 [PubMed - as supplied by publisher]

HERVs in Neuropathogenesis.
Christensen T.
Department of Medical Microbiology and Immunology, University of Aarhus, Bartholin Building, Wilhelm Meyers Allé 4, 8000, Aarhus C, Denmark, tc@microbiology.au.dk.
In humans, exogenous retroviruses are known to cause immunodeficiency and neurological disease. While endogenous retroviruses are firmly established pathogens in other species, the human endogenous retroviruses (HERVs) may well be considered as emerging pathogens. HERVs also exhibit complex interactions with exogenous retroviruses and herpesviruses. Two neurological disorders in particular are associated with HERVs: multiple sclerosis (MS) and schizophrenia. HERV-H/F and HERV-W are specifically activated both in the circulation and the central nervous system (CNS) in a majority of MS patients, and particularly, the envelopes (env transcription and Env proteins) appear strongly associated with disease activity. Interferon beta (IFN-beta) therapy is well-established for MS. IFN-beta is also known to have anti-retroviral activities toward exogenous retroviruses (HIV and HTLV-I). New reports show that IFN-beta also mediate down-regulation of HERV-H/F and HERV-W in MS patients. HERV-W and HERV-K transcription (gag and pol) appears, to some extent, to be up-regulated in the circulation and the CNS of patients with schizophrenia. The expression of anti-HERV-W Gag reactive epitopes is reported to be down-regulated in the brain but up-regulated in the blood from schizophrenia patients. The pathogenic potential of HERVs certainly merits further studies.
PMID: 20422298 [PubMed - as supplied by publisher]
Molecular Regulation of JC Virus Tropism: Insights into Potential Therapeutic Targets for Progressive Multifocal Leukoencephalopathy.
Marshall LJ, Major EO.
Laboratory of Molecular Medicine and Neuroscience, Molecular Medicine and Virology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, 10 Center Drive, Building 10 Room 3B14 MSC 1295, Bethesda, MD, 20892-1296, USA, marshalllj@ninds.nih.gov.
Progressive multifocal leukoencephalopathy (PML) is a growing concern for patients undergoing immune modulatory therapies for treatment of autoimmune diseases such as multiple sclerosis. Currently, there are no drugs approved for the treatment of PML that have been demonstrated in the patient to effectively and reproducibly alter the course of disease progression. The human polyoma virus JC is the causative agent of PML. JC virus (JCV) dissemination is tightly controlled by regulation of viral gene expression from the promoter by cellular transcription factors expressed in cells permissive for infection. JCV infection likely occurs during childhood, and latent virus containing PML-associated promoter sequences is maintained in lymphoid cells within the bone marrow. Because development of PML is tightly linked to suppression and or modulation of the immune system as in development of hematological malignancies, AIDS, and monoclonal antibody treatments, further scrutiny of the course of JCV infection in immune cells will be essential to our understanding of development of PML and identification of new therapeutic targets.

Studies in the Modulation of Experimental Autoimmune Encephalomyelitis.
Libbey JE, Tsunoda I, Fujinami RS.
Department of Pathology, University of Utah School of Medicine, 30 North 1900 East, 3R330 SOM, Salt Lake City, UT, 84132, USA.
Experimental autoimmune encephalomyelitis (EAE), an experimental model for multiple sclerosis, can be induced through inoculation with several different central nervous system (CNS) proteins or peptides. Modulation of EAE, resulting in either protection from EAE or enhancement of EAE, can also be accomplished through either vaccination or DNA immunization with molecular mimics of self-CNS proteins. Previously published data on this method of EAE modulation will be reviewed. New data is presented, which demonstrates that EAE can also be modulated through the administration of the beta-(1,3)-D-glucan, curdlan. Dendritic cells stimulated by curdlan are involved in the differentiation of the interleukin-17 producing subset of CD4(+) T cells that are recognized effector cells in EAE. Using two different systems to study the effects of curdlan on EAE, it was found that curdlan increased the incidence of EAE and/or the severity of the disease course.

Epstein-Barr Virus Infection and Multiple Sclerosis: A Review.
Ascherio A, Munger KL.
Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave, Bldg. 2, 3rd Fl, Boston, MA, 02115, USA, aascheri@hsph.harvard.edu.
Epstein-Barr virus (EBV) infection results in a life-long persistence of the virus in the host's B-lymphocytes and has been associated with numerous cancers including Burkitt's lymphoma, Hodgkin lymphoma, and nasopharyngeal carcinoma. There is considerable evidence that EBV infection is a strong risk factor for the development of multiple sclerosis. Early age at primary EBV infection is typically asymptomatic, but primary infection during adolescence or adulthood often manifests as infectious mononucleosis, which has been associated with a two- to threefold increased risk of MS. Most importantly, MS risk is extremely low in individuals who are EBV negative, but it increases several folds following EBV infection. Additional evidence supporting a role for EBV in MS pathogenesis includes the observations of elevated antibodies to EBV antigens (especially EBV nuclear antigen-1) prior to the onset of MS, and an increased risk of MS among EBV-positive children. The biological mechanism by which EBV may cause MS is not known, but several possibilities are discussed.

PMID: 20369303 [PubMed - as supplied by publisher]
Pathogenesis of Murine Coronavirus in the Central Nervous System.
Bender SJ, Weiss SR.
Department of Microbiology, University of Pennsylvania School of Medicine, 36th Street and Hamilton Walk, Philadelphia, PA, 19104-6076, USA.
Murine coronavirus (mouse hepatitis virus, MHV) is a collection of strains that induce disease in several organ systems of mice. Infection with neurotropic strains JHM and A59 causes acute encephalitis, and in survivors, chronic demyelination, the latter of which serves as an animal model for multiple sclerosis. The MHV receptor is a carcinoembryonic antigen-related cell adhesion molecule, CEACAM1a; paradoxically, CEACAM1a is poorly expressed in the central nervous system (CNS), leading to speculation of an additional receptor. Comparison of highly neurovirulent JHM isolates with less virulent variants and the weakly neurovireulent A59 strain, combined with the use of reverse genetics, has allowed mapping of pathogenic properties to individual viral genes. The spike protein, responsible for viral entry, is a major determinant of tropism and virulence. Other viral proteins, both structural and nonstructural, also contribute to pathogenesis in the CNS. Studies of host responses to MHV indicate that both innate and adaptive responses are crucial to antiviral defense. Type I interferon is essential to prevent very early mortality after infection. CD8 T cells, with the help of CD4 T cells, are crucial for viral clearance during acute disease and persist in the CNS during chronic disease. B cells are necessary to prevent reactivation of virus in the CNS following clearance of acute infection. Despite advances in understanding of coronavirus pathogenesis, questions remain regarding the mechanisms of viral entry and spread in cell types expressing low levels of receptor, as well as the unique interplay between virus and the host immune system during acute and chronic disease. PMID: 20369302 [PubMed - as supplied by publisher]

Genetic association of CASP8 polymorphisms with primary progressive multiple sclerosis.
We investigated caspase 8 (CASP8) as a candidate gene for multiple sclerosis (MS) susceptibility. Three SNPs (rs2037815, rs12990906 and rs1035140) were genotyped in 546 MS patients and 547 controls. For SNP rs2037815, GG homozygosity was associated with primary progressive multiple sclerosis (PPMS) when compared with relapse-onset MS and controls. We identified risk (GCA) and protective (ACT) haplotypes associated with PPMS when compared with relapse-onset MS and controls. GG homozygosity for SNP rs2037815 in PPMS patients was associated with a trend towards faster disease progression. These findings point to a role of CASP8 polymorphisms in the MS genetic risk in PPMS patients. Copyright 2010 Elsevier B.V. All rights reserved.
PMID: 20363033 [PubMed - in process]
What's in a name? Experimental encephalomyelitis: 'Allergic' or 'autoimmune'
Mackay IR, Anderson WH.
The Department of Biochemistry and Molecular Biology, School of Biomedical Sciences, Monash University, Clayton, Victoria, 3800, Australia.
New linguistic coinage can signify new practices and fresh perceptions in science: descriptors therefore are not trivial. Here, we consider the shifting valence of 'allergic' and 'autoimmune' in conceptions of experimental encephalomyelitis (EE). Ehrlich's dismissal of the relevance to disease of autoimmunity resulted in its 'long struggle for recognition' notwithstanding the convincing attribution in 1904 of the hemolysis of paroxysmal cold hemoglobinuria. Yet allergy did take hold because of its assumption that harmful effects could be ascribed to an extrinsic agent against which immune responses were supposed to be directed, in line with contemporary microbiological research. In 1885 the history of EE began with Pasteur's anti-rabies vaccine, dried virus-infected rabbit spinal cord, with use occasionally inducing a post-vaccinal encephalomyelitis (PVE). From 1933 to 1935, PVE was investigated by Rivers who reported that some monkeys immunized with normal rabbit CNS extracts developed an inflammatory demyelinating EE and anti-brain antibodies: no cause was attributed. In the 1940s Freund developed an adjuvant that greatly potentiated immunization and in 1947 this was applied to animals immunized for EE: induction was accelerated and the disease was called 'E allergic E', initiating the EAE acronym. As recorded, 'the study of autoimmune disease leapt from nothing in 1945 to a vigorous field in the 1950s'. Yet researchers sedulously retained allergic in the EAE acronym until the 1980s, long after 'autoimmune' had become available to them. Eventually practitioners for whom autoimmunity had meaning influenced the transition to 'E autoimmune E' as the laboratory analogue of human autoimmune multiple sclerosis. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20427093 [PubMed - as supplied by publisher]

Elevated plasma C4a levels in multiple sclerosis correlate with disease activity.
Ingram G, Hakobyan S, Robertson NP, Morgan PB.
Department of Neurosciences, Cardiff University, Heath Park, Cardiff, CF14 4XN, UK.
Complement plays a pivotal role in the pathogenesis of multiple sclerosis. C4a, an activated fragment of complement component C4, has been linked to disease activity. We correlated plasma C4 and plasma and CSF C4a with clinical disease in a well-characterised cohort of patients and controls. Plasma C4 was non-significantly and CSF C4a was significantly elevated overall in patients compared to controls. Plasma C4a was raised only in acute relapse, decreasing over 2 months. Results demonstrate intrathecal and systemic activation of complement, reflected in changes in CSF and plasma C4a. The data support a role for complement activation in pathogenesis and suggest a systemic component to the disease. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20409594 [PubMed - as supplied by publisher]

IL8 and CXCL13 are potent chemokines for the recruitment of human neural precursor cells across brain endothelial cells.
Weiss N, Deboux C, Chaverot N, Miller F, Baron-Van Evercooren A, Couraud PO, Cazaubon S. CNRS (UMR8104), Institut Cochin, Université Paris Descartes, Paris 75014, France; U1016, INSERM, Paris 75014, France.
It has been recently shown that systemically injected neural precursor cells (NPCs) could cross brain endothelium and favor functional recovery in animal models of multiple sclerosis (MS). Here we show that human NPCs express receptors of the chemokines IL8 and CXCL13 (CXCR1 and CXCR5, respectively) and migrate across brain endothelial cells in vitro, in response to these chemokines. Considering that these chemokines have been found overexpressed in MS in active, but not inactive areas of demyelination, our data suggest that systemically injected human NPCs may be considered for targeting active areas of demyelination in therapeutic approaches of MS. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20400187 [PubMed - as supplied by publisher]
No evidence for an effect of DNA methylation on multiple sclerosis severity at HLA-DRB1*15 or HLA-DRB5.
Handel AE, De Luca GC, Morahan J, Handunnetthi L, Sadovnick AD, Ebers GC, Ramagopalan SV.
Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, United Kingdom; Department of Clinical Neurology, University of Oxford, The West Wing, John Radcliffe Hospital, Oxford, OX3 9DU, United Kingdom.
Multiple sclerosis (MS) is a complex neurological disease with huge variability in disease outcome. The majority of MS genetic susceptibility is determined by major histocompatibility complex (MHC) alleles, in particular haplotypes carrying HLA-DRB1*1501. HLA-DRB1*1501 also affects the clinical outcome of the disease and animal research has suggested that HLA-DRB5 interacts with HLA-DRB1*1501 to influence disease severity. We used an extremes-of-outcome design with 48 benign and 20 malignant MS patients to assess whether or not DNA methylation at HLA-DRB1*1501 and/or HLA-DRB5 also contributes to MS phenotypic heterogeneity. We found no significant effect of DNA methylation across HLA-DRB1*1501 and HLA-DRB5 on severity, although we cannot rule out time- or tissue-specific effects of DNA methylation.

Anti-myelin antibodies modulate clinical expression of childhood multiple sclerosis.
Department of Neurology and Center for Neurologic Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.
Anti-myelin basic protein (MBP) antibodies in pediatric-onset MS and controls were characterized. Serum samples were obtained from 94 children with MS and 106 controls. Paired CSF and serum were obtained from 25 children with MS at time of their initial episode of acute demyelinating syndrome (ADS). Complementary assays were applied across samples to evaluate the presence, and the physical binding properties, of anti-MBP antibodies. While the prevalence and titers of serum anti-MBP antibodies against both immature and mature forms of MBP were similar in children with MS and in controls, binding characteristics and formal Surface Plasmon Resonance (SPR) studies indicated surprisingly high binding affinities of all pediatric anti-MBP antibodies. Serum levels of anti-MBP antibodies correlated significantly with their CSF levels, and their presence in children with MS was associated with significantly increased risk of an acute disseminated encephalomyelitis-like initial clinical presentation. While antibodies to both immature and mature forms of MBP can be present as part of the normal pediatric humoral repertoire, these anti-myelin antibodies are of surprisingly high affinity, can access the CNS during inflammation, and have the capacity to modulate disease expression. Our findings identify an immune mechanism that could contribute to the observed heterogeneity in spectrum of clinical presentations in early-onset MS. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20381173 [PubMed - as supplied by publisher]
*Cyclooxygenase-2 expression in oligodendrocytes increases sensitivity to excitotoxic death.*
ABSTRACT: BACKGROUND: We previously found that cyclooxygenase 2 (COX-2) was expressed in dying oligodendrocytes at the onset of demyelination in the Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD) model of multiple sclerosis (MS) (Carlson et al. J.Neuroimmunology 2006, 149:40). This suggests that COX-2 may contribute to death of oligodendrocytes. OBJECTIVE: The goal of this study was to examine whether COX-2 contributes to excitotoxic death of oligodendrocytes and potentially contributes to demyelination. METHODS: The potential link between COX-2 and oligodendrocyte death was approached using histopathology of MS lesions to examine whether COX-2 was expressed in dying oligodendrocytes. COX-2 inhibitors were examined for their ability to limit demyelination in the TMEV-IDD model of MS and to limit excitotoxic death of oligodendrocytes in vitro. Genetic manipulation of COX-2 expression was used to determine whether COX-2 contributes to excitotoxic death of oligodendrocytes. A transgenic mouse line was generated that overexpressed COX-2 in oligodendrocytes. Oligodendrocyte cultures derived from these transgenic mice were used to examine whether increased expression of COX-2 enhanced the vulnerability of oligodendrocytes to excitotoxic death. Oligodendrocytes derived from COX-2 knockout mice were evaluated to determine if decreased COX-2 expression promotes a greater resistance to excitotoxic death. RESULTS: COX-2 was expressed in dying oligodendrocytes in MS lesions. COX-2 inhibitors limited demyelination in the TMEV-IDD model of MS and protected oligodendrocytes against excitotoxic death in vitro. COX-2 expression was increased in wild-type oligodendrocytes following treatment with kainic acid (KA). Overexpression of COX-2 in oligodendrocytes increased the sensitivity of oligodendrocytes to KA-induced excitotoxic death eight-fold compared to wild-type. Conversely, oligodendrocytes prepared from COX-2 knockout mice showed a significant decrease in sensitivity to KA induced death. CONCLUSIONS: COX-2 expression was associated with excitotoxic death in MS lesions and appeared to increase excitotoxic death of oligodendrocytes in culture. An understanding of how COX-2 expression influences oligodendrocyte death leading to demyelination may have important ramifications for future treatments for MS.
PMID: 20388219 [PubMed - as supplied by publisher]

*Prolyl oligopeptidase is inhibited in relapsing-remitting multiple sclerosis.*
ABSTRACT: BACKGROUND: Multiple sclerosis (MS) is a complex, inflammatory and neurodegenerative disease of the central nervous system leading to long-term disability. Recent studies indicate a close association between inflammation and neurodegeneration in all lesions and disease stages of MS. Prolyl oligopeptidase (POP) is a proline-specific serine protease that cleaves several neuroactive peptides. This peptidase has been implicated in neurodegeneration, as well as in the modulation of the inflammatory response. METHODS: We examined plasma POP and the levels of an endogenous POP inhibitor from relapsing remitting MS patients and compared these with healthy controls, by monitoring the fluorescent changes due to standard fluorescently labelled substrate cleavage. We analysed the data in relationship to patient age and disability status. RESULTS: We observed a significant decrease in POP activity in plasma of relapsing remitting MS patients relative to healthy controls, coupled with an increase of POP endogenous inhibitor. The POP activity was also correlated with patient age and disability status. The lowered POP activity from plasma of MS patients could be rescued by reductants CONCLUSIONS: The decrease in circulating POP activity measured in MS is reverted by reductants. This suggests that POP inactivation in MS might be a result of the oxidative conditions prevailing in the plasma of the diseased patients. Plasma levels of POP activity as well as those of their endogenous inhibitor are suggested as biomarkers of inflammation and oxidative stress in MS.
PMID: 20370893 [PubMed - as supplied by publisher]
**Diffusion-weighted imaging in noncompressive myelopathies: a 33-patient prospective study.**
Marcel C, Kremer S, Jeantroux J, Blanc F, Dietemann JL, De Sève J.
Clinique Neurologique, Hôpital Civil, 1 place de l'Hôpital, Strasbourg, France, chrismarcel@free.fr.
Diffusion-weighted imaging (DWI) is frequently used to differentiate cerebral lesions. The aim of our study was to evaluate the diagnostic value of DWI and the measurement of the apparent diffusion coefficient (ADC) in noncompressive myelopathy explorations. Thirty-three patients presenting a spinal cord syndrome due to a noncompressive myelopathy underwent spinal cord MRI between September 2005 and November 2008. For each patient, the ADC was calculated in the pathological spinal cord. ADC values were also measured in the healthy spinal cord of ten control subjects. Statistical analysis was based on the Student's t test. Twenty-one patients presented an inflammatory myelopathy: Nine patients presented multiple sclerosis, three patients presented a parainfectious myelopathy, two patients acute disseminated encephalomyelitis, one patient neuromyelitis optica, one patient systemic lupus erythematosus, and five patients a myelopathy of unknown aetiology. Six patients presented a spinal cord infarction. ADC values were significantly lower in spinal cord infarct (mean ADC = 0.81 +/- 0.08 x 10(-3) mm(2)/s) than in inflammatory spinal cord lesions (mean ADC = 1.37 +/- 0.23 x 10(-3) mm(2)/s) and in healthy control spinal cord (mean ADC = 0.93 +/- 0.07 x 10(-3) mm(2)/s). These results are important to differentiate ischaemic from inflammatory myelopathies, especially at the acute phase when clinical presentation and extensive work-up are not able to show an aetiologic diagnosis. Although these results are similar to those described in cerebral explorations, ADC measurements remain technically limited for the moment.
PMID: 20425119 [PubMed - as supplied by publisher]

**Epstein-Barr virus, 9.4 T MRI and phosphodiesterase inhibitors in multiple sclerosis.**
Strupp M.
Department of Neurology, Ludwig Maximilian University, Klinikum Grosshadern, Marchioninstr. 15, 81377, Munich, Germany, Michael.strupp@med.uni-muenchen.de.
PMID: 20419309 [PubMed - as supplied by publisher]

114. J Neurol. 2010 Apr 10. [Epub ahead of print]
**Characteristics of multiple sclerosis at onset and delay of diagnosis and treatment in Spain (The Novo Study).**
Hospital Regional Universitario Carlos Haya, Málaga, Spain, oscar.fernandez.sspa@juntadeandalucia.es.
Multiple sclerosis (MS) is a disease supposedly of autoimmune origin, with reactivity directed against myelin antigens. From the neuropathological point of view, MS produces inflammation, demyelination and axonal and neuronal degeneration. Inflammatory phenomena are predominant in the initial phase of the disease, followed later by neurodegenerative processes. Over the last decade, early treatment, during the most inflammatory phase of the disease, has been considered the best strategy to treat MS. Accordingly, we decided to determine the periods of delay between the first symptoms and the time to the first medical visit, the time to referral to a specialised MS unit, the delay in undertaking clinical and paraclinical tests, the diagnostic criteria used and the overall delay in diagnosis and treatment. The median time from onset of first symptoms to the first visit to a physician was 19.2 months, which represented the greatest delay. The median time between this initial medical consultation and the confirmation of the diagnosis by a specialised MS unit was 5.7 months, and the overall time from symptom onset to diagnosis was 24.9 months (2.08 years). The median time between onset of the first symptoms and the decision to give the first treatment was 2 years. The most important delay was that from symptom onset to the first medical visit, with the other delays being less. Thus, it is during this initial period that greater effort is required in order to reduce the time to diagnosis, by increasing awareness of the problem of MS among the general population and primary care physicians.
PMID: 20383518 [PubMed - as supplied by publisher]
Pseudobulbar affect: prevalence and quality of life impact in movement disorders.

Strowd RE, Cartwright MS, Okun MS, Haq I, Siddiqui MS.
Department of Neurology, Medical Center Blvd, Wake Forest University School of Medicine, Winston-Salem, NC, 27157, USA, rstrowd@wfubmc.edu.

Pseudobulbar affect (PBA) is an affective disinhibition syndrome characterized by sudden, involuntary outbursts of inappropriate crying or laughing. We have previously reported the prevalence of PBA in movement disorders using an interviewer-administered questionnaire that had not been validated. In the current study, a validated self-administered screening instrument, the Center for Neurologic Study-Lability Scale (CNS-LS), was used to study the prevalence of PBA, its association with mood symptoms, and the quality of life impact. Two hundred sixty-nine patients met inclusion criteria (consent, age > 18 years, formal diagnosis, and completion of the CNS-LS). The CNS-LS was used to assess PBA at a cutoff score of 17 (utilized from multiple sclerosis studies). The Beck Depression Inventory (BDI) scale and Parkinson’s disease questionnaire (PDQ-39) were used to assess depressive symptoms and quality of life. Logistic regression analysis was used to predict associations with PBA. PBA was prevalent in 7.1% (n = 19) of movement disorder patients. No significant difference in prevalence was observed by patient diagnosis: 7.1% (12/168) in Parkinson’s disease (PD), 11.4% (4/35) in essential tremor, 0% (0/16) in psychogenic movement disorders, 0% (0/16) in dystonia, 0% (0/16) in dystonia, and 11.4% (4/35) in essential tremor. Patients with PBA had higher BDI depression scores (p < 0.0001) and lower PDQ-39 emotional well-being subscores (p < 0.0001). Patients taking antidepressant medications had significantly higher rates of PBA (p = 0.0008). The prevalence of PBA symptoms was 7.1% in PD and all movement disorders patients. Patients with PBA tend to have more depressive symptoms and poorer quality of life.

PMID: 20376475 [PubMed - as supplied by publisher]

Erratum to: Oligoclonal bands and MRI in clinically isolated syndromes: predicting conversion time to multiple sclerosis.

Rojas JI, Patrucco L, Cristiano E.
MS Section, Neurology Department, Italian Hospital of Buenos Aires, Gascomicronn 450, C1181ACH, Buenos Aires, Argentina, juan.rojas@hospitalitaliano.org.ar.

PMID: 20376472 [PubMed - as supplied by publisher]

Atrophy mainly affects the limbic system and the deep grey matter at the first stage of multiple sclerosis.


Background The existence of grey matter (GM) atrophy right after the first clinical event suggestive of multiple sclerosis (MS) remains controversial. The aim of this study was therefore to establish whether regional GM atrophy is already present in the earliest stage of MS assessing regional GM atrophy in a large group of patients. Methods Sixty-two patients with a clinically isolated syndrome (CIS) were examined on a 1.5 T MR imager within 6 months after their first clinical events. A group of 37 matched healthy control subjects were also included in the study. An optimised voxel-based morphometry (VBM) method customised for MS was applied on volumetric T(1)-weighted images. The functional status of patients was assessed using the Expanded Disability Status Scale (EDSS) and the Brief Repeatable Battery. Results VBM analysis (p<0.005, familywise error corrected) on patients versus control subjects showed the presence of significant focal GM atrophy in patients involving the bilateral insula, the bilateral orbitofrontal cortices, the bilateral internal and inferior temporal regions, the posterior cingulate cortex, the bilateral thalami, the bilateral caudate nuclei, the bilateral lenticular nuclei and the bilateral cerebellum. EDSS was slightly correlated (r = 0.37, p = 0.0027) with the atrophy of the right cerebellum. No correlations have been evidenced between the cognitive status of patients and the regional GM atrophy. Conclusion The present study performed on a large group of CIS patients demonstrated that regional GM atrophy is present right after the first clinical event of multiple sclerosis and mainly affects the deep GM and the limbic system.

PMID: 20392976 [PubMed - as supplied by publisher]
Magnetic resonance spectroscopy evaluation in patients with neuromyelitis optica.
Department of Neurology, Hôpital Civil, 1 place de l'hôpital, BP 426, 67091, Strasbourg cedex, France.
jerome.de.seze@chru-strasbourg.fr
OBJECTIVE: Neuromyelitis optica (NMO) is an inflammatory disease associated with optic neuritis and myelitis. Although some studies have reported multiple sclerosis (MS)-like lesions in 10-30% of NMO patients, brain MRI is usually normal. Several studies have observed metabolic abnormalities on MR spectroscopy in MS, even in normal-appearing white matter (NAWM). To the authors’ knowledge, MR spectroscopy has never been used to investigate NMO. The aim of this study was to evaluate metabolic abnormalities in the NAWM and normal-appearing grey matter (NAGM) of NMO patients. METHODS: The authors evaluated 24 patients (17 women and seven men, with a mean age of 44.6 years). NMO was diagnosed according to revised criteria. All patients had a brain and spinal cord MR imaging including MR spectroscopy sequences in both NAWM and NAGM. Patients were compared with 12 healthy subjects. RESULTS: NAA/creatinine ratios in NAWM (1.89 + or - 0.26 in NMO compared with 1.91 + or - 0.15 in control subjects) and NAGM (1.62 + or - 0.21 compared with 1.59 + or - 0.18) were normal, as were choline/creatinine ratios in NAWM (1.03 + or - 0.18 compared with 1.08 + or - 0.14) and NAGM (0.89 + or - 0.2 compared with 0.94 + or - 0.2). Myo-inositol values in NAWM were also normal (0.42 + or - 0.12 compared with 0.42 + or - 0.18). CONCLUSION: Our results are clearly different from those found in MS, where NAA is frequently decreased and choline increased, even in NAWM. Our findings could have an impact on the differentiation between MS and NMO.
PMID: 20360165 [PubMed - indexed for MEDLINE]

Impaired information processing speed and attention allocation in multiple sclerosis patients versus controls: A high-density EEG study.
Department of Neurology, St. Vincent's University Hospital/University College Dublin, Ireland; Trinity Center for Bioengineering, Trinity College Dublin, Ireland.
BACKGROUND: The no-go P3a is a variant of the P300 event-related potential (ERP) that indexes speed of information processing and attention allocation. The aim of this study was to compare ERP findings with results from the paced auditory serial addition test (PASAT) and to quantify latency, amplitude and topographical differences in P3a ERP components between multiple sclerosis (MS) patients and controls.
PATIENTS AND METHODS: Seventy-four subjects (20 relapsing remitting (RRMS) patients, 20 secondary progressive (SPMS) patients and 34 controls) completed a three-stimulus oddball paradigm (target, standard, and non-target). Subjects participated in separate visual and auditory tasks while data were recorded from 134 EEG channels. Latency differences were tested using an ANCOVA. Topographical differences were tested using statistical parametric mapping. RESULTS: Visual P3a amplitude correlated with PASAT score in all MS patients over frontal and parietal areas. There were significant differences in latency, amplitude, and topography between MS patients and controls in the visual condition. RRMS and SPMS patients differed in visual P3a latency and amplitude at frontal and parietal scalp regions. In the auditory condition, there were latency differences between MS patients and controls only over the parietal region. CONCLUSION: The present results demonstrate that information processing speed and attention allocation are impaired in MS. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20399448 [PubMed - as supplied by publisher]
120. J Neurol Sci. 2010 Apr 13. [Epub ahead of print]
Factors influencing the health-related quality of life in Hungarian multiple sclerosis patients.
Department of Neurology, Albert Szent-Györgyi Clinical Centre, University of Szeged, Szeged, Hungary.
BACKGROUND: The 'Multiple Sclerosis Quality of Life Instrument' (MSQOL-54) was recently validated in Hungarian, on more than 400 multiple sclerosis (MS) patients. The aim of the present study was to examine the impact on their overall quality of life (QoL) of the demographic and clinical data on these patients, and their scores on different QoL scales. METHODS: The Hungarian version of MSQOL-54 was given to patients at the outpatient units at the Department of Neurology, University of Szeged, and two other Hungarian MS centres. Additional data, including the EDSS scores of the patients, and relevant clinical and demographic data, were also collected. RESULTS: The questionnaires scales relating to social function, general health, mental health and satisfaction with the sexual function mostly determined the overall QoL ratings. 62.1% of the patients indicated at least one comorbid condition. Depressed patients had a significantly worse quality of life (p<0.0001). CONCLUSIONS: MSQOL-54 is a useful tool for the recognition of possibly treatable factors influencing the QoL, but not assessed by the EDSS. Quality of life data have emerged on more than 400 patients, i.e. a considerable proportion of the Hungarian MS patient population. Copyright © 2010 Elsevier B.V. All rights reserved.
PMID: 20394948 [PubMed - as supplied by publisher]

121. J Neuroophthalmol. 2010 Apr 12. [Epub ahead of print]
Midbrain Cleft as a Cause of Chronic Internuclear Ophthalmoplegia, Progressive Ataxia, and Facial Weakness.
Ahmad O, Reddel S, Lueck CJ.
Department of Neurology, The Canberra Hospital and Australian National University Medical School (OA, CJo), Canberra, Australia; and Departments of Neurology and Molecular Medicine, Concord Hospital and University of Sydney (SR), Sydney, Australia.
A 44-year-old man with progressive ataxia, facial weakness, bilateral adduction deficits, and abducting nystagmus was initially misdiagnosed and treated for multiple sclerosis because a midbrain anatomic cleft had been overlooked on brain MRI. Six cases of "midbrain (or mesencephalic) cleft" or "keyhole aqueduct syndrome" have been previously reported. This developmental anatomic abnormality always manifests bilateral internuclear ophthalmoplegia (INO), often together with ataxia, which may be progressive and debilitating. Because the INO is so chronic, patients may have no visual symptoms. The cause of a midbrain cleft is uncertain, but it may be the midbrain version of a syrinx. There is no known effective treatment.
PMID: 20393349 [PubMed - as supplied by publisher]

Abnormal Anterior Pretectal Nucleus Activity Contributes to Central Pain Syndrome.
Murray PD, Masri R, Keller A.
1Univ. of Maryland School of Medicine, Program in Neuroscience.
Central pain syndrome (CPS) is a debilitating condition that affects a large number of patients with a primary lesion or dysfunction in the central nervous system, most commonly due to spinal cord injury, stroke, and multiple sclerosis lesions. The pathophysiological processes underlying the development and maintenance of CPS are poorly understood. We have recently shown, in an animal model of CPS, that neurons in the posterior thalamic nucleus (PO) have increased spontaneous and evoked activity. We also demonstrated that these changes are due to suppressed inhibitory inputs from the zona incerta (ZI). The anterior pretectal nucleus (APT) is a diencephalic nucleus that projects upon both the PO and ZI, suggesting that it might be involved in the pathophysiology of CPS. Here we test the hypothesis that CPS is associated with abnormal APT activity by recording single units from APT in anesthetized rats with CPS resulting from spinal cord lesions. The firing rate of APT neurons was increased in spinal-lesioned animals, compared to sham-operated controls. This increase was due to a selective increase in firing of Tonic neurons that project to and inhibit ZI, and an increase in bursts in Fast Bursting and Slow Rhythmic neurons. We also show that, in normal animals, suppressing APT results in increased PO spontaneous activity and evoked responses in a sub-population of PO neurons. Taken together, these findings suggest that APT regulates ZI inputs to PO, and that enhanced APT activity during CPS contributes to the abnormally high activity of PO neurons in CPS.
PMID: 20357063 [PubMed - as supplied by publisher]
Activated T-cells inhibit neurogenesis by releasing granzyme B: rescue by Kv1.3 blockers.
Department of Neurology, The Johns Hopkins University, Baltimore, Maryland 21287, USA.
There is a great need for pharmacological approaches to enhance neural progenitor cell (NPC) function particularly in neuroinflammatory diseases with failed neuroregeneration. In diseases such as multiple sclerosis and stroke, T-cell infiltration occurs in periventricular zones where NPCs are located and is associated with irreversible neuronal loss. We studied the effect of T-cell activation on NPC functions. NPC proliferation and neuronal differentiation were impaired by granzyme B (GrB) released by the T-cells. GrB mediated its effects by the activation of a Gi-protein-coupled receptor leading to decreased intracellular levels of cAMP and subsequent expression of the voltage-dependent potassium channel, Kv1.3. Importantly, blocking channel activity with margatoxin or blocking its expression reversed the inhibitory effects of GrB on NPCs. We have thus identified a novel pathway in neurogenesis. The increased expression of Kv1.3 in pathological conditions makes it a novel target for promoting neurorestoration.
PMID: 20371822 [PubMed - indexed for MEDLINE]

A Novel Autotaxin Inhibitor Reduces Lysophosphatidic Acid Levels in Plasma and the Site of Inflammation.
Pfizer.
Autotaxin is the enzyme responsible for the production of lysosphatidic acid (LPA) from lysosphatidyl choline (LPC) and is upregulated in many inflammatory conditions, including but not limited to cancer, arthritis and multiple sclerosis. LPA signaling causes angiogenesis, mitosis, cell proliferation and cytokine secretion. Inhibition of autotaxin may have anti-inflammatory properties in a variety of diseases, however, this hypothesis has not been tested pharmacologically due to the lack of potent inhibitors. Here we report the development of a potent autotaxin inhibitor (PF-8380) with an IC(50) of 2.8 nM in isolated enzyme assay and 101 nM in human whole blood. PF-8380 has adequate oral bioavailability and exposures required for in vivo testing of autotaxin inhibition. Autotaxin's role to produce LPA in plasma and at the site of inflammation was tested in a rat air pouch model. The specific inhibitor PF-8380, dosed orally at 30 mg/kg, provided > 95% reduction in both plasma and air pouch LPA within 3 hours, indicating autotaxin is a major source of LPA during inflammation. 30 mg/kg PF-8380 reduced inflammatory pain with the same maximal efficacy as naproxen. Inhibition of plasma autotaxin activity correlated with inhibition of autotaxin at the site of inflammation and in ex vivo whole blood. Furthermore a close PK/PD relationship was observed, which suggests that LPA is rapidly formed and degraded in vivo. PF-8380 can serve as a tool compound to elucidate LPA's role in inflammation.
PMID: 20392816 [PubMed - as supplied by publisher]
Efficacy and Safety of Tadalafil for Erectile Dysfunction in Patients with Multiple Sclerosis.
Lombardi G, Macchiarella A, Del Popolo G.
Neuro-Urology, Careggi Hospital, University of Florence, Florence, Italy.

ABSTRACT
Introduction. Data are sparse concerning the effects of phosphodiesterase type 5 (PDE5) inhibitors for erectile dysfunction (ED) in subjects with multiple sclerosis (MS). Aim. To evaluate the efficacy and safety of tadalafil use in subjects with ED because of MS. Methods. Ninety-six MS patients with ED after a 4-week treatment-free period were given tadalafil 10 mg. All patients were re-evaluated after 4 weeks. Those with a score lower than 26 on the International Index of Erectile Function (IIEF-15) and with less than 75% of total successful sexual attempts assessed by the Sexual Encounter Profile Questions 2 and 3 (SEP2-3) had their dosage of tadalafil increased to 20 mg, whereas responding subjects continued with 10 mg. Subsequently, all patients had a final follow-up visit after 8 weeks. Main Outcome Measures. SEP2-3, IIEF-15 questionnaire. The Life Satisfaction Checklist (LSC) questionnaire composed of eight questions was used prior to starting tadalafil and at the end of the 12-week treatment. Results. Ninety-two subjects completed the study. Seventy-two responded, 30 of whom used 10 mg. Two subjects discontinued the therapy because of moderate side effects: one suffered from headache and one from tachycardia. Responding patients reached a significant statistical improvement in all follow-ups compared with baseline on the erectile domain and overall sexual satisfaction scores of the IIEF-15 using the Wilcoxon test P < 0.01. Furthermore, they showed statistical improvement through the Wilcoxon test P < 0.01 on the sexual life, family life, and partner relationship questions of the LSC compared with baseline. Conclusion. Tadalafil is an effective and safe treatment for males with MS suffering from ED. Further studies are needed on MS patients to evaluate the efficacy and safety of long-term use, and to detect predictable parameters for the success of PDE5 inhibitors. Lombardi G, Macchiarella A, and Del Popolo G. Efficacy and safety of tadalafil for erectile dysfunction in patients with multiple sclerosis. J Sex Med **;**:**-**.

PMID: 20384939 [PubMed - as supplied by publisher]

Intrathecal baclofen for spasticity management: a comparative analysis of spasticity of spinal vs cortical origin.
Saval A, Chiodo AE.
SCI Program, Department of Physical Medicine and Rehabilitation, University of Michigan Medical Center, 325 E. Eisenhower Parkway, Ann Arbor, MI 48108. USA.

BACKGROUND/OBJECTIVE: To examine the differences in intrathecal baclofen management of individuals with spasticity of cortical vs spinal etiologies. DESIGN: Retrospective chart review of 57 individuals with the diagnoses of severe cortical and spinal spasticity requiring an intrathecal baclofen pump. METHODS: Parameters evaluated included daily dosage of medication required, flex vs simple continuous delivery modes, dosing changes, need for other local spasticity treatment, and catheter complications. RESULTS: There were no statistically significant differences between individuals with cortical spasticity and spinal spasticity when comparing daily dosage, number of contacts, and mode of delivery. At 6 months, there was a statistically significant difference in dosing between individuals with multiple sclerosis and those without. Within groups, there was a significant difference in average daily dosing over 3 years. A significant difference was found comparing the use of botulinum toxin type A for upper extremity spasticity within the cortical group. Nine individuals had catheter complications. CONCLUSIONS: Cortical and spinal spasticity appear to parallel each other with no significant differences in daily dosing, dosing changes, and mode of delivery of intrathecal baclofen. This did not hold true at all time points for the multiple sclerosis subgroup. The significant difference noted within groups for daily dosing over the first 3 years challenges the notion of stable dosing over time. Focal injections of Botox/phenol in the upper extremities are an important adjunct therapy for patients with cortical spasticity, even after the placement of an intrathecal baclofen pump. Our complication rate was slightly lower than that reported in the literature.

The Th17 immune response in renal inflammation.

Turner JE, Paust HJ, Steinmetz OM, Panzer U.

III Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

The discovery of interleukin (IL)-17-producing CD4(+) T (Th17) cells as a unique T-helper cell lineage has revised our understanding of T-cell-mediated tissue injury. Recent data from studies in humans and mice indicate that autoimmune diseases such as multiple sclerosis and rheumatoid arthritis, classically believed to be Th1-mediated, are predominantly driven by a Th17 immune response. IL-17 (IL-17A), IL-17F, IL-21, IL-22, and possibly also IL-9 produced by Th17 cells promote inflammation by directly causing tissue injury and enhancing secretion of pro-inflammatory cytokines and chemokines by resident cells. This results in augmented infiltration of leukocytes, in particular neutrophils, to the affected tissue where they induce organ inflammation and injury. Recent studies have highlighted the potential importance of the Th17 immune response also in renal inflammatory disease. This includes the identification and characterization of IL-17-producing T cells in nephritic kidneys of mice and humans, as well as evidence for the contribution of IL-17 and the IL-23/Th17 axis to renal tissue injury in glomerulonephritis. In this review, we will briefly summarize general characteristics of Th17 cells and discuss in detail the potential role of the Th17 immune response in human and experimental renal inflammation with a special focus on glomerulonephritis. Kidney International advance online publication, 14 April 2010; doi:10.1038/ki.2010.102.

PMID: 20375986 [PubMed - as supplied by publisher]

The changing demographic pattern of multiple sclerosis epidemiology.

Koch-Henriksen N, Sørensen PS.

Department of Neurology, Aarhus University Hospital in Aalborg, Aalborg, Denmark. koch-henriksen@stofanet.dk

The uneven distribution of multiple sclerosis (MS) across populations can be attributed to differences in genes and the environment and their interaction. Prevalence and incidence surveys could be affected by inaccuracy of diagnosis and ascertainment, and prevalence also depends on survival. These sources of error might play a part in the geographical and temporal variations. Our literature search and meta-regression analyses indicated an almost universal increase in prevalence and incidence of MS over time; they challenge the well accepted theory of a latitudinal gradient of incidence of MS in Europe and North America, while this gradient is still apparent for Australia and New Zealand; and suggest a general, although not ubiquitous, increase in incidence of MS in females. The latter observation should prompt epidemiological studies to focus on changes in lifestyle in females. New insights into gene-environment and gene-gene interactions complicate interpretations of demographic epidemiology and have made obsolete the idea of simple causative associations between genes or the environment and MS. Copyright 2010 Elsevier Ltd. All rights reserved.

PMID: 20398859 [PubMed - in process]

Venous abnormalities and multiple sclerosis: another breakthrough claim?

Qiu J.

ejane@janeqiu.com

PMID: 20398855 [PubMed - in process]

Oral therapies for multiple sclerosis: are we there yet?

Hartung HP, Aktas O.

PMID: 20398852 [PubMed - in process]
**Applying functional MRI to the spinal cord and brainstem.**
Leitch JK, Figley CR, Stroman PW.
Centre for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada K7L 3N6.
Functional magnetic resonance imaging of the spinal cord (spinal fMRI) has facilitated the noninvasive visualization of neural activity in the spinal cord (SC) and brainstem of both animals and humans. This technique has yet to gain the widespread usage of brain fMRI, due in part to the intrinsic technical challenges spinal fMRI presents and to the narrower scope of applications it fulfills. Nonetheless, methodological progress has been considerable and rapid. To date, spinal fMRI studies have investigated SC function during sensory or motor task paradigms in spinal cord injury (SCI), multiple sclerosis (MS) and neuropathic pain (NP) patient populations, all of which have yielded consistent and sensitive results. The most recent study in our laboratory has successfully used spinal fMRI to examine cervical SC activity in a SCI patient with a metallic fixation device spanning the C(4) to C(6) vertebrae, a critical step in realizing the clinical utility of the technique. The literature reviewed in this article suggests that spinal fMRI is poised for usage in a wide range of patient populations, as multiple groups have observed intriguing, yet consistent, results using standard, readily available MR systems and hardware. The next step is the implementation of this technique in the clinic to supplement standard qualitative behavioral assessments of SCI. Spinal fMRI may offer insight into the subtleties of function in the injured and diseased SC, and support the development of new methods for treatment and monitoring. Copyright © 2010 Elsevier Inc. All rights reserved. PMID: 20409662 [PubMed - as supplied by publisher]

**Specialized support programs increase treatment adherence, reducing relapses for multiple sclerosis patients.**
Sipkoff M.
MSipkoff@ManagedCareMag.com
PMID: 20361542 [PubMed - in process]

**Preclinical testing of strategies for therapeutic targeting of human T-cell trafficking in vivo.**
Coisne C, Engelhardt B.
Theodor Kocher Institute, University of Bern, Bern, Switzerland.
Naive T cells are migratory cells that continuously recirculate between blood and lymphoid tissues. Antigen-specific stimulation of T cells within the lymph nodes reprograms the trafficking properties of T cells by inducing a specific set of adhesion molecules and chemokine receptors on their surface which allow these activated and effector T cells to effectively and specifically home to extralymphoid organs. The observations of organ-specific homing of T cells initiated the development of therapeutic strategies targeting adhesion receptors for organ-specific inhibition of chronic inflammation. As most adhesion receptors have additional immune functions besides mediating leukocyte trafficking, these drugs may have additional immunomodulatory effects. Therapeutic targeting of T-cell trafficking to the central nervous system is the underlying concept of a novel treatment of relapsing remitting multiple sclerosis with the humanized anti-alpha-4-integrin antibody natalizumab. In this chapter, we describe a possible preclinical in vivo approach to directly visualize the therapeutic efficacy of a given drug in inhibiting T-cell homing to a certain organ at the example of the potential of natalizumab to inhibit the trafficking of human T cells to the inflamed central nervous system in an animal model of multiple sclerosis.
PMID: 20379881 [PubMed - in process]

**[Progress of therapy in patients with multiple sclerosis]**
[Article in German]
Kümpefl T, Havla J, Hohlfeld R.
Institut für Klinische Neuroimmunologie, Klinikum der Universität München, Grosshadern-Ludwig-Maximilians-Universität München. tania.kuempefl@med.uni-muenchen.de
PMID: 20384096 [PubMed - in process]
**Differential ICAM-1 isoform expression regulates the development and progression of experimental autoimmune encephalomyelitis.**  
Hu X, Barnum SR, Wohler JE, Schoeb TR, Bullard DC.  
Department of Microbiology, University of Alabama at Birmingham, Birmingham, AL 35294, USA.  
Intercellular adhesion molecule-1 (ICAM-1) functions in leukocyte trafficking, activation, and the formation of the immunological synapse. ICAM-1 is a member of the immunoglobulin superfamily of adhesion proteins, which share a similar structure of repeating Ig-like domains. Many genes in this family, including ICAM-1, show alternative splicing leading to the production of different protein isoforms, although little functional information is available regarding the expression patterns, ligand interactions, and functions of these isoforms, especially those arising from the ICAM-1 gene. In this study, we show using different lines of mutant mice (Icam1(tm1Jcgr) and Icam1(tm1Bay)) that alterations in the expression of the alternatively spliced ICAM-1 isoforms can significantly influence the disease course during the development of EAE. Icam1(tm1Jcgr) mutant mice, unlike Icam1(tm1Bay) mutants, do not express isoforms containing the Mac-1 binding domain and had significantly attenuated of EAE. In contrast, Icam1(tm1Bay) mice developed severe EAE in both active and adoptive transfer models compared to both Icam1(tm1Jcgr) and wild type mice. We also observed that T cells from Icam1(tm1Bay) mice displayed increased proliferation kinetics and produced higher levels of IFN-gamma compared to Icam1(tm1Jcgr) and wild type mice. Thus, our investigations show that the alternatively spliced ICAM-1 isoforms are functional, and play key roles during the progression of CNS inflammation and demyelination in EAE. Furthermore, our findings suggest that these isoforms may also play key roles in controlling the development of inflammatory diseases such as multiple sclerosis, possibly through differential engagement with ICAM-1 ligands such as Mac-1. (c) 2010. Published by Elsevier Ltd.  
PMID: 20371120 [PubMed - in process]  

**Heparanase upregulates Th2 cytokines, ameliorating experimental autoimmune encephalitis.**  
Department of Bone Marrow Transplantation, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel; Department of Oncology, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel.  
Heparanase is an endo-beta-d-glucuronidase that cleaves heparan sulfate (HS) saccharide chains. The enzyme promotes cell adhesion, migration and invasion and plays a significant role in cancer metastasis, angiogenesis and inflammation. The present study focuses on the involvement of heparanase in autoimmunity, applying the murine experimental autoimmune encephalitis (EAE) model, a T-cell dependent disease often used to investigate the pathophysiology of multiple sclerosis (MS). Intraperitoneal administration of recombinant heparanase ameliorated, in a dose dependent manner, the clinical signs of the disease. In vitro and in vivo studies revealed that heparanase inhibited mitogen induced splenocyte proliferation and mixed lymphocyte reaction (MLR) through modulation of their repertoire of cytokines indicated by a marked increase in the levels of IL-4, IL-6 and IL-10, and a parallel decrease in IL-12 and TNF-alpha. Similar results were obtained with active, latent, or point mutated inactive heparanase, indicating that the observed inhibitory effect is attributed to a non-enzymatic activity of the heparanase protein. We suggest that heparanase induces upregulation of Th2 cytokines, resulting in inhibition of the inflammatory lesion of EAE. Copyright © 2010 Elsevier Ltd. All rights reserved.  
PMID: 20399501 [PubMed - as supplied by publisher]
139. Mol Nutr Food Res. 2010 Apr 1. [Epub ahead of print]
The estimated benefits of vitamin D for Germany.
Zittermann A.
Clinic for Thoracic and Cardiovascular Surgery, Heart Center North Rhine-Westphalia, Ruhr University Bochum, Bad Oeynhausen, Germany.
This article gives an overview of the vitamin D status in Germany, provides evidence for an independent association of vitamin D deficiency with various chronic diseases, and discusses preventive measures for improving vitamin D status in Germany. The prevalence of vitamin D insufficiency is 40-45% in the general German population. An additional 15-30% are vitamin D deficient. Vitamin D can prevent falls and osteoporotic fractures in older people. There is also accumulating evidence that vitamin D may prevent excess mortality and may probably prevent some chronic diseases that occur in early life such as type 1 diabetes and multiple sclerosis. Adherence to present sun safety policy (avoidance of the sun between 11 am and 3 pm) and dietary recommendations (5-10 mug daily for adults) would, however, definitively lead to vitamin D deficiency. The estimated cost saving effect of improving vitamin D status in Germany might be up to 37.5 billion euro annually. It should be the goal of nutrition and medical societies to erase vitamin D deficiency in Germany within the next 5-10 years. To achieve this goal, the daily production of at least 25 mug of vitamin D in the skin or an equivalent oral intake should be guaranteed.
PMID: 20373291 [PubMed - as supplied by publisher]

140. Mol Ther. 2010 Apr 27. [Epub ahead of print]
Successful Treatment of Metachromatic Leukodystrophy Using Bone Marrow Transplantation of HoxB4 Overexpressing Cells.
Miyake N, Miyake K, Karlsson S, Shimada T.
Department of Biochemistry and Molecular Biology, Division of Gene Therapy Research, Center for Advanced Medical Technology, Nippon Medical School, Tokyo, Japan.
To evaluate the contribution of bone marrow (BM) cells to treat neurological disorders, we examined the effectiveness of BM cells expressing the homeobox B4 (HoxB4) gene to cure mice with metachromatic leukodystrophy (MLD) through transplantation. Increased number of donor cells was observed in brains of the MLD mice transplanted with HoxB4-transduced BM cells (B4MLD) in contrast to those transplanted with control green fluorescent protein (GFP)-transduced BM cells (MIGMLD). Immunohistochemical staining showed that most of the GFP(+) cells were Iba1(+) microglia. In addition, O4(+) oligodendrocytes were identified only in the B4MLD brains but not in the MIGMLD brain. Alcian blue staining showed that accumulation of sulfatide was dramatically reduced in brain tissue from B4MLD mice, and there was a corresponding improvement in the animals' ability to walk a balance beam 8 months after transplantation. Thus transplantation of BM cells overexpressing HoxB4 appears to effectively prevent the progression of MLD in this mouse model. These findings support the idea that hematopoietic stem cells (HSCs) transduced with a HoxB4 expression vector could be the useful carriers of therapeutic proteins into the brain for regeneration of oligodendrocytes to treat such demyelinating disorders as MLD, Krabbe disease, and multiple sclerosis.
PMID: 20424597 [PubMed - as supplied by publisher]

A window of opportunity for no treatment in early multiple sclerosis?
Gilmore C, Cottrell D, Scolding N, Wingerchuk D, Weinschenker B, Boggild M.
Department of Neurology, Nottingham University Hospitals NHS Trust, Nottingham, UK.
PMID: 20427417 [PubMed - as supplied by publisher]
142. Mult Scler. 2010 Apr 8. [Epub ahead of print]

**Analysis of multiple candidate genes in association with phenotypes of multiple sclerosis.**


Department of Neurology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.

Multiple sclerosis is a heterogeneous neurological disease with varying degrees of severity. The common hypothesis is that susceptibility to multiple sclerosis and its phenotype are caused by a combination of environmental and genetic factors. The genetic part exerts its effect through several genes, each having modest effects. We evaluated whether disease severity could be predicted by a model based on clinical data and data from a DNA chip. The DNA chip was designed containing several single nucleotide polymorphisms in 44 genes, previously described to be associated with multiple sclerosis. A total of 605 patients with multiple sclerosis were included in this analysis, using gender, onset type and age at onset as clinical covariates. We correlated 80 single nucleotide polymorphisms to the degree of disease severity using the following three outcome measures: linear Multiple Sclerosis Severity Score, dichotomous Multiple Sclerosis Severity Score (using a cut-off point of 2.5) and time to reach Expanded Disability Status Scale score 6. Sixty-nine single nucleotide polymorphisms were included in the analysis. No individual single nucleotide polymorphism showed a significant association; however, a combination of single nucleotide polymorphisms significantly improved the prediction of disease severity in addition to the clinical variables. In all three models the Interleukin 2 gene was included, confirming a previously reported modest effect on disease severity. The highest power was obtained using the dichotomized Multiple Sclerosis Severity Score as outcome. Several single nucleotide polymorphisms showed their added predictive value over the clinical data in the predictive models. These results support our hypothesis that disease severity is determined by clinical variables and genetic influences (through several genes with small effects) in concert. PMID: 20378664 [PubMed - as supplied by publisher]

143. Mult Scler. 2010 Apr 8. [Epub ahead of print]

**Disease onset in familial and sporadic primary progressive multiple sclerosis.**


Faculty of Med., Div. of Neurology, Uni. of British Columbia, Vancouver, Canada/Dept. of Neurology; Uni. of Groningen; Groningen, The Netherlands.

The pathophysiology of primary progressive (PP) multiple sclerosis (MS) involves diffuse axonal degeneration which is believed to start early in the disease process, even before the onset of clinical symptoms. Symptomatic onset then occurs when this process reaches a threshold after which the axonal loss can no longer be compensated. A preliminary study showed that patients with familial PPMS had an earlier clinical onset than patients with sporadic disease, suggesting a hereditary component to the disease process of PPMS. In this study, we combined data from two large, population-based, longitudinal MS databases to investigate disease onset in familial and sporadic PPMS. We examined 411 patients with PPMS. There were no differences in gender distribution or onset symptoms between familial and sporadic PPMS. Patients with familial PPMS were significantly younger at disease onset (n = 84, median age: 37.6 years) than patients with sporadic disease (n = 327, median age: 42.7, p = 0.007). This difference was due to a greater proportion of familial cases with a disease onset before the age of 30 and a smaller proportion with disease onset between 40 and 50 years of age (p = 0.002). Gender had no significant effect on the age at disease onset. Further analyses showed that these findings were unlikely to be due to ascertainment bias towards an earlier diagnosis in familial cases. Our findings suggest a hereditary component to the disease process of PPMS. It would be worthwhile to identify patients with familial PPMS for future research on disease modifying genes in MS. PMID: 20378663 [PubMed - as supplied by publisher]

Bayer Vital GmbH, Specialty Medicine  
http://www.bayer-vital.de/  
http://www.betaferon.de  
http://www.ms-gateway.de
144. Mult Scler. 2010 Apr 7. [Epub ahead of print]
Clinical trial of a formal group fatigue program in multiple sclerosis.
Hugos C, Copperman L, Fuller B, Yadav V, Lovera J, Bourdette D.
Department of Rehabilitation Services, Department of Neurology Oregon Health and Science University, Portland, OR, USA.
Fatigue: Take Control is a novel program to teach fatigue management to people with multiple sclerosis (MS) following recommendations in the Fatigue and Multiple Sclerosis guideline. Fatigue: Take Control includes six 2-hour group sessions with DVD viewing, discussion and homework and accompanying participant and leader workbooks. While many people have participated in Fatigue: Take Control programs, its efficacy has not been determined. The objective of this study was to determine whether participation in Fatigue: Take Control reduces fatigue and increases self-efficacy in people with MS. Thirty participants were randomly assigned to a group who immediately participated in the program (FTC) or a wait-list group (WL). The primary outcome was the Modified Fatigue Impact Scale (MFIS) and secondary outcomes were the Multiple Sclerosis Self-Efficacy Scale (MSSE) and the Fatigue Severity Scale (FSS). The MFIS was administered on 10 occasions. Other measures were administered on four occasions. A mixed model tested the effects using all observations. Compared with the WL, the FTC group had significantly more improvement on the MFIS \(F(1, 269) = 7.079, p = 0.008\) and the MSSE \(F(1, 111) = 5.636, p = 0.019\). No significant effect was found for the FSS. Across all visits, fatigue was significantly lower and self-efficacy was significantly higher for the FTC group compared with the WL group. This pilot study demonstrated significant effects in fatigue and self-efficacy among subjects taking the Fatigue: Take Control program, suggesting that this comprehensive program based on the Fatigue and Multiple Sclerosis guideline may be beneficial in MS.
PMID: 20375125 [PubMed - as supplied by publisher]

Mesenchymal stem cells for multiple sclerosis: can we find the answer?
Tyndall A; EULAR Stromal Cell Translational Group.
PMID: 20385716 [PubMed - in process]

146. Mult Scler. 2010 Mar 30. [Epub ahead of print]
Interleukin 18 Receptor 1 expression distinguishes patients with multiple sclerosis.
Department of Clinical Neuroscience, Neuroimmunology Unit, Sweden.
Definition of dysregulated immune components in multiple sclerosis may help in the identification of new therapeutic targets. Deviation of the interleukin 18 receptor 1 (IL18R1) is of particular interest since the receptor is critical for experimental neuroinflammation. The objective of this study was to determine whether expression of IL18R1 varies between multiple sclerosis patients and controls, and to test genetic association of IL18R1 with multiple sclerosis. We used quantitative real-time PCR to assess mRNA levels of IL18R1 in cerebrospinal fluid and peripheral blood mononuclear cells of 191 patients with multiple sclerosis, 61 patients with clinically isolated syndrome and 168 controls having other neurological disorders. Association was tested in 2153 patients with multiple sclerosis and 1733 controls using 13 tagging single nucleotide polymorphisms within the IL18R1 gene. We found that patients with multiple sclerosis had increased IL18R1 mRNA expression in both cerebrospinal fluid cells (p < 0.05) and peripheral blood mononuclear cells (p < 0.05) compared with controls. Patients with clinically isolated syndrome had elevated levels compared with controls in cerebrospinal fluid cells (p < 0.001) but not in peripheral blood mononuclear cells. The gene was not associated to multiple sclerosis. We conclude that the increased expression of IL18R1 may contribute pathogenically to disease and is therefore a potential therapeutic target. The absence of a genetic association in the IL18R1 gene itself suggests regulation from other parts of the genome, or as part of the inflammatory cascade in multiple sclerosis without a prime genetic cause.
PMID: 20354066 [PubMed - as supplied by publisher]

Alzheimer drug worsens neurological dysfunction in multiple sclerosis.
[No authors listed]
PMID: 20411602 [PubMed]
**Behind the paper: saved from the drain.**  
Dolgin E.  
PMID: 20376044 [PubMed - indexed for MEDLINE]

**Molecular oracles for multiple sclerosis therapy.**  
Wekerle H, Hohlfeld R.  
PMID: 20376043 [PubMed - indexed for MEDLINE]

150. Nat Rev Neurol. 2010 Apr 20. [Epub ahead of print]  
**Stem cell transplantation in multiple sclerosis: current status and future prospects.**  
Martino G, Franklin RJ, Van Evercooren AB, Kerr DA; the Stem Cells in Multiple Sclerosis (STEMS) Consensus Group.  
Institute of Experimental Neurology-DIBIT 2, Division of Neuroscience, San Raffaele Scientific Institute, Via Olgettina 58, 20132 Milan, Italy.  
This article provides an overview of the current knowledge relating to the potential use of transplanted stem cells in the treatment of patients with multiple sclerosis (MS). Two types of stem cells, CNS-derived neural stem/precursor cells (NPCs) and bone marrow-derived mesenchymal stem cells (MSCs) are considered to provide reproducible and robust therapeutic effects when intravenously or intrathecally injected into both rodents and primates with experimental autoimmune encephalomyelitis. Furthermore, preliminary safety data concerning the use of intrathecally injected autologous MSCs in patients with progressive MS are available. We discuss how the data gathered to date challenge the narrow view that the therapeutic effects of NPCs and MSCs observed in the treatment of MS are accomplished solely by cell replacement. Both types of stem cell, when transplanted systemically, might instead influence disease outcome by releasing a plethora of factors that are immunomodulatory or neuroprotective, thereby directly or indirectly influencing the regenerative properties of intrinsic CNS stem/precursor cells.  
PMID: 20404843 [PubMed - as supplied by publisher]

151. Nat Rev Neurol. 2010 Apr 20. [Epub ahead of print]  
**Signals to promote myelin formation and repair.**  
Taveggia C, Feltl ML, Wrabetz L.  
Division of Neuroscience and INSPE, San Raffaele Scientific Institute, DIBIT, Via Olgettina 58, Milan 20132, Italy.  
The myelin sheath wraps large axons in both the CNS and the PNS, and is a key determinant of efficient axonal function and health. Myelin is targeted in a series of diseases, notably multiple sclerosis (MS). In MS, demyelination is associated with progressive axonal damage, which determines the level of patient disability. The few treatments that are available for combating myelin damage in MS and related disorders, which largely comprise anti-inflammatory drugs, only show limited efficacy in subsets of patients. More-effective treatment of myelin disorders will probably be accomplished by early intervention with combinatorial therapies that target inflammation and other processes—for example, signaling pathways that promote remyelination. Indeed, evidence suggests that such pathways might be impaired in pathology and, hence, contribute to the failure of remyelination in such diseases. In this article, we review the molecular basis of signaling pathways that regulate myelination in the CNS and PNS, with a focus on signals that affect differentiation of myelinating glia. We also discuss factors such as extracellular molecules that act as modulators of these pathways. Finally, we consider the few preclinical and clinical trials of agents that augment this signaling.  
PMID: 20404842 [PubMed - as supplied by publisher]
**Genome, epigenome and RNA sequences of monozygotic twins discordant for multiple sclerosis.**  
Department of Neurology, University of California at San Francisco, San Francisco, California 94143, USA. sebaran@cgl.ucsf.edu  
Monozygotic or 'identical' twins have been widely studied to dissect the relative contributions of genetics and environment in human diseases. In multiple sclerosis (MS), an autoimmune demyelinating disease and common cause of neurodegeneration and disability in young adults, disease discordance in monozygotic twins has been interpreted to indicate environmental importance in its pathogenesis. However, genetic and epigenetic differences between monozygotic twins have been described, challenging the accepted experimental model in disambiguating the effects of nature and nurture. Here we report the genome sequences of one MS-discordant monozygotic twin pair, and messenger RNA transcriptome and epigenome sequences of CD4(+) lymphocytes from three MS-discordant, monozygotic twin pairs. No reproducible differences were detected between co-twins among approximately 3.6 million single nucleotide polymorphisms (SNPs) or approximately 0.2 million insertion-deletion polymorphisms. Nor were any reproducible differences observed between siblings of the three twin pairs in HLA haplotypes, confirmed MS-susceptibility SNPs, copy number variations, mRNA and genomic SNP and insertion-deletion genotypes, or the expression of approximately 19,000 genes in CD4(+) T cells. Only 2 to 176 differences in the methylation of approximately 2 million CpG dinucleotides were detected between siblings of the three twin pairs, in contrast to approximately 800 methylation differences between T cells of unrelated individuals and several thousand differences between tissues or between normal and cancerous tissues. In the first systematic effort to estimate sequence variation among monozygotic co-twins, we did not find evidence for genetic, epigenetic or transcriptome differences that explained disease discordance. These are the first, to our knowledge, female, twin and autoimmune disease individual genome sequences reported.  
PMID: 20428171 [PubMed - in process]

**Twin study surveys genome for cause of multiple sclerosis.**  
Katsnelson A.  
PMID: 20428135 [PubMed - in process]

**[Radiologically isolated syndrome : Multiple sclerosis based solely on MRI findings?]**  
[Article in German]  
Sellner J, Schirmer L, Hemmer B, Mühlau M.  
Neurologische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Ismaninger Strasse 22, 81675, München, Deutschland, sellner@lrz.tum.de.  
Incidental brain magnetic resonance imaging (MRI) findings are the result of an increasing usage of MRI in the diagnostic work-up of patients. An adequate assessment of patients in which brain lesions typical for multiple sclerosis (MS) are determined but who have been asymptomatic so far is problematic, especially when Barkhof-Tintoré criteria for spatial dissemination are fulfilled and no other differential diagnosis can be confirmed. This entity, the so-called radiologically isolated syndrome, constitutes a major diagnostic and therapeutic challenge. Two recent studies revealed that a subgroup of patients with radiologically isolated syndrome are at high risk for near-term development of MR-based progression and occurrence of the first clinical event. Hence, the radiologically isolated syndrome has to be classified as a possible preliminary phase of the clinical manifestation of MS in a subgroup of patients and entails in-depth therapeutic considerations. This article covers the current literature for this syndrome and, in the absence of official guidelines, provides a pragmatic diagnostic and therapeutic approach for patient management.  
PMID: 20422146 [PubMed - as supplied by publisher]
"Chronic cerebrospinal venous insufficiency" and multiple sclerosis: Critical analysis and first observation in an unselected cohort of MS patients.
[Article in German]
Krogias C, Schröder A, Wiendl H, Hohlfeld R, Gold R.
Neurologische Klinik, St. Josefs-Hospital, Ruhr-Universität Bochum, Gudrunstrasse 56, 44791, Bochum, Deutschland, christos.krogias@rub.de.
Currently, the hypothesis that altered venous hemodynamics might play a causative role in the pathogenesis of multiple sclerosis (MS) is being controversially discussed. This new "venous hypothesis" postulates that obstructions of the cervical venous system cause an increased pressure of the intracranial venous system and that in turn intracranial congestion disintegrates the blood-brain barrier initiating the inflammatory process in MS. The "venous hypothesis" is analyzed and evaluated with regard to the following aspects: first concerning the validity of published data, second with regard to the plausibility in view of the currently approved pathogenetic model of MS, and third with regard to the compatibility with preliminary neurosonological findings in a small but unselected cohort of patients at our department. The authors conclude that the "chronic cerebrospinal venous insufficiency (CCSVI)" cannot represent the exclusive pathogenetic factor in the pathogenesis of MS. In our cohort, only 20% of the patients fulfilled the required neurosonological features of CCSVI. So far, the pathogenetic relevance of these findings remains speculative. Thus, based on the current scientific position we cannot justify invasive "therapeutic" approaches, especially if they are performed outside of clinical trials.
PMID: 20386873 [PubMed - as supplied by publisher]

Subvocal articulatory rehearsal during verbal working memory in multiple sclerosis.
Sweet LH, Vanderhill SD, Jerskey BA, Gordon NM, Paul RH, Cohen RA.
The Warren Alpert Medical School of Brown University, Butler Hospital, Providence, RI, USA.
This study was designed to examine verbal working memory (VWM) components among multiple sclerosis (MS) patients and determine the influence of information processing speed. Of two frequently studied VWM sub-components, subvocal rehearsal was expected to be more affected by MS than short-term memory buffering. Furthermore, worse subvocal rehearsal was predicted to be specifically related to slower cognitive processing. Fifteen MS patients were administered a neuropsychological battery assessing VWM, processing speed, mood, fatigue, and disability. Participants performed a 2-Back VWM task with modified nested conditions designed to increase subvocal rehearsal (via inter-stimulus interval) and short-term memory buffering demands (via phonological similarity). Performance during these 2-Back conditions did not significantly differ and both exhibited strong positive correlations with disability. However, only scores on the subvocal rehearsal 2-Back were significantly related to performance on the remaining test battery, including processing speed and depressive symptoms. Findings suggest that performance during increased subvocal rehearsal demands is specifically influenced by cognitive processing speed and depressive symptoms.
PMID: 20401804 [PubMed - as supplied by publisher]
In vivo multi-slice mapping of myelin water content using T(2)(*) decay.
Hwang D, Kim D, DuYP.
School of Electrical and Electronic Engineering, Yonsei University, Seoul, Republic of Korea.
Quantitative assessment of the myelin water content in the brain can substantially improve our understanding of white matter diseases such as multiple sclerosis. In this study, in vivo myelin water content was estimated using T(2)* relaxation with multi-slice acquisitions in magnetic resonance imaging (MRI). The main advantages of using T(2)* relaxation are (1) a low specific absorption rate (SAR), which is especially beneficial for imaging at high field strengths, (2) a short first-echo time (approximately 2ms) and short echo spacing (approximately 1ms), which allows for the acquisition of multiple sampling points during the fast decay of the myelin water signal, and (3) fast multi-slice acquisitions. High-resolution and multi-slice myelin water fraction (MWF) maps were obtained in a clinically acceptable scan time at 3T. Five healthy adults were scanned with a multi-gradient-echo sequence to acquire T(2)(*) signal decay data. Images with a dimension of 256x256 at eight slice locations were acquired in 8.5min with a signal-to-noise ratio (SNR) of 94.8 in the first-echo images. The SNR was further increased by using an anisotropic diffusion filter. Local field gradients (LFG) were estimated from the acquired multi-slice data, and the LFG-induced signal decays were corrected with a first-order approximation of LFG using the sinc function. The corrected T(2)(*) signal decays were analyzed with a three-pool model to quantify MWF. Our results demonstrate the feasibility of in vivo multi-slice mapping of MWF using multi-compartmental analysis of the T(2)(*) signal decay. Copyright © 2010. Published by Elsevier Inc.
PMID: 20398770 [PubMed - as supplied by publisher]

158. Neuroimage. 2010 Apr 1. [Epub ahead of print]
Disease modeling in multiple sclerosis: Assessment and quantification of sources of variability in brain parenchymal fraction measurements.
Sampat MP, Healy BC, Meier DS, Dell'oglio E, Liguori M, Guttmann CR.
Advanced Imaging in Multiple Sclerosis Laboratory, Department of Neurology, University of California San Francisco, San Francisco, CA, USA.
The measurement of brain atrophy from magnetic resonance imaging (MRI) has become an established method of estimating disease severity and progression in multiple sclerosis (MS). Most commonly reported in the form of brain parenchymal fraction (BPF), it is more sensitive to the degenerative component of the disease and shows progression more reliably than lesion burden. Typically, the reliability of BPF and other morphometric measurements is assessed by evaluating scan-rescan experiments. While these experiments provide good estimates of real-life error related to imperfect patient repositioning in the MRI scanner, measurement variance due to physiological and reversible pathological fluctuations in brain volume are not taken into account. In this work, we propose a new model for estimating variability in serial morphometry, particularly the BPF measurement. Specifically, we attempt to detect and explicitly model the remaining sources of error to more accurately describe the overall variability in BPF measurements. Our results show that sources of variability beyond subject repositioning error are important and cannot be ignored. We demonstrate that scan-rescan experiments only provide a lower bound on the true error in repeated measurements of patients’ BPF. We have estimated the variance due to patient repositioning during scan-rescan (sigma(sr)(2) = 3.0e-06), variance assigned to physiological fluctuations (sigma(p)(2) = 5.74e-06) and the variance associated with lesion activity (sigma(les)(2) = 1.09e-05). These variance components can be used to determine the relative impact of their sources on sample size estimates for studies investigating change over time in MS patients. Our results demonstrate that sample size calculations based exclusively on scan-rescan variability (sigma(sr)) are likely to underestimate the number of patients required. If the physiological variability (sigma(p)) is incorporated in sample size calculations, the required sample size would increase by a factor of 5.69 based on standard t-test sample size calculation. Copyright © 2010. Published by Elsevier Inc.
PMID: 20362675 [PubMed - as supplied by publisher]

**Immunization with pVAXhsp65 Decreases Inflammation and Modulates Immune Response in Experimental Encephalomyelitis.**


Department of Microbiology and Immunology, Biosciences Institute, São Paulo State University, Botucatu, Brazil.

Background: A DNA vaccine (pVAXhsp65) containing the gene of a heat-shock protein (hsp65) from *Mycobacterium leprae* showed high immunogenicity and protective efficacy against tuberculosis in BALB/c mice. A possible deleterious effect related to autoimmunity needed to be tested because hsp65 is highly homologous to the correspondent mammalian protein. In this investigation we tested the effect of a previous immunization with DNAhsp65 in the development of experimental autoimmune encephalomyelitis (EAE), a rat model of multiple sclerosis. Methods: Female Lewis rats were immunized with 3 pVAXhsp65 doses by intramuscular route. Fifteen days after the last DNA dose the animals were evaluated for specific immunity or submitted to induction of EAE. Animals were evaluated daily for weight loss and clinical score, and euthanized during the recovery phase to assess the immune response and inflammatory infiltration in the central nervous system. Results: Immunization with pVAXhsp65 induced a specific immune response characterized by production of IgG(2b) anti-hsp65 antibodies and IFN-gamma secretion. Previous immunization with pVAXhsp65 did not change EAE clinical manifestations (weight and clinical score). However, the vaccine clearly decreased brain and lumbar spinal cord inflammation. In addition, it downmodulated IFN-gamma and IL-10 production by peripheral lymphoid organs. Conclusion: Our data demonstrated that this vaccine does not trigger a deleterious effect on EAE development and also points to a potential protective effect. Copyright © 2010 S. Karger AG, Basel.

PMID: 20407280 [PubMed - as supplied by publisher]


**Evaluation of postural balance control in patients with multiple sclerosis - effect of different sensory conditions and arithmetic task execution. A pilot study.**

Porosińska A, Pierzchała K, Mentel M, Karpe J.

Kliniczny Oddział Neurologii, Samodzielnego Publicznego Szpitala Klinicznego nr 1, Śląskiego Uniwersytetu Medycznego, w Katowicach, Zabrze, Polska. alpia@interia.eu

BACKGROUND AND PURPOSE: The purpose of this study was to investigate the effect of concomitant cognitive task execution and different sensory conditions on balance control in patients with multiple sclerosis (MS). MATERIAL AND METHODS: Thirty-two subjects with MS and 30 healthy age- and sex-matched control subjects were included in the study. Balance Performance Oriented Mobility Assessment was performed in all subjects. Their spontaneous sway characteristics while standing with different sensory conditions and during execution of a simple arithmetic task were analysed. Mean sway in the coronary and sagittal plane, as well as sway velocity, were measured. RESULTS: The values of all evaluated variables obtained in all tests were significantly higher in the MS group than in controls. In the MS group, more pronounced progression of changes in response to increased difficulty of the test was also observed. Analysis of risk of falls in MS revealed a significant increase of sway velocity and mean sway in the mediolateral and anteroposterior plane in the majority of tests. CONCLUSIONS: Postural stability in patients with MS is significantly decreased in comparison with the control group in all evaluated conditions. Stability deficit is enhanced in response to more difficult conditions of evaluation. Increased risk of falls is related to the increased postural sway velocity and length of mean sway; this association is most pronounced in the coronary plane.

PMID: 20358484 [PubMed - in process]
161. Neurol Res. 2010 Apr 27. [Epub ahead of print]
Clinical and electronystagmographical evaluation of vestibular symptoms in relapsing remitting multiple sclerosis.
Degirmenci E, Bir LS, Ardic FN.
OBJECTIVE: Multiple sclerosis (MS) may give rise to a variety of clinical signs and symptoms including vertigo and/or other problems related with equilibrium. In this study, we aimed to evaluate clinical and electronystagmographical (ENG) characteristics of relapsing remitting MS (RRMS) patients. DESIGN: This is a prospective controlled study consisting of 30 patients who were diagnosed as definite RRMS according to McDonald's diagnostic criteria and 30 healthy individuals. SETTING: Entire population of patients were examined and followed up at the same tertiary centre during the period of September 2003 and March 2005. Clinical examination and detailed electronystagmographic investigations were performed in each group. METHODS: Vestibular laboratory testing was carried out by a computerized ENG system. All ENG subtests including tracking, saccade, optokinetic, gaze, positional and Dix-Hallpike tests were performed in each group but caloric, which is relatively an invasive test, was performed only in the patient group. MAIN OUTCOME MEASURES: We aimed to find the ratio of abnormal tests indicating, central and/or peripheral pathology in ENG. We also analyzed the correlation of total number of abnormal tests in ENG with clinical parameters. RESULTS: Differences of ENG abnormality indicating central and/or peripheral pathology and ENG abnormality indicating only central pathology between the two groups were statistically significant. Correlation of total number of abnormal tests in ENG with EDSS score was statistically significant. CONCLUSION: ENG is sensitive in detecting the vestibular system involvement in RRMS patients if all subtests are performed and evaluated in detail with clinical symptoms and signs.
PMID: 20426898 [PubMed - as supplied by publisher]

Multiple sclerosis impairs ability to detect abrupt appearance of a subliminal stimulus.
Carrubba S, Minagar A, Gonzalez-Toledo E, Chesson AL Jr, Frilot C 2nd, Marino AA.
Department of Orthopaedic Surgery, LSU Health Sciences Center, Shreveport, LA 71130-3932, USA.
OBJECTIVES: The study was designed to find evidence that brain electrical activity associated with processing the abrupt appearance or disappearance of a sensory stimulus differed in the presence and absence of the neuropsychological changes that are characteristic of multiple sclerosis (MS). METHODS: A subliminal stimulus (electrical field) was applied, and the onset and offset responses from patients with MS were compared with the responses of study participants in two age- and gender-matched control groups, using a novel type of non-linear dynamical analysis that had been developed in earlier studies. RESULTS: An onset response occurred in 27% of the patients with MS, compared with 85% in the control groups. Among the three patients who exhibited onset-induced changes in brain electrical activity, the average latency of the effect was less and the magnitude of the change was greater than the corresponding values in the control group. DISCUSSION: Non-linear analysis of electroencephalograms recorded during the sudden presentation of a subliminal stimulus potentially could serve as the basis of a functional test to help diagnose MS. A larger cohort of patients with MS needs to be assessed to validate the results of this study.
PMID: 20406608 [PubMed - in process]

A case of neurofibromatosis and multiple sclerosis.
Spinicci G, Cherchi MV, Murru R, Conti M, Marrosu MG.
Dipartimento di Scienze Cardiovascolari e Neurologiche, Centro Sclerosi Multipla, University of Cagliari, Cagliari, Italy, gspinicci@tiscali.it.
Neurofibromatosis 1 (NF1), also called von Recklinghausen disease or peripheral NF, is a common autosomal-dominant neurocutaneous disorder associated with mutations of the NF 1 gene. The pathogenesis is poorly understood and the disease is characterized by café-au-lait spots, neurofibromatous tumors of the skin, Lisch nodules of the iris and many pleiotropic manifestations. The gene responsible for the disorder has been isolated on chromosome 17q11.2. The association of multiple sclerosis with NF is rarely reported in literature. We describe a patient with NF1, who subsequently developed relapsing-remitting multiple sclerosis.
PMID: 20424878 [PubMed - as supplied by publisher]
**Clinical spectrum associated with aquaporin-4 antibodies (NMO-IgG).**  
[Article in English, Spanish]  
Blanco Y, Hankiewicz K, Llufríu S, Sabater L, Graus F, Saiz A.  
Servei de Neurologia, Hospital Clinic, Universitat de Barcelona e Institut d'Investigació August Pi i Sunyer (IDIBAPS), Barcelona, España.  
INTRODUCTION: The description of a highly sensitive and specific biomarker for neuromyelitis optica (NMO-IgG/aquaporin-4 antibody) extended the clinical spectrum of NMO to limited forms such as optic neuritis (ON) and longitudinally extensive myelitis (LEM). OBJECTIVE: To assess the sensitivity and specificity of our assay, and to describe the clinical characteristics of the patients who were tested for NMO-IgG. METHODS: NMO-IgG was analysed by immunohistochemistry and confirmed by assay on HEK cells transfected with aquaporin-4. The clinical information was obtained from forms filled in by the referring neurologists. RESULTS: A total of 580 samples from 518 patients were analysed from November 2005 to September 2008. Clinical information was available from 358 (68%) patients. All 33 (100%) positive cases were followed up. Twenty-eight of the 43 (65%) patients diagnosed with NMO by the revised criteria of 2006 were positive; the sensitivity was 62.5% when applying the same criteria, but discounting the criterion of NMO-IgG status, or 57% when applying the criteria of 1999. NMO-IgG was detected in 3 (13%) of the recurrent LEM and 2 (4%) of the recurrent ON. NMO-IgG was not detected in the remaining patients (96 with multiple sclerosis; 80 with myelitis; 28 with non-recurrent ON; and 33 other diagnosis). CONCLUSIONS: No false positive cases were found in this large and non-selected study. NMO-IgG positive cases were mostly associated with NMO, and only in a low percentage with recurrent ON or LEM.  
PMID: 20388455 [PubMed - as supplied by publisher]

**Cardiotoxicity and other adverse events associated with mitoxantrone treatment for MS.**  
From the Faculty of Medicine, Division of Neurology (E.K., M.K., B.L., P.R., H.T.), and Faculty of Medicine, Division of Cardiology (S.I.), University of British Columbia, Vancouver, British Columbia, Canada; Department of Nursing (J.G.), Vancouver Coastal Health, British Columbia, Canada; and Department of Neurology (M.K.), University Medical Center Groningen, University of Groningen; Groningen, The Netherlands.  
BACKGROUND: Mitoxantrone is used for aggressive multiple sclerosis (MS), but concerns about safety, including cardiotoxicity and other laboratory measures, prevail. OBJECTIVE: To evaluate the incidence and potential predictors of adverse events associated with mitoxantrone at the MS Clinic, University of British Columbia, Canada. METHODS: Retrospective review of patients treated with mitoxantrone by standard protocol; maximum cumulative dose = 120 mg/m(2). Left ventricular ejection fraction (LVEF) was measured with regular multiple-gated acquisition (MUGA) scans; blood cell counts and biochemical liver tests were performed before infusions. Generalized estimating equations were used to examine potential predictors of adverse events (graded according to the Common Toxicity Criteria, version 4) in patients with normal baseline and >/=1 follow-up MUGA or laboratory assessment. RESULTS: All 163 patients (58% women) treated with mitoxantrone from 1999 to 2007 were reviewed. Mean baseline age was 41.9 (SD 10.8) years, cumulative dose was 59.7 (SD 26.0) mg/m(2), and median follow-up duration was 14 months (maximum 6.5 years). By study end, 14% developed de novo cardiotoxicity (grade >/=2) as measured by decreased LVEF, 27% neutropenia (grade >/=1), 15% anemia (grade >/=1), and 15% liver toxicity (grade >/=1). Possible predictors of adverse events included sex, age, disease duration, and cumulative dose; only women exposed to a higher cumulative dose were at a greater risk of anemia (adjusted odds ratio 1.26, 95% confidence interval 1.08-1.48 per 10 mg/m(2)). CONCLUSIONS: Based on cardiac and laboratory assessments, mitoxantrone was reasonably well tolerated. However, cardiotoxicity was evident after doses well below current maximum recommended levels. A dose-response effect was not apparent. Findings emphasize the importance of monitoring; the long-term effects of mitoxantrone in multiple sclerosis require investigation.  
PMID: 20427751 [PubMed - as supplied by publisher]

**A phase I/II dose-escalation trial of vitamin D3 and calcium in multiple sclerosis.**


From the Division of Neurology (J.M.B., P.O.), St. Michael's Hospital, Toronto; University of Toronto (J.M.B., S.K., R.V., H.-M.D., R.C., C.D., P.O.), Toronto; Department of Nutritional Sciences and Laboratory Medicine and Pathology (S.K., R.V.), Mount Sinai Hospital, Toronto; Montreal Neurological Institute (A.B.-O., D.G.), Montreal; McGill University (A.B.-O., D.G.), Montreal; The Neurosciences & Mental Health Program (H.-M.D., R.C.), Hospital for Sick Children, Toronto; Center for Research in Neurodegenerative Diseases (C.D.), University of Toronto; and Division of Neurology (M.U.), Etobicoke General Hospital, Toronto, Canada.

**OBJECTIVE:** Low vitamin D status has been associated with multiple sclerosis (MS) prevalence and risk, but the therapeutic potential of vitamin D in established MS has not been explored. Our aim was to assess the tolerability of high-dose oral vitamin D and its impact on biochemical, immunologic, and clinical outcomes in patients with MS prospectively. METHODS: An open-label randomized prospective controlled 52-week trial matched patients with MS for demographic and disease characteristics, with randomization to treatment or control groups. Treatment patients received escalating vitamin D doses up to 40,000 IU/day over 28 weeks to raise serum 25-hydroxyvitamin D [25(OH)D] rapidly and assess tolerability, followed by 10,000 IU/day (12 weeks), and further downtitrated to 0 IU/day. Calcium (1,200 mg/day) was given throughout the trial. Primary endpoints were mean change in serum calcium at each vitamin D dose and a comparison of serum calcium between groups. Secondary endpoints included 25(OH)D and other biochemical measures, immunologic biomarkers, relapse events, and Expanded Disability Status Scale (EDSS) score. RESULTS: Forty-nine patients (25 treatment, 24 control) were enrolled [mean age 40.5 years, EDSS 1.34, and 25(OH)D 78 nmol/L]. All calcium-related measures within and between groups were normal. Despite a mean peak 25(OH)D of 413 nmol/L, no significant adverse events occurred. Although there may have been confounding variables in clinical outcomes, treatment group patients appeared to have fewer relapse events and a persistent reduction in T-cell proliferation compared to controls. CONCLUSIONS: High-dose vitamin D (approximately 10,000 IU/day) in multiple sclerosis is safe, with evidence of immunomodulatory effects. Classification of evidence: This trial provides Class II evidence that high-dose vitamin D use for 52 weeks in patients with multiple sclerosis does not significantly increase serum calcium levels when compared to patients not on high-dose supplementation. The trial, however, lacked statistical precision and the design requirements to adequately assess changes in clinical disease measures (relapses and Expanded Disability Status Scale scores), providing only Class level IV evidence for these outcomes.

PMID: 20427749 [PubMed - as supplied by publisher]


**Combined effects of smoking, anti-EBNA antibodies, and HLA-DRB1*1501 on multiple sclerosis risk.**

Simon KC, van der Mei IA, Munger KL, Ponsonby A, Dickinson J, Dwyer T, Sundström P, Ascherio A.

Departments of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115, USA.

**OBJECTIVE:** To examine the interplay between smoking, serum antibody titers to the Epstein-Barr virus nuclear antigens (anti-EBNA), and HLA-DR15 on multiple sclerosis (MS) risk. METHODS: Individual and pooled analyses were conducted among 442 cases and 865 controls from 3 MS case-control studies—a nested case-control study in the Nurses’ Health Study/Nurses’ Health Study II, the Tasmanian MS Study, and a Swedish MS Study. Conditional logistic regression models were used to calculate odds ratios (ORs) and 95% CIs for the association between smoking, anti-EBNA titers, HLA-DR15, and MS risk. Study estimates were pooled using inverse variance weights to determine a combined effect and p value. RESULTS: Among MS cases, anti-EBNA titers were significantly higher in ever smokers compared to never smokers. The increased risk of MS associated with high anti-EBNA Ab titers was stronger among ever smokers (OR = 3.9, 95% CI = 2.7-5.7) compared to never smokers (OR = 1.8, 95% CI = 1.4-2.3; p for interaction = 0.001). The increased risk of MS associated with a history of smoking was no longer evident after adjustment for anti-EBNA Ab titers. No modification or confounding by HLA-DR15 was observed. The increased risk of MS associated with ever smoking was only observed among those who had high anti-EBNA titers (OR = 1.7, 95% CI = 1.1-2.6). CONCLUSIONS: Smoking appears to enhance the association between high anti-EBNA titer and increased multiple sclerosis (MS) risk. The association between HLA-DR15 and MS risk is independent of smoking. Further work is necessary to elucidate possible biologic mechanisms to explain this finding.

PMID: 20375311 [PubMed - in process]
**Default-mode network dysfunction and cognitive impairment in progressive MS.**  
Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute and University Ospedale San Raffaele, Milan, Italy.  
OBJECTIVE: This study explores default-mode network (DMN) abnormalities in patients with secondary progressive (SP) and primary progressive (PP) multiple sclerosis (MS) and whether such abnormalities correlate with cognitive impairment and damage to selected white matter (WM) fiber bundles, quantified using diffusion tensor (DT) MRI tractography. METHODS: Resting state (RS) functional MRI and DT MRI data were acquired from 33 patients with SPMS, 24 patients with PPMS, and 24 controls. Independent component analysis (ICA) was used to identify the DMN. SPM5 was used to assess within- and between-group activations. RESULTS: Between-group differences in DMN activity were found in the left medial prefrontal cortex (mPFC), left precentral gyrus (PcG), and anterior cingulate cortex (ACC). Compared to controls, patients with SPMS had reduced activity in the mPFC (p = 0.01) and PcG (p = 0.02), while patients with PPMS had reduced activity in the PcG (p = 0.008) and the ACC (p = 0.002). Compared to patients with PPMS, patients with SPMS had increased ACC activity (p = 0.008). Reduction of RS activity in the ACC was more pronounced in cognitively impaired vs cognitively preserved patients with MS (p = 0.02). In patients with MS, DMN abnormalities correlated with the PASAT and word list test scores (r values ranging from 0.35 to 0.45) and DT MRI changes in the corpus callosum and the cingulum (r values ranging from 0.82 to 0.87). CONCLUSION: These results suggest that a dysfunction of the anterior components of the default-mode network may be among the factors responsible for the accumulation of cognitive deficits in patients with progressive multiple sclerosis.  
PMID: 20404306 [PubMed - in process]

**The limits of functional reorganization in multiple sclerosis.**  
Schoonheim MM, Geurts JJ, Barkhof F.  
PMID: 20404304 [PubMed - in process]

**Role of Cytokines as Mediators and Regulators of Microglial Activity in Inflammatory Demyelination of the CNS.**  
Merson TD, Binder MD, Kilpatrick TJ.  
Florey Neuroscience Institutes and the Centre for Neuroscience, University of Melbourne, Parkville, VIC, 3010, Australia, t.merson@florey.edu.au.  
As the resident innate immune cells of the central nervous system (CNS), microglia fulfill a critical role in maintaining tissue homeostasis and in directing and eliciting molecular responses to CNS damage. The human disease Multiple Sclerosis and animal models of inflammatory demyelination are characterized by a complex interplay between degenerative and regenerative processes, many of which are regulated and mediated by microglia. Cellular communication between microglia and other neural and immune cells is controlled to a large extent by the activity of cytokines. Here we review the role of cytokines as mediators and regulators of microglial activity in inflammatory demyelination, highlighting their importance in potentiating cell damage, promoting neuroprotection and enhancing cellular repair in a context-dependent manner.  
PMID: 20411441 [PubMed - as supplied by publisher]
Kinetics of IL-17- and interferon-gamma-producing PLPp-specific CD4 T cells in EAE induced by coinjection of PLPp/IFA with pertussis toxin in SJL mice.
Hofstetter HH, Forsthuber TG.
Clinical Research Group for Multiple Sclerosis and Neuroimmunology, Department of Neurology, University of Würzburg, Würzburg, Germany; Department of Pathology, Case Western Reserve University, Cleveland, OH 44106, USA.
Systemic administration of Pertussis toxin (PTX) abrogates T cell tolerance mediated by injection of neuroantigens in incomplete Freund's adjuvant (IFA) and causes experimental autoimmune encephalomyelitis (EAE). PTX concomitantly induces high frequencies of neuroantigen-specific IFN-gamma- and IL-17-producing T cells. Both IL-17 and IFN-gamma have been implicated as a key effector cytokines in the pathogenesis of EAE, possibly with different functions. We therefore investigated potential differences in the temporal and spatial kinetics of the PTX-induced neuroantigen-specific IFN-gamma- and IL-17-producing T cell effector populations. IFN-gamma- and IL-17-producing PLPp-specific T cells initially arose in comparable frequencies in the local draining lymph nodes (drLN) after immunization as measured by cytokine ELISPOT. High frequencies of both IFN-gamma- and IL-17-producing T cells were present in the immune periphery before onset of EAE. The highest frequencies of PTX-induced IFN-gamma- and IL-17-producing PLPp-specific cells coincided in the inflamed CNS during acute EAE. During recovery, both IFN-gamma- and IL-17-producing PLPp-specific T cells simultaneously disappeared from the CNS, whereas high frequencies of these cells remained present in the immune periphery. The functional affinity of both IFN-gamma- and IL-17-producing T cells did not change during EAE. Therefore, autoimmune pathology in this model did not correlate with specific PTX effects either on Th1 or Th17 cells regarding their kinetics and CNS migration. Copyright © 2010. Published by Elsevier Ireland Ltd.
PMID: 20398738 [PubMed - as supplied by publisher]

Progesterone attenuates neurological behavioral deficits of experimental autoimmune encephalomyelitis through remyelination with nucleus-sublocalized Olig1 protein.
Yu HJ, Fei J, Chen XS, Cai QY, Liu HL, Liu GD, Yao ZX.
Department of Rehabilitation, Southwest Hospital, Third Military Medical University, Chongqing 400038, China; Department of Histology and Embryology, Third Military Medical University, Chongqing 400038, China.
Multiple sclerosis (MS) is the most common demyelination disease of central nervous system (CNS). The deterioration of the disease is characterized by the axonal loss with defective remyelination. Progesterone can promote the remyelination, but whether it exerts beneficial effect on treatment of MS still remains unclear. Olig1 protein is a key regulator in the remyelination, when the intracellular sublocalization plays an import role too. We observed the effect of progesterone on experimental autoimmune encephalomyelitis (EAE) in rats by injecting the progesterone after the neurological behavioral deficits were shown up. The results showed no continuous increase of the nervous function score from day 10 after injection (p<0.05). Electron microscopy and LFB staining found prominent increase of OD value of normal myelin in the brain from day 6 after injection (p<0.05). Olig1 protein was localized almost completely in the cytoplasm of Olig1-positive cells from normal rats' brain. In EAE rats, the Olig1 protein has been translocated to the nucleus of 32.17% of Olig1-positive cells, which was increased to 68.52% after injection with progesterone at day 6 after injection (p<0.01). The results indicate that the progesterone is beneficial to attenuating neurological behavioral deficits, for it can promote more successful remyelination of EAE with aid of the nucleus-sublocalized Olig1 protein. Copyright © 2010 Elsevier Ireland Ltd. All rights reserved.
PMID: 20381586 [PubMed - as supplied by publisher]
Matrix metalloproteinases and neurotrauma: evolving roles in injury and reparative processes.  
Department of Neurosurgery, University of California, San Francisco, CA 94143-0110, USA.  
haoqian.zhang@ucsf.edu  
Matrix metalloproteinases (MMPs) are involved in a wide range of proteolytic events in fetal development and normal tissue remodeling as well as wound healing and inflammation. In the CNS, they have been implicated in a variety of neurodegenerative diseases ranging from multiple sclerosis to Alzheimer disease and are integral to stroke-related cell damage. Although studies implicate increased activity of MMPs in pathogenesis in the CNS, there is also a growing literature to support their participation in events that support recovery processes. Here the authors provide a brief overview of MMPs and their regulation, address their complex roles following traumatic injuries to the adult and developing CNS, and consider their time- and context-dependent signatures that influence both injury and reparative processes.  

Multiple sclerosis: understanding a complex neurological condition.  
MacLean R.  
MS Society, MS National Centre, London. rmaclean@mssociety.org.uk  
This article provides a brief overview of the pathophysiology of multiple sclerosis (MS). The symptoms experienced, including their management and treatment by members of the multidisciplinary team, are discussed, with a particular focus on the role of the nurse. Promoting and/or enabling self-management is an integral part of the nurse’s role. Although there is no cure for MS, good management can enable all people affected by the condition to come to terms with their diagnosis and have a positive outlook for the future.  
PMID: 20391676 [PubMed - indexed for MEDLINE]

Modulation of inflammation by chondroitin sulfate.  
Vallières M, du Souich P.  
Department of Pharmacology, Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada H3C 3J7.  
OBJECTIVE AND METHODS: To evaluate the immune-modulator effect of chondroitin sulfate (CS) by means of the review of the literature. RESULTS: Inflammatory reactions are primarily originated by infectious agents, immune reactions and by sterile tissue lesions that activate membrane receptors by means of pathogen-associated molecular patterns, tissue breakdown products and cytokines. The activation of membrane receptors triggers the phosphorylation of mitogen activated protein kinases and of the nuclear factor kappaB (NF-kappaB). The binding of NF-kappaB to the promoter of target genes enhances the expression of pro-inflammatory cytokines, inducible nitric oxide synthase, cyclooxygenase 2, phospholipase A2, and matrix metalloproteases, proteins that contribute to tissue damage and to the inflammatory reaction. The activation of NF-kappaB has a key role in the immune homeostasis and the inflammatory response and therefore, in the pathogenesis of numerous diseases. Chondroitin sulfate (CS) is able to diminish NF-kappaB activation and nuclear translocation in chondrocytes and synovial membrane, effects that may explain the benefits of CS in osteoarthritis. In addition, systemic CS reduces NF-kappaB nuclear translocation in macrophages and hepatocytes, raising the hypothesis that CS might be of benefit to treat other diseases with a strong inflammatory component. There is preliminary evidence in humans that CS improves moderate to severe psoriasis. Moreover, experimental and clinical data suggest that CS might be a useful therapeutic agent in diseases such as inflammatory bowel diseases, atherosclerosis, Parkinson’s and Alzheimer’s diseases, multiple sclerosis, amyotrophic lateral sclerosis, rheumatoid arthritis and systemic lupus erythematosus. DISCUSSION: These results urge for double blinded placebo-controlled trials to confirm the utility of CS in diseases with immune and inflammatory components. Copyright © 2010 Osteoarthritis Research Society International. Published by Elsevier Ltd. All rights reserved.  
PMID: 20399900 [PubMed - as supplied by publisher]
177. Pain. 2010 Apr 15. [Epub ahead of print]
A diminished response to formalin stimulation reveals a role for the glutamate transporters in the altered pain sensitivity of mice with experimental autoimmune encephalomyelitis (EAE).
Multiple Sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS) in which neuropathic pain is now recognized as a major symptom. To date, few studies have examined the underlying mechanisms of neuropathic pain in MS. Recently we showed that in a chronic-relapsing animal model of MS, experimental autoimmune encephalomyelitis (EAE), characteristic neuropathic behaviours develop. However, responses to persistent noxious stimuli in EAE remain unexplored. We, therefore set out to characterize the changes in pain sensitivity in our EAE model to subcutaneous injection of formalin. We show here that female C57BL/6 mice immunized with myelin oligodendrocyte glycoprotein (MOG(35-55)) display a significant decrease in elicited pain behaviours in response to formalin injection. These effects were found to involve dysregulation of the glutamatergic system in EAE. We show here that these effects are mediated by decreased glutamate transporter expression associated with EAE. Our findings demonstrate that dysregulation of glutamate transporter function in EAE mice is an important mechanism underlying the abnormal pain sensitivity in response to persistent noxious stimulation of mice with EAE and also sheds light on a potential mechanism underlying neuropathic pain behaviours in this model. Copyright © 2010 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved. PMID: 20399559 [PubMed - as supplied by publisher]

Multiple sclerosis (MS) is a disease of the CNS, typically striking adults during the primary productive time of their life. The symptoms of MS can restrict the individual's physical activity and income-earning ability, resulting in a major financial burden on the patient, family, health system and society. This systematic literature review was conducted to document the economic burden of MS. Employing pre-defined search terms and inclusion/exclusion criteria, systematic searches were conducted in MEDLINE, EMBASE, PsycINFO, the Health Economic Evaluations Database (HEED), the NHS Economic Evaluation Database (EED) and the UK National Institute for Health and Clinical Excellence (NICE) website as well as conference abstracts. We identified 29 cost-of-illness studies that met the a priori inclusion criteria. The cost categories responsible for the majority of costs associated with MS varied across countries. There was a significant increase in costs associated with an increase in disease severity as measured by the Kurtzke Expanded Disability Status Scale (EDSS) score. The increase in magnitude was coupled with changes in the distribution of costs; although direct medical costs were important contributors in earlier stages of disease, they were outweighed by indirect costs in later stages, mainly due to relapses and productivity losses. Considering the increased costs associated with relapse occurrence and increasing disease severity, pharmaceutical or non-pharmaceutical interventions aimed at delaying the progression of disease may help to reduce the economic burden of MS. PMID: 20402540 [PubMed - in process]
The effect of single nucleotide polymorphisms from genome wide association studies in multiple sclerosis on gene expression.
Handel AE, Handunnetthi L, Berlanga AJ, Watson CT, Morahan JM, Ramagopalan SV.
Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom.
BACKGROUND: Multiple sclerosis (MS) is a complex neurological disorder. Its aetiology involves both environmental and genetic factors. Recent genome-wide association studies have identified a number of single nucleotide polymorphisms (SNPs) associated with susceptibility to (MS). We investigated whether these genetic variations were associated with alteration in gene expression. METHODS/PRINCIPAL FINDINGS: We used a database of mRNA expression and genetic variation derived from immortalised peripheral lymphocytes to investigate polymorphisms associated with MS for correlation with gene expression. Several SNPs were found to be associated with changes in expression: in particular two with HLA-DQA1, HLA-DQA2, HLA-DQB1, HLA-DRB1, HLA-DRB4 and HLA-DRB5, one with ZFP57, one with CD58, two with IL7 and FAM164A, and one with FAM119B, TSFM and KUB3. We found minimal cross-over with a recent whole genome expression study in MS patients. DISCUSSION: We have shown that many susceptibility loci in MS are associated with changes in gene expression using an unbiased expression database. Several of these findings suggest novel gene candidates underlying the effects of MS-associated genetic variation.
PMCID: PMC2854120 PMID: 20405052 [PubMed - in process]

Multiple sclerosis susceptibility-associated SNPs do not influence disease severity measures in a cohort of Australian MS patients.
Recent association studies in multiple sclerosis (MS) have identified and replicated several single nucleotide polymorphism (SNP) susceptibility loci including CLEC16A, IL2RA, IL7R, RPL5, CD58, CD40 and chromosome 12q13-14 in addition to the well established allele HLA-DR15. There is potential that these genetic susceptibility factors could also modulate MS disease severity, as demonstrated previously for the MS risk allele HLA-DR15. We investigated this hypothesis in a cohort of 1006 well characterised MS patients from South-Eastern Australia. We tested the MS-associated SNPs for association with five measures of disease severity incorporating disability, age of onset, cognition and brain atrophy. We observed trends towards association between the RPL5 risk SNP and time between first demyelinating event and relapse, and between the CD40 risk SNP and symbol digit test score. No associations were significant after correction for multiple testing. We found no evidence for the hypothesis that these new MS disease risk-associated SNPs influence disease severity.
PMCID: PMC2848851 PMID: 20368992 [PubMed - in process]

Imaging evaluation of demyelinating processes of the central nervous system.
Smith AB, Smirniotopoulos JG.
Department of Radiology and Radiological Sciences, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Rd, Bethesda, MD 20814, USA. alsmith@usuhs.mil
Demyelinating processes involving the central nervous system have a variety of aetiologies and can be separated into primary and secondary demyelinating processes. The classic example of primary demyelination is multiple sclerosis. Secondary demyelination, where the aetiology is known, includes infectious, metabolic and toxic disease processes. The underlying component of all demyelinating disorders is damage to the myelin sheath and/or the oligodendrocyte, the cell forming the myelin sheath. These processes often have similar imaging findings, making knowledge of the patient's history, physical examination and laboratory evaluation imperative for developing a differential diagnosis. This pictorial essay provides a review of the imaging of these diverse disorders.
PMID: 20354045 [PubMed - in process]
Estradiol inhibits ongoing autoimmune neuroinflammation and NFκB-dependent CCL2 expression in reactive astrocytes.
Giraud SN, Caron CM, Pham-Dinh D, Kitabgi P, Nicot AB.
Institut National de la Santé et de la Recherche Médicale, Unité Mixte de Recherche en Santé 546, Hôpital Pitié-Salpêtrière, Paris F-75013, France.
Astroglial reactivity associated with increased production of NFκB-dependent proinflammatory molecules is an important component of the pathophysiology of chronic neurological disorders such as multiple sclerosis (MS). The use of estrogens as potential anti-inflammatory and neuroprotective drugs is a matter of debate. Using mouse experimental allergic encephalomyelitis (EAE) as a model of chronic neuroinflammation, we report that implants reproducing pregnancy levels of 17beta-estradiol (E2) alleviate ongoing disease and decrease astrocytic production of CCL2, a proinflammatory chemokine that drives the local recruitment of inflammatory myeloid cells. Immunohistochemistry and confocal imaging reveal that, in spinal cord white matter EAE lesions, reactive astrocytes express estrogen receptor (ER)alpha (and to a lesser extent ERbeta) with a preferential nuclear localization, whereas other cells including infiltrated leukocytes express ERs only in their membranes or cytosol. In cultured rodent astrocytes, E2 or an ERalpha agonist, but not an ERbeta agonist, inhibits TNFalpha-induced CCL2 expression at nanomolar concentrations, and the ER antagonist ICI 182,170 blocks this effect. We show that this anti-inflammatory action is not associated with inhibition of NFκB nuclear translocation but rather involves direct repression of NFκB-dependent transcription. Chromatin immunoprecipitation assays further indicate that estrogen suppresses TNFalpha-induced NFκB recruitment to the CCL2 enhancer. These data uncover reactive astrocytes as an important target for nuclear ERalpha inhibitory action on chemokine expression and suggest that targeting astrocytic nuclear NFκB activation with estrogen receptor alpha modulators may improve therapies of chronic neurodegenerative disorders involving astroglial neuroinflammation.
PMID: 20404154 [PubMed - as supplied by publisher]

EATING OURSELVES TO DEATH AND DESPAIR: THE CONTRIBUTION OF ADIPOSITY AND INFLAMMATION TO DEPRESSION.
Shelton RC, Miller AH.
Vanderbilt University, 1500 21st Avenue South, Suite 2200, Nashville, TN 37212.
Obesity and related metabolic conditions are of epidemic proportions in most of the world, affecting both adults and children. The accumulation of lipids in the body in the form of white adipose tissue in the abdomen is now known to activate innate immune mechanisms. Lipid accumulation causes adipocytes to directly secrete the cytokines interleukin (IL) 6 and tumor necrosis factor alpha (TNFalpha), but also monocyte chemoattractant protein 1 (MCP-1), which results in the accumulation of leukocytes in fat tissue. This sets up a chronic inflammatory state which is known to mediate the association between obesity and conditions such as cardiovascular disease, type 2 diabetes, and cancer. There is also a substantial literature linking inflammation with risk for depression. This includes the observations that: 1. People with inflammatory diseases such as multiple sclerosis, cardiovascular disease, and psoriasis have elevated rates of depression; 2. Many people administered inflammatory cytokines such as interferon alpha develop depression that is indistinguishable from depression in non-medically ill populations; 3. A significant proportion of depressed persons show upregulation of inflammatory factors such as IL-6, C-reactive protein, and TNFalpha; and 4) Inflammatory cytokines can interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function, and synaptic plasticity. While many factors may contribute to the association between inflammatory mediators and depression, we hypothesize that increased adiposity may be one causal pathway. Mediational analysis suggests a bi-directional association between adiposity and depression, with inflammation possibly playing an intermediary role. Copyright © 2010. Published by Elsevier Ltd.
PMID: 20417247 [PubMed - as supplied by publisher]
Structural and functional hippocampal changes in multiple sclerosis patients with intact memory function.
Roosendaal SD, Hulst HE, Vrenken H, Feenstra HE, Castelijns JA, Pouwels PJ, Barkhof F, Geurts JJ. Department of Radiology, MS Center Amsterdam, VU University Medical Center, De Boelelaan 1117, 1007 MB Amsterdam, the Netherlands. s.roosendaal@vumc.nl
PURPOSE: To investigate changes in hippocampal functional connectivity and structural measures of hippocampal damage in multiple sclerosis (MS) patients with intact spatial memory, a cognitive domain frequently affected in progressive MS. MATERIALS AND METHODS: The study protocol was approved by the institutional ethics review board; all subjects gave written informed consent prior to participation. Twenty-five MS patients with intact spatial memory function were compared with 30 age- and sex-matched controls. Hippocampal volume differences, based on manually drawn masks, were evaluated by using the Student t test. Additionally, focal hippocampal lesions and mean diffusivity were obtained as descriptive measures of structural hippocampal damage. Multiple regression analyses of the resting-state functional magnetic resonance (MR) imaging data were performed for each subject by using hippocampal time series. Between-group analyses were conducted with a mixed-effects model, corrected for multiple comparisons by a cluster defining threshold level of z = 2 and a corrected cluster size significance level of P < .05. RESULTS: Right hippocampal volume was significantly lower in MS patients as compared with controls (P < .01). Left hippocampal volume was also lower in MS patients compared with controls, but not significantly so (P = .09). Resting-state functional connectivity between the hippocampus and its anatomic input or target areas, including the anterior cingulate gyrus, thalamus, and prefrontal cortex, were significantly decreased in MS patients. Decreased hippocampal functional connectivity was more pronounced in a subgroup of MS patients with hippocampal atrophy, although subtle decreases of functional connectivity were also found in patients with normal hippocampal volume. CONCLUSION: In MS patients, substantial abnormalities of hippocampal functional connectivity are already present before spatial memory function is impaired, especially in those patients with more pronounced hippocampal atrophy. Longitudinal studies should now assess whether these functional connectivity and structural changes may precede memory impairment in MS.
PMID: 20413769 [PubMed - in process]

[Oral therapy for multiple sclerosis!]
Article in French
de Seze J.
Clinique neurologique, hôpital Civil, 1, place de l'hôpital, BP 426, 67091 Strasbourg cedex, France.
PMID: 20385331 [PubMed - in process]

[Multiple sclerosis. What about treatment with monoclonal antibodies?]
Article in French
Marignier R, Confavreux C.
Service de neurologie A, centre de coordination EDMUS pour la sclérose en plaques, hôpital neurologique Pierre-Wertheimer, CHU de Lyon, 69677 Bron Cedex. romain.marignier@chu-lyon.fr
PMID: 20402115 [PubMed - in process]
A role for VAV1 in experimental autoimmune encephalomyelitis and multiple sclerosis.
Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.
Multiple sclerosis, the most common cause of progressive neurological disability in young adults, is a chronic inflammatory disease. There is solid evidence for a genetic influence in multiple sclerosis, and deciphering the causative genes could reveal key pathways influencing the disease. A genome region on rat chromosome 9 regulates experimental autoimmune encephalomyelitis, a model for multiple sclerosis. Using interval-specific congenic rat lines and association of single-nucleotide polymorphisms with inflammatory phenotypes, we localized the gene of influence to Vav1, which codes for a signal-transducing protein in leukocytes. Analysis of seven human cohorts (12,735 individuals) demonstrated an association of rs2546133-rs2617822 haplotypes in the first VAV1 intron with multiple sclerosis (CA: odds ratio, 1.18; CG: odds ratio, 0.86; TG: odds ratio, 0.90). The risk CA haplotype also predisposed for higher VAV1 messenger RNA expression. VAV1 expression was increased in individuals with multiple sclerosis and correlated with tumor necrosis factor and interferon-gamma expression in peripheral blood and cerebrospinal fluid cells. We conclude that VAV1 plays a central role in controlling central nervous system immune-mediated disease and proinflammatory cytokine production critical for disease pathogenesis.
PMID: 20368159 [PubMed - in process]

Risks vs benefits of glatiramer acetate: a changing perspective as new therapies emerge for multiple sclerosis.
Johnson KP.
Maryland Center for MS, Baltimore, Maryland, USA.
An understanding of the risks, benefits, and relative value of glatiramer acetate (GA) in multiple sclerosis (MS) has been evolving based on recently completed head-to-head studies: REGARD (REbif vs Glatiramer Acetate in Relapsing MS Disease); BEYOND (Betaseron Efficacy Yielding Outcomes of a New Dose); and BECOME (Betaseron vs Copaxone in Multiple Sclerosis with Triple-Dose Gadolinium and 3-Tesla MRI Endpoints). Outcomes in the primary endpoints of these trials showed no significant differences between GA and high-dose beta-interferons (IFNbets). Results of the PreCISel (Early GA Treatment in Delaying Conversion to Clinically Definite Multiple Sclerosis [CDMS] in Subjects Presenting With a Clinically Isolated Syndrome [CIS]) trial led to the US Food and Drug Administration approval of GA in patients with a CIS. Furthermore, the ongoing follow-up study to the original pivotal GA trial, now extending beyond 15 years, continues to support the safety of GA. Currently, GA and IFNbets are no longer the only immunomodulators available for MS. Introduction of the monoclonal antibody, natalizumab (Tysabri(R)); Biogen Idec, Inc., Cambridge, MA, USA) provides an alternative immunomodulator for MS and has changed the therapeutic landscape dramatically. However, the rare but serious cases of progressive multifocal leukoencephalopathy that have occurred with natalizumab have raised concerns among clinicians and patients about using this agent and some of the emerging agents. The potential risks and benefits of the emerging therapies ( cladribine, alemtuzumab, rituximab, fingolimod, laquinimod, teriflunomide, and dimethyl fumarate) based on phase II/III trials, as well as their use for indications other than MS, will be presented. This review provides available data on GA, natalizumab, and the emerging agents to support new developments in our understanding of GA and how its long-standing role as a first-line therapy in MS will evolve within the increasingly complex MS therapeutic landscape.
PMCID: PMC2857614 PMID: 20421914 [PubMed - in process]
Necrotizing meningoencephalitis of Pug Dogs associates with dog leukocyte antigen class II and resembles acute variant forms of multiple sclerosis.
Greer KA, Wong AK, Liu H, Famula TR, Pedersen NC, Ruhe A, Wallace M, Neff MW.
School of Natural Sciences and Mathematics, Indiana University East, Richmond, IN, USA.
Necrotizing meningoencephalitis (NME) is a disorder of Pug Dogs that appears to have an immune etiology and high heritability based on population studies. The present study was undertaken to identify a genetic basis for the disease. A genome-wide association scan with single tandem repeat (STR) markers showed a single strong association near the dog leukocyte antigen (DLA) complex on CFA12. Fine resolution mapping with 27 STR markers on CFA12 further narrowed association to the region containing DLA-DRB1, -DQA1 and -DQB1 genes. Sequencing confirmed that affected dogs were more likely to be homozygous for specific alleles at each locus and that these alleles were linked, forming a single high risk haplotype. The strong DLA class II association of NME in Pug Dogs resembles that of human multiple sclerosis (MS). Like MS, NME appears to have an autoimmune basis, involves genetic and nongenetic factors, has a relatively low incidence, is more frequent in females than males, and is associated with a vascularity orientated non supplicative inflammation. However, NME of Pug Dogs is more aggressive in disease course than classical human MS, appears to be relatively earlier in onset, and involves necrosis rather than demyelination as the central pathobiologic feature. Thus, Pug Dog encephalitis (PDE) shares clinical features with the less common acute variant forms of MS. Accordingly, NME of Pug Dogs may represent a naturally occurring canine model of certain idiopathic inflammatory disorders of the human central nervous system.
PMID: 20403140 [PubMed - as supplied by publisher]

Characterization of D6S2806 and D6S2879 short tandem repeat loci in HLA-DRB1 region in Iranian population.
Vallian S, Tajadod M, Hojati Z.
Division of Genetics, Department of Biology, Faculty of Science, University of Isfahan, Isfahan, Islamic Republic of Iran.
Genomewide screen analysis has shown the close association of the human leukocyte antigen (HLA)-DRB1 region with susceptibility to multiple sclerosis and a number of autoimmune diseases. Using bioinformatics software, several potential short tandem repeat (STR) markers have been introduced in this region in the major histocompatibility complex data base (dbMHC). In this study, the identity and characteristics of two putative STR markers, D6S2879 and D6S2806, in this region were examined in Iranian population. The loci were genotyped in 85 individuals using polymerase chain reaction followed by polyacrylamide gel electrophoresis and sequencing. Analysis of the allelic frequency showed the presence of six and four alleles for D6S2806 and D6S2879, respectively. Analysis of deviations from Hardy-Weinberg equilibrium (HWE) showed that D6S2806 was in equilibrium (P > 0.05). However, the D6S2879 locus showed a significant deviation from HWE (P < 0.05). Therefore, the D6S2806 locus could be suggested as a marker for linkage analysis and disease-susceptibility investigations in the MHC-DRB1 gene region.
PMID: 20403136 [PubMed - as supplied by publisher]

Infection, inflammation, and chronic diseases: consequences of a modern lifestyle.
Ehlers S, Kaufmann SH; the Participants of the 99(th) Dahlem Conference.
Cluster of Excellence "Inflammation at Interfaces" (Borstel-Kiel-Lübeck-Plön), Research Center Borstel, Microbial Inflammation Research, Parkallee 1, D-23845 Borstel, Germany.
Infectious diseases, including tuberculosis, malaria, hepatitis, pneumonia, dysentery, and helminth infestations, still constitute a profound threat in developing countries. Curiously, their decline in high-income societies is paralleled by an unprecedented emergence of allergic disorders, notably asthma and atopy, and chronic inflammatory and autoimmune diseases, such as Crohn's disease, type 1 diabetes, and multiple sclerosis. Several changes in lifestyle are associated with this transition, including diminished exposure to soil and animals, nutritional bias, obesity and increased exposure to pollutants and antibiotics, which all impact the intestinal microbiota. Understanding the mechanistic links behind the epidemiological observations, the complexity of a changing microbiome, and the immunoregulatory consequences of microbial exposure in barrier organs was the subject of the 99(th) Dahlem Conference. Copyright © 2010 Elsevier Ltd. All rights reserved.
PMID: 20399709 [PubMed - as supplied by publisher]
A critical role for virus-specific CD8(+) CTLs in protection from Theiler's virus-induced demyelination in disease-susceptible SJL mice.
Getts MT, Richards MH, Miller SD.
Department of Microbiology and Immunology and Interdepartmental Immunobiology Center, Northwestern University Feinberg School of Medicine, 303 E. Chicago Ave., Chicago, IL 60611, USA.
Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease (TMEV-IDD) is a relevant mouse model of multiple sclerosis. Infection of susceptible SJL/J mice leads to life-long CNS virus persistence and development of a chronic T cell-mediated autoimmune demyelinating disease triggered via epitope spreading to endogenous myelin epitopes. Potent CNS-infiltrating CD8(+) T cell responses to TMEV epitopes have previously been shown to be induced in both disease-susceptible SJL/J and resistant C57BL/6 mice, in which the virus is rapidly cleared. Specific tolerization of SJL CD8(+) T cells specific for the immunodominant TMEV VP3(159)(−)(166) epitope has no effect on viral load or development of clinical TMEV-IDD, but adoptive transfer of activated CD8(+) VP3(159)(−)(166)-specific T cell blasts shortly after TMEV infection to boost the early anti-viral response leads to clearance of CNS virus and protection from subsequent TMEV-IDD. These studies have important implications for vaccine strategies and treatment of chronic infections in humans. Copyright © 2010 Elsevier Inc. All rights reserved.
PMID: 20381109 [PubMed - as supplied by publisher]

[A clinical comparative study of multiple sclerosis and neuromyelitis optica.]
[Article in Chinese]
Liu JG, Qi XK, Xiong B, Li LP, Yao S, Qiu F.
Department of Neurology, Navy General Hospital of PLA, Beijing 100048, China.
OBJECTIVE: To compare the clinical characteristics of multiple sclerosis (MS) and neuromyelitis optica (NMO) for better diagnosis and differential diagnosis of them. METHODS: The characteristics of 40 MS and 38 NMO cases were retrospectively studied on clinic manifestations, electroneurophysiology, some laboratory indices, imaging characteristics and so on. RESULTS: The ratios of male to female were 1:1.35 and 1:4.43 respectively in patients with MS and NMO, so patients with NMO were more likely to be female as compared with MS (P < 0.05). The mean onset age was (35.5 +/- 13.9) years in MS patients and (30.6 +/- 15.6) years in NMO patients, but no significant difference was found (P > 0.05). The cases of visual acuity </= 0.1 in patients NMO was 13, which of MS was merely 1. The cases of visual acuity less than 0.5 after treatment in NMO patients was 19, which in MS was only 1. The cases of cognitive impairment in NMO was 3, which of MS was 10. The cases of cerebrospinal fluid oligoclonal bands in MS was 16, which in NMO patients was 9. The lesions of spinal cord shown in MRI of MS patients were typically oval, peripheral and asymmetric, but those in NMO patients extended longitudinally and converged centrally. The mean number of involved vertebral segments in NMO patients was significantly greater than that in MS patients (6.6 vs 2.2, P < 0.01). Furthermore, the number of spinal cord lesions in MS patients was also remarkably greater than that in NMO patients (2.0 vs 1.2, P < 0.01). CONCLUSIONS: NMO may be a distinct clinical entity, which is likely to be differentiated from MS by its tendency to affect women, younger age at onset, and other features clinical manifestations, electroneurophysiology, laboratory parameters, neuroimaging show. PMID: 20356505 [PubMed - in process]

[Construction and clinical application of lentivirus-AQP4 expressing vector]
[Article in Chinese]

Department of Neurology, Xuanwu Hospital, Capital Medical University, Beijing 100053, China.

OBJECTIVE: To construct the human aquaporin-4 (AQP4) expressing vector and detect anti-AQP4 antibody in serum of patients with neuromyelitis optica (NMO).

METHODS: RNA was extracted from human glioblastoma and AQP4 cDNA obtained through RT-PCR. The fragment was cloned into the lentiviral expressing vector (iDUET101) and transformed into competent strain Hb101 for later amplification; plasmids were extracted from the amplified positive-bacteria-colony, sequenced and transfected into HEK-293T cells. Expression of AQP4 was identified by RT-PCR, Western blot and immunofluorescence assay. And anti-AQP4 antibody in human serum was tested.

RESULTS: The sequence of target fragment matched with that of human AQP4 fragment sequences (NM_001650) completely. The constructed AQP4 fragment transfected in HEK-293T cell was tested by immunofluorescent examination and it exhibited obvious fluorescence located in cell membrane. Western blot test was positive. And the fragment was about 34 KD. Cellular immunofluorescence examination showed 11 examples of 12 NMO patient serums (91.7%) were positive, 4 in 34 multiple sclerosis (11.8%) positive and negative in all 50 serum samples of healthy controls.

CONCLUSION: The HEK-293T cell transfected with lentivirus-AQP4 vector can express stably. And the expressed fragment may be applied in clinical examination.

PMID: 20356560 [PubMed - in process]