Literatur-Dauerrecherche **Multiple Sklerose**

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1. Polymicrobial Diseases.


Polymicrobial Diseases is a collection of chapters from investigators researching a variety of diseases with multiple etiologies. These diseases can be categorized as those originating from polyviral infections, polybacterial infections, viral and bacterial infections, and polymicrobial mycotic infections, and those that result in immunosuppression. The book begins with a section on an integrated view of polymicrobial diseases in animals and humans, including a representative list of these diseases, the etiologic agents, and the underlying mechanisms of pathogenesis (chapter 1). Also included in this section is a chapter on the in vitro methods for the study of polymicrobial diseases (chapter 2). Section II contains information on polyviral infections in animals (chapter 3), infections with multiple hepatotropic viruses (chapter 4), multiple retroviral infections (chapter 5), and viruses associated with multiple sclerosis (chapter 6). Section III discusses polybacterial infections, including bacterial vaginosis (chapter 7), periodontal disease (chapter 8), abscesses (chapter 9), and atrophic rhinitis in swine (chapter 10). Section IV comprises polymicrobial diseases involving viruses and bacteria. These are infections seen in respiratory diseases in humans (chapter 11) and animals (chapters 12 and 13), otitis media (chapter 14), and intestinal disorders (chapter 15). The emerging role of viruses in periodontal disease is also discussed (chapter 16). Section V discusses polymicrobial infections involving fungi (chapter 17) and Candida interactions with bacterial biofilms (chapter 18). Section VI focuses on polymicrobial diseases that result from microbe-induced immunosuppression (chapter 19), which often allows other microbes to become established (chapter 20). In conclusion, section VII summarizes the state of polymicrobial infections in animals and humans (chapter 21).

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This study has tested the feasibility of using physical delivery methods, employing static and oscillating field "magnetofection" techniques, to enhance magnetic nanoparticle-mediated gene transfer to rat oligodendrocyte precursor cells derived for transplantation therapies. These cells are a major transplant population to mediate repair of damage as occurs in spinal cord injury and neurological diseases such as multiple sclerosis. We show for the first time that magnetic nanoparticles mediate effective transfer of reporter and therapeutic genes to oligodendrocyte precursors; transfection efficacy was significantly enhanced by applied static or oscillating magnetic fields, the latter using an oscillating array employing high-gradient NdFeB magnets. The effects of oscillating fields were frequency-dependent, with 4 Hz yielding optimal results. Transfection efficiencies obtained using magnetofection methods were highly competitive with or better than current widely used nonviral transfection methods (e.g., electroporation and lipofection) with the additional critical advantage of high cell viability. No adverse effects were found on the cells' ability to divide or give rise to their daughter cells, the oligodendrocytes-key properties that underpin their regeneration-promoting effects. The transplantation potential of transfected cells was tested in three-dimensional tissue engineering models utilizing brain slices as the host tissue; modified transplanted cells were found to migrate, divide, give rise to daughter cells, and integrate within host tissue, further evidencing the safety of the protocols used. Our findings strongly support the concept that magnetic nanoparticle vectors in conjunction with state-of-the-art magnetofection strategies provide a technically simple and effective alternative to current methods for gene transfer to oligodendrocyte precursor cells.

PMID: 21721568 [PubMed - as supplied by publisher]

**Impaired heart rate variability as a marker of cardiovascular autonomic dysfunction in multiple sclerosis.**

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Multiple sclerosis (MS) can cause alterations in autonomic cardiovascular functions. We aimed to investigate the correlation of disease activity and disability with heart rate variability (HRV) of cardiovascular autonomic dysfunction (CAD) demonstrated by 24-h Holter monitoring. Thirty-four patients with clinically active relapsing-remitting MS, age 33.8 +/- 7.6 years, were studied. Twenty healthy volunteers served as controls. The time domain long-term HRV parameters were recorded by a digicorder recorder calculated by ambulatory electrocardiograms. Variabilities in time domain were lower in the MS patients: SDNN (standard deviation of all R-R intervals, p = 0.019), SDANN (standard deviation of the averages of R-R intervals in all 5-minute segments of the entire recordings, p = 0.040), RMSSD (the square root of the mean of the sum of the squares of differences between adjacent R-R intervals, p = 0.026), HRVM (mean of the SDNN in all the 5-minute intervals, p = 0.029), HRVSD (standard deviation of the SDNN in all the 5-minute, p = 0.043). These results suggest that MS causes CAD manifesting as long-term HRV abnormalities. This illness seems to cause a dysfunction in parasympathetic cardiovascular tone. Depressed HRV parameters are independent from the clinical findings, but the illness progression partially seems to provoke a decrease in such parameters.

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**The role of magnetic resonance imaging in the study of multiple sclerosis: diagnosis, prognosis and understanding disease pathophysiology.**

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Magnetic resonance imaging (MRI) has become an established tool to diagnose multiple sclerosis (MS) and to monitor its evolution. In patients at presentation with clinically isolated syndromes suggestive of MS, MRI criteria for MS diagnosis have been proposed and are updated on a regular basis. In addition, MRI "red flags" useful for the differential diagnosis from other neurological conditions which can mimic MS have been identified. In patients with established MS, the ability of MR measures in explaining patients’ clinical status and progression of disability is still suboptimal. This has prompted the extensive application of modern MR-based technologies to estimate the overall disease burden in patients at different stages of the disease. The use of these techniques has allowed to grade in vivo the heterogeneity of MS pathology not only in focal lesions, but also in the normal-appearing white matter and grey matter. Combined with the use of functional MRI, this is ameliorating progressively our understanding of the factors associated to MS evolution. This review summarizes how MRI has improved our ability to diagnose MS and to predict its course, as well as how it is changing our understanding of the factors associated with the accumulation of irreversible disability in this condition.

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Incidence of multiple sclerosis in Chile. A hospital registry study.
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Objective - To study the incidence of MS in Chile by examining the hospitalizations across all geographical regions of the country and to examine whether there is a correlation between these rates and the latitude or ultraviolet radiation. Methods - This is a descriptive study examining the national registry of hospitalizations because of MS (code G35 in ICD-10) from January 1, 2001, to December 31, 2006. Incidence rates were calculated by gender and geographical region and standardized to the world population estimated for 2010. Results - A total of 6857 hospitalizations were analyzed. There were 935 individuals; 63.9% were women. The mean incidence rate for 2002-2006 period was 0.90 (95% CI: 0.75-1.05). The annualized incidence rates for regions from North to South were as follows: I Tarapaca 0.54 (95% CI: 0.0-1.21), II Antofagasta 0.93 (0.10-1.75), III Atacama 1.07 (0.0-2.31), IV Coquimbo 0.63 (0.01-1.24), V Valparaiso 0.83 (0.38-1.27), VI O'Higgins 0.72 (0.14-1.30), VII Maule 0.52 (0.06-0.98), VIII BIO BIO 0.81 (0.41-1.21), IX Araucania 0.43 (0.0-0.86), X Los Lagos 0.91 (0.35-1.46), XI Aysen 0.99 (0.0-2.98), XII Magallanes 3.54 (0.57-6.51), and XIII Metropolitana 1.10 (0.84-1.36). There were no significant correlations between hospitalization rates and latitude, except for region XII. UV radiation levels showed significant differences only for region XII. Conclusion - There is a moderate risk of MS in Chile. The southernmost region showed significantly higher incidence rates than those in the rest of the country (a cluster zone). We did not find any correlation between incidence rates and latitude or UV radiation.

Cognitive deficits in multiple sclerosis: correlations with T2 changes in normal appearing brain tissue.
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Objective - Although disease load in multiple sclerosis (MS) often is based on T2 lesion volumes, the changes in T2 of normal appearing brain tissue (NABT) are rarely considered. By means of magnetic resonance, (MR) we retrospectively investigated whether T2 changes in NABT explain part of the cognitive impairment seen in MS and constitute a supplement to traditional measurement of T2 lesion volume. Methods - Fifty patients with clinically definite MS were included (38 women, 12 men). Patients were MR scanned, neuropsychologically tested, and evaluated clinically with the Kurtzke Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Impairment Scale (MSIS). Voxel-wise T2 estimates and total T2 lesion volume were tested for correlations with eight cognitive domains, a general cognitive dysfunction factor (CDF), and the two clinical scales. Results - We found distinct clusters of voxels with T2 estimates correlating with CDF, mental processing speed, complex motor speed, verbal fluency, and MSIS. A significant negative correlation was found between total lesion volume and CDF ($r = -0.34, P = 0.02$), verbal intelligence ($r = -0.40, P = 0.005$), mental processing speed ($r = -0.34, P = 0.03$), visual problem solving ($r = -0.40, P = 0.01$), and complex motor speed ($r = -0.39, P = 0.01$). No significant correlation was detected between total lesion load and the clinical measures EDSS and MSIS. Conclusion - Our results suggest that even in the NABT MR detects changes likely to be associated with an underlying pathology and possibly contributes to the cognitive impairment in MS.

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**Intrathecal levels of vitamin D and IgG in multiple sclerosis.**

Holmøy T, Lossius A, Gundersen TE, Moen SM, Castellazzi M, Fainardi E, Casetta I.

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Holmøy T, Lossius A, Gundersen TE, Moen SM, Castellazzi M, Fainardi E, Casetta I. Intrathecal levels of vitamin D and IgG in multiple sclerosis. Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2011.01577.x. © 2011 John Wiley & Sons A/S. Background - Intrathecal synthesis of IgG is a hallmark of multiple sclerosis (MS). Vitamin D may modulate B-cell function and dampen the synthesis of IgG. Objective - To investigate the relation between vitamin D levels in cerebrospinal fluid and serum and intrathecal synthesis of IgG. Methods - 25-hydroxyvitamin D (25(OH)D) and IgG were assessed in cerebrospinal fluid and serum in 40 patients with MS. Results - There was no significant correlation between the IgG index and 25(OH)D levels in cerebrospinal fluid or serum. The levels of 25(OH)D in cerebrospinal fluid and serum did not differ between patients with and without intrathecal synthesis of IgG. There was a non-significant trend towards a positive correlation between the concentrations of 25(OH)D and IgG in the cerebrospinal fluid, but not in serum. Conclusion - Physiological variation in vitamin D does not exert a major impact on intrathecal synthesis of IgG in MS.

PMID: 21781056 [PubMed - as supplied by publisher]


**Fractures and falls in patients with newly diagnosed clinically isolated syndrome and multiple sclerosis.**

Moen SM, Celius EG, Nordsletten L, Holmøy T.

Department of Neurology, Oslo University Hospital Ullevål, Oslo, Norway Orthopedic Department, Oslo University Hospital Ullevål, Oslo, Norway Department of Neurology, Akershus University Hospital, Lørenskog, Norway Institute of Clinical Medicine, University of Oslo, Oslo, Norway.

Moen SM, Celius EG, Nordsletten L, Holmøy T. Fractures and falls in patients with newly diagnosed clinically isolated syndrome and multiple sclerosis. Acta Neurol Scand: 2011: 124 (Suppl. 191): 79-82. © 2011 John Wiley & Sons A/S. Background - Increased risk of falls and reduced bone strength may both contribute to enhanced fracture risk in patients with multiple sclerosis (MS). Fall tendency and fractures have not been investigated in newly diagnosed patients. Objectives - The aim was to compare the fall tendency and fracture risk in a cohort of newly diagnosed clinically isolated syndrome (CIS) and MS patients with that in the general population. Methods - We performed a population-based case-control study in Oslo of self-reported fall tendency and fracture history in consecutive patients diagnosed with either a CIS suggestive of demyelinating disease or MS between January 2005 and January 2008. Two age-, sex-, and ethnicity-matched control groups were included: one group from the population registry and one group recruited by the patients. Results - Ninety-nine patients (mean time since the first symptom 1.6 ± 1.3 years, mean expanded disability status scale [EDSS] score 1.4 ± 1.1) and 159 controls were included. Whereas no difference in the number of fractures was reported, 20% of the patients and 3% of the controls reported a tendency to fall (P < 0.001). Fall tendency was associated with degree of disability (mean EDSS score among patients with and without self-reported fall tendency was 2.4 ± 1.4 and 1.1 ± 0.9, respectively; P = 0.001). Fall tendency was also reported in two of 22 patients with EDSS 0. Conclusions - Fall tendency may occur early in the disease course of MS, before impairment of locomotion and balance becomes evident on clinical examination.

PMID: 21711261 [PubMed - in process]
Multiple sclerosis, a cause of secondary osteoporosis? What is the evidence and what are the clinical implications?

Kampman MT, Eriksen EF, Holmøy T.
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Kampman MT, Eriksen EF, Holmøy T. Multiple sclerosis, a cause of secondary osteoporosis? What is the evidence and what are the clinical implications? Acta Neurol Scand: 2011: 124 (Suppl. 191): 44-49. © 2011 John Wiley & Sons A/S. Background - Both women and men with multiple sclerosis (MS) are at increased risk of developing osteoporosis. Methods - A non-systematic review of the prevalence, pathogenesis and treatment of osteoporosis in patients with multiple sclerosis. Results - MS and osteoporosis share aetiological risk factors such as smoking and hypovitaminosis D, as well as pathogenetic players such as osteopontin and osteoprotegerin. Recently, low bone mineral density (BMD) values have been measured shortly after diagnosis of clinically isolated syndrome and MS and in fully ambulatory persons with MS below 50 years of age. Studies consistently show that BMD at the femoral neck decreases with increasing MS-related disability. Osteoporosis-related fractures cause increased morbidity and mortality and add to the burden of having MS. Conclusion - We argue that MS, like a number of other chronic diseases, is a cause of secondary osteoporosis. Therefore, bone health assessment should be a part of the integral management of persons with MS. We suggest that BMD be measured shortly after diagnosis, that BMD measurements be repeated depending on BMD values and individual osteoporosis risk profile, and that serum 25-hydroxyvitamin D be monitored. All persons with MS should receive bone health advice.

PMID: 21711256 [PubMed - in process]

Modeling a complex disease multiple sclerosis.

Kurschus FC, Wörtge S, Waisman A.
The recent decades have shown that multiple sclerosis (MS) is not a uniform disease entity with common etiology, but rather a disease or syndrome characterized by a heterogeneous pattern of manifestations and pathological principles. Apart from the older distinctions of the Devic's disease from the standard Western form of relapsing remitting MS or the more Asian form of opticospinal MS, specific pathological patterns indicating distinct etiologies have been established by analyses of biopsies and autopsies. Further, the distinct responses of patients to drugs targeting either specific cell types or immunoregulatory mechanisms such as Rituximab or IFNβ clearly demonstrate the heterogeneity of the disease and their driving mechanisms. Finally, the late neurodegenerative phase, which severe cases of MS patients experience, is now in the focus of research. Here, a mechanism independent of or with low participation of the adaptive immune system takes place, which is therefore not treatable by current immunotargeting drugs. In this review, we will summarize previous and latest efforts to establish new mouse models mirroring these distinct disease patterns and pathways.

PMID: 21762817 [PubMed - in process]

Diffusion Tensor Imaging of the Optic Nerve in Multiple Sclerosis: Association with Retinal Damage and Visual Disability.

Smith SA, Williams ZR, Ratchford JN, Newsome SD, Farrell SK, Farrell JA, Gifford A, Miller NR, van Zijl PC, Calabresi PA, Reich DS.

Department of Radiology and Radiological Sciences, Biomedical Engineering, Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee; Russell H. Morgan Department of Radiology and Radiological Science, Baltimore, Maryland; F. M. Kirby Research Center for Functional Brain Imaging, Kennedy Krieger Institute, Baltimore, Maryland; Wilmer Eye Institute and Departments of Neurology and Neurogenetics, Johns Hopkins University, Baltimore, Maryland; and National Institute for Neurological Disease and Stroke, National Institutes of Health, Bethesda, Maryland.

BACKGROUND AND PURPOSE: There is a well-known relationship between MS and damage to the optic nerve, but advanced, quantitative MR imaging methods have not been applied to large cohorts. Our objective was to determine whether a short imaging protocol (<10 minutes), implemented with standard hardware, could detect abnormal water diffusion in the optic nerves of patients with MS. MATERIALS AND METHODS: We examined water diffusion in human optic nerves via DTI in the largest MS cohort reported to date (104 individuals, including 38 optic nerves previously affected by optic neuritis). We also assessed whether such abnormalities are associated with loss of visual acuity (both high and low contrast) and damage to the retinal nerve fiber layer (assessed via optical coherence tomography). RESULTS: The most abnormal diffusion was found in the optic nerves of patients with SPMS, especially in optic nerves previously affected by optic neuritis (19% drop in FA). DTI abnormalities correlated with both retinal nerve fiber layer thinning (correlation coefficient, 0.41) and loss of visual acuity, particularly at high contrast and in nerves previously affected by optic neuritis (correlation coefficient, 0.54). However, diffusion abnormalities were overall less pronounced than retinal nerve fiber layer thinning. CONCLUSIONS: DTI is sensitive to optic nerve damage in patients with MS, but a short imaging sequence added to standard clinical protocols may not be the most reliable indicator of optic nerve damage.

PMID: 21799043 [PubMed - as supplied by publisher]


Comparison of MR and Contrast Venography of the Cervical Venous System in Multiple Sclerosis.

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BACKGROUND AND PURPOSE: MRV has been proposed as a possible screening method to identify chronic cerebrospinal venous insufficiency, which may play a role in MS. We report our initial experience comparing MRV and CV in MS patients to evaluate venous stenosis and collateral venous drainage.

MATERIALS AND METHODS: Time-of-flight and time-resolved imaging of contrast kinetics MRV and CV were performed in 39 MS patients. The presence and severity of both IJ vein caliber changes and non-IJ collaterals were graded by using a 4-point scale by 2 radiologists in an independent and blinded manner.

RESULTS: Both studies frequently showed venous abnormalities, most commonly IJ flattening at the C1 level and in the lower neck. There was moderate-to-good agreement between the modalities (κ = 0.55; 95% CI, 0.45%-0.65%). For collaterals, agreement was only fair (κ = 0.30; 95% CI, 0.09%-0.50%). The prevalence of IJ segments graded mild or worse on CV was 54%. If CV was considered a standard, the sensitivity and specificity of MRV was 0.79 (0.71-0.86) and 0.76 (0.67-0.83), respectively. Degree of stenosis was related to the severity of collaterals for CV but not for MRV. CONCLUSIONS: IJ caliber changes were seen in characteristic locations on both MRV and CV in MS patients. Agreement between modalities was higher for stenosis than for collaterals. If CV is considered a standard, MRV performance is good but may require additional improvement before MRV can be used for screening.

PMID: 21757521 [PubMed - as supplied by publisher]
Multiple sclerosis (MS) is a complex chronic, progressing disease that contributes to poor quality of life (QOL) for patients and high costs for managed care organizations. Currently, disease-modifying treatments (DMTs) constitute the platform pharmacotherapy for MS patients. Despite their efficacy, for many patients taking DMTs there is little evidence of their effect on QOL in general or symptom management. Impaired mobility contributes to direct and indirect costs. Annual direct medical costs for MS with gait impairment average nearly $21,000 per patient. Decreased mobility is also associated with higher absenteeism rates, thus raising indirect costs. Dalfampridine has been shown to improve walking in patients with MS. The effects of dalfampridine can complement those of DMTs by improving walking ability as a key component of overall mobility and a primary concern among many MS patients. Improved walking could potentially help contain some of the direct and indirect costs associated with MS care.

PMID: 21761954  [PubMed - in process]

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Disease-modifying treatments (DMTs), which are the foundation of multiple sclerosis (MS) care, reduce clinical exacerbations (relapses) and slow disease progression; however, improving quality of life (QOL) is an unmet need for many individuals with MS. DMTs, including interferon-beta, glatiramer acetate, natalizumab, mitoxantrone, and fingolimod, reduce the rate and severity of relapses, the accumulation of brain and spinal cord lesions as shown on magnetic resonance imaging (MRI), and disability progression. Many studies link diminished QOL with specific MS symptoms (fatigue, impaired mobility, spasticity, etc). Even in patients already receiving DMTs, symptoms and QOL may improve with additional agents that treat specific symptoms, thereby improving patient function and ability to perform activities of daily living (ADLs). Patients have reported that mobility impairment is one of the worst aspects of MS. Almost half of patients treated with DMTs reported no improvement in mobility. However, blocking the voltage-dependent potassium channels on the surface of demyelinated nerve fibers may improve signal conduction. Dalfampridine, a potassium channel blocker, received Food and Drug Administration (FDA) approval for all forms of MS specifically to improve walking, which was demonstrated by increased walking speed. By improving walking in some patients with MS, the effects of dalfampridine may complement those of DMTs and address the stated priorities of many patients.
PMID: 21761953  [PubMed - in process]

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Multiple sclerosis (MS) affects approximately 400,000 people in the United States and 2.1 million people worldwide. It is the most common chronic, non-traumatic neurological disorder afflicting young people during their peak productive ages. MS can diminish quality of life (QOL) by interfering with the ability to work, pursue leisure activities, and carry on usual life roles. Symptoms that affect QOL may include impaired mobility, fatigue, depression, pain, spasticity, cognitive impairment, sexual dysfunction, bowel and bladder dysfunction, vision and hearing problems, seizures, and swallowing and breathing difficulties. Direct medical costs of MS in the United States are estimated in excess of $10 billion per year. Indirect costs of MS include costs of reduced employment or unemployment, assistive equipment, disability related home modifications, and paid and unpaid personal care. Although direct medical costs predominate in the earlier stages of MS, indirect costs of productivity loss are responsible for higher costs later. Disease-modifying therapies (DMTs) lessen symptoms, reduce relapses, and delay disability progression. Unfortunately, many DMTs might produce only modest improvements in QOL. Although symptom-specific therapies do not delay disease progression, they may delay unemployment and dependency, thereby reducing indirect costs.
PMID: 21761952  [PubMed - in process]
**Solitary lesion in magnetic resonance imaging: tumor versus multiple sclerosis.**
Kalavakunta JK, Tokala H, Loehrke M.  
*Department of Internal Medicine, Michigan State University/Kalamazoo Center for Medical Studies, Kalamazoo, Michigan (E-mail: jkalavakunta@gmail.com).*  
PMID: 21799469 [PubMed - in process]

**Cerebrospinal fluid analysis in the 2010 revised McDonald’s multiple sclerosis diagnostic criteria.**
Galea I, Freedman MS, Thompson EJ.  
Division of Clinical Neurosciences, University of Southampton, Southampton General Hospital, Southampton, United Kingdom.  
PMID: 21786311 [PubMed - in process]

**Proposed chronic cerebrospinal venous insufficiency criteria do not predict multiple sclerosis risk or severity.**
Department of Neuroscience, University Hospital Tor Vergata, Rome, Italy; Santa Lucia Foundation/European Center for Brain Research, centonze@uniroma2.it.  
OBJECTIVE: It is still unclear whether chronic cerebrospinal venous insufficiency (CCSVI) is associated with multiple sclerosis (MS), because substantial methodological differences have been claimed by Zamboni to account for the lack of results of other groups. Furthermore, the potential role of venous malformations in influencing MS severity has not been fully explored. This information is particularly relevant, because uncontrolled surgical procedures are increasingly offered to MS patients to treat their venous stenoses.  
METHODS: In the present study, CCSVI was studied in 84 MS patients and in 56 healthy subjects by applying the Zamboni method for CCSVI identification. RESULTS: We found no significant differences (p = 0.12) in CCSVI frequency between MS and control subjects. Furthermore, no differences were found between CCSVI-positive and CCSVI-negative patients in terms of relevant clinical variables such as disease duration, time between onset and first relapse, relapsing or progressive disease course, and risk of secondary progression course. Statistically significant differences were not found between CCSVI-positive and CCSVI-negative MS subjects by analyzing direct measures of disability such as mean Expanded Disability Status Scale (EDSS) (p = 0.07), mean progression index (p > 0.1), and mean MS severity score (p > 0.1). The percentage of subjects who reached EDSS 4.0 and 6.0 milestones was not different among CCSVI-negative and CCSVI-positive subjects, and no significant correlation was found between severity of disability and number of positive CCSVI criteria. INTERPRETATION: Our results indicate that CCSVI has no role in either MS risk or MS severity. Ann Neurol 2011;  
PMID: 21786298 [PubMed - in process]

**Gestational vitamin D and the risk of multiple sclerosis in offspring.**
Mirzaei F, Michels KB, Munger K, O'Reilly E, Chitnis T, Forman MR, Giovannucci E, Rosner B, Ascherio A.  
Department of Nutrition, Harvard School of Public Health, Boston, MA; Department of Epidemiology, Harvard School of Public Health, Boston, MA. fmirzaei@hsph.harvard.edu.  
OBJECTIVE: Vitamin D may have a protective role in the etiology of multiple sclerosis (MS), but the effect of gestational vitamin D on adult onset MS has not been studied. METHODS: In 2001, 35,794 mothers of participants of the Nurses’ Health Study II completed a questionnaire inquiring about their experiences and diet during pregnancy with their nurse daughters. We studied the association of maternal milk intake, maternal dietary vitamin D intake, and predicted maternal serum 25-hydroxyvitamin D (25(OH)D) during pregnancy and their daughters’ risk of developing MS. RESULTS: MS was diagnosed in 199 women. The relative risk of MS was lower among women born to mothers with high milk or vitamin D intake during pregnancy. The multivariate adjusted rate ratio (RR) of MS was 0.62 (95% confidence interval [CI], 0.40-0.95; p trend = 0.001) for nurses whose mothers consumed 2 to 3 glasses of milk per day compared with those whose mothers consumed <3 glasses per month, and 0.57 (95% CI, 0.35-0.91; p trend = 0.002) for nurses with mothers in the highest quintile of dietary vitamin D intake compared with those in the lowest. The predicted 25(OH)D level in the pregnant mothers was also inversely associated with the risk of MS in their daughters. Comparing extreme quintiles, the adjusted RR was 0.59. (95% CI, 0.37-0.92; p trend = 0.002). INTERPRETATION: Higher maternal milk and vitamin D intake during pregnancy may be associated with a lower risk of developing MS in offspring. ANN NEUROL 2011;  
PMID: 21786297 [PubMed - in process]

Bayer Vital GmbH, Specialty Medicine  
http://www.bayer-vital.de/  
http://www.betaferon.de  
http://www.ms-gateway.de
Vitamin D deficiency diminishes the severity and delays onset of experimental autoimmune encephalomyelitis.
Deluca HF, Plum LA.
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Multiple sclerosis incidence is clearly inversely related to sun exposure. This observation led to the idea that vitamin D might be responsible for this relationship. Providing super-physiologic doses of the hormonal form of vitamin D, 1α,25-dihydroxyvitamin D(3), suppresses an animal model of multiple sclerosis, i.e. experimental autoimmune encephalomyelitis (EAE) but causes unwanted hypercalcemia. Further, dietary calcium is needed for this activity of 1α,25-dihydroxyvitamin D(3). B10PL mice were maintained on a vitamin D-deficient diet for two generations to produce frank vitamin D deficiency. These animals showed delayed onset and reduced severity of EAE compared to control animals on the same diet and given vitamin D(3) or provided a vitamin D-containing chow diet. Thus, vitamin D deficiency interferes with the development of this autoimmune disease rather than increasing susceptibility.
PMID: 21784056 [PubMed - as supplied by publisher]

Repeated Treatment With Rituximab Based on the Assessment of Peripheral Circulating Memory B Cells in Patients With Relapsing Neuromyelitis Optica Over 2 Years.
Kim SH, Kim W, Li XF, Jung IJ, Kim HJ.
Research Institute and Hospital, National Cancer Center, Goyang, Korea.
OBJECTIVE: To evaluate the efficacy and safety of repeated rituximab treatment based on the assessment of peripheral circulating memory B cells over 24 months in patients with relapsing neuromyelitis optica (NMO). DESIGN: Prospective open-label study. SETTING: Institutional referral center for multiple sclerosis. Patients Thirty patients with relapsing NMO or NMO spectrum disorder. Intervention Treatment protocol of rituximab consisted of an induction therapy (375 mg/m(2) once weekly for 4 weeks or 1000 mg infused twice, with a 2-week interval between the infusions) followed by maintenance therapy. The maintenance therapy was repeated treatment with rituximab (375 mg/m(2), once) whenever the frequency of reemerging CD27(+) memory B cells was more than 0.05% in peripheral blood mononuclear cells by flow cytometric analysis. MAIN OUTCOME MEASURES: Annualized relapse rate, disability (Expanded Disability Status Scale score), anti-aquaporin 4 antibody level, and safety of rituximab treatment. RESULTS: Of 30 patients, 28 showed a marked reduction in relapse rate while taking rituximab over 24 months. The relapse rate was reduced significantly, by 88%, and 70% of patients became relapse-free over 24 months. Disability either improved or stabilized in 97% of patients. Anti-aquaporin 4 antibody levels declined significantly following treatment with rituximab, consistent with the clinical response and the effect on CD27(+) memory B cells. Repeated treatment with rituximab was generally well tolerated, and no clinically relevant adverse event leading to discontinuation of treatment was observed. CONCLUSION: Repeated treatment with rituximab appeared to produce consistent and sustained efficacy over 24 months with good tolerability in patients with NMO.
PMID: 21747007 [PubMed - as supplied by publisher]

Chronic Cerebrospinal Venous Insufficiency and Multiple Sclerosis.
Bagert BA, Marder E, Stüve O.
Ochsner Clinic Foundation, New Orleans, Louisiana (Dr Bagert); and Neurology Section, Medical Service, Veterans Affairs North Texas Health Care System and Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center at Dallas (Drs Marder and Stüve).
Chronic cerebrospinal venous insufficiency has recently been proposed to be etiologic to multiple sclerosis. Independent investigation into this theory during the past 2 years has not succeeded in verifying this relationship. A critical analysis of the scientific methods used in the original studies of chronic cerebrospinal venous insufficiency in multiple sclerosis reveals several methodological problems with regard to potential bias and confounding. The current evidence calls into question whether chronic cerebrospinal venous insufficiency in multiple sclerosis exists at all.
PMID: 21747006 [PubMed - as supplied by publisher]

How safe could intrathecal transplantation of mesenchymal stem cells be considered in multiple sclerosis?
Karacostas D, Hadjigeorgiou G, Ioannidis P, Milonas I.
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PMID: 21747040 [PubMed - in process]
A benign form of neuromyelitis optica: does it exist?


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BACKGROUND: Few data exist on a possible benign form of neuromyelitis optica (NMO). OBJECTIVES: To identify NMO with a good outcome (go-NMO) among a large population of patients and to describe demographic and clinical variables associated with go-NMO vs standard NMO and benign multiple sclerosis.

DESIGN: Observational retrospective multicenter study. SETTING: Twenty-five medical centers in metropolitan France (MF) and 3 medical centers in the French West Indies (FWI). Patients A total of 175 patients with NMO were retrospectively analyzed from 2 cohorts: 125 in MF and 50 patients of nonwhite race/ethnicity in the FWI. Patients in MF fulfilled the 2006 NMO criteria, whereas patients in the FWI fulfilled the 1999 or 2006 NMO criteria. Neuromyelitis optica and multiple sclerosis databases were reviewed, and patients with a score of 3 or lower on the Expanded Disability Status Scale after a 10-year follow-up period were considered to have go-NMO. MAIN OUTCOME MEASURES: Clinical, laboratory, and magnetic resonance imaging data and course of disability. RESULTS: In MF, go-NMO was observed in 11 patients, including 3 untreated patients. In the FWI, NMO was severe because of disability related to optic neuritis. Compared with standard NMO, go-NMO was associated with a lower annualized relapse rate (0.3 vs 1.0, P < .01), and 8 of 11 patients with go-NMO showed complete regression of myelitis on magnetic resonance imaging during the disease course. Three patients experienced a disabling attack of NMO after 15 years of follow-up. A good outcome occurred less frequently among patients with NMO than among patients with multiple sclerosis (12.0% vs 22.4%, P = .03). CONCLUSIONS: Among patients in MF, go-NMO occurs rarely. However, because a disabling attack may occur after a long follow-up period, a benign form of NMO cannot be defined.

PMID: 21747032 [PubMed - in process]

Markedly elevated soluble intercellular adhesion molecule 1, soluble vascular cell adhesion molecule 1 levels, and blood-brain barrier breakdown in neuromyelitis optica.

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OBJECTIVE: To evaluate the degree of blood-brain barrier disruption in patients with neuromyelitis optica (NMO) and to clarify whether the levels of soluble intercellular adhesion molecule 1 (sICAM-1) and soluble vascular cell adhesion molecule 1 (sVCAM-1) in patients with NMO can be useful biomarkers for blood-brain barrier breakdown. DESIGN: Descriptive historical cohort. SETTING: Department of Neurology, Graduate School of Medicine, Chiba University. Patients The levels of sICAM-1 and sVCAM-1 in 25 patients with NMO, 21 patients with multiple sclerosis, and 20 patients with other noninflammatory neurologic disorders in the serum and cerebrospinal fluid (CSF) were measured using a multiplexed fluorescent magnetic bead-based immunoassay. MAIN OUTCOME MEASURES: Levels of the soluble adhesion molecules in serum and CSF and their associations with blood-brain barrier disruption. RESULTS: The CSF levels of sICAM-1 and sVCAM-1 increased in patients with NMO compared with patients with multiple sclerosis and other noninflammatory neurologic disorders (P < .001), and serum levels of sICAM-1 increased in patients with NMO compared with healthy control individuals (P = .003). The CSF sICAM-1 levels from patients with NMO were correlated with the albumin quotient (P = .02) and the presence of lesions detected via gadolinium-enhanced magnetic resonance imaging. CONCLUSIONS: Severe blood-brain barrier breakdown occurs in patients with NMO. Measuring adhesion molecules is useful to evaluate this barrier disruption.

PMID: 21747031 [PubMed - in process]
Classical immunomodulatory therapy in multiple sclerosis: how it acts, how it works.
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Interferon beta (IFNβ) and glatiramer acetate (GA) were the first immunomodulators approved to the treatment of relapsing-remitting multiple sclerosis (MS) and clinically isolated syndromes. Despite the enlargement of the therapeutic armamentarium, IFNβ and GA remain the most widely used drugs and the therapeutic mainstay of MS.OBJECTIVE: To review the mechanisms of action of IFNβ and GA and main clinical results in MS. RESULTS: IFNβ modulates T and B-cell activity and has effects on the blood-brain barrier. The well proved mechanism of GA is an immune deviation by inducing expression of anti-inflammatory cytokines. Some authors favor the neuroprotective role of both molecules. Clinical trials showed a 30% reduction on the annualized relapse rate and of T2 lesions on magnetic resonance.
CONCLUSION: Although the precise mechanisms how IFNβ and GA achieve their therapeutics effects remain unclear, these drugs have recognized beneficial effects and possess good safety and tolerability profiles. The large clinical experience in treating MS patients with these drugs along almost two decades deserves to be emphasized, at a time where the appearance of drugs with more selective mechanisms of action, but potentially less safer, pave the way to a better selection of the most appropriate individualized treatment.
PMD: 21755136 [PubMed - in process]

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Multiple sclerosis (MS) is a chronic neurological disease that typically affects young adults. A recent publication suggested that MS might originate from insufficient blood drainage in certain areas of the central nervous system. The condition was named chronic cerebrospinal venous insufficiency (CCSVI). Other papers have not confirmed these findings and, therefore, the matter remains controversial. Nineteen months after the original publication on CCSVI and MS, another 22 papers have been published addressing the matter. No clinical trials have been carried out on the subject and there is no evidence-based indication to perform surgical vascular procedures in MS patients. However, over the same nineteen-month period, the internet discussion on the subject of CCSVI and MS has led to countless websites advertising treatment using vascular surgery for patients with MS all over the world. The treatment based on the CCSVI theory has appealingly been called "liberation treatment", thus making it difficult to explain to patients why a treatment that has been highly praised (on the internet) cannot be recommended based on partial medical results that await confirmation.
PMD: 21755134 [PubMed - in process]

Balance Rehabilitation Unit (BRU TM) posturography in relapsing-remitting multiple sclerosis.
Kessler N, Ganança MM, Ganança CF, Ganança FF, Lopes SC, Serra AP, Caovilla HH. Federal University of São Paulo, São Paulo, SP, Brazil.
OBJECTIVE: To evaluate balance control with Balance Rehabilitation Unit (BRU TM) posturography in patients with multiple sclerosis (MS). METHOD: A cross controlled study was performed including 39 relapsing-remitting multiple sclerosis patients with scores less than or equal to 4 in the Expanded Disability Status Scale (EDSS), and a homogeneous control group consisting of 65 healthy individuals, matched by the age and gender. The experimental group was distributed according to the EDSS scale scores in 0-2.5 and 3-4. To assess the vestibular system function, the patients underwent a neurotological evaluation, including posturography of the Balance Rehabilitation Unit (BRU TM). RESULTS: Statistically significant differences were observed when comparing the values of the sway velocity and the ellipse area of the MS 0-2.5 group with the control and the MS 3-4 group with the control. A statistically significant difference was verified between the MS 0-2.5 and the MS 3-4 groups in the condition 3 ellipse area values. CONCLUSION: The evaluation of the balance control with posturography of Balance Rehabilitation Unit (BRU TM) enables the identification of abnormalities of the sway velocity and confidential ellipse in patients with relapsing-remitting multiple sclerosis.
PMD: 21755127 [PubMed - in process]

Paced auditory serial addition test (PASAT): a very difficult test even for individuals with high intellectual capability.

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OBJECTIVE: To assess the difficulty of paced auditory serial addition test (PASAT) in a population of high intellectual level, under ideal cognitive testing circumstances. METHOD: One hundred medical students underwent PASAT testing. They had slept well the night before, they had eaten before the assessment, they were not using any drugs that could affect the central nervous system and they did not have depression, anxiety or any chronic disease. RESULTS: The average result from the three-second version of PASAT was 57.5% and, from the two-second version, it was 44.3%. CONCLUSION: Even under ideal circumstances, PASAT is a very difficult test for the general population. It may not be ideal for neurologists to screen, assess and follow up patients with cognitive function in multiple sclerosis.

PMID: 21755126 [PubMed - in process]


Emerging role of high density lipoproteins as a player in the immune system.

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High density lipoproteins (HDL) possess a number of physiological activities. The most studied and, perhaps, better understood is the ability of HDL to promote excess cholesterol efflux from peripheral tissues and transport to the liver for excretion, a mechanism believed to confer protection against atherosclerotic cardiovascular disease. The ability of HDL to modulate cholesterol bioavailability in the lipid rafts, membrane microdomains enriched in glycosphingolipids and cholesterol, is evolutionary conserved and affects the properties of cells involved in the innate and adaptive immune response, tuning inflammatory response and antigen presentation functions in macrophages as well as B and T cell activation. Also sphingosine-1 phosphate (S1P), a major active sphingolipid carried by HDL, is of relevance in the pathogenesis of several immuno-inflammatory disorders through the modulation of macrophage and lymphocyte functions. Furthermore, HDL influence the humoral innate immunity by modulating the activation of the complement system and the expression of pentraxin 3 (PTX3). Finally, in humans, HDL levels and functions are altered in several immune-mediated disorders, such as rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease and multiple sclerosis as well as during inflammatory responses. Altogether these observations suggest that the effects of HDL in immunity could be related, to either the ability of HDL to modulate cholesterol content in immune cell lipid rafts and to their role as reservoir for several biologically active substances that may impact the immune system.

PMID: 21783193 [PubMed - as supplied by publisher]


Autoimmunity in 2010.

Selmi C.

There is now growing evidence that autoimmunity is the common trait connecting multiple clinical phenotypes albeit differences in tissue specificity, pathogenetic mechanisms, and therapeutic approaches cannot be overlooked. Over the past years we witnessed a constant growth of the number of publications related to autoimmune diseases in peer-reviewed journals of the immunology area. Original data referred to factors from common injury pathways (i.e. T helper 17 cells, serum autoantibodies, or vitamin D) and specific diseases such as multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis. As an example, the issue of a latitudinal gradient in the prevalence and incidence rates has been proposed for all autoimmune diseases and was recently coined as geoepidemiology to suggest new environmental triggers for tolerance breakdown. The present article is aimed at reviewing the articles that were published over the past year in the major autoimmune and immunology journals.

PMID: 21763468 [PubMed - as supplied by publisher]
The effects of omega-3 Fatty acids on matrix metalloproteinase-9 production and cell migration in human immune cells: implications for multiple sclerosis.
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Department of Neurology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, CR 120, Portland, OR 97239, USA.
In multiple sclerosis (MS), compromised blood-brain barrier (BBB) integrity contributes to inflammatory T cell migration into the central nervous system. Matrix metalloproteinase-9 (MMP-9) is associated with BBB disruption and subsequent T cell migration into the CNS. The aim of this paper was to evaluate the effects of omega-3 fatty acids on MMP-9 levels and T cell migration. Peripheral blood mononuclear cells (PBMC) from healthy controls were pretreated with two types of omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Cell supernatants were used to determine MMP-9 protein and activity levels. Jurkat cells were pretreated with EPA and DHA and were added to fibronectin-coated transwells to measure T cell migration. EPA and DHA significantly decreased MMP-9 protein levels, MMP-9 activity, and significantly inhibited human T cell migration. The data suggest that omega-3 fatty acids may benefit patients with multiple sclerosis by modulating immune cell production of MMP-9.
PMCID: PMC3140187 PMID: 21799946 [PubMed - in process]

Multiple sclerosis.
Ramagopalan S, Dyment D, Farrell R, Isobe N.
Department of Clinical Neurology, University of Oxford, Oxford OX3 9DU, UK.
PMCID: PMC3130332 PMID: 21747986 [PubMed]

Sleep problems and fatigue in chronically ill women.
Parker White C, White MB.
a Department of Child Development and Family Relations, East Carolina University.
The objective of this study was to understand the quality and quantity of sleep in women with multiple sclerosis (MS) or rheumatoid arthritis (RA), who also had young children, and how their sleep behaviors were associated with their fatigue. A cross-sectional sample of mothers with MS and RA and a well comparison group completed mailed surveys. Participants included 103 mothers with MS, 68 mothers with RA, and 91 well mothers. Mothers answered questions about their sleep, fatigue, pain, and depression. Women with chronic illnesses reported more problems going to sleep than did well women, with pain, depression, or both as significant covariates. Women with chronic illnesses reported that their sleep was interrupted less often by their children than did well women. Sleep quality and quantity were worse for women with RA who were experiencing a flare. Mothers with chronic illnesses experienced more sleep problems, which was associated with their pain and depression.
PMID: 21722010 [PubMed - in process]

Activation of P38 MAPK in CD4 T cells controls IL-17 production and autoimmune encephalomyelitis.
Department of Medicine, Immunobiology Program, University of Vermont, Burlington, VT, United States; Although several transcription factors have been shown to be critical for the induction and maintenance of IL-17 expression by CD4 T helper cells, less is known about the role of non-transcriptional mechanisms. Here we show that the p38 MAP kinase (MAPK) signaling pathway is essential for in vitro and in vivo IL-17 production by regulating IL-17 synthesis in CD4 T cells through the activation of the eIF-4E/MNK pathway. We also show that p38 MAPK activation is required for the development and progression of both chronic and relapsing-remitting forms of experimental allergic encephalomyelitis (EAE), the principal autoimmune model of multiple sclerosis. Furthermore, we show that regulation of p38 MAPK activity specifically in T cells is sufficient to modulate EAE severity. Thus, mechanisms other than the regulation of gene expression also contribute to Th17 cell effector functions and, potentially, to the pathogenesis of other Th17 cell mediated diseases.
PMID: 21791428 [PubMed - as supplied by publisher]
**ABSTRACT:** BACKGROUND: There is evidence that at least 5% of Multiple Sclerosis (MS) cases manifest in childhood. Children with MS present with a demyelinating episode involving single or multiple symptoms prior to developing a second event (usually within two years) to then meet criteria for diagnosis. There is evidence from adult cohorts that the incidence and sex ratios of MS are changing and that children of immigrants have a higher risk for developing MS. A paediatric population should reflect the vanguard of such changes and may reflect trends yet to be observed in adult cohorts. Studying a paediatric population from the first demyelinating event will allow us to test these hypotheses, and may offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS. METHODS: The Paediatric UK Demyelinating Disease Longitudinal Study (PUDDLS) is a prospective longitudinal observational study which aims to determine the natural history, predictors and outcomes of childhood CNS inflammatory demyelinating diseases. PUDDLS will involve centres in the UK, and will establish a cohort of children affected with a first CNS inflammatory demyelinating event for long-term follow up by recruiting for approximately 5 years. PUDDLS will also establish a biological sample archive (CSF, serum, and DNA), allowing future hypothesis driven research. For example, the future discovery of a biomarker will allow validation within this dataset for the evaluation of novel biomarkers. Patients will also be requested to consent to be contacted in the future. A secondary aim is to collaborate internationally with the International Paediatric Multiple Sclerosis Group when future collaborative studies are proposed, whilst sharing a minimal anonymised dataset. PUDDLS is the second of two jointly funded studies. The first (UCID-SS) is an epidemiological surveillance study that already received ethical approvals, and started on the 1st September 2009. There is no direct patient involvement, and UCID-SS aims to determine the UK and Ireland incidence of CNS demyelinating disorders in children under 16 years. DISCUSSION: A paediatric population should reflect the vanguard of MS epidemiological changes and may reflect trends yet to be observed in adult MS cohorts. The restricted window between clinical expression of disease and exposure to environmental factors in children offers a unique research opportunity. Studying a paediatric population from the first demyelinating event will allow us to investigate the changing epidemiology of MS, and may offer further valuable insights into the genetic and environmental interactions in the pathogenesis of MS. 

PMID: 21798048 [PubMed - as supplied by publisher]

**ABSTRACT:** BACKGROUND: The relapsing-remitting dynamics is a hallmark of autoimmune diseases such as Multiple Sclerosis (MS). Although current understanding of both cellular and molecular mechanisms involved in the pathogenesis of autoimmune diseases is significant, how their activity generates this prototypical dynamics is not understood yet. In order to gain insight about the mechanisms that drive these relapsing-remitting dynamics, we developed a computational model using such biological knowledge. We hypothesized that the relapsing dynamics in autoimmunity can arise through the failure in the mechanisms controlling cross-regulation between regulatory and effector T cells with the interplay of stochastic events (e.g. failure in central tolerance, activation by pathogens) that are able to trigger the immune system. RESULTS: The model represents five concepts: central tolerance (T-cell generation by the thymus), T-cell activation, T-cell memory, cross-regulation (negative feedback) between regulatory and effector T-cells and tissue damage. We enriched the model with reversible and irreversible tissue damage, which aims to provide a comprehensible link between autoimmune activity and clinical relapses and active lesions in the magnetic resonances studies in patients with Multiple Sclerosis. Our analysis shows that the weakness in this negative feedback between effector and regulatory T-cells, allows the immune system to generate the characteristic relapsing-remitting dynamics of autoimmune diseases, without the need of additional environmental triggers. The simulations show that the timing at which relapses appear is highly unpredictable. We also introduced targeted perturbations into the model that mimicked immunotherapies that modulate effector and regulatory populations. The effects of such therapies happened to be highly dependent on the timing and/or dose, and on the underlying dynamic of the immune system. CONCLUSION: The relapsing dynamic in MS derives from the emergent properties of the immune system operating in a pathological state, a fact that has implications for predicting disease course and developing new therapies for MS. 

PMID: 21762505 [PubMed - as supplied by publisher]
Risk factors for progressive axonal degeneration of the retinal nerve fibre layer in multiple sclerosis patients.
Aim To quantify structural and functional degeneration in the retinal nerve fibre layer (RNFL) of patients with multiple sclerosis (MS) over a 2-year time period, and to analyse the effect of prior optic neuritis (ON) as well as the duration and incidence of MS relapses. Methods 166 MS patients and 120 healthy controls underwent assessment of visual acuity and colour vision, visual field examination, optical coherence tomography, scanning laser polarimetry and visual evoked potentials (VEPs). All subjects were re-evaluated after a period of 12 and 24 months. Results Changes in the optic nerve were detected by structural measurements but not by functional assessments. Changes registered in MS patients were greater than changes in healthy controls (p<0.05). Eyes with previous ON showed a greater reduction of parameters in the baseline evaluation, but RNFL atrophy was not significantly greater in the longitudinal study. Patients with MS relapses showed a greater reduction of RNFL thickness and VEP amplitude compared with non-relapsing cases. Patients with and without treatment showed similar measurement reduction, but the non-treated group had a significantly higher increase in Expanded Disability Status Scale (p=0.029). Conclusions MS causes progressive axonal loss in the optic nerve, regardless of a history of ON. This ganglion cell atrophy occurs in all eyes but is more marked in MS eyes than in healthy eyes.
PMID: 21785155 [PubMed - as supplied by publisher]

Oral fingolimod rescues the functional deficits of synapses in experimental autoimmune encephalomyelitis.
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Background and purpose. Alterations of glutamate-mediated synaptic transmission occur early during neuroinflammatory insults, and lead to degenerative neuronal damage in multiple sclerosis (MS) and in experimental autoimmune encephalomyelitis (EAE), which models MS in mice. Fingolimod is an effective orally active agent for the treatment of MS, able to interfere with lymphocyte invasion of the brain. It is still unclear if fingolimod can be neuroprotective in this disorder. Experimental approach. By means of neurophysiological recordings and morphological evaluation of dendritic integrity, here we explored if the beneficial effects of oral fingolimod on the clinical score of EAE mice were associated with some degree of synaptic transmission preservation. Key results. Oral fingolimod was able to prevent and to reverse the pre- and post-synaptic alterations of glutamate transmission occurring in EAE mice. This effect was associated with a dramatic amelioration of the clinical deficits of EAE mice, and with a significant inhibition of neuronal dendritic pathology also accompanying EAE. Fingolimod did not alter per se spontaneous excitatory postsynaptic currents in control animals, indicating that only the pathological process behind inflammation-induced glutamate transmission defect is modulated by this compound. Conclusions and implications. The effects of fingolimod on the clinical, synaptic and dendritic abnormalities of EAE might represent a possible correlate of the neuroprotective action of this agent in MS.
PMID: 21740406 [PubMed - as supplied by publisher]
The MAO inhibitor phenelzine improves functional outcomes in mice with experimental autoimmune encephalomyelitis (EAE).
Musgrave T, Benson C, Wong G, Browne I, Tenorio G, Rauw G, Baker GB, Kerr BJ. Centre for Neuroscience, University of Alberta, Edmonton, AB, Canada; Department of Anesthesiology and Pain Medicine, University of Alberta, Edmonton, AB, Canada.

Multiple sclerosis (MS) and the animal model, experimental autoimmune encephalomyelitis (EAE), are both accompanied by motor and non-motor symptoms. Pathological changes in the activities of key neurotransmitters likely underlie many of these symptoms. We have previously described disturbances in the levels of 5-hydroxytryptamine (5-HT/serotonin), noradrenaline (NE) and γ-aminobutyric acid (GABA) in a mouse model of EAE. The potential therapeutic effect of a drug that targets these three neurotransmitters, the antidepressant and anti-panic drug phenelzine (PLZ), was assessed in mice with MOG(35-55) induced EAE. The neurotransmitter content of EAE and control tissue after PLZ administration was first evaluated by HPLC. The ability of PLZ treatment to modulate EAE disease course and clinical signs was then assessed. Daily PLZ treatment, starting seven days after disease induction, delayed EAE onset, reduced disease severity in the chronic phase and was associated with substantial improvements in exploratory behavior and a novel measure of sickness and/or depression. Upon completion of the experiment, PLZ's effects on histopathological markers of the disease were examined. No differences were observed in T cell infiltration, microglia/macrophage reactivity, demyelination or axonal injury in PLZ-treated spinal cords. However, EAE mice treated with PLZ showed a normalization of 5-HT levels in the ventral horn of the spinal cord that might account for the improvements in behavioral outcomes. These results demonstrate the therapeutic potential of MAO inhibitors such as PLZ in MS. Additionally, the behavioral changes observed in EAE mice indicate that alterations in non-motor or ‘affective’ measures may be valuable to consider in addition to traditional measures of gross locomotor function.
PMID: 21723939 [PubMed - as supplied by publisher]

Distinct spatio-temporal extracellular matrix accumulation within demyelinated spinal cord lesions in Thelier's murine encephalomyelitis.
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Accumulation of extracellular matrix (ECM) and glial scar formation are considered important factors for the failure of regeneration in CNS injury and multiple sclerosis. Thelier’s murine encephalomyelitis (TME) as a model of multiple sclerosis served to evaluate the spatio-temporal course of ECM alterations in demyelinating conditions. Microarray analysis revealed only mildly up-regulated gene expression of ECM molecules, their biosynthesis pathways, and pro-fibrotic factors, while up-regulation of matrix remodeling enzymes was more prominent. Immunohistochemistry demonstrated progressive accumulation of chondroitin sulfate proteoglycans, glycoproteins and collagens within demyelinated TME lesions, paralleling the development of astrogliosis. Deposition of collagen IV, laminin, perlecan and tenascin-C started 28 days post infection (dpi), collagen I, decorin, entactin and neurocan accumulated from 56 dpi on, and fibronectin from 98 dpi on. The basement membrane (BM) molecules collagen IV, entactin, fibronectin, laminin and perlecan showed perivascular and parenchymal deposition, while the non-BM components collagen I, decorin, neurocan and tenascin-C only accumulated in a non-vascular pattern in demyelinated areas. Contrary, phosphacan expression progressively decreased during TME. The immunoreactivity of aggrecan and brevican remained unchanged. The spatio-temporal association of matrix accumulation with astrogliosis suggests a mainly astrocytic origin of ECM deposits, which in turn may contribute to remyelination failure in TME.
PMID: 21767322 [PubMed - as supplied by publisher]
Intercellular interactomics of human brain endothelial cells and th17 lymphocytes: a novel strategy for identifying therapeutic targets of CNS inflammation.
Haqqani AS, Stanimirovic DB.
Institute for Biological Sciences, National Research Council, Ottawa, ON, Canada K1A 0R6.
Leukocyte infiltration across an activated brain endothelium contributes to the neuroinflammation seen in many neurological disorders. Recent evidence shows that IL-17-producing T-lymphocytes (e.g., Th17 cells) possess brain-homing capability and contribute to the pathogenesis of multiple sclerosis and cerebral ischemia. The leukocyte transmigration across the endothelium is a highly regulated, multistep process involving intercellular communications and interactions between the leukocytes and endothelial cells. The molecules involved in the process are attractive therapeutic targets for inhibiting leukocyte brain migration. We hypothesized and have been successful in demonstrating that molecules of potential therapeutic significance involved in Th17-brain endothelial cell (BEC) communications and interactions can be discovered through the combination of advanced membrane/submembrane proteomic and interactomic methods. We describe elements of this strategy and preliminary results obtained in method and approach development. The Th17-BEC interaction network provides new insights into the complexity of the transmigration process mediated by well-organized, subcellularly localized molecular interactions. These molecules and interactions are potential diagnostic, therapeutic, or theranostic targets for treatment of neurological conditions accompanied or caused by leukocyte infiltration.
PMCID: PMC3130966 PMID: 21755032 [PubMed]

Acute demyelinating disease after oral therapy with herbal extracts.
Kostianovsky A, Maskin P, Noriega MM, Soler C, Bonelli I, Riley CS, O'Connor KC, Saubidet CN, Alvarez PA.
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Central nervous system demyelinating processes such as multiple sclerosis and acute disseminated encephalomyelitis constitute a group of diseases not completely understood in their physiopathology. Environmental and toxic insults are thought to play a role in priming autoimmunity. The aim of the present report is to describe a case of acute demyelinating disease with fatal outcome occurring 15 days after oral exposure to herbal extracts.
PMCID: PMC3130893 PMID: 21738505 [PubMed]

The effect of ankle foot orthosis stiffness on the energy cost of walking: A simulation study.
Bregman DJ, van der Krogt MM, de Groot V, Harlaar J, Wisse M, Collins SH.
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BACKGROUND: In stroke and multiple sclerosis patients, gait is frequently hampered by a reduced ability to push-off with the ankle caused by weakness of the plantar-flexor muscles. To enhance ankle push-off and to decrease the high energy cost of walking, spring-like carbon-composite Ankle Foot Orthoses are frequently prescribed. However, it is unknown what Ankle Foot Orthoses stiffness should be used to obtain the most efficient gait. The aim of this simulation study was to gain insights into the effect of variation in Ankle Foot Orthosis stiffness on the amount of energy stored in the Ankle Foot Orthosis and the energy cost of walking.
METHODS: We developed a two-dimensional forward-dynamic walking model with a passive spring at the ankle representing the Ankle Foot Orthosis and two constant torques at the hip for propulsion. We varied Ankle Foot Orthosis stiffness while keeping speed and step length constant. FINDINGS: We found an optimal stiffness, at which the energy delivered at the hip joint was minimal. Energy cost decreased with increasing energy storage in the ankle foot orthosis, but the most efficient gait did not occur with maximal energy storage. With maximum storage, push-off occurred too late to reduce the impact of the contralateral leg with the floor. Maximum return prior to foot strike was also suboptimal, as push-off occurred too early and its effects were subsequently counteracted by gravity. The optimal Ankle Foot Orthosis stiffness resulted in significant push-off timed just prior to foot strike and led to greater ankle plantar-flexion velocity just before contralateral foot strike. INTERPRETATION: Our results suggest that patient energy cost might be reduced by the proper choice of Ankle Foot Orthosis stiffness.
PMID: 21723012 [PubMed - as supplied by publisher]
Proteinuria with fumaric acid ester treatment for psoriasis. 
Ogilvie S, Lewis Jones S, Dawe R, Foerster J. 
Departments of Dermatology Photobiology Division of Medical Sciences, Ninewells Hospital, Dundee, UK. 
Fumaric acid esters (FAE) have been used in the treatment of psoriasis for many years. In general, they are regarded as relatively safe compared with other antipsoriatic systemic treatments, with the most notable adverse effects being gastrointestinal upset, lymphopenia and transient flushing. Renal toxicity has only rarely been reported, and was not found in two independent prospective trials nor in a large retrospective evaluation of almost 1000 patients treated for a median of 44 months. We report three patients developing reversible proteinuria during FAE treatment. One of these displayed the same pattern upon repeated drug administration, thereby clearly indicating FAE treatment to be the causal trigger. The presented cases highlight proteinuria as a clinical concern in FAE treatment. Furthermore, as the novel FAE agent dimethylfumaric (DMF) ester (contained in BG00012/Panacler) has previously been shown to be effective in psoriasis in a phase III trial and not shown renal toxicity in a large trial for multiple sclerosis, the current report suggests that market introduction of DMF for psoriasis should be pursued. 
PMID: 21771009 [PubMed - in process]

Shams K, Grindlay DJ, Williams HC. 
Alan Lyell Centre for Dermatology, Southern General Hospital, Glasgow, UK NHS Evidence Skin Disorders, Centre for Evidence Based Dermatology, University of Nottingham, Nottingham, UK. 
This review provides a summary of key findings from 18 systematic reviews on atopic eczema, published or indexed between January 2009 and 24 August 2010. There was no good evidence on the possible benefit of organic food consumption and eczema. Maternal intake of fish or fish oil may be associated with a reduced risk of eczema in offspring, although further studies are needed. There is some evidence that partially hydrolysed infant formulas rather than standard formulas may be associated with a reduced risk of eczema in infants, but there are shortcomings in the existing evidence. An inverse relationship has been found between gliomas/acute lymphoblastic leukaemia and allergic disease/eczema, but there appears to be no association between multiple sclerosis and eczema. Attention deficit hyperactivity disorder does appear to be associated with eczema, but there is no evidence of a causal link. The risk of eczema seems to be increased in urban compared with rural areas. Some new evidence has suggested superiority of 1% pimecrolimus over potent and mild corticosteroids at 6 months but not 12 months, and there is some evidence for superiority of 0.03% and 0.1% tacrolimus over 1% pimecrolimus. An updated Cochrane Review still found no evidence of a benefit from any form of antistaphylococcal treatment in managing clinically infected or uninfected eczema. The evidence base is poor for bath emollients, occlusive treatments (e.g. wet and dry wraps) and woven silk clothing in treating eczema. In general, the methods used in most systematic reviews of eczema need to be reported more clearly, especially with regard to a more vigorous quality assessment of included studies. Included studies are frequently heterogeneous, proxy reporting is common, and appropriate disease definitions are often lacking. Better adherence to existing guidance on trial reporting and prospective registration of clinical trials may help improve the quality of studies. 
PMID: 21718344 [PubMed - in process]

Dalfampridine in multiple sclerosis: From symptomatic treatment to immunomodulation. 
Espejo C, Montalban X. 
Multiple sclerosis (MS) is a neurodegenerative disease that is deemed to affect more than 2.1 million people worldwide, and for which there is no cure. Early symptoms of MS are believed to result from axonal demyelination leading to slowing or blockade of impulse conduction. The blockade of K+ channels has been proven to improve conduction deficiencies secondary to demyelination in patients with MS. Dalfampridine is a K+ channel blocker that was recently approved by FDA for the symptomatic treatment of ambulation hardship in MS. Understanding the mechanisms by which Dalfampridine exerts its therapeutic effects is a complex issue as it blocks a wide variety of K+ channels that are distributed across multiple cell types in the nervous system but also in the immune system, and because of their molecular identities remaining unknown. This review describes Dalfampridine potential roles at the cellular and molecular levels in MS pathogenesis. 
PMID: 21742559 [PubMed - as supplied by publisher]
Cladribine as a therapeutic option in multiple sclerosis.
Warnke C, Leussink VI, Goebels N, Aktas O, Boyko A, Kieseier BC, Hartung HP.
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There is an unmet need for more potent and convenient drugs in the treatment of patients diagnosed with multiple sclerosis (MS). Among five currently investigated oral drugs with an ongoing or completed phase III program, promising efficacy data for oral cladribine have recently been published. However, benefits need to be weighed against potential risks to define the role of this compound within current treatment regimens. Here we review present data on efficacy of oral cladribine and discuss known and anticipated risks of this drug.
PMID: 21733757  [PubMed - as supplied by publisher]

Combined evoked potentials as markers and predictors of disability in early multiple sclerosis.
Schlaeger R, D'Souza M, Schindler C, Grize L, Kappos L, Fuhr P.
Department of Neurology, University Hospital Basel, Switzerland.
OBJECTIVE: To prospectively assess combined evoked potentials (EP) as markers and predictors of the disease course of early MS over 3years. METHODS: Fifty patients in the early phase of relapsing remitting MS prospectively received visual, somatosensory and motor EP and EDSS assessments at baseline (T1) and at 6months intervals during 3years. Spearman rank correlation was used to determine the relationship between z-transformed EP-latencies (z-EPL) and EDSS. Multivariable linear regression was performed to predict EDSS at year 3 (T7) in function of z-EPL(T1). Validity of the models was assessed using group cross-validation. RESULTS: At each of the seven points in time, EDSS correlated with the sum of z-EPL (0.64 ≤ ρ ≤ 0.79, p<0.001). The change of the sum of z-EPL(T7-T1) correlated with the change of EDSS(T7-T1) (ρ=0.51, p=0.001). EDSS(T7) as predicted by the sum of z-scores of EP latencies or by the number of pathological EP results at baseline correlated with the observed clinical values after 3years (ρ>0.70, p<0.001, for both measures). CONCLUSIONS: Multimodal EPs correlate well with clinical disability in cross-sectional and longitudinal comparison in early MS and allow prediction of disease evolution over 3years. SIGNIFICANCE: EPs seem well suited as markers of the disease course in early MS in clinical trials and bear potential for supporting decision-finding in individual patients.
PMID: 21778106  [PubMed - as supplied by publisher]
Scott LJ.

Oral fingolimod (Gilenya™), a sphingosine 1-phosphate (S1P) receptor agonist, is the first oral agent and the first in a novel class of disease-modifying therapies (DMTs) to be approved for use in the US for the treatment of relapsing forms of multiple sclerosis (MS). In the EU, fingolimod is approved for use as a single-agent DMT in selected patients with highly-active, relapsing-remitting (RR) MS. This article reviews the pharmacological properties and clinical use of the drug in patients with RRMS. Fingolimod is rapidly converted in vivo to the active moiety S-fingolimod-phosphate, which binds with high affinity to S1P receptors, thereby sequestering lymphocytes in the lymph nodes and preventing their egress into the peripheral circulation. As a consequence, there is a reduction in the infiltration of autoaggressive lymphocytes into the CNS. Fingolimod-phosphate also acts as a functional antagonist, as its binding to S1P receptors results in their internalization and degradation, thereby downregulating S1P receptors on the lymphocyte cell surface. Since fingolimod crosses the blood-brain barrier, it also potentially acts at S1P receptors on neural cells in the CNS to mitigate neuropathological processes associated with MS. In large multinational trials in adult patients with RRMS, oral fingolimod 0.5 mg/day was more effective than oral placebo (FREEDOMS) and recommended dosages of intramuscular interferon-β (IFNβ)-1a (TRANSFORMS) in reducing the annualized relapse rate and was also generally more effective at slowing progression of neurological disability and at reducing the burden and activity of disease. Fingolimod was generally well tolerated in these trials of up to 2 years’ duration, with most adverse events being manageable and of mild to moderate severity; there were two deaths from opportunistic infections, albeit these occurred with fingolimod 1.25 mg/day (higher than the recommended dosage). Limited long-term data indicated that no new safety concerns had arisen after 5 years of fingolimod treatment. However, further clinical experience is required to fully determine the long-term safety profile of fingolimod, particularly with regard to any potentially serious or life-threatening adverse events. In the absence of robust pharmacoeconomic studies and of head-to-head trials comparing fingolimod with other formulations of IFNβ and glatiramer acetate, the relative position of fingolimod with respect to other DMTs remains to be fully determined. In the meantime, given its convenient once-daily oral treatment regimen and better efficacy than intramuscular IFNβ-1a, fingolimod is a valuable emerging option for the treatment of adult patients with relapsing forms of MS.

PMID: 21790210 [PubMed - in process]

Fingolimod for Multiple Sclerosis: Mechanism of Action, Clinical Outcomes, and Future Directions.
Mehling M, Kappos L, Derfuss T.
Department of Neurology and Department of Biomedicine, University Hospital Basel, Petersgraben 4, CH-4031, Basel, Switzerland.
The oral sphingosine 1-phosphate receptor (S1PR) modulator fingolimod functionally antagonizes S1PR hereby blocking lymphocyte egress from secondary lymphoid organs to the peripheral blood circulation. This results in a reduction in peripheral lymphocyte counts, including potentially encephalitogenic T cells. In patients with relapsing multiple sclerosis fingolimod has been shown to be an effective treatment. In phase 2 and phase 3 studies fingolimod-treated patients had reduced disease activity clinically and in MRI. Although severe infectious complications occurred in single cases treated with fingolimod, the frequency of overall infections was comparable in fingolimod-treated patients and controls. Overall, in clinical studies fingolimod was well tolerated and had a favorable safety profile. In follow-up studies with continuous fingolimod, treatment showed sustained efficacy while being well tolerated.

PMID: 21789537 [PubMed - as supplied by publisher]
Gait Abnormalities in Multiple Sclerosis: Pathogenesis, Evaluation, and Advances in Treatment.
Cameron MH, Wagner JM.
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Multiple sclerosis (MS) is a demyelinating disease of the central nervous system characterized by episodic decline in various neurologic functions. Gait dysfunction in MS is distinguished by decreased gait speed, walking endurance, step length, cadence and joint motion, as well as increased metabolic cost of walking and increased variability of gait. Standardized clinical, timed, and patient-based measures can identify MS patients with gait dysfunction, and observational gait analysis, instrumented walkways, or three-dimensional gait analysis can help determine which problem underlies their gait dysfunction to help direct effective treatment. Exercise may ameliorate all types of gait dysfunction. In addition, gait dysfunction due to weakness may be alleviated by orthoses or functional electrical stimulation; gait dysfunction due to spasticity may be relieved by oral, intrathecal, or intramuscular medications. Assistive devices and balance training may reduce gait dysfunction from imbalance, and dalfampridine may accelerate gait in people with MS who walk slowly.
PMID: 21779953 [PubMed - as supplied by publisher]

The Radiologically Isolated Syndrome: Look (Again) Before You Treat.
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The advent and wide use of magnetic resonance brain imaging has led to the unexpected detection of lesions that appear typical of multiple sclerosis (MS) in otherwise asymptomatic patients. Several cohorts of patients with the "radiologically isolated syndrome (RIS)" have been studied mainly retrospectively, and a proportion of them do go on to have clinical symptoms of MS. This has led to the not infrequent clinical conundrum of whether or not to treat patients with MRI lesions suggestive of MS, given the knowledge that MS disease-modifying therapies work best when given early in the disease course. However, the decision to proactively treat patients with RIS is countered by the increasing risks associated with MS disease-modifying therapies as well as the uncertain prognostic outcome of RIS. This review will highlight what is and is not known about the long-term outcomes of RIS and present recommendations for clinicians when faced with this challenging situation.
PMID: 21748263 [PubMed - as supplied by publisher]

Inflammasome activation in obesity-related inflammatory diseases and autoimmunity.
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The inflammasome is a highly regulated protein complex that triggers caspase-1 activation and subsequent secretion of IL-1β and IL-18. Recognition of microbial components and danger signals by NOD-like receptor (NLR) family members in the cytosol promotes inflammasome activation and downstream inflammatory cytokine production. Pathogen recognition by NLRs and downstream release of inflammasome-derived cytokines are important in host defense against numerous infections. Recent studies have also identified a unique role for inflammasome regulation in the induction and pathogenesis of multiple autoimmune and inflammatory disorders. We now know that obesity-related factors and endogenous markers of cellular stress can lead to unchecked activation of the inflammasome and provoke inflammation and subsequent destruction of vital organs. This review will highlight recent findings that link inflammasome signaling to the progression of autoinflammatory and autoimmune diseases. We will focus on the contribution of inflammasome activation to the pathogenesis of autoinflammatory and autoimmune diseases that are of major significance to human health including type 2 diabetes, atherosclerosis, multiple sclerosis, and type 1 diabetes.
PMID: 21794210 [PubMed - in process]

**Five-day regimen of intramuscular or subcutaneous self-administered adrenocorticotropic hormone gel for acute exacerbations of multiple sclerosis: a prospective, randomized, open-label pilot trial.**

Simsarian JP, Saunders C, Smith DM.

Neurology Center of Fairfax Ltd, Fairfax, VA, USA.

**BACKGROUND:** Despite over 50 years of experience with adrenocorticotropic hormone (ACTH) as a treatment for acute exacerbations of multiple sclerosis, there have been no trials examining the options of the 2-3-week dosing regimen or intramuscular injection protocol used in the original trials. At our clinic, we performed a small, prospective, randomized pilot study to examine the efficacy and safety of, and patient satisfaction with, a short (five-day) self-administered ACTH dosing protocol for exacerbations of multiple sclerosis, and to compare the subcutaneous and intramuscular routes of administration.

**METHODS:** Patients for this study were recruited from an outpatient treatment clinic. Each patient self-administered natural ACTH gel 80 U/day by subcutaneous or intramuscular injection for five consecutive days and was evaluated at baseline and on days 7 and 14. Patient feedback was collected using the Patient Global Impression of Change (PGI-C, the primary efficacy measure), a patient global visual analog scale, the Expanded Disability Status Scale, a timed walk, the Nine-hole Peg Test, and the Clinical Global Impression of Change.

**RESULTS:** Of the 20 enrolled patients (mean age 39.5 years), 19 completed the study. On day 14, 61.1% of patients (11 of 18 with day 14 scores) were treatment responders, and rated their condition as "very much improved" or "much improved" on the PGI-C. The intramuscular group had numerically more responders, but there was no significant difference in the proportion of responders between the intramuscular and subcutaneous groups at day 14 (P = 0.3). The intramuscular route of injection was associated with more injection site pain than the subcutaneous route.

**CONCLUSION:** A shorter five-day course of intramuscular or subcutaneous ACTH gel may improve symptoms associated with acute exacerbations of multiple sclerosis. Larger studies with standard of care controls are needed to confirm whether this shorter course of intramuscular or subcutaneous ACTH gel is effective and could potentially be substituted for the standard 14-day treatment.

PMCID: PMC3140290 PMID: 21792296 [PubMed - in process]

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**An estimate of the global reduction in mortality rates through doubling vitamin D levels.**

Grant WB.

Sunlight, Nutrition, and Health Research Center, San Francisco, CA, USA.

**Background/Objectives:** The goal of this work is to estimate the reduction in mortality rates for six geopolitical regions of the world under the assumption that serum 25-hydroxyvitamin D (25(OH)D) levels increase from 54 to 110 nmol/l. Subjects/Methods: This study is based on interpretation of the journal literature relating to the effects of solar ultraviolet-B (UVB) and vitamin D in reducing the risk of disease and estimates of the serum 25(OH)D level-disease risk relations for cancer, cardiovascular disease (CVD) and respiratory infections. The vitamin D-sensitive diseases that account for more than half of global mortality rates are CVD, cancer, respiratory infections, respiratory diseases, tuberculosis and diabetes mellitus. Additional vitamin D-sensitive diseases and conditions that account for 2 to 3% of global mortality rates are Alzheimer's disease, falls, meningitis, Parkinson's disease, maternal sepsis, maternal hypertension (pre-eclampsia) and multiple sclerosis. Increasing serum 25(OH)D levels from 54 to 110 nmol/l would reduce the vitamin D-sensitive disease mortality rate by an estimated 20%. Results: The reduction in all-cause mortality rates range from 7.6% for African females to 17.3% for European females. Reductions for males average 0.6% lower than for females. The estimated increase in life expectancy is 2 years for all six regions. Conclusions: Increasing serum 25(OH)D levels is the most cost-effective way to reduce global mortality rates, as the cost of vitamin D is very low and there are few adverse effects from oral intake and/or frequent moderate UVB irradiance with sufficient body surface area exposed.

European Journal of Clinical Nutrition advance online publication, 6 July 2011; doi:10.1038/ejcn.2011.68.

PMID: 21731036 [PubMed - as supplied by publisher]

Anti-aquaporin-4 antibodies in the context of assorted immune-mediated diseases.

Dellavance A, Alvarenga RR, Rodrigues SH, Kok F, de Souza AW, Andrade LE.

Research and Development Division, Fleury Group Rheumatology Division, Universidade Federal de São Paulo - UNIFESP Neurology Department, Universidade de São Paulo - USP, São Paulo, SP, Brasil.

Background and purposes: Anti-aquaporin 4 antibodies are specific markers for Devic's disease. This study aimed to test if this high specificity holds in the context of a large spectrum of systemic autoimmune and non-autoimmune diseases. Methods: Anti-aquaporin-4 antibodies (NMO-IgG) were determined by indirect immunofluorescence (IIF) on mouse cerebellum in 673 samples, as follows: group I (clinically defined Devic's disease, n = 47); group II [inflammatory/demyelinating central nervous system (CNS) diseases, n = 41]; group III (systemic and organ-specific autoimmune diseases, n = 250); group IV (chronic or acute viral diseases, n = 35); and group V (randomly selected samples from a general clinical laboratory, n = 300).

Results: NMO-IgG was present in 40/47 patients with classic Devic's disease (85.1% sensitivity) and in 13/22 (59.1%) patients with disorders related to Devic's disease. The latter 13 positive samples had diagnosis of longitudinally extensive transverse myelitis (n = 10) and isolated idiopathic optic neuritis (n = 3). One patient with multiple sclerosis and none of the remaining 602 samples with autoimmune and miscellaneous diseases presented NMO-IgG (99.8% specificity).

Conclusions: The available data clearly point to the high specificity of anti-aquaporin-4 antibodies for Devic's disease and related syndromes also in the context of miscellaneous non-neurologic autoimmune and non-autoimmune disorders.

PMID: 21771203 [PubMed - as supplied by publisher]


Serum and CSF PDGF-AA and FGF-2 in relapsing-remitting multiple sclerosis: a case-control study.


Department of Neurology, Imam Khomeini Hospital, Iranian Centre of Neurological Research, Tehran University of Medical Sciences, Tehran Department of Neurology, Sina Hospital, Tehran University of Medical Sciences, Tehran Department of biology, Faculty of science, University of Tarbiat Moallem, Tehran, Iran.

Background and purpose: Fibroblast growth factor-2 (FGF-2) and platelet-derived growth factor-A (PDGF-AA) are potent modulators of oligodendrocytes, the main responsible cells for myelin regeneration. We measured FGF-2 and PDGF-AA in the sera and cerebrospinal fluid (CSF) of patients with relapsing-remitting multiple sclerosis (RR-MS) and compared these values with control subjects. Methods: Twenty-three patients with RR-MS and 23 subjects without inflammatory and demyelinating diseases were included. Serum samples of the patients were collected in both relapse and remission phases and were analyzed with ELISA method. CSF was drawn during the relapse period. Blood and CSF were drawn from control subjects for comparison. Wilcoxon and Mann-Whitney U-test and Spearman's rank correlation were used for analysis. P values of <0.05 were considered significant. Results: Age and sex distribution were similar in both groups. Serum values of FGF-2 were higher in relapse phase compared with remission phase, with a trend toward significance (P = 0.052). CSF PDGF-AA showed significant negative correlation with disease duration (correlation coefficient = -0.58, P = 0.004). Serum levels of PDGF did not differ between two phases significantly. There was no difference in serum and CSF values of these factors between patients and controls. When we compared patients with prolonged disease with controls, a significant difference between the CSF levels of PDGF-AA was observed (mean ± SEM 2.78 ± 0.8 in controls vs. 0.55 ± 0.29 in patients with MS ≥ 2 years, P < 0.05). Conclusion: Our study was the first to show that CSF PDGF-AA is related to disease duration. Supporting previous findings we showed that serum and CSF levels of these factors are weak indicators of disease severity.

PMID: 21771201 [PubMed - as supplied by publisher]
Weekly IM interferon beta-1a in multiple sclerosis patients over 50 years of age.
Lamp C, You X, Limmroth V.
Department of Neurology and Pain Medicine, Kovinhospital Barmherzige Brüder Linz, Linz, Austria Biogen Idec Inc., Weston, MA, USA Cologne City Hospitals, University of Cologne, Germany.

Background: Efficacy and safety data have not previously been compiled for intramuscular interferon beta-1a (IM IFNβ-1a) in patients with multiple sclerosis (MS) ≥ 50 years of age. We investigated the efficacy and safety of IM IFNβ-1a in patients segregated by 50 and 40 years of age in separate meta-analyses. Methods: The MS Clinical Research Group Study, the Controlled High-Risk Subjects AVONEX® (IM IFNβ-1a) MS Prevention Study, the IFNβ-1a European Dose-Comparison Study, and a multicenter, open-label antigenicity and safety study of human serum albumin-free IM IFNβ-1a were analyzed. Results: Overall, 906 patients (68 aged ≥ 50 years and 838 aged <50 years, or 323 aged ≥ 40 years and 583 aged <40 years) received IM IFNβ-1a for ≥ 24 months. At baseline, patients ≥ 50 years had significantly higher Expanded Disability Status Scale scores than patients <50 years (3.4 vs. 2.8; P < 0.001), but fewer relapses in the three preceding years (2.6 vs. 3.4; P < 0.001); patients ≥ 40 years and <40 years exhibited similar differences. After 2 years of treatment, there were no significant differences in annualized relapse rate, sustained disability progression, time to sustained disability progression, or number of MRI-identified gadolinium-enhanced lesions between age groups in either analysis. The cumulative probability of relapse was significantly lower in patients ≥ 40 years versus patients <40 years (0.601 vs. 0.702; P < 0.001). Adverse event incidence did not differ significantly between age groups in either analysis. Conclusions: IM IFNβ-1a is effective and well tolerated in patients with MS ≥ 40 and ≥ 50 years as well as younger patients.

PMID: 21718390 [PubMed - as supplied by publisher]
Multiple sclerosis in familial Mediterranean fever.
Yahalom G, Livneh A.
Department of Neurology, the Chaim Sheba Medical Center, Tel-Hashomer, Israel Department of Medicine F, the Chaim Sheba Medical Center, Tel-Hashomer, Israel Tel Aviv University, Tel-Aviv, Israel.
PMID: 21749569 [PubMed - in process]

Is there any association between multiple sclerosis and familial Mediterranean fever?
Zahednasab H, Esmaeili A, Bahreini SA.
Department of Clinical Biochemistry, Faculty of Medical Sciences, University of Tarbiat Modares, Tehran Cell, Molecular & Developmental Division, Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan, Iran.
PMID: 21749568 [PubMed - in process]

Romi F, Helgeland G, Gilhus NE.
Department of Neurology, Haukeland University Hospital, Bergen, Norway.
Heat-shock proteins (HSPs) are antigen-presenting protein-aggregation-preventing chaperones, induced by cellular stress in eukaryotic cells. In this review, we focus on recent HSP advances in neurological disorders. In myasthenia gravis, patients responding to immunosuppressive therapy have reduced serum HSP-71 antibodies. Generalized and ocular myasthenia gravis patients have elevated serum HSP-70 antibodies, indicating common pathogenic mechanisms. In Guillain-Barré syndrome, HSP-70 antibodies are elevated in serum and cerebrospinal fluid, and serum levels are higher than in myasthenia gravis and multiple sclerosis. In multiple sclerosis, serum HSP-27 antibodies are elevated during relapses providing disease activation marker, while α,β-crystallin expression in brain lesions indicates remission phase initiation. In acute stroke, serum HSP-27 antibodies are elevated irrespective of stroke type and duration. In epilepsy, HSP-27 is induced in patients' astrocytes and cerebral blood vessel walls, and α,β-crystallin is expressed in epileptic foci. In neurodegenerative disorders such as Alzheimer dementia and Parkinson's disease, HSPs are upregulated in brain tissue, and α,β-crystallin modulates superoxide dismutase-1 (SOD-1) tissue accumulation in familial amyotrophic lateral sclerosis. HSPs play an important role in antigen-presentation and tolerance development. Antibody-mediated interference with their function alters immune responses causing neuropathology. The role of HSPs in clinical neurology should be the subject of future investigation.
PMID: 21757921 [PubMed - as supplied by publisher]
Efficacy and Safety of OnabotulinumtoxinA in Patients with Urinary Incontinence Due to Neurogenic Detrusor Overactivity: A Randomised, Double-Blind, Placebo-Controlled Trial.
Department of Urology & IBMC, Hospital São João & Universidade Do Porto, Porto, Portugal.
BACKGROUND: Neurogenic detrusor overactivity (NDO) frequently results in urinary incontinence (UI) which impairs quality of life (QOL) and puts the upper urinary tract at risk. OBJECTIVE: To assess the effects of onabotulinumtoxinA (BOTOX®, Allergan, Inc.) on UI, urodynamic variables, and QOL in incontinent patients with NDO. DESIGN, SETTING, AND PARTICIPANTS: This multicentre, randomised, double-blind, placebo-controlled study enrolled patients with multiple sclerosis (MS; n=154) or spinal cord injury (SCI; n=121) with UI due to NDO (≥14 UI episodes per week). INTERVENTION: Patients received 30 intradetrusor injections of onabotulinumtoxinA 200 U (n=92), 300 U (n=91), or placebo (n=92), avoiding the trigone. MEASUREMENTS: Primary end point was change from baseline in UI episodes per week (week 6). Secondary end points included urodynamics (maximum cystometric capacity [MCC], maximum detrusor pressure during first involuntary detrusor contraction [P(detmaxIDC)], and Incontinence Quality of Life [I-QOL] total score. Adverse events (AEs) were assessed. RESULTS AND LIMITATIONS: At baseline, mean UI episodes per week (33.5) were similar across groups. At week 6, onabotulinumtoxinA 200 U and 300 U significantly reduced UI episodes per week (-21.8 and -19.4, respectively) compared with placebo (-13.2; p<0.01); onabotulinumtoxinA benefit was observed by the first posttreatment study visit at week 2. Improvements in MCC, P(detmaxIDC), and I-QOL at week 6 were significantly greater with both onabotulinumtoxinA doses than with placebo (p<0.001). Benefits were observed in both the MS and SCI populations. The median time to patient request for retreatment was the same for both onabotulinumtoxinA doses (42.1 wk) and greater than placebo (13.1 wk; p<0.001). Most frequent AEs were localised urological events (urinary tract infections and urinary retention, which were dose related in patients not using clean intermittent catheterisation [CIC] at baseline). Significant increases in postvoid residual were observed in patients using CIC prior to treatment, and 12%, 30%, and 42% of patients in the placebo, 200-U, and 300-U groups, respectively, initiated CIC posttreatment. CONCLUSIONS: OnabotulinumtoxinA significantly reduced UI and improved urodynamics and QOL in MS and SCI patients with NDO. Both doses were well tolerated with no clinically relevant differences in efficacy or duration of effect between the two doses (http://www.clinicaltrials.gov; NCT00461292). PMID: 21798658 [PubMed - as supplied by publisher]

Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial.
Department of Nursing and Physical Therapy, University of Almeria (UAL), Carretera de Sacramento s/n, 04120 Almeria, Granada, Spain.
Background. Multiple sclerosis (MS) is a chronic demyelinating neurological disease. Several studies have reported that complementary and alternative therapies can have positive effects against pain in these patients. Objective. The objective was to investigate the effectiveness of an Ai-Chi aquatic exercise program against pain and other symptoms in MS patients. Methods. In this randomized controlled trial, 73 MS patients were randomly assigned to an experimental or control group for a 20-week treatment program. The experimental group underwent 40 sessions of Ai-Chi exercise in swimming pool and the control group 40 sessions of abdominal breathing and contraction-relaxation exercises in therapy room. Outcome variables were pain, disability, spasm, depression, fatigue, and autonomy, which were assessed before the intervention and immediately and at 4 and 10 weeks after the last treatment session. Results. The experimental group showed a significant (P < 0.028) and clinically relevant decrease in pain intensity versus baseline, with an immediate posttreatment reduction in median visual analogue scale scores of 50% that was maintained for up to 10 weeks. Significant improvements were also observed in spasm, fatigue, disability, and autonomy. Conclusion. According to these findings, an Ai-Chi aquatic exercise program improves pain, spasms, disability, fatigue, depression, and autonomy in MS patients. PMCID: PMC3138085 PMID: 21785645 [PubMed - in process]
68. Exp Brain Res. 2011 Jul 20. [Epub ahead of print]

**Trunk sway in mildly disabled multiple sclerosis patients with and without balance impairment.**

Finding O, Sellner J, Meier N, Allum JH, Vibert D, Lienert C, Mattle HP.

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Multiple sclerosis (MS) causes a broad range of neurological symptoms. Most common is poor balance control. However, knowledge of deficient balance control in mildly affected MS patients who are complaining of balance impairment but have normal clinical balance tests (CBT) is limited. This knowledge might provide insights into the normal and pathophysiological mechanisms underlying stance and gait. We analysed differences in trunk sway between mildly disabled MS patients with and without subjective balance impairment (SBI), all with normal CBT. The sway was measured for a battery of stance and gait balance tests (static and dynamic posturography) and compared to that of age- and sex-matched healthy subjects. Eight of 21 patients (38%) with an Expanded Disability Status Scale of 1.0-3.0 complained of SBI during daily activities. For standing on both legs with eyes closed on a normal and on a foam surface, patients in the no SBI group showed significant differences in the range of trunk roll (lateral) sway angle and velocity, compared to normal persons. Patients in the SBI group had significantly greater lateral sway than the no SBI group, and sway was also greater than normal in the pitch (anterior-posterior) direction. Sway for one-legged stance on foam was also greater in the SBI group compared to the no SBI and normal groups. We found a specific laterally directed impairment of balance in all patients, consistent with a deficit in proprioceptive processing, which was greater in the SBI group than in the no SBI group. This finding most likely explains the subjective symptoms of imbalance in patients with MS with normal CBT.

PMID: 21773798 [PubMed - as supplied by publisher]


**Vascular pathology in multiple sclerosis: mind boosting or myth busting?**

Waschbisch A, Manzel A, Linker RA, Lee DH.

ABSTRACT: The investigation of central nervous system vascular changes in the pathophysiology of multiple sclerosis (MS) is a time-honored concept. Yet, recent reports on changes in venous cerebrospinal outflow, the advent of new magnetic resonance imaging techniques and the investigation of immunomodulatory properties of several vascular mediators on the molecular level have added new excitement to hypotheses centering around vascular pathology as determining factor in the pathophysiology of MS. Here we critically review the concept of chronic cerebrospinal venous insufficiency in MS patients and describe new imaging techniques including perfusion weighted imaging, susceptibility weighted imaging and diffusion weighted imaging which reveal central nervous system hypoperfusion, perivascular iron deposition and diffuse structural changes in the MS brain. On a molecular basis, vascular mediators represent interesting targets connecting vascular pathology with immunomodulation. In summary, the relation of venous changes to the pathophysiology of MS may not be as simple as initially described and it certainly seems awkward to think of the complex disease MS solely as result of a simple venous outflow obstruction. Yet, the investigation of new vascular concepts as one variable in the pathophysiology of the autoimmune attack seems very worthwhile and may add to a better understanding of this devastating disorder.

PMID: 21756314 [PubMed - as supplied by publisher]


**A new electronic device for subcutaneous injection of IFN β-1a.**

Exell S, Verdun E, Driebergen R.


Disease-modifying drugs (DMDs) can provide important benefits for patients with multiple sclerosis (MS), but nonadherence to treatment is associated with an increased risk of relapse. All first-line DMDs used in MS require regular injection, but injection-related problems are common barriers to treatment adherence. Autoinjectors that allow automatic injection at the press of a button have increased the ease and convenience of injection, compared with manual injection. A new electronic autoinjector has recently been introduced for the administration of subcutaneous IFN β-1a. This device is the first electronic autoinjector for use with any MS therapy, and includes several innovative features that may be advantageous to patients. One of these features is an accurate electronic dosing log, which can be viewed by the patient and the healthcare provider. This article discusses this new electronic device in the context of other autoinjectors currently used to self-inject first-line DMDs in MS.

PMID: 21728909 [PubMed - as supplied by publisher]
Adherence to treatment in multiple sclerosis.


OBJECTIVE: To find out if patients with multiple sclerosis adhere to treatment with beta interferons and glatiramer acetate, the percentage of withdrawal and its causes. METHODS: Observational, longitudinal, prospective, national, multicentre study which selected multiple sclerosis patients who attended the hospital pharmacy department to collect their medication. The main variable was the adherence percentage during a year, measured as the relationship between the dose of the dispensed and necessary drug. Treatment withdrawals and their causes were then measured. RESULTS: Over a six-month period, 543 patients from 39 pharmacy departments were included. The average time exposed to the drugs during the study period was 312 days and the average adherence in this period was 61.5% (95% CI: 59.4-63.5). Thirty-four (6.26%) of the 543 study participants withdrew treatment, which for most cases was decided by the doctor. CONCLUSIONS: Multiple sclerosis patients' treatment adherence during a period of one year has been lower than the ideal. The causes should therefore be analysed and corrective measures established.

Clinical and laboratory study of pro-inflammatory and antiinflammatory cytokines in women with multiple sclerosis.

Trenova AG, Manova MG, Kostadinova II, Murdjeva MA, Hristova DR, Vasileva TV, Zahariev ZI.

AIM: The aim of the present study was to investigate the serum levels of cytokines TNF-a, IFN-gamma, IL-4 and IL-10 in female patients with MS and healthy individuals, the changes occurring in the relapse and remission phases of the disease and their correlation with the severity of the neurological deficit. PATIENTS AND METHODS: Thirty-five women with relapsing-remitting MS were examined. The patients' age ranged between 18 and 50 years and MS was verified clinically and by magnetic resonance imaging according to the McDonald criteria. Thirteen of the patients were treated with interferon-beta-1b. The serum concentrations of TNF-a, IFN-y, IL-4 and IL-10 were determined twice - in relapse and in remission - using an enzyme-linked immunosorbent assay (ELISA). The control group consisted of 35 age-matched healthy females. RESULTS: The comparison of cytokine serum concentrations during the two phases of the disease showed significant elevation of the TNF-alpha serum levels in the relapse phase and of IL-4 - in the remission phase. The comparison between the patients and the healthy control subjects demonstrated statistically significant lower concentrations of TNF-a in remission patients and higher concentrations of IL-10 in relapse patients. The patients with interferon-beta-1b treatment showed different profile of cytokine secretion from the patients without interferon-beta-1b treatment. Interferon-beta-1b-treated patients showed significantly lower serum levels of TNF-a and IFN-gamma during the relapse phase and higher TNF-a and IL-10 serum levels during the remission phase compared with the untreated patients. CONCLUSIONS: Serum levels of TNF-a and IL-4 objectively reflect the immune response during relapse and remission of the disease. The severity of neurological deficit as estimated with the expanded disability status scale (EDSS) does not depend on the serum levels of TNF-a, IL-10 and IFN-gamma in the two phases of MS.

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PMID: 21797104 [PubMed - in process]

**A cytokine gene screen uncovers SOCS1 as genetic risk factor for multiple sclerosis.**


Cytokine and cytokine receptor genes, including IL2RA, IL7R and IL12A, are known risk factors for multiple sclerosis (MS). Excitotoxic oligodendroglial death mediated by glutamate receptors contributes to demyelinating reactions. In the present study, we screened 368 single-nucleotide polymorphisms (SNPs) in 55 genes or gene clusters coding for cytokines, cytokine receptors, suppressors of cytokine signaling (SOCS), complement factors and glutamate receptors for association with MS in a Spanish-Basque resident population. Top-scoring SNPs were found within or nearby the genes coding for SOCS-1 (P=0.0005), interleukin-28 receptor, alpha chain (P=0.0008), oncostatin M receptor (P=0.002) and interleukin-22 receptor, alpha 2 (IL22RA2; P=0.003). The SOCS1 rs243324 variant was validated as risk factor for MS in a separate cohort of 3919 MS patients and 4003 controls (combined Cochran-Mantel-Haenszel P=0.00006; odds ratio (OR)=1.13; 95% confidence interval (CI)=1.07-1.20). In addition, the T allele of rs243324 was consistently increased in relapsing-remitting/secondary progressive versus primary-progressive MS patients, in each of the six data sets used in this study (P (CMH)=0.0096; OR=1.24; 95% CI 1.05-1.46). The association with SOCS1 appears independent from the chr16MS risk locus CLEC16A.

Genes and Immunity advance online publication, 30 June 2011; doi:10.1038/gene.2011.44.

PMID: 21716315 [PubMed - as supplied by publisher]


**Epstein-Barr virus and multiple sclerosis: interaction with HLA.**


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Epstein-Barr virus (EBV) infection, history of infectious mononucleosis (IM) and HLA-A and DRB1 have all been proposed as risk factors for multiple sclerosis (MS). Our aim was to analyse possible interactions between antibodies against Epstein-Barr virus nuclear antigen 1 (EBNA1) or EBNA1 fragments, presence of DRB1(*)15 and absence of A(*)02. The study population includes newly diagnosed cases and matched controls. Interaction on the additive scale was calculated using attributable proportion due to interaction (AP), which is the proportion of the incidence among individuals exposed to two interacting factors that is attributable to the interaction per se. IM showed association with MS, odds ratio (OR)=1.89 (1.45-2.48% confidence interval (CI)), as did raised EBNA1 IgG OR=1.74 (1.38-2.18 95%CI). All EBNA1 fragment IgGs were associated with MS risk. However, EBNA1 fragment 385-420 IgG levels were more strongly associated to MS than total EBNA1 IgG, OR=3.60 (2.75-4.72 95%CI), and also interacted with both DRB1(*)15 and absence of A(*)02, AP=0.60 (0.45-0.76 95%CI) and AP=0.39 (0.18-0.61 95%CI), respectively. The observed interaction between HLA class I and II genotype and reactivity to EBV-related epitopes suggest that the mechanism through which HLA genes influence the risk of MS may, at least in part, involve the immune control of EBV infection.

Genes and Immunity advance online publication, 21 July 2011; doi:10.1038/gene.2011.42.

PMID: 21776012 [PubMed - as supplied by publisher]

**Headache in Systemic Lupus Erythematosus vs Multiple Sclerosis: A Prospective Comparative Study.**

Katsiari CG, Vikelis M, Paraskevopoulou ES, Sfikakis PP, Mitsikostas DD.

From the First Department of Propedeutic and Internal Medicine, Athens University Medical School, Athens, Greece (C.G. Katsiari and P.P. Sfikakis); Department of Neurology, Athens Naval Hospital, Athens, Greece (M.G. Vikelis, E.S. Paraskevopoulou, and D.D. Mitsikostas).

Objective. - To clarify whether headache, and particularly migraine, belongs to the spectrum of neurologic manifestations of systemic lupus erythematosus (SLE), the archetypal autoimmune disease. Methods. - Consecutive SLE patients were matched 1:1 for age, gender, and level of education with healthy control subjects. A representative subgroup of SLE patients were also matched with patients suffering from multiple sclerosis (MS), a nervous system-specific autoimmune disease. All study participants were assessed for headache present in the previous year. Anxiety, depression, and quality of life were also estimated at baseline. During the following year, all participants were assessed every 3 months using specific headache diaries. Results. - Seventy-two SLE/control pairs and 48 MS patients completed 12 months of follow-up. Prevalence of migraine, with or without aura, was similar between SLE patients (21%), MS patients (23%), and controls (22%), as was the prevalence of frequent tension-type headache. Duration and severity of migraine attacks were milder in SLE patients than controls. Only chronic tension-type headache was significantly more prevalent in SLE patients (12.5%) compared to controls (1.4%). MS patients also presented increased frequency of chronic tension-type headache (8.3%). No associations of any headache type with particular clinical manifestations, autoantibody, or disease activity, either in SLE or MS patient groups, were found. Irrespective of the presence of headache, anxiety symptoms and impaired quality of life were more frequent among SLE than MS patients or controls. Conclusion. - Migraine should be no longer considered a neurologic manifestation of systemic or organ-specific autoimmunity. Increased migraine prevalence in these patients found in previous studies could be due to methodological weaknesses.

PMID: 21797859  [PubMed - as supplied by publisher]


**Identification of a new susceptibility variant for multiple sclerosis in OAS1 by population genetics analysis.**


Bioinformatic Lab, Scientific Institute IRCCS E. Medea, Via don L. Monza 20, 23842, Bosisio Parini, LC, Italy.

Contrasting results have been reported concerning the association of a splice-site polymorphism (rs10774671) in OAS1 with multiple sclerosis (MS). We analysed two OAS1 regions encompassing alternatively spliced exons. While the region carrying the splice-site variant is neutrally evolving, a signature of long-standing balancing selection was observed across an alternative exon 7. Analysis of variants in this exon identified an insertion/deletion polymorphism (rs11352835, A/-) that originates predicted products with distinct C termini. This variant is located along the major branch of the haplotype genealogy, suggesting that it may represent the selection target. A case/control study for MS indicated that rs11352835 is associated with disease susceptibility (for an allelic model with the deleted allele predisposing to MS, OR 1.27, 95% CI 1.072-1.513, p = 0.010). No association was found between rs10774671 and MS. As the two SNPs are in linkage disequilibrium in Europeans, the previously reported association between rs10774671 and MS susceptibility might be driven by rs11352835, possibly explaining the contrasting results previously observed for the splice-site polymorphism. Thus, we describe a novel susceptibility variant for MS in OAS1 and show that population genetic analyses can be instrumental to the identification of selection targets and, consequently, of functional polymorphisms with an effect on phenotypic traits.

PMID: 21735172  [PubMed - as supplied by publisher]
Implementation of an absolute brain (1)H-MRS quantification method to assess different tissue alterations in multiple sclerosis.
Magnetic resonance spectroscopy has emerged as a sensitive modality to detect early and diffuse alterations in multiple sclerosis. Recently, the hypothesis of neurodegenerative pathogenesis has highlighted the interest for measurement of metabolites concentrations, to gain specificity, in a large brain volume encompassing different tissue alterations. Therefore, we proposed in this work the implementation of an absolute quantification method based on localized spectroscopy at short (30 ms) and long (135 ms) echo time of a volume including normal appearing white matter, cortical grey matter and lesions. Firstly, methodological developments were implemented including external calibration, and corrections of phased-array coil sensitivity and cerebrospinal fluid volume contribution. Secondly, these improvements were validated and optimized using an original methodology based on simulations of brain images with lesions. Finally, metabolic alterations were assessed in 65 patients including 26 relapsing-remitting (RR), 17 primaryprogressive patients (PP), 22 secondary-progressive (SP), and in 23 normal subjects. Results showed increases of choline, creatine and myo-Inositol concentrations in PP and SP patients compared to controls, whereas the concentration of N-acetyl compounds remained constant. The major finding of this study was the identification of Cho concentration and Cho/tNA ratio as putative markers of progressive onset, suggesting interesting perspectives in detection and follow-up of neurodegenerative processes.
PMID: 21768043 [PubMed - as supplied by publisher]

78. Immunobiology. 2011 Jul 8. [Epub ahead of print]
CD46 processing: A means of expression.
Ni Choléain S, Astier AL.
MRC Centre for Inflammation Research, Centre for MS Research, University of Edinburgh, UK.
CD46 is a ubiquitously expressed type I transmembrane protein, first identified as a regulator of complement activation, and later as an entry receptor for a variety of pathogens. The last decade has also revealed the role of CD46 in regulating the adaptive immune response, acting as an additional costimulatory molecule for human T cells and inducing their differentiation into Tr1 cells, a subset of regulatory T cells. Interestingly, CD46 regulatory pathways are defective in T cells from patients with multiple sclerosis, asthma and rheumatoid arthritis, illustrating its importance in regulating T cell homeostasis. Indeed, CD46 expression at the cell surface is tightly regulated in many different cell types, highlighting its importance in several biological processes. Notably, CD46 is the target of enzymatic processing, being cleaved by metalloproteinases and by the presenilin/gamma secretase complex. This processing is required for its functions, at least in T cells. This review will summarize the latest updates on the regulation of CD46 expression and on its effects on T cell activation.
PMID: 21742405 [PubMed - as supplied by publisher]

Recognition of the kind of stress coping in patients of multiple sclerosis.
Hajhashemi A, Vaziripour HD, Baratian H, Kajbaf MB, Etemadifar M.
Department of Psychology, Islamic Azad University, Khorasgan Branch, Isfahan, Iran.
BACKGROUND: Investigations have shown that some factors like stress can increase the recurrence and severity of multiple sclerosis (MS). Considering the direct influences of depression and anxiety on our body immunity system, and also the relation between stress and factors, such as Insulin Growth Factor (IGF-1), involved in neurogenesis and myelin repairing, it is an essential issue to identify the most common method used in relieving stress by such patients. OBJECTIVE: To identify the type of common coping methods for stressful situation. MATERIALS AND METHODS: This case-control study was performed on 50 patients of both the genders with MS in Esfahan (Esfahan MS Association). The data were collected and then analyzed using analysis of variance (ANOVA) method with the help of SPSS software version 15. The P value less than 0.05 was considered as statistically significant. RESULTS: In our study, coping method for stressful situation was significantly different in MS patients versus the healthy group (P=0.02). Descriptive indices showed that these patients use avoidant method more commonly than the control group (mean=45.01, SD=8.9 vs. mean=40.8, SD=11.8, respectively). CONCLUSION: Due to the different methods used by MS patients to cope with stressful situation in comparison with the healthy ones, more appropriate techniques can be introduced to modify them, and hence, less stress-induced side effects could be expected in this population.
PMCID: PMC3122554 PMID: 21716783 [PubMed]

Increased T-cell immunity against aquaporin-4 and proteolipid protein in neuromyelitis optica.


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In neuromyelitis optica (NMO), B-cell autoimmunity to aquaporin-4 (AQP4) has been shown to be essential. However, the role of T cells remains ambiguous. Here, we first showed an increase in CD69+ activated T cells in PBMCs during NMO relapses. Next, T-cell responses to AQP4 and myelin peptides were studied in 12 NMO patients, 10 multiple sclerosis (MS) patients and 10 healthy subjects (HS). Four hours after adding 1 of 28 overlapping AQP4 peptides, a mixture of AQP4 peptides (AQP4-M) or one of six distinct myelin peptides to 2-day cultured PBMC, CD69 expression on CD4+ T cells was examined. Data were analyzed by paired t-test, frequency of samples with 3-fold increase of CD69 on CD4+ cells (fSI3) and mean stimulation index (mSI). The T-cell response to AQP4-M was significantly increased in NMO (fSI3 = 10/12, mSI = 5.50), with AQP4 (11-30) and AQP4 (91-110) representing the two major epitopes (AQP4 (11-30), fSI3 = 11/12, mSI = 16.0 and AQP4 (91-110), fSI3 = 11/12, mSI = 13.0). Significant but less extensive responses to these two epitopes were also observed in MS and HS. Significant reactivities against AQP4 (21-40), AQP4 (61-80), AQP4 (101-120), AQP4 (171-190) and AQP4 (211-230) were exclusively found in NMO. In addition, responses to AQP4 (81-100) were higher and more frequently detected in NMO, without reaching statistical significance. Interestingly, among the six myelin peptides studied, proteolipid protein (95-116) induced a significant T-cell response in NMO (fSI3 = 7/12, mSI = 4.60). Our study suggests that cellular as well as humoral responses to AQP4 are necessary for NMO development and that the immune response to myelin protein may contribute to disease pathogenesis.

PMID: 21795759  [PubMed - as supplied by publisher]


CTLA-4 +49 A/G gene polymorphism in Croatian and Slovenian multiple sclerosis patients.

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Postgraduate Study, School of Medicine, University of Rijeka, Rijeka, Croatia.

Polymorphisms in the CTLA-4 gene are known to be important in several autoimmune diseases, including multiple sclerosis (MS). Previous studies on the impact of CTLA-4 +49 A/G gene polymorphism have given contradictory results. We investigated the possible influence of this polymorphism on MS susceptibility and disease behaviour in Croatian and Slovenian populations. Genotyping was performed in 367 patients with MS and 480 control subjects using PCR-RFLP method. The G allele was present in 216 (58.9%) patients with MS vs. 282 (58.7%) healthy controls (P = 0.975, OR = 1.01, 95% CI = 0.76-1.32). No significant differences were observed in CTLA-4 +49 A or G allele distribution between patients and controls, indicating that this polymorphism does not influence susceptibility to MS in the surveyed populations. No correlation was observed between G allele carrier status and age at disease onset, disease course or severity.

PMID: 21797987  [PubMed - as supplied by publisher]
Genetic polymorphisms associated with the development and clinical course of multiple sclerosis (Review).
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Health Sciences Postgraduation Program, Health Sciences Center, State University of Londrina, Londrina, Parana, Brazil.

Multiple sclerosis (MS) is an autoimmune disease characterized by areas of inflammation, demyelination and axonal damage. The etiology of MS is multifactorial with an interaction between genetic, environmental and geographical factors. The objective of this study was to review the physiopathology and the genetic polymorphisms associated with the development and clinical course of MS. Studies carried out in populations worldwide showed that polymorphisms in the genes of the major histocompatibility complex (MHC) class II and class III have been associated with susceptibility, resistance and clinical forms of MS. Considerable attention has been focused on studies evaluating disease-modifying effects in MS that identified seven genes of probable importance such as the HLA class II, ApoE, IL-1ra, IL-1β, TNF-α, TNF-β and CCR5 genes. However, the results described in the literature about genetic biomarkers in MS are not consistent in the worldwide population. The detection of a single nucleotide polymorphism involved in the etiology and physiopathology of MS is very difficult and, it is likely that, several genetic polymorphisms are involved, each with a small contribution to the susceptibility or resistance to MS. Taken together the results show the need for continued research in genetically heterogeneous populations to identify new biomarkers associated with MS that could be used as prognostic markers or as therapeutic targets to modulate the autoimmune response in MS patients. This information may contribute to a better understanding of the physiopathology and treatment of MS, with the possibility of developing different therapeutic strategies according to the genetic profile of each individual.

Distinct pathological patterns in relapsing-remitting and chronic models of experimental autoimmune encephalomyelitis and the neuroprotective effect of glatiramer acetate.
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The respective roles of inflammatory and neurodegenerative processes in the pathology of multiple sclerosis (MS) and in its animal model experimental autoimmune encephalomyelitis (EAE) are controversial. Novel treatment strategies aim to operate within the CNS to induce neuroprotection and repair processes in addition to their anti-inflammatory properties. In this study we analyzed and compared the in situ pathological manifestations of EAE utilizing two different models, namely the relapsing-remitting PLP-induced and the chronic MOG-induced diseases. To characterize pathological changes, both transmission electron microscopy (TEM) and immunohistochemistry were employed. The effect of the approved MS drug glatiramer acetate (GA, Copaxone) on myelin damage/repair and on motor neuron loss/preservation was studied in both EAE models. Ultrastructural spinal cord analysis revealed multiple white matter damage foci, with different patterns in the two EAE models. Thus, the relapsing-remitting model was characterized mainly by widespread myelin damage and by remyelinating fibers, whereas in the chronic model axonal degeneration was more prevalent. Loss of lower motor neurons was manifested only in mice with chronic MOG-induced disease. In the GA-treated mice, smaller lesions, increased axonal density and higher prevalence of normal appearing axons were observed, as well as decreased demyelination and degeneration. Furthermore, quantitative analysis of the relative remyelination versus demyelination, provides for the first time evidence of significant augmentation of remyelination after GA treatment. The loss of motor neurons in GA-treated mice was also reduced in comparison to that of EAE untreated mice. These effects were obtained even when GA treatment was applied in a therapeutic schedule, namely after the appearance of clinical symptoms. Hence, the remyelination and neuronal preservation induced by GA are in support of the neuroprotective consequences of this treatment.

PMID: 21752599 [PubMed - as supplied by publisher]

**Kinetic analysis of Autotaxin reveals substrate-specific catalytic pathways and a mechanism for lysophosphatidic acid distribution.**

Saunders LP, Cao W, Chang WC, Albright RA, Braddock DT, De La Cruz EM. Yale University, United States.

Autotaxin (ATX) is a secreted lysophospholipase D that hydrolyzes lysophosphatidylcholine (LPC) into lysophosphatidic acid (LPA), initiating signaling cascades leading to cancer metastasis, wound healing, and angiogenesis. Knowledge of the pathway and kinetics of LPA synthesis by ATX is critical for developing quantitative physiological models of LPA signaling. We measured the individual rate constants and pathway of the LPA synthase cycle of ATX using the fluorescent lipid substrates FS-3 and NBD-LPC. FS-3 binds rapidly ($k_1 \geq 500 \mu M^{-1} s^{-1}$) and is hydrolyzed slowly ($k_2 = 0.024 s^{-1}$). Release of the first hydrolysis product is random and rapid ($\geq 1s^{-1}$), while release of the second is slow and rate-limiting (0.005 - 0.007 s$^{-1}$). Substrate binding and hydrolysis are slow and rate limiting with LPC. Product release is sequential with choline preceding LPA. The catalytic pathway and kinetics depend strongly on the substrate, suggesting that ATX kinetics could vary for the various in vivo substrates. Slow catalysis with LPC reveals the potential for LPA signaling to spread to cells distal to the site of LPC substrate binding by ATX. An ATX mutant in which catalytic threonine at position 210 is replaced with alanine binds substrate weakly, favoring a role for T210 in binding as well as catalysis. FTY720P, the bioactive form of a drug currently used to treat multiple sclerosis, inhibits ATX in an uncompetitive manner and slows the hydrolysis reaction, suggesting that ATX inhibition plays a significant role in lymphocyte immobilization in FTY720P-based therapeutics.

PMID: 21719699 [PubMed - as supplied by publisher]


**Tight junction proteins expression and modulation in immune cells and multiple sclerosis.**

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The tight junction proteins (TJPs) are major determinants of endothelial cells comprising physiological vascular barriers such as the blood-brain-barrier, but little is known about their expression and role in immune cells. In this study we assessed TJP expression in human leukocyte subsets, their induction by immune activation, and modulation associated with autoimmune disease states and therapies. A consistent expression of tight junction protein complexes was detected in peripheral blood leukocytes (PBLs), predominantly in B and T lymphocytes and monocytes, while the in vitro application of various immune cell activators led to an increase of claudin 1 levels, yet not of claudin 5. Claudin 1 and claudin 5 levels were elevated in PBLs of multiple sclerosis (MS) patients in relapse, relative to patients in remission, healthy controls, and subjects with other neurological disorders. Interestingly, claudin 1 protein levels were elevated also in PBLs of patients with type 1 diabetes (T1D). Following glucocorticoid treatment of MS patients in relapse, RNA levels of JAM3 and CLDN5 and claudin 5 protein levels in PBLs decreased. Furthermore, a correlation between CLDN5 pre-treatment levels and clinical response phenotype to interferon-β therapy was detected. Our findings indicate that higher levels of leukocyte Claudins are associated with immune activation and specifically, increased levels of claudin 5 are associated with MS disease activity. This study highlights a potential role of leukocyte TJPs in physiological states, and autoimmunity and suggests they should be further evaluated as biomarkers for aberrant immune activity and response to therapy in immune-mediated diseases such as MS.

PMID: 21762372 [PubMed - as supplied by publisher]
A novel mitochondrial DNA deletion producing progressive external ophthalmoplegia associated with multiple sclerosis.
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We report a previously undescribed 7676 base pair mitochondrial (mt)DNA deletion involving genes of complex I, complex IV subunits 2 and 3 (cytochrome oxidase [Cox] II, III), adenosine triphosphatase 8 and 6, cytochrome b and 8 transfer (t)RNA genes producing myopathy and progressive external ophthalmoplegia (PEO) in a 44-year-old right-handed Caucasian man with features of multiple sclerosis (MS). We performed complete mtDNA sequencing and deletion analysis, spectrophotometric analysis of muscle and platelet respiratory chain activity, measurement of platelet mitochondrial membrane potential with the potentiometric dye JC-1 and magnetic resonance spectroscopy (MRS) and MRI studies of normal-appearing and lesional cerebral tissue. The deletion resulted in significant respiratory chain deficiency in muscle and blood and abnormalities of the platelet mitochondrial membrane potential. However, cerebrospinal fluid analysis, magnetic resonance spectroscopy and MRI features suggested inflammatory central nervous system demyelination rather than a primary respiratory chain disorder. We conclude that this novel mtDNA deletion causing myopathy and PEO is associated with severe muscle and platelet cellular energetic abnormalities. Furthermore, clinical and paraclinical features of multiple sclerosis were found. The potential pathomechanistic interaction between mtDNA variation and multiple sclerosis is reviewed.
PMID: 21795050 [PubMed - as supplied by publisher]

Interleukin-17-secreting T cells in neuromyelitis optica and multiple sclerosis during relapse.
Multiple Sclerosis Center, Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University,
No. 600 Tianhe Road, Guangzhou 510630, Guangdong Province, China.
Growing evidence suggests that interleukin (IL)-17 and IL-17-secreting CD4(+)T (Th17) cells are involved in the pathogenic mechanisms of multiple sclerosis (MS). IL-17-secreting CD8(+)T cells were recently identified as a novel subset of CD8(+) T cells. We aimed to analyze the role of Th17 and IL-17 secreting CD8(+)T cells in the pathogenesis of neuromyelitis optica (NMO) as well as MS. Fourteen patients with NMO, 20 with MS and 16 control participants (CTL) were enrolled between November 2008 and December 2009. The proportion of Th17 cells and IL-17 secreting CD8(+)T cells were counted using flow cytometry, and serum levels of IL-6, IL-17, IL-21, IL-23, and transforming growth factor-beta (TGF-β) were measured by enzyme-linked immunosorbent assay. Patients with NMO had a larger proportion of Th17 cells than patients with MS (3.72% versus [vs.] 2.58%, p=0.02) and CTL (3.72% vs. 1.36%, p<0.001). The proportion of Th17 cells in patients with MS was also markedly higher than in the CTL (2.58% vs. 1.36%, p<0.001). IL-17-secreting CD8(+) T cell counts in NMO patients were markedly higher than in MS patients (1.61% vs. 1.09%, p=0.036) and CTLs (1.61% vs. 0.58%, p<0.001). The proportion of IL-17-secreting CD8(+) T cells in MS patients was also higher than in CTLs (1.09% vs. 0.58%, p=0.002). Serum IL-17 and IL-23 levels were increased in patients with NMO and MS, while serum IL-21 concentration was higher only in NMO patients compared to CTL. We concluded that Th17 cells were highly activated in patients with NMO. IL-17-secreting CD8(+) T cells were increased in patients with NMO and MS during relapse and have an important role in the pathological mechanism of NMO and MS.
PMID: 21795048 [PubMed - as supplied by publisher]

**Serum bilirubin concentrations and multiple sclerosis.**


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Bilirubin is the end product of heme catabolism by heme oxygenases. Although bilirubin has long been considered as a toxic waste product, it is now recognized as an endogenous antioxidant. It has been reported that bilirubin is an effective treatment in both acute and chronic experimental autoimmune encephalomyelitis (EAE) disease models. However, the relationship between bilirubin and multiple sclerosis (MS) has not been fully explored. The serum bilirubin concentrations were measured in 340 individuals comprising 88 healthy subjects, 133 patients with MS and 119 patients with cerebral infarction. Serum total bilirubin (Tbil), direct bilirubin (Dbil) and indirect bilirubin (Ibil) concentrations were significantly lower in patients with MS than in either patients with cerebral infarction or healthy controls (p<0.001). The correlation identified between bilirubin and MS was still highly significant when the effect of gender was eliminated.

Among patients with MS, Tbil, Dbil and Ibil concentrations were lower in patients with MS with longer duration (>2years), less disabling disease (Expanded Disability Status Scale score<3), and inactive MRI appearance, although the differences did not reach statistical significance. Our results suggest that there are reduced serum bilirubin concentrations in patients with MS.

PMID: 21782448 [PubMed - as supplied by publisher]

89. J Commun Disord. 2011 Jul 2. [Epub ahead of print]

**Speech and pause characteristics associated with voluntary rate reduction in Parkinson's disease and Multiple Sclerosis.**

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The primary purpose of this study was to investigate how speakers with Parkinson's disease (PD) and Multiple Sclerosis (MS) accomplish voluntary reductions in speech rate. A group of talkers with no history of neurological disease was included for comparison. This study was motivated by the idea that knowledge of how speakers with dysarthria voluntarily accomplish a reduced speech rate would contribute toward a descriptive model of speaking rate change in dysarthria. Such a model has the potential to assist in identifying rate control strategies to receive focus in clinical treatment programs and also would advance understanding of global speech timing in dysarthria. All speakers read a passage in Habitual and Slow conditions. Speech rate, articulation rate, pause duration, and pause frequency were measured. All speaker groups adjusted articulation time as well as pause time to reduce overall speech rate. Group differences in how voluntary rate reduction was accomplished were primarily one of quantity or degree. Overall, a slower-than-normal rate was associated with a reduced articulation rate, shorter speech runs that included fewer syllables, and longer more frequent pauses. Taken together, these results suggest that existing skills or strategies used by patients should be emphasized in dysarthria training programs focusing on rate reduction. Results further suggest that a model of voluntary speech rate reduction based on neurologically normal speech shows promise as being applicable for mild to moderate dysarthria. Learning outcomes: The reader will be able to: (1) describe the importance of studying voluntary adjustments in speech rate in dysarthria, (2) discuss how speakers with Parkinson's disease and Multiple Sclerosis adjust articulation time and pause time to slow speech rate.

PMID: 21767851 [PubMed - as supplied by publisher]


**A profile of support group use and need among middle-aged and older adults with multiple sclerosis.**

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This study compared middle-aged and older adults with multiple sclerosis (MS, N = 1,275) according to their use of support groups and identified factors associated with perceived need. Over 64.6% (n = 824) of participants had attended a MS support group meeting at least once. Individuals who had never attended a group were more likely to reside in urban or suburban communities, report lower symptom interference, and fewer activity limitations. Women, individuals without a helper, and people with greater symptom interference were more likely to perceive a need for a support group. Findings raise questions for professionals involved in developing and implementing multiple sclerosis support groups.

PMID: 21714616 [PubMed - in process]

**Cutting Edge: Regulator of G Protein Signaling-1 Selectively Regulates Gut T Cell Trafficking and Colitic Potential.**


Peter Gorer Department of Immunobiology, King's College London, London SE1 9RT, United Kingdom; The RGS1 gene is associated with celiac disease, multiple sclerosis, and type I diabetes, which are all T cell-mediated pathologies, yet there is no reported analysis of regulator of G protein signaling (RGS1) biology in human T cells. This study shows that RGS1 expression is substantially higher in T cells from human gut versus peripheral blood and that this can be exaggerated in intestinal inflammation. Elevated RGS1 levels profoundly reduce T cell migration to lymphoid-homing chemokines, whereas RGS1 depletion selectively enhances such chemotaxis in gut T cells and impairs their colitogenic potential. These findings provide a revised framework in which to view the linkage of RGS1 to inflammatory disease.

PMID: 21795595 [PubMed - as supplied by publisher]


**Delta-Like Ligand 4 Regulates CNS T Cell Accumulation during Experimental Autoimmune Encephalomyelitis.**

Reynolds ND, Lukacs NW, Long N, Karpus WJ.

Department of Pathology, Feinberg School of Medicine, Northwestern University, Chicago, IL 60611; Experimental autoimmune encephalomyelitis (EAE) is a CD4(+) T cell-mediated inflammatory demyelinating disease of the CNS that serves as a model for multiple sclerosis. Notch receptor signaling in T lymphocytes has been shown to regulate thymic selection and peripheral differentiation. In the current study, we hypothesized that Notch ligand-receptor interaction affects EAE development by regulating encephalitogenic T cell trafficking. We demonstrate that CNS-infiltrating myeloid dendritic cells, macrophages, and resident microglia expressed Delta-like ligand 4 (DLL4) after EAE induction. Treatment of mice with a DLL4-specific blocking Ab significantly inhibited the development of clinical disease induced by active priming. Furthermore, the treatment resulted in decreased CNS accumulation of mononuclear cells in the CNS. Anti-DLL4 treatment did not significantly alter development of effector cytokine expression by Ag-specific T cells. In contrast, anti-DLL4 treatment reduced T cell mRNA and functional cell surface expression of the chemokine receptors CCR2 and CCR6. Adoptive transfer of Ag-specific T cells to mice treated with anti-DLL4 resulted in decreased clinical severity and diminished Ag-specific CD4(+) T cell accumulation in the CNS. These results suggest a role for DLL4 regulation of EAE pathogenesis through modulation of T cell chemokine receptor expression and migration to the CNS.

PMID: 21788444 [PubMed - as supplied by publisher]


**Silencing MicroRNA-155 Ameliorates Experimental Autoimmune Encephalomyelitis.**

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IFN-γ-producing Th1 and IL-17-producing Th17 cells are the key participants in various autoimmune diseases, including multiple sclerosis and its animal model, experimental autoimmune encephalomyelitis (EAE). Although both of these T cell subsets are known to be regulated by specific transcription factors and cytokines, the role of microRNAs that control these two inflammatory T cell subsets and whether targeting microRNAs can have therapeutic effects are not known. In this study, we show that microRNA-155 (Mir-155) expression is elevated in CD4(+) T cells during EAE, and Mir-155(-/-) mice had a delayed course and reduced severity of disease and less inflammation in the CNS. The attenuation of EAE in Mir-155(-/-) mice was associated with a decrease in Th1 and Th17 responses in the CNS and peripheral lymphoid organs. The T cell-intrinsic function of Mir-155(-/-) was demonstrated by the resistance of Mir-155(-/-) CD4(+) T cell-repleted Rag-1(-/-) mice to EAE. Finally, we found that anti-Mir-155 treatment reduced clinical severity of EAE when given before and after the appearance of clinical symptoms. These findings demonstrate that Mir-155 confers susceptibility to EAE by affecting inflammatory T cell responses and identify Mir-155 as a new target for therapeutic intervention in multiple sclerosis.

PMID: 21788439 [PubMed - as supplied by publisher]
Cytosolic Phospholipase A2 (α) Blockade Abrogates Disease during the Tissue-Damage Effector Phase of Experimental Autoimmune Encephalomyelitis by Its Action on APCs.


Inflammation and Immunology Research Unit, Pfizer Research and Development, Cambridge, MA 02140; Cytosolic phospholipase A(2)α (cPLA(2)α) is the rate-limiting enzyme for release of arachidonic acid, which is converted primarily to PGs via the cyclooxygenase 1 and 2 pathways and to leukotrienes via the 5-lipoxygenase pathway. We used adoptive transfer and relapsing-remitting forms of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis, in two different strains of mice (SJL or C57BL/6) to demonstrate that blockade of cPLA(2)α with a highly specific small-molecule inhibitor during the tissue-damage effector phase abrogates the clinical manifestation of disease. Using the adoptive transfer model in SJL mice, we demonstrated that the blockade of cPLA(2)α during the effector phase of disease was more efficacious in ameliorating the disease pathogenesis than the blockade of each of the downstream enzymes, cyclooxygenase-1/2 and 5-lipoxygenase. Similarly, blockade of cPLA(2)α was highly efficacious in ameliorating disease pathogenesis during the effector phase of EAE in the adoptive transfer model of EAE in C57BL/6 mice. Investigation of the mechanism of action indicates that cPLA(2)α inhibitors act on APCs to diminish their ability to induce Ag-specific effector T cell proliferation and proinflammatory cytokine production. Furthermore, cPLA(2)α inhibitors may prevent activation of CNS-resident microglia and may increase oligodendrocyte survival. Finally, in a relapsing-remitting model of EAE in SJL mice, therapeutic administration of a cPLA(2)α inhibitor, starting from the peak of disease or during remission, completely protected the mice from subsequent relapses.

PMID: 21746963 [PubMed - in process]


Integrative visualization of temporally varying medical image patterns.

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We have developed a tool for the visualization of temporal changes of disease patterns, using stacks of medical images collected in time-series experiments. With this tool, users can generate 3D surface models from different time points. Visual integration enables the tool to show 2D images, 3D models and statistical data simultaneously. As an example, the tool has been used to visualize brain MRI scans of several multiple sclerosis patients. It has been developed in Java™, to ensure portability and platform independence, with a user-friendly interface and can be downloaded free of charge for academic users.

PMID: 21778531 [PubMed - in process]


Fifty years on: against the stigmatising myths, taboos and traditions embedded within the Suicide Act 1961 (UK).

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Although assisted suicide carries a maximum of 14 years imprisonment in England, courts and juries have historically demonstrated a reluctance to convict, most specifically in relation to those travelling abroad to accompany a terminally ill person seeking assisted dying. The possibility of prosecution is still present, however, and there have recently been a number of challenges to the law on assisted dying. During the consultation period of the Coroners and Justice Act 2009 (UK) an amendment was proposed that would have legalised, among other things, assisting suicide overseas. However, it was voted down by peers who believed it to be dangerously radical. In 2008 a multiple sclerosis sufferer requested a clear policy statement, should her partner help her to seek assisted dying abroad in the future. After her application was initially rejected, Mrs Purdy was granted leave to appeal and following a favourable ruling by the House of Lords in 2009, the Director of Public Prosecutions clarified the law on assisted suicide, introducing a Full Code Test which includes the consideration of ”public interest factors”. Although the new guidelines are not a direct threat to the 50-year-old Suicide Act 1961 (UK), it is clearly an historic development: the latest in a series of high-profile cases and debates which have taken place over the last decade. It is suggested that English law on assisted dying continues to rely on a range of inappropriate concepts, taboos and superstitions, and it is from this perspective that the implications for future legislative reform are addressed.

PMID: 21774275 [PubMed - in process]

The pursuit of transparency and quality improvement in cost-effectiveness analysis - a case study in disease-modifying drugs for the treatment of multiple sclerosis.
Bell CF.
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Cost-effectiveness analysis (CEA) can be a powerful analytic tool for assessing the value of health care interventions when used in conjunction with efficacy, safety, and other supporting data in an evidence-based decision making environment. CEA is commonly defined in terms of the comparison of costs, expressed in monetary units, with outcomes that may be expressed in a variety of ways. One of the most common forms of CEA compares costs in monetary units with outcomes quantified in nonmonetary units (e.g., cancer avoided, death avoided, or successfully treated patient). Cost-utility analysis (CUA) is a form of CEA that compares costs in monetary units with outcomes quantified as a multidimensional measure of effectiveness (e.g., utilities that are used to estimate quality-adjusted life-years [QALYs]). Cost benefit analysis (CBA), another form of CEA that is used less frequently, compares costs and benefits (i.e., outcomes) both of which are quantified in monetary units. Overall, there has been an increasing trend in the use of CEA (CEA, CUA, and CBA) to inform decision making. This trend can be implicitly measured by the frequency of published CEA over time.

PMID: 21787032 [PubMed - in process]


Reliability of the Thai version of SF-36 questionnaire for an evaluation of quality of life in multiple sclerosis patients in multiple sclerosis clinic at Siriraj Hospital.
Laosanguanek N, Wiroteurairuang T, Siritho S, Prayoonwiwat N.
Neurology Division, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.

BACKGROUND: To study the application, validity and reliability of a Thai version of SF-36 questionnaires in Thai multiple sclerosis (MS) patients. MATERIAL AND METHOD: An evaluation of quality of life using a Thai version of SF-36 was performed in 70 MS or clinical isolated syndrome (CIS) patients. Statistical analysis: Measurement of internal consistency was done by Cronbach’s alpha coefficient and inter-item correlation; measurement of The test-retest reliability assessing consistency of the measure was done by Pearson correlation. RESULTS: There were 55 clinical definite MS patients, 12 laboratory-supported definite MS patients, and 3 clinical-probable MS patients, according to Poser criteria. MS types were classified as PP-primary progressive MS(2), RR-relapsing remitting MS (59), SP-secondary progressive MS(3) and CIS(6). Internal consistency measured by Cronbach’s Alpha exceeded 0.7 except social functions, which was 0.69. The item correlation coefficient ranged from 0.47-0.88. Reliability of test-retest all items determined by Pearson correlation was significant, ranging from 0.84-0.94. CONCLUSION: Thai version SF-36 questionnaire is reliable for the assessment of quality of life in Thai multiple sclerosis patients.

PMID: 21721432 [PubMed - in process]

O'Day K, Meyer K, Miller RM, Agarwal S, Franklin M. Xcenda, Palm Harbor, FL, USA.

Abstract Background: With the addition of new agents for the treatment of multiple sclerosis (MS) (e.g., fingolimod), there is a need to evaluate the relative value of newer therapies in terms of cost and effectiveness, given healthcare resource constraints in the United States. Objective: To assess the cost-effectiveness of natalizumab vs fingolimod in patients with relapsing MS. Methods: A decision analytic model was developed to estimate the incremental cost per relapse avoided of natalizumab and fingolimod from a U.S. managed care payer perspective. Two-year costs of treating patients with MS included drug acquisition costs, administration and monitoring costs, and costs of treating MS relapses. Effectiveness was measured in terms of MS relapses avoided (data from AFFIRM and FREEDOMS trials). One-way and probabilistic sensitivity analyses were conducted to assess uncertainty. Results: Mean 2-year estimated treatment costs were $86,461 (natalizumab) and $98,748 (fingolimod). Patients receiving natalizumab had a mean of 0.74 relapses avoided per 2 years vs 0.59 for fingolimod. Natalizumab dominated fingolimod in the incremental cost-effectiveness analysis, as it was less costly and more effective in reducing relapses. One-way sensitivity analysis showed the results of the model were robust to changes in drug acquisition costs, administration costs, and costs of treating MS relapses. Probabilistic sensitivity analysis showed natalizumab was cost-effective 95.1% of the time, at a willingness-to-pay (WTP) threshold of $0 per relapse avoided, increasing to 96.3% of the time at a WTP threshold of $50,000 per relapse avoided. Limitations: Absence of data from direct head-to-head studies comparing natalizumab and fingolimod, use of relapse rate reduction rather than sustained disability progression as primary model outcome, assumption of 100% adherence to MS treatment, and not capturing adverse event costs in the model. Conclusions: Natalizumab dominates fingolimod in terms of incremental cost per relapse avoided, as it is less costly and more effective.

PMID: 21777161 [PubMed - as supplied by publisher]

Serum nitric oxide concentrations in patients with multiple sclerosis and patients with epilepsy.

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Nitric oxide (NO), a neurotransmitter and a free radical, has been purported to be involved in numerous neurological diseases. We investigated the serum nitric oxide concentration in 30 patients with multiple sclerosis (MS), in 30 patients with epilepsy and in 30 control subjects. The aim was also to determine whether a statistically significant difference in serum NO concentrations exists between the groups of interest. The total serum nitric oxide concentration was measured using the Griess reaction after reducing nitrates to nitrites with elemental zinc. In the group multiple sclerosis, the mean NO concentrations were $X \pm \text{SEM} = 31.02 \pm 1.79 \mu\text{mol/l}$, in the control group $X \pm \text{SEM} = 25.31 \pm 1.44 \mu\text{mol/l}$ and in the group epilepsy $X \pm \text{SEM} = 22.51 \pm 1.28 \mu\text{mol/l}$. Student's $t$ test showed a statistically significant difference between subjects with multiple sclerosis and the control group ($p = 0.013$), as well as between the groups multiple sclerosis and epilepsy ($p = 0.0002$). This data confirms that NO may play an important role in the pathogenesis of multiple sclerosis, whereas its role in epilepsy still remains unclear.

PMID: 21779769 [PubMed - as supplied by publisher]
Brain endothelial barrier passage by monocytes is controlled by the endothelin system.

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Homeostasis of the brain is dependent on the blood-brain barrier (BBB). This barrier tightly regulates the exchange of essential nutrients and limits the free flow of immune cells into the central nervous system (CNS). Perturbations of BBB function and the loss its immune quiescence are hallmarks of a variety of brain diseases, including multiple sclerosis (MS), vascular dementia, and stroke. In particular, diapedesis of monocytes and subsequent trafficking of monocyte-derived macrophages into the brain are key mediators of demyelination and axonal damage in MS. Endothelin-1 (ET-1) is considered as a potent pro-inflammatory peptide and has been implicated in the development of cardiovascular diseases. Here we studied the role of different components of the endothelin system, i.e. endothelin-1, its type B receptor (ET(B)) and endothelin-converting enzyme-1 (ECE-1) in monocyte diapedesis of a human brain endothelial cell barrier. Our pharmacological inhibitory and specific gene knockdown studies point to a regulatory function of these proteins in transendothelial passage of monocytes. Results from this study suggest that the endothelin system is a putative target within the brain for anti-inflammatory treatment in neurological diseases.

PMID: 21777246 [PubMed - as supplied by publisher]

Tumor Necrosis Factor-alpha and the Roles it Plays in Homeostatic and Degenerative Processes Within the Central Nervous System.

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Tumor Necrosis Factor-alpha (TNF-α) is a prototypic pro-inflammatory cytokine involved in the innate immune response. TNF-α ligation and downstream signaling with one of its cognate receptors, TNF-RI or TNF-RII, modulates fundamental processes in the brain including synapse formation and regulation, neurogenesis, regeneration, and general maintenance of the central nervous system (CNS). During states of chronic neuroinflammation, extensive experimental evidence implicates TNF-α as a key mediator in disease progression, gliosis, demyelination, inflammation, blood-brain-barrier deterioration, and cell death. This review explores the complex roles of TNF-α in the CNS under normal physiologic conditions and during neurodegeneration. We focus our discussion on Multiple Sclerosis, Parkinson's disease, and Alzheimer's disease, relaying the outcomes of preclinical and clinical testing of TNF-α directed therapeutic strategies, and arguing that despite the wealth of functions attributed to this central cytokine, surprisingly little is known about the cell type- and stage-specific roles of TNF-α in these debilitating disorders.

PMID: 21728035 [PubMed - as supplied by publisher]

Comparison of a classical Th1 bacteria versus a Th17 bacteria as adjuvant in the induction of experimental autoimmune encephalomyelitis.

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The relative contribution of myelin-specific Th1 and Th17 cells in the pathology of multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), is controversial. IL-12, the key cytokine necessary for the differentiation of Th1 cells, has been found to be dispensable for EAE induction; while the related cytokine associated with Th17 cells, IL-23, is a critical factor for inducing EAE. Since EAE is induced by immunization with myelin proteins in CFA which contains M. tuberculosis that generates a prototypical Th1-mediated immune response, we sought to determine if replacing the M. tuberculosis in the adjuvant with a bacterium that induces an IL-23-dependent Th17 cell response during infection would induce EAE with a different phenotype. C. rodentium, a bacterium that requires IL-23 for protective immunity, was used as the adjuvant in EAE and compared to CFA. Mice immunized with C. rodentium adjuvant (CRA) developed classical signs of EAE, similar to CFA-immunized mice, but disease was less severe with a later onset and slower progression than CFA. Surprisingly, the peripheral cytokine profile revealed similar numbers of Th1 and Th17 cells for both CFA and CRA-immunized mice; however, the number of Th1 and Th17 cells was significantly reduced in the CNS of CRA-immunized mice. The development of EAE in CRA-immunized mice was associated with epitope spreading. The unique clinical course of CRA immunizations helps serve as a useful alternative model for studying EAE pathogenesis and potential therapeutics for MS.

PMID: 21715026 [PubMed - as supplied by publisher]

No influence on disease progression of non-HLA susceptibility genes in MS.
The Multiple Sclerosis Research group, Centre for Molecular Medicine, Department of Clinical neuroscience, Karolinska Institutet, Stockholm, Sweden.
Recently, several non-HLA loci have been shown to be convincingly associated with Multiple Sclerosis (MS) susceptibility, assumingly indicating important pathways in the pathogenesis. A genotype influence on disease outcome measures by these genes would support a role of these pathways in ongoing tissue damage. Here, however, we report a consistent dissociation between causation and progression for five non-HLA genotypes (IL7R, IL2RA, CLEC16A, CD226 and SH2B3) in 1776 Scandinavian MS patients.
PMID: 21742385  [PubMed - as supplied by publisher]


Parenchymal accumulation of CD163(+) macrophages/microglia in multiple sclerosis brains.
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Reactive macrophages/microglia exert both protective or damaging effects in multiple sclerosis (MS), which contribute to the relapsing-remitting nature of MS. CD163 is considered a marker of M2 (alternatively activated) macrophages. In the MS brain, CD163(+) perivascular macrophages express molecules for antigen recognition and presentation. Here we further investigated the accumulation of CD163(+) macrophages/microglia in the parenchyma of MS brains. CD163 expression pattern was investigated in different lesions of brain tissue specimens from five MS brains and five neuropathologically unaffected controls by immunohistochemistry. In the parenchyma of normal brain samples, immunoreactivity (IR) of CD163 was absent. In acute active lesions and at the rim of chronic active lesions of MS, strong accumulation of CD163(+) macrophages/microglia was seen. In chronic inactive lesions and in the center of chronic active lesion, CD163(+) macrophages/microglia were rare. Further, double-labeling showed that parenchymal and perivascular CD163(+) macrophages/microglia were myelin basic protein positive and HLA-DR(+), suggesting that CD163(+) macrophages/microglia could ingest and present antigen. In addition, in vitro incubating macrophage RAW264.7 cells with myelin turned LPS-induced inflammatory macrophages into an anti-inflammatory phenotype, indicating that myelin basic protein positive, CD163(+) macrophages/microglia in MS might have anti-inflammatory effects. The parenchymal CD163(+) macrophages/microglia, which had the capacity for antigen ingestion and presentation, might contribute to the resolution of inflammation in MS.
PMID: 21737148  [PubMed - as supplied by publisher]


Intrathecal human herpesvirus 6 antibodies in multiple sclerosis and other demyelinating diseases presenting as oligoclonal bands in cerebrospinal fluid.
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Department of Virology, Haartman Institute, University of Helsinki, Finland; Department of Virology, HUSLAB Laboratory Services, Helsinki, Finland.
Demyelinating diseases of the central nervous system (CNS) often include elevated IgG production in intrathecal space presenting as oligoclonal bands (OCBs) in cerebrospinal fluid (CSF). In most demyelinating diseases, e.g. in multiple sclerosis (MS), the underlying cause is not known. We used isoelectric focusing and affinity immunoblot to study the specificity of CSF OCBs to human herpesvirus-6 (HHV-6) in patients with demyelinating diseases of the CNS including MS. Eighty patients with positive OCB finding were included in the study. The OCBs reacted with the HHV-6 antigen in 18 cases (23%). Twelve of 46 MS patients (26%), 5 of 24 other demyelinating diseases (21%) and 1 of 10 other neurological disorders (10%) had HHV-6 specific OCBs in CSF. A specific intrathecal HHV-6 A and B antibody production was shown in a proportion of patients with demyelinating diseases and might suggest a role in the pathogenesis of these diseases.
PMID: 21767883  [PubMed - as supplied by publisher]
Lympohcyte calcium influx kinetics in multiple sclerosis treated without or with interferon beta.
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Kv1.3 and IKCa1 potassium channels play an important role in the maintenance of calcium-influx during lymphocyte activation and present a possible target for selective immunomodulation. We investigated the calcium-influx characteristics of Th1, Th2, CD4, CD8 T-lymphocytes isolated from multiple sclerosis patients without or with interferon-beta therapy, and its modulation by Kv1.3 and IKCa1 channel inhibitors using flow cytometry. Specific immunomodulation of the CD8 subset can be reached through inhibition of Kv1.3 channels in multiple sclerosis patients without interferon-beta. However, this effect is not specific enough concerning all lymphocyte subsets influencing the autoimmune response, since it also affects anti-inflammatory Th2 cells.

PMID: 21764463 [PubMed - as supplied by publisher]

Fingolimod modulates microglial activation to augment markers of remyelination.
Jackson SJ, Giovannoni G, Baker D.

ABSTRACT: INTRODUCTION: Microglial activation in multiple sclerosis has been postulated to contribute to long-term neurodegeneration during disease. Fingolimod has been shown to impact on the relapsing remitting phase of disease by modulating autoreactive T-cell egress from lymph organs. In addition, it is brain penetrant and has been shown to exert multiple effects on nervous system cells. METHODS: In this study, the impact of fingolimod and other sphingosine-1-phosphate receptor active molecules following lysophosphatidyl choline-induced demyelination was examined in the rat telencephalon reaggregate, spheroid cell culture system. The lack of immune system components allowed elucidation of the direct effects of fingolimod on CNS cell types in an organotypic situation. RESULTS: Following demyelination, fingolimod significantly augmented expression of myelin basic protein in the remyelination phase. This increase was not associated with changes in neurofilament levels, indicating de novo myelin protein expression not associated with axonal branching. Myelin wrapping was confirmed morphologically using confocal and electron microscopy. Increased remyelination was associated with down-regulation of microglial ferritin, tumor necrosis factor alpha and interleukin 1 during demyelination when fingolimod was present. In addition, nitric oxide metabolites and apoptotic effectors caspase 3 and caspase 7 were reduced during demyelination in the presence of fingolimod. The sphingosine-1-phosphate receptor 1 and 5 agonist BAF312 also increased myelin basic protein levels, whereas the sphingosine-1-phosphate receptor 1 agonist AUY954 failed to replicate this effect on remyelination. CONCLUSIONS: The results presented indicate that modulation of S1P receptors can ameliorate pathological effectors associated with microglial activation leading to a subsequent increase in protein and morphological markers of remyelination. In addition, sphingosine-1-phosphate receptor 5 is implicated in promoting remyelination in vitro. This knowledge may be of benefit for treatment of chronic microglial inflammation in multiple sclerosis.

PMID: 21729281 [PubMed - as supplied by publisher]
Myelin-phagocytosing macrophages modulate autoreactive T cell proliferation.
Bogie JF, Stinissen P, Hellings N, Hendriks JJ.

ABSTRACT: INTRODUCTION: Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) in which macrophages play a central role. Initially, macrophages where thought to be merely detrimental in MS, however, recent evidence suggests that their functional phenotype is altered following myelin phagocytosis. Macrophages that have phagocytosed myelin may be less inflammatory and may exert beneficial effects. The presence of myelin-containing macrophages in CNS-draining lymph nodes and perivascular spaces of MS patients suggests that these cells are ideally positioned to exert an immune regulatory role. Therefore we evaluated in this study the effect of myelin-phagocytosing macrophages on lymphocyte reactivity.

METHODS: Thioglycolate-elicited rat peritoneal macrophages were loaded with myelin and cocultured with myelin-basic protein (MBP) or ovalbumin (OVA) reactive lymphocytes. Lymphocyte proliferation was determined by CFSE-labeling. The role of nitric oxide in regulating lymphocyte proliferation was assessed by addition of an inhibitor of inducible nitric oxide synthase to the coculture. In vivo immune regulation was investigated by treating MBP- and OVA-immunized animals subcutaneously with myelin. Cognate antigen specific lymphocyte proliferation and nitric oxide production were determined 9d post-immunization.

RESULTS: In this study we demonstrate that myelin-phagocytosing macrophages inhibit TCR-triggered lymphocyte proliferation in an antigen-independent manner. The observed immune suppression is mediated by an increase in NO production by myelin-phagocytosing macrophages upon contact with lymphocytes. Additionally, myelin delivery to primarily CD169+ macrophages in popliteal lymph nodes of OVA-immunized animals results in a reduced cognate antigen specific proliferation. In contrast to OVA-immunized animals, lymphocytes from MBP-immunized animals displayed an increased proliferation after stimulation with their cognate antigen, indicating that myelin-phagocytosing macrophages have dual effects depending on the specificity of surrounding lymphocytes.

CONCLUSIONS: Collectively our data show that myelin phagocytosis leads to an altered macrophage function that inhibits lymphocyte proliferation. Additionally, results from this study indicate that myelin-phagocytosing macrophages fulfill a dual role in vivo. On one hand they aggravate autoimmunity by activating myelin-reactive lymphocytes and on the other hand they suppress lymphocyte reactivity by producing NO.

CD8 T cell deficiency impairs control of Epstein-Barr virus and worsens with age in multiple sclerosis.
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The University of Queensland, School of Medicine, Brisbane, Queensland, Australia.
PMID: 21791511 [PubMed - as supplied by publisher]


Glanz BI, Healy BC, Hviid LE, Chitnis T, Weiner HL.
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Objective The objective was to investigate changes in cognitive functioning in subjects with early multiple sclerosis (MS) over 5&emsp14;years. Methodological issues associated with longitudinal cognitive research such as practice effects and drop-outs were also examined. Methods Ninety subjects with a diagnosis of clinically isolated syndrome or MS and disease duration from a first symptom of ≤6&emsp14;years participated in the study. Subjects were administered the Brief Repeatable Battery of Neuropsychological Tests in MS, which includes five measures assessing four cognitive domains. As a means of stabilising practice effects, the battery was administered 1-2&emsp14;weeks apart at enrolment and then annually for up to 5&emsp14;years. Results Significant deterioration was found on a measure of working memory and speed of information processing. Significant deterioration was also found on measures of immediate and delayed visual spatial memory. Verbal memory was unchanged over the course of the study. Improved performance was observed on a second measure of speed of information processing and on a measure of verbal fluency. Among subjects with longitudinal follow-up, the drop-out rate was 30%, but subjects who dropped out did not differ from those who completed the study in terms of baseline cognitive performance or the change in cognitive performance from year 1 to year 2. Conclusions Subjects with early MS showed a deterioration in working memory and visual spatial memory over a period of up to 5&emsp14;years. Although significant practice effects were associated with several cognitive measures, the Symbol Digit Modality Test may be useful for longitudinal evaluations of cognitive functioning in MS.
PMID: 21746743 [PubMed - as supplied by publisher]


HLA associations with multiple sclerosis in Greece.
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BACKGROUND: Multiple sclerosis (MS) is a demyelinating inflammatory disease of the central nervous system originated by a complex interplay of environmental and genetic factors. The association of MS with the human leukocyte antigen (HLA) class II alleles was investigated in MS patients in northwest Greece, in the geographical region of Epirus. OBJECTIVE: Our aim was to estimate the prevalence of the HLA-DRB1*1501, HLA-DQB1*0602 and HLA-DQA1*0102 alleles, consisting the most common susceptibility haplotype in North European and North American Caucasians. METHODS: We studied 126 MS patients and 93 age and sex matched healthy controls. HLA typing was performed by a polymerase chain reaction (PCR) amplification with sequence-specific primers (PCR-SSP) method. RESULTS: We found that HLA-DRB1*1501, HLA-DQB1*0602 and HLA-DQA1*0102 alleles were significantly more frequent among patients (34% versus 11%, p=0.00015; 69% versus 51%, p=0.01; 76% versus 55%, p=0.002, respectively). HLA-DRB1*1501, HLA-DQB1*0602, HLA-DQA1*0102 haplotype was significantly more common among patients (p=0.00067). HLA-DRB1*1501 and HLA-DQB1*0602 alleles were more frequently detected in patients with initial symptoms from the brainstem or the cerebellum (p=0.024). No significant correlation was observed among these alleles with sex, disease clinical course, or age at onset. CONCLUSION: This is the first study to investigate genetic susceptibility to MS in Greece. Our results are in line with previous reports in North European and North American patients.
PMID: 21741664 [PubMed - as supplied by publisher]

The effect of FTY720 in the Theiler’s virus model of multiple sclerosis.
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FTY720 (fingolimod) has demonstrated efficacy in multiple sclerosis (MS). We evaluated the effects of FTY720 on progressive disability, viral load, and antibody responses in mice infected with Theiler's murine encephalomyocarditis virus (TMEV). FTY720 and phosphorylated FTY720 (FTY720-P) were detected in the brain after intraperitoneal injection of the drug. Bioactivity of FTY720 was confirmed by reduced numbers of mononuclear cells in the spleen and blood after treatment. No significant differences were found in disability progression, viral load, and serum antibody responses between the FTY720-treated versus the PBS-treated mice. There was less production of IgG within the CNS in the FTY-treated group on some measures.

PMID: 21726878  [PubMed - as supplied by publisher]


Vitamin D: Evidence for its role as a prognostic factor in multiple sclerosis.
Mowry EM.

Vitamin D insufficiency has been shown to be associated with increased susceptibility to multiple sclerosis (MS), but until recently, it was unclear if vitamin D status also influences the prognosis of the disease. In experimental autoimmune encephalomyelitis, a mouse model of MS, the administration of vitamin D reduces the severity of the disease. Initial reports in MS of inverse associations between vitamin D levels and disability or relapse rate were encouraging, but the cross-sectional or retrospective study designs limited their interpretability. More recently, studies of pediatric-onset and adult MS have demonstrated that among those with established MS, those with lower vitamin D levels are at higher risk for subsequent relapse. These observational data provide strong support for randomized controlled trials of vitamin D supplementation in MS.

PMID: 21762931  [PubMed - as supplied by publisher]


Characterization of the multiple sclerosis traits: Nuclear receptors (NR) impaired apoptosis pathway and the role of 1-alpha 25-dihydroxyvitamin D(3).
Achiron A, Feldman A, Gurevich M.

Low expression of NR4A gene family members (NR4A1, NR4A3) and 1-alpha, 25-dihydroxyvitamin D(3) receptor (VDR) genes was demonstrated in peripheral blood mononuclear cells (PBMC) of subjects evaluated during the pre-disease state of multiple sclerosis (MS-to-be, MS2b), in patients with clinically isolated syndrome (CIS) during the very early presentation of neurological symptomatology and in relapsing-remitting MS (RRMS) patients. Both NR4A1 and NR4A3 are known to be involved in T-cell receptor-induced apoptosis and are regulated by VDR. We further evaluated the precise implications of apoptosis signaling regulators in relation to MS pathogenesis at the cellular level by studying the effects of 1-alpha, 25-dihydroxyvitamin D(3) (Vit D(3)) upon NR4A1 expression. We demonstrated that the low apoptotic level in MS patients was repaired by Vit D(3) mainly through NR4A1 and to a lesser extent thorough BCL2-associated X protein (BAX). These findings prove a role for Vit D(3) as a possible therapeutic intervention in MS patients aimed to activate the repressed apoptosis and enhance better control of the disease.

PMID: 21752397  [PubMed - as supplied by publisher]
Vitamin D-mediated immune regulation in Multiple Sclerosis.
Correale J, Ysraeilit MC, Gaitán MI.
Although Vitamin D is best known as a modulator of calcium homeostasis, it also has immune modulating potential. A protective effect of Vitamin D on Multiple Sclerosis (MS) is supported by the reduced risk associated with sun exposure and use of Vitamin D supplements. Moreover, high circulating levels of Vitamin D have been associated with lower risk of MS. To gain more insight into putative regulatory mechanisms of Vitamin D in MS pathogenesis, we studied 132 Hispanic patients with clinically definite MS, 58 with relapsing remitting MS (RR MS) during remission, 34 RR MS patients during relapse, and 40 primary progressive MS cases (PP MS). Sixty healthy individuals matched with respect to place of residence, race/ethnicity, age and gender served as controls. Levels of 25(OH) Vitamin D and 1,25(OH)(2) Vitamin D, measured by ELISA were significantly lower in RR MS patients than in controls. In addition, levels in patients suffering relapses were lower than during remissions. By contrast, PP MS patients showed similar values to controls. Proliferation of both freshly isolated CD4+ T cells and MBP-specific T cells was significantly inhibited by 1,25(OH)(2) Vitamin D. Moreover, activated Vitamin D enhanced the development of IL-10 producing cells, and reduced the number of IL-6 and IL-17 secreting cells. Notably, VDR expression was induced by 1,25(OH)(2) Vitamin D in both activated and resting cells. Interestingly, T cells were able to metabolize 25(OH) Vitamin D into biologically active 1,25(OH)(2) Vitamin D, since T cells express 1α-hydroxylase constitutively. Finally, 1,25(OH)(2) Vitamin D also increased the expression and biological activity of IDO, triggering significant increase in the number of CD4+CD25+ T regulatory cells. Collectively, these findings suggest that 1,25(OH)(2) Vitamin D plays an important role in T cell homeostasis during the course of MS, suggesting correction of its deficiency may be useful during treatment of the disease.
PMID: 21723567 [PubMed - as supplied by publisher]

Leber Hereditary Optic Neuropathy Mimicking Neuromyelitis Optica.
McClelland CM, Van Stavern GP, Tselis AC.
Department of Ophthalmology (CMM, GPVS), Washington University, St. Louis, Missouri; Department of Neurology (ACT), Wayne State University, Detroit, Michigan.
Leber hereditary optic neuropathy (LHON) is rarely associated with multiple sclerosis-like features. We present a case of a 65-year-old African American woman with LHON masquerading as neuromyelitis optica (NMO). We highlight the features of the clinical examination and MRI that were suggestive of an alternative diagnosis and review the literature regarding LHON and multiple sclerosis. The diagnosis of LHON should be considered in all cases of acute or subacute bilateral optic neuropathy, including presumed seronegative NMO.
PMID: 21734595 [PubMed - as supplied by publisher]

Modulation of inhibitory strength and kinetics facilitates regulation of persistent inward currents and motoneuron excitability following spinal cord injury.
Venugopal S, Hamm TM, Crook SM, Jung R.
1Arizona State University.
Spasticity is commonly observed after chronic spinal cord injury (SCI) and many other central nervous system disorders (e.g., multiple sclerosis, stroke). SCI-induced spasticity has been associated with motoneuron hyperexcitability partly due to enhanced activation of intrinsic persistent inward currents (PICs). Disrupted spinal inhibitory mechanisms have also been implicated. Altered inhibition can result from complex changes in the strength, kinetics and reversal potential (E(Cl)-) of γ-aminobutyric acidA (GABA(A)) and glycine receptor currents. Development of optimal therapeutic strategies requires an understanding of the impact of these interacting factors on motoneuron excitability. We employed computational methods to study the effects of conductance, kinetics, and E(Cl)- of a dendritic inhibition on PIC activation and motoneuron discharge. A two-compartment motoneuron with enhanced PICs characteristic of SCI and receiving recurrent inhibition from Renshaw cells was utilized in these simulations. This dendritic inhibition regulated PIC onset and offset and exerted its strongest effects at motoneuron recruitment and in the secondary range of the I-F relationship during PIC activation. Increasing inhibitory conductance compensated for moderate depolarizing shifts in E(Cl)- by limiting PIC activation and self-sustained firing. Furthermore, GABA(A) currents exerted greater control on PIC activation than glycnergic currents, an effect attributable to their slower kinetics. These results suggest that modulation of the strength and kinetics of GABA(A) currents could provide treatment strategies for uncontrollable spasms.
PMID: 21775715 [PubMed - as supplied by publisher]
Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system. Exogenous cell replacement in MS lesions has been proposed as a means of achieving remyelination when endogenous remyelination has failed. However, the ability of exogenous cells to remyelinate axons in the presence of inflammation remains uncertain. We have explored the remyelinating capacity of an oligodendrocyte progenitor cell line CG-4 transduced with the GFP gene and transplanted adjacent to a zymosan-induced focal demyelination model in the rat spinal cord. The resulting zymosan-induced lesions were characterized by persistent macrophage/microglia activation, focal demyelination, degeneration of axons, and reactive astrogliosis. GFP(+) CG-4 cells were found to migrate preferentially toward the inflammatory lesion and survive inside the lesion. A proportion of GFP(+) CG-4 cells differentiated into mature oligodendrocytes and remyelinated axons within the lesion. These findings suggest that grafted oligodendrocyte progenitors may migrate toward areas of inflammation in the adult rat spinal cord, where they can survive and differentiate into myelinating oligodendrocytes. © 2011 Wiley-Liss, Inc.

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Social cognitive correlates of physical activity: findings from a cross-sectional study of adults with relapsing-remitting multiple sclerosis.

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BACKGROUND: Persons with multiple sclerosis (MS) are often physically inactive and sedentary. This observation has prompted the search for modifiable variables derived from established theories that act as correlates of physical activity. Such variables would presumably represent targets for interventions designed to promote change in physical activity behavior among persons with MS. The current study examined social cognitive variables as correlates of physical activity in persons with MS. METHODS: Persons (N = 218) with relapsing-remitting MS completed a questionnaire battery that assessed physical activity behavior; self-efficacy for physical activity; physical, social, and self-evaluative outcome expectations for exercise, functional limitations as an impediment for physical activity, and exercise goal-setting. The battery was delivered and returned through the US postal service. Data were analyzed using covariance modeling in Mplus 3.0.

RESULTS: Self-efficacy had indirect effects on physical activity via impediments (path coefficient = .10, P < .005), self-evaluative outcome expectations (path coefficient = .07, P < .025), and goal-setting (path coefficient = .09, P < .01). The model explained 40% of variance in self-reported physical activity.

CONCLUSIONS: This cross-sectional study suggests that self-efficacy is indirectly associated with physical activity by way of goals, self-evaluative outcome expectations, and impediments in persons with relapsing-remitting MS.

PMID: 21734307 [PubMed - in process]

Lipidomic investigations for the characterization of circulating serum lipids in multiple sclerosis.

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Multiple Sclerosis (MS) is a neurodegenerative autoimmune demyelinating disease affecting young adults. The aetiology still remains a mystery and diagnosis is impaired by the lack of defined molecular markers. Autoimmune response remains the main topic under investigation and recent studies suggest additional non-proteic mediators of brain inflammation such as lipids. We carried out an LC-MS based lipidomics approach to highlight serum lipids profiling in MS. Method was optimised and applied in a preliminary clinical cross-sectional investigation of MS patients vs Healthy Controls (HC) and patients with Other Neurological Diseases (OND). Ten significant metabolites were highlighted and tentatively identified by accurate mass and MS/MS experiments. Our most relevant data show altered level of lyso-glycerophosphatidylcholine (lysoPC) and glycerophosphatidylcholine (PC) species. Total lysoPC/PC ratio showed significant decrease in pathological groups (MS, OND) and, in addition, MS subjects had a relevant decrease of this ratio also in respect to OND. These findings suggest that there may be an altered phospholipid metabolism in MS that can be evaluated in serum. Some of these features are distinctive and may be considered specific for MS. Our lipidomics data show, for the first time, evidence in serum of a relationship between LysoPC/PC ratio and MS. PMID: 21757039 [PubMed - as supplied by publisher]

**The L coding region of DA strain of TMEV causes dysfunction and death of myelin-synthesizing cells.**

Ghadge GD, Wollmann R, Baida G, Traka M, Roos RP.
Departments of Neurology.

DA strain and other members of the TO subgroup of Theiler's murine encephalomyelitis virus (TMEV) induce an early transient subclinical neuronal disease followed by a chronic progressive inflammatory demyelination, with persistence of the virus in the central nervous system (CNS) for the life of the mouse. Although Theiler's virus induced demyelinating disease (TMEV-IDD) is thought to be immune-mediated, there is also evidence that supports a role for the virus in directly inducing demyelination. In order to clarify the function of DA virus genes, we generated a transgenic mouse that had tamoxifen-inducible expression of the DA L coding region in oligodendrocytes (and Schwann cells), a cell type in which the virus is known to persist. Tamoxifen-treated young transgenic mice usually developed an acute progressive fatal paralysis with abnormalities of the oligodendrocyte and Schwann cell and demyelination, but without significant lymphocytic infiltration; later treatment led to transient weakness with demyelination and persistent expression of the recombined transgene. These findings demonstrate that a high level of expression of DA L can cause the death of myelin-synthesizing cells and death of the mouse, while a lower level of L expression (which can persist) can lead to cellular dysfunction with survival. The results suggest that expression of DA L plays an important role in the pathogenesis of TMEV-IDD. Virus-induced infection and death of oligodendrocytes may play a role in the demyelination of other diseases in which an immune-mediated mechanism has been stressed, including multiple sclerosis.

PMID: 21752920  [PubMed - as supplied by publisher]


**Surgical transplantation of mouse neural stem cells into the spinal cords of mice infected with neurotropic mouse hepatitis virus.**

Carbajal KS, Weinger JG, Whitman LM, Schaumburg CS, Lane TE.
Department of Molecular Biology and Biochemistry, University of California, Irvine.

Mice infected with the neurotropic JHM strain of mouse hepatitis virus (MHV) develop pathological and clinical outcomes similar to patients with the demyelinating disease Multiple Sclerosis (MS). We have shown that transplantation of NSCs into the spinal cords of sick mice results in a significant improvement in both remyelination and in clinical outcome. Cell replacement therapies for the treatment of chronic neurologic diseases are now a reality and in vivo models are vital in understanding the interactions between the engrafted cells and host tissue microenvironment. This presentation provides an adapted method for transplanting cells into the spinal cord of JHMV-infected mice. In brief, we provide a procedure for i) preparation of NSCs prior to transplant, ii) pre-operative care of mice, iii) exposure of the spinal cord via laminectomy, iv) stereotactic injection of NSCs, and iv) post-operative care.

PMID: 21775959  [PubMed - in process]


**Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring.**

University Hospital, Basel, Switzerland.

Natalizumab, a highly specific α4-integrin antagonist, is approved for treatment of patients with active relapsing-remitting multiple sclerosis (RRMS). It is generally recommended for individuals who have not responded to a currently available first-line disease-modifying therapy or who have very active disease. The expected benefits of natalizumab treatment have to be weighed against risks, especially the rare but serious adverse event of progressive multifocal leukoencephalopathy. In this Review, we revisit and update previous recommendations on natalizumab for treatment of patients with RRMS, based on additional long-term follow-up of clinical studies and post-marketing observations, including appropriate patient selection and management recommendations.

PMID: 21777829  [PubMed - in process]


**Natalizumab for multiple sclerosis: a complicated treatment.**

Keegan BM.
Department of Neurology, Mayo Clinic, Rochester, MN 55905, USA.

PMID: 21777819  [PubMed - in process]
Combining statins with interferon beta in multiple sclerosis: think twice, it might not be all right.
Zamvil SS, Steinman L.
Department of Neurology and Program in Immunology, University of California, San Francisco, San Francisco, CA 94143, USA; Department of Neurology and Neurological Sciences and Interdepartmental Program in Immunology, Stanford University, Stanford, CA 94305, USA.
PMID: 21742557 [PubMed - in process]

Simvastatin as add-on therapy to interferon beta-1a for relapsing-remitting multiple sclerosis (SIMCOMBIN study): a placebo-controlled randomised phase 4 trial.
Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark.
BACKGROUND: Treatment of relapsing-remitting multiple sclerosis with interferon beta is only partly effective. We aimed to establish whether add-on of simvastatin, a statin with anti-inflammatory properties, improves this efficacy. METHODS: We enrolled treatment-naive patients with relapsing-remitting multiple sclerosis in a multicentre, placebo-controlled, double-blind, randomised, parallel-group trial of simvastatin (80 mg daily) as add-on treatment to intramuscular interferon beta-1a (30 µg weekly). After starting treatment with interferon beta, patients were randomly assigned (in computer-generated blocks of four patients) to simvastatin 80 mg per day or placebo for 1-3 years. Patients and treating and evaluating physicians were masked to treatment allocation. The primary outcome measure was annual rate of documented relapses; analysis was by intention to treat. This trial is registered at ClinicalTrials.gov, NCT00492765. FINDINGS: We randomly assigned 307 patients to interferon beta plus simvastatin (n=151) or plus placebo (n=156). Annual rate of documented relapses was 0.19 (95% CI 0.13 to 0.28) in the simvastatin group and 0.14 (95% CI 0.09 to 0.23) in the placebo group (absolute difference 0.059, 95% CI -0.09 to 0.23; p=0.35). Time to first documented relapse (20th percentile) was 18.1 months in patients on simvastatin and 21.5 months in those on placebo (hazard ratio 1.21, 95% CI 0.74 to 1.99; p=0.51). Mean number of new or enlarging T2 lesions was 0.7 (95% CI 0.5 to 1.0) in the simvastatin group and 1.0 (95% CI 0.8 to 1.3) in the placebo group (ratio of new lesions, 0.78, 95% CI 0.58 to 1.04; p=0.08). Eight (6%) patients on simvastatin and 17 (13%) on placebo had no disease activity (odds ratio 0.42, 95% CI 0.17 to 1.00; p=0.05). No unexpected adverse events were seen. Generally, adverse events were mild and there were no group differences in infectious or musculoskeletal disorders, including myalgia (five [3%] patients on simvastatin and nine [6%] on placebo). Rhabdomyolysis and myoglobinuria were not reported and there were no differences in serum creatine phosphokinase. INTERPRETATION: We found no beneficial effect of simvastatin as add-on therapy to interferon beta-1a. Although unlikely, we can not exclude that combination of other statins with other disease-modifying drugs still could be beneficial. FUNDING: Biogen Idec.
PMID: 21742556 [PubMed - as supplied by publisher]

Reconstitution of the human biome as the most reasonable solution for epidemics of allergic and autoimmune diseases.
Bilbo SD, Wray GA, Perkins SE, Parker W.
Department of Psychology and Neuroscience, Systems and Integrative Neuroscience Group, Duke University, Durham, NC 27710, United States.
A wide range of hyperimmune-associated diseases plague post-industrial society, with a prevalence and impact that is staggering. Strong evidence points towards a loss of helminths from the ecosystem of the human body (the human biome) as the most important factor in this epidemic. Helminths, intestinal worms which are largely eradicated by elements of post-industrial culture including toilets and water treatment facilities, have an otherwise ubiquitous presence in vertebrates, and have co-evolved with the immune system. Not only do helminths discourage allergic and autoimmune reactions by diverting the immune system away from these pathologic processes and stimulating host regulatory networks, helminths release a variety of factors which down-modulate the immune system. A comprehensive view of hyperimmune-related disease based on studies in immunology, parasitology, evolutionary biology, epidemiology, and neurobiology indicates that the effects of biome depletion may not yet be fully realized, and may have an unexpectedly broad impact on many areas of human biology, including cognition. Fortunately, colonization with helminths results in a cure of numerous autoimmune and allergic diseases in laboratory rodents, and clinical studies in humans have indicated their utility for treatment of both multiple sclerosis and inflammatory bowel disease. Based on these considerations, commitment of considerable resources toward understanding the effects of "biome depletion" and systematically evaluating the most effective approach toward biome reconstitution is strongly encouraged. PMID: 21741180 [PubMed - as supplied by publisher]
Hypothesis: Everyday products induce multiple sclerosis.
Buchter B, Dunkel M, Li J.
Alberta, Bertastrasse 18a, CH-8003 Zürich, Switzerland.
PMID: 21788105 [PubMed - as supplied by publisher]

Vascular Dysfunction and Physical Activity in Multiple Sclerosis.
Ranadive SM, Yan H, Weikert M, Lane AD, Linden MA, Baynard T, Motl RW, Fernhall B.
From the Department of Kinesiology and Community Health, University of Illinois, Urbana-Champaign, IL.
BACKGROUND:: Multiple sclerosis (MS) is an inflammatory disorder of the brain and spinal cord. Disability status and progression are associated with reduced physical activity (PA) and cardiovascular function. Lack of adequate PA combined with inflammation may create high susceptibility to subclinical atherosclerosis and vascular dysfunction. PURPOSE:: The purpose of this study was to compare subclinical atherosclerosis and arterial function between individuals with and without MS matched on age, sex and BMI. METHODS:: 33 individuals diagnosed with MS and 33 controls, underwent strain-gauge plethysmography for resting forearm blood flow (FBF) and peak reactive hyperemia (RHpeak) for the micro-vascular function. Intima media thickness (IMT) and arterial compliance (AC) were measured using carotid ultrasound for vascular function. C-reactive protein (CRP) and PA (7-day accelerometer data) were also measured. RESULTS:: There was a significant difference (p<.05) in resting FBF, RHpeak, cPWV and AC between the MS and control group respectively. PA was associated with peak FBF and cPWV, but not FBF and carotid AC. Individuals with MS exhibit reduced arterial function but similar IMT compared to controls. Persons with MS had significantly reduced PA levels compared with controls, and physical activity accounted for differences in arterial function between groups. CONCLUSIONS:: These results indicate that subclinical markers of atherosclerosis are higher in individuals with MS, suggesting a higher risk of CVD in this population. However, the higher levels of subclinical atherosclerosis was accounted for by the low PA in persons with MS, suggesting that increasing PA may reduce the increase in CVD risk in patients with MS.
PMID: 21775908 [PubMed - as supplied by publisher]

Cross-Talk between Apolipoprotein E and Cytokines.
Zhang H, Wu LM, Wu J.
Department of Neurology, The First Hospital of Jilin University, Jilin University, 130021 Changchun, China.
Apolipoprotein E (apoE) is a multifunctional glycosylated protein characterized by its wide tissue distribution. Despite its importance in lipid transport and atherosclerosis pathogenesis, apoE is associated with neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson disease, and autoimmune disorders such as multiple sclerosis and psoriasis. Among others, the role of apoE in modulating inflammation and oxidation is crucial in elucidating the risk factors of the above diseases since the function of apoE is closely linked with both proinflammatory and antiinflammatory cytokines. Moreover, apoE modulates inflammatory and immune responses in an isoform-dependent manner. Correspondingly, inflammatory cytokines can either upregulate or downregulate the production of apoE in various tissue types. However, studies on the interactions between apoE and cytokines occasionally yield conflicting results, highlighting the complex roles of apoE and cytokines in various disorders. The present paper summarizes the current knowledge about the cross-talk between apoE and cytokines, with emphasis on the effects of apoE on the Th1/Th2 balance.
PMCID: PMC3136159 PMID: 21772670 [PubMed - in process]

**Overexpression and purification of U24 from Human Herpesvirus Type-6 in E. coli: unconventional use of oxidizing environments with a maltose binding protein-hexahistidine dual tag to enhance membrane protein yield.**

Tait AR, Straus SK.

**ABSTRACT:** BACKGROUND: Obtaining membrane proteins in sufficient quantity for biophysical study and biotechnological applications has been a difficult task. Use of the maltose binding protein / hexahistidine dual tag system with E.coli as an expression host is emerging as a high throughput method to enhance membrane protein yield, solubility, and purity, but fails to be effective for certain proteins. Optimizing the variables in this system to fine-tune for efficiency can ultimately be a daunting task. To identify factors critical to success in this expression system, we have selected to study U24, a novel membrane protein from Human Herpesvirus type-6 with potent immunosuppressive ability and a possible role in the pathogenesis of the disease multiple sclerosis. RESULTS: We expressed full-length U24 as a C-terminal fusion to a maltose binding protein / hexahistidine tag and examined the effects of temperature, growth medium type, cell strain type, oxidizing vs. reducing conditions and periplasmic vs. cytoplasmic expression location. Temperature appeared to have the greatest effect on yield; at 37°C full-length protein was either poorly expressed (periplasm) or degraded (cytoplasm) whereas at 18°C, expression was improved especially in the periplasm of C41(DE3) cells and in the cytoplasm of oxidizing Dtrx/Dgor mutant strains, Origami 2 and SHuffle. Expression of the fusion protein in these strains were estimated to be 3.2, 5.3 and 4.3 times greater, respectively, compared to commonly-used BL21(DE3) cells. We found that U24 is isolated with an intramolecular disulfide bond under these conditions, and we probed whether this disulfide bond was critical to high yield expression of full-length protein. Expression analysis of a C21SC37S cysteine-free mutant U24 demonstrated that this disulfide was not critical for full-length protein expression, but it is more likely that strained metabolic conditions favour factors which promote protein expression. This hypothesis is supported by the fact that use of minimal media could enhance protein production compared to nutrient-rich LB media. CONCLUSIONS: We have found optimal conditions for heterologous expression of U24 from Human Herpesvirus type-6 in E.coli and have demonstrated that milligram quantities of pure protein can be obtained. Strained metabolic conditions such as low temperature, minimal media and an oxidizing environment appeared essential for high-level, full-length protein production and this information may be useful for expressing other membrane proteins of interest.

PMID: 21714924  [PubMed - as supplied by publisher]


**1,25-Dihydroxyvitamin D3 Ameliorates Th17 Autoimmunity Via Transcriptional Modulation of IL-17A.**


Department of Biochemistry and Molecular Biology, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, NJ, USA.

A new class of inflammatory CD4(+)-T cells production IL-17 (Th17) has been identified which plays a critical role in numerous inflammatory conditions and autoimmune diseases. The active form of vitamin D, 1,25(OH)(2)D(3), has a direct repressive effect on the expression of IL-17A in both human and mouse T cells. In vivo treatment of mice with ongoing experimental autoimmune encephalomyelitis (EAE; a mouse model of multiple sclerosis) diminishes paralysis and progression of the disease and reduces IL-17A secreting CD4(+) T cells in the periphery and CNS. The mechanism of 1,25(OH)(2)D(3) repression of IL-17A expression was found to be transcriptional repression mediated by VDR. Transcription assays, gel shift and ChiP assays indicate that the negative effect of 1,25(OH)(2)D(3) on IL-17A involves blocking of NFAT, recruitment of HDAC, sequestration of Runx1 by 1,25(OH)(2)D(3)/VDR as well as direct effect of 1,25(OH)(2)D(3) on induction of Foxp3. Our results describe novel mechanisms and new concepts with regard to vitamin D and the immune system and suggest therapeutic targets for the control of autoimmune diseases.

PMID: 21746882  [PubMed - as supplied by publisher]
Sphingosine 1-phosphate receptor modulator fingolimod (FTY720) does not promote remyelination in vivo.
Hu Y, Lee X, Ji B, Guckian K, Apicco D, Pepinsky RB, Miller RH, Mi S.
Biogen Idec Inc., Neuro-Discovery Biology, 14 Cambridge Center, Cambridge, Massachusetts 02142, United States.
The sphingosine 1-phosphate (S1P) receptor modulators have emerged as a new therapeutic opportunity paradigm for the treatment of immune-mediated demyelinating diseases such as multiple sclerosis (MS). The S1P analog fingolimod (FTY720) has been shown to alleviate disease burden in immune-mediated animal models of MS, and has been approved for treatment in clinical trials in patients with MS in the United States. While the immunological effects of FTY720 are well established, there is controversy in the literature regarding the contribution of FTY720 on myelin repair. Here, we directly assessed the impact of FTY720 on myelin repair in cuprizone and lysolecithin (LPC) demyelination models that have a minimal immunological component. FTY720 failed to promote remyelination in either animal model. These studies suggest that while FTY720 may be effective at modulating the immunological attack in MS, it may benefit from an add-on therapy to enhance the myelin repair required for long-term functional restoration in MS.
PMID: 21740973 [PubMed - as supplied by publisher]

139. Mol Pharm. 2011 Jul 19. [Epub ahead of print]
A Single Intrathecal Injection of DNA and an Asymmetric Cationic Lipid as Lipoplexes Ameliorates Experimental Autoimmune Encephalomyelitis.
Yellayi S, Hilliard B, Ghazanfar M, Tsingalia A, Nantz MH, Bollinger L, de Kok-Mercado F, Hecker JG.
Department of Pathology and Laboratory Medicine, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6112, United States.
Intrathecal delivery of gene therapeutics is a route of administration that overcomes several of the limitations that plague current immunosuppressive treatments for autoimmune diseases of the central nervous system (CNS). Here we report intrathecal delivery of small amounts (3 µg) of plasmid DNA that codes for an immunomodulatory fusion protein, OX40-TRAIL, composed of OX40, a tumor necrosis factor receptor, and tumor necrosis factor related apoptosis inducing ligand (TRAIL). This DNA was delivered in a formulated nucleic acid-lipid complex (lipoplexes) with an asymmetric two-chain cationic lipid myristoyl (14:0) and lauroyl (12:1) rosenthal inhibitor-substituted compound (MLRI) formed from the tetraalkylammonium glycerol-based compound N-(1-(2,3-dioleoyloxy)-propyl-N-1-(2-hydroxy)ethyl)-N,N-dimethyl ammonium iodide. Delivery and expression in the CNS of OX40-TRAIL in the mouse prior to onset of experimental autoimmune encephalomyelitis (EAE), an animal model for multiple sclerosis, decreased the severity of clinical disease. We believe this preclinical demonstration of rapid, widespread, and biologically therapeutic nonviral gene delivery to the CNS is important in further development of clinical lipid-based therapeutics for CNS disorders.
PMID: 21732666 [PubMed - as supplied by publisher]

140. Mol Pharm. 2011 Jul 13. [Epub ahead of print]
Hematopoietic Stem Cell Gene Therapy as a Treatment for Autoimmune Diseases.
Alderuccio F, Nasa Z, Chung J, Ko HJ, Chan J, Toh BH.
Department of Immunology, Monash Central Clinical School, and Centre for Inflammatory Diseases, Department of Medicine, Southern Clinical School, Monash University, Victoria, Australia.
A key function of the immune system is to protect us from foreign pathogens such as viruses, bacteria, fungi and multicellular parasites. However, it is also important in many other aspects of human health such as cancer surveillance, tissue transplantation, allergy and autoimmune disease. Autoimmunity can be defined as a chronic immune response that targets self-antigens leading to tissue pathology and clinical disease. Autoimmune diseases, as a group of diseases that include type 1 diabetes, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus, have no effective cures, and treatment is often based on long-term broad-spectrum immunosuppressive regimes. While a number of strategies aimed at providing disease specific treatments are being explored, one avenue of study involves the use of hematopoietic stem cells to promote tolerance. In this manuscript, we will review the literature in this area but in particular examine the relatively new experimental field of gene therapy and hematopoietic stem cell transplantation as a molecular therapeutic strategy to combat autoimmune disease.
PMID: 21732672 [PubMed - as supplied by publisher]

Deussing E; Armed Forces Health Surveillance Center (AFHSC).
PMID: 21793602 [PubMed - in process]

**Multiple sclerosis relapses are not associated with exercise.**

Tallner A, Waschbisch A, Wenny I, Schwab S, Hentschke C, Pfeifer K, Mäurer M.

Institute of Sport Science and Sport, University of Erlangen-Nürnberg, Germany.

Since multiple sclerosis (MS) often affects physically active young individuals, it is important to know if exercise can result in increased disease activity. Therefore we used a self-report questionnaire to examine the relationship of different levels of sports activity and relapses in 632 patients with MS. In order to analyse whether subjective recall might have biased the results, we performed, in a subgroup of our sample, an objective assessment of clinical data and physical fitness parameters. We were unable to find any association between sports activity and clinical relapses in either of the two analyses. The group with highest activity even shows the lowermost mean values, standard deviations and range concerning the number of relapses. Our data suggest that physical activity has no significant influence on clinical disease activity.

PMID: 21733890 [PubMed - as supplied by publisher]

143. Mult Scler. 2011 Jul 5. [Epub ahead of print]

**Contact dermatitis induced by glatiramer acetate.**

Haltmeier S, Yıldız M, Müller S, Anliker M, Heinzinger L.

Department of Dermatology and Allergy, Cantonal Hospital of St Gallen, Switzerland.

Glatiramer acetate (Copaxone®) is an immunomodulatory polypeptide used in patients with relapsing-remitting multiple sclerosis. It represents a safe treatment option with mild side effects. In this study, we look at a 39-year-old woman who received glatiramer acetate as subcutaneous injections for two months and developed contact dermatitis. The drug had to be stopped, and treatment with topical prednisone was initiated. Prick/scratch testing was negative but the lymphocyte transformation test was highly positive for glatiramer acetate. This is the first report on contact dermatitis induced by glatiramer acetate injections. The treatment consisted of local topical steroids and cessation of the drug.

PMID: 21729979 [PubMed - as supplied by publisher]

144. Mult Scler. 2011 Jul 5. [Epub ahead of print]

**Pronounced focal and diffuse brain damage predicts short-term disease evolution in patients with clinically isolated syndrome suggestive of multiple sclerosis.**


Department of Neurology, Psychiatry and Psychology, "Sapienza" University of Rome, Italy.

Background: In clinically isolated syndrome (CIS), the role of quantitative magnetic resonance imaging (MRI) in detecting prognostic markers is still debated. Objective: To evaluate measures of diffuse brain damage (such as brain atrophy and the ratio of N-acetylaspatic acid to creatine (NAA/Cr)) in patients with CIS, in addition to focal damage, as predictors of 1-year disease evolution. Methods: 49 patients with CIS underwent MRI scans to quantify T2-lesions (T2-L) and gadolinium-enhanced lesion (GEL) number at baseline and after 1 year. Along with 25 healthy volunteers, they also underwent combined MRI/magnetic resonance spectroscopy examination to measure normalized brain volumes (NBVs) and NAA/Cr. Occurrence of relapses and new T2-L was recorded over 1 year to assess disease evolution. Results: Occurrence of relapses and/or new T2-L over 1 year divided patients with CIS into 'active' and 'stable' groups. Active patients had lower baseline NAA/Cr and NBV. Baseline T2-L number, GEL, NAA/Cr and NBV predicted subsequent disease activity. Multivariable logistic regression models showed that both 'focal damage' (based on T2-L number and GEL) and 'diffuse damage' (based on NBV and NAA/Cr) models predicted disease activity at 1 year with great sensitivity, specificity and accuracy. This was best when the four MRI measures were combined (80% sensitivity, 89% specificity, 83% accuracy). Conclusions: Quantitative MRI measures of diffuse tissue damage such as brain atrophy and NAA/Cr, in addition to measures of focal demyelinating lesions, may predict short-term disease evolution in patients with CIS, particularly when used in combination. If confirmed in larger studies, these findings may have important clinical and therapeutic implications.

PMID: 21729978 [PubMed - as supplied by publisher]

Oral fingolimod (FTY720) in relapsing multiple sclerosis: impact on health-related quality of life in a phase II study.
Unitat de Neuroimmunologia Clinica, Vall d'Hebron University Hospital, Barcelona, Spain.
Background: Health-related quality of life (HRQoL) worsens with multiple sclerosis (MS) relapses and disease progression. Common symptoms including depression and fatigue may contribute to poor HRQoL. Objectives: To report exploratory analyses assessing the impact of fingolimod (FTY720) on HRQoL and depression in a phase II study of relapsing MS. Methods: The Hamburg Quality of Life Questionnaire in MS (HAQUAMS) and Beck Depression Inventory second edition (BDI-II) scores were assessed during a 6-month, placebo-controlled study and optional extension. Results: HAQUAMS total score improved with fingolimod and worsened with placebo. Mean score change from baseline to month 6 was +0.02 with fingolimod 1.25 mg (p<0.05 versus placebo), -0.01 with fingolimod 5.0 mg and p0.12 with placebo. Categorical data supported a clinically important effect of fingolimod on HRQoL. Fingolimod 1.25 mg was also beneficial over placebo in the fatigue/thinking HAQUAMS sub-domain (p<0.05 versus placebo). Change in mean BDI-II scores from baseline to month 6 and the proportion of patients with BDI-II scores indicative of clinical depression favored fingolimod 1.25 mg over placebo (p<0.05 for both). At month 4, mean BDI-II and HAQUAMS total scores appeared to be maintained in fingolimod-treated patients. Conclusion: Fingolimod 1.25 mg may improve HRQoL and depression at 6 months compared with placebo in patients with relapsing MS.
PMID: 21727148 [PubMed - as supplied by publisher]


Focal multiple sclerosis lesions abound in 'normal appearing white matter'
Mistry N, Tallantyre EC, Dixon JE, Galazis N, Jaspan T, Morgan PS, Morris P, Evangelou N.
Division of Clinical Neurology, University of Nottingham, Queen's Medical Centre, UK.
Background: The 'normal appearing white matter' (NAWM) in multiple sclerosis (MS) is known to be abnormal using quantitative magnetic resonance (MR) techniques. The aetiology of the changes in NAWM remains debatable. Objective: To investigate whether high-field and ultra high-field T(1)-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) MRI enables detection of MS white matter lesions in areas defined as NAWM using high-field T(2)-weighted fluid attenuation inversion recovery (FLAIR) MRI; that is, to ascertain whether undetected lesions are likely contributors to the burden of abnormality in similarly defined NAWM. Methods: Fourteen MS patients underwent MRI scans using 3T FLAIR and MPRAGE and 7 Tesla (7T) MPRAGE sequences. Independent observers identified lesions on 3T FLAIR and (7T and 3T) MPRAGE images. The detection of every individual lesion was then compared for each image type. Results: We identified a total of 812 white matter lesions on 3T FLAIR. Using 3T MPRAGE, 186 additional lesions were detected that were not detected using 3T FLAIR. Using 7T MPRAGE, 231 additional lesions were detected that were not detected using 3T FLAIR. Conclusions: MRI with 3T and 7T MPRAGE enables detection of MS lesions in areas defined as NAWM using 3T FLAIR. Focal MS lesions contribute to the abnormalities known to exist in the NAWM.
PMID: 21788249 [PubMed - as supplied by publisher]
**A randomized placebo-controlled cross-over study using a low frequency magnetic field in the treatment of fatigue in multiple sclerosis.**
Carvalho ML, Motta R, Konrad G, Battaglia MA, Brichetto G.
Italian Multiple Sclerosis Society, Genova, Italy.
Background: Fatigue is one of the most common disabling symptoms in multiple sclerosis (MS). There is growing evidence in the literature for beneficial effects of magnetic fields on different MS symptoms and this has been reported to be beneficial in patients with MS, especially those with fatigue. Objectives: The aim of the study was to assess the effects on primary fatigue with a pulsed systemic low frequency magnetic field by means of clinical scales in a population of MS subjects. Methods: Randomized double-blind cross-over trial with 50 MS subjects with primary fatigue who were recruited among those followed as outpatients at the AISM Rehabilitation Centre, Genova, Italy. Subjects were randomized into two groups: magnetic field group and sham therapy group and evaluated with the Modified Fatigue Impact Scale (MFIS), the Fatigue Severity Scale (FSS), VAS and Time Walking Test 10 meter (TWT10m.) at the time points of the study. Each group received both sham therapy and magnetic field therapy with a wash-out period of 5 months. Subjects were treated for 24 min per session, three times per week, for 8 weeks. Statistical analysis was performed using multivariate analysis. Results: Results showed a statistically significant improvement in MFIS Physical Score for T0 - T1 (p < 0.05) for TIME but not for TREATMENT and TIME*TREATMENT factors. No statistically significant differences were found for all other parameters considered in the study. Conclusions: Exposure to a low frequency magnetic field, within the parameters of this treatment protocol, has no advantage over sham exposure in reducing the impact of fatigue.
PMID: 21788248 [PubMed - as supplied by publisher]

**Modelling the distribution of cortical lesions in multiple sclerosis.**
Sormani M, Stromillo ML, Battaglini M, Signori A, De Stefano N.
Biostatistics Unit, Department of Health Sciences, University of Genoa, Italy.
Recent studies have shown the relevance of the cerebral grey matter involvement in multiple sclerosis (MS). Cortical lesions (CLs), detected by specific MRI sequences, are likely to become a new research outcome in MS studies. The aim of this study was to infer the optimal statistical model describing the distribution of CLs in patients with relapsing-remitting (RR)MS. The negative binomial model gave the best fit to the observed distribution of CLs in a group of 44 RRMS patients with one MRI scan of the brain. This observation has important implications for the statistical analysis of CLs in MS studies.
PMID: 21757533 [PubMed - as supplied by publisher]

**High frequency of co-infection by Epstein-Barr virus types 1 and 2 in patients with multiple sclerosis.**
Department of Pathology, Ramón y Cajal University Hospital, IRYCIS, Madrid, Spain.
Background: The existence of Epstein-Barr virus (EBV) strains specifically associated with multiple sclerosis (MS) is a matter of controversy. Little is also known about the prevalence of EBV types 1 and 2 in MS patients and the presence of co-infections by both strains. Objective: To make EBV strain type assignment and compare the frequencies of types 1, 2 and co-infections by both in MS patients and healthy controls. Methods: Blood samples from 75 consecutive MS patients and 186 controls were collected. EBV was simultaneously detected and typed using a polymerase chain reaction (PCR) which amplified a strain-specific sequence in the EBV nuclear antigen 2. Results: EBV was detected in 70 out of 75 patients (93.3%) and in 123 of 186 controls (66.1%). Among positive cases, type 1 was found in 6 patients (8.6%) and 40 controls (32.5%), type 2 in 1 patient (1.4%) and 37 controls (30.1%), and dual-infections by both EBV types were detected in 63 patients (90%) and 46 controls (37.4%). Logistic regression models showed that MS was significantly associated with the presence of EBV (p<0.001) and also with dual type infections (p<0.001). Conclusion: This study provides molecular evidence associating co-infection of type 1 and 2 EBV with MS.
PMID: 21757537 [PubMed - as supplied by publisher]


Oxford Outcomes Ltd, Oxford, UK.

Objective: The aim of this study was to assess the psychometric properties of the FAMS within two clinically distinct populations, CIS and early relapsing-remitting MS (RRMS), and discern the appropriateness of the FAMS within these populations. Methods: Secondary analysis was conducted on FAMS data from two clinical trials assessing interferon beta-1b in early RRMS and CIS. The statistical analysis assessed the scale acceptability, reliability, validity and responsiveness of the FAMS. Item response theory (IRT) was also conducted on the early RRMS sample in order to assess how well the FAMS discriminated amongst individuals with less severe MS. Results: Results from both trials demonstrated an improvement in the FAMS psychometric properties with increased baseline disease severity. However, high ceiling effects were evident amongst less severe patients, and there was an overall lack of responsiveness to improvement and poor construct validity. IRT also demonstrated its lack of discrimination/sensitivity in early RRMS. Conclusions: In trials involving patients with early stage RRMS and CIS, modifications to the FAMS based on a qualitative assessment of its content validity in these populations would be required in order to potentially improve the FAMS psychometric properties and sensitivity.

PMID: 21757536 [PubMed - as supplied by publisher]


Epstein-Barr virus nuclear antigen-1 B-cell epitopes in multiple sclerosis twins.


Centre for Experimental Neurological Therapies, S. Andrea Hospital Hospital-site, Faculty of Medicine and Psychology, Sapienza University, Rome, Italy.

Background: Compared with quantitative observations, the search for qualitative changes that may characterize the immune response to Epstein-Barr virus (EBV) in multiple sclerosis (MS) has been less intense. Objective: To examine the B-cell epitopes of antibodies against the Epstein-Barr nuclear antigen-1 (EBNA-1) and their relevance for MS, through a study in disease-discordant identical twins. Methods: We evaluated the antibodies to all unique, maximally overlapping octapeptides of EBNA-1 in 12 pairs of monozygotic (MZ) twins (9 MS-discordant, 3 healthy), 3 non-twin patients and 2 healthy subjects. All except one of the patients were untreated. The EBV serology of these individuals had been assessed in advance using commercially available and in-house enzyme-linked immunosorbent assay (ELISA) kits, including assays for antibodies against select peptides of EBNA-1: EBNA-72 (GAGGGAGAGG) and EBNA-206 (EADYFEYHQEGGPDGE). Results: The glycine-alanine rich domain of EBNA-1 was immunodominant in all subjects. Compared with healthy individuals, and similarly to what has been described in infectious mononucleosis (IM) patients, affected co-twins and non-twin patients had a significantly increased response to another EBNA-1 epitope (aa. 401-411). Conclusion: In a study that controls for confounders, our data focus an EBNA-1 specificity that may be associated with MS pathogenesis.

PMID: 21757535 [PubMed - as supplied by publisher]
Percutaneous posterior tibial nerve stimulation as an effective treatment of refractory lower urinary tract symptoms in patients with multiple sclerosis: preliminary data from a multicentre, prospective, open label trial.
Neurocentre of Southern Switzerland, Ente Ospedaliero Cantonale, Ospedale Regionale di Lugano, Lugano, Switzerland.
Background: Percutaneous tibial nerve stimulation (PTNS) has been proposed as a new, minimally invasive neuromodulation technique to treat lower urinary tract symptoms (LUTS). Objective: To evaluate efficacy, safety and impact on quality of life (QoL) of PTNS on patients with multiple sclerosis (MS) who have LUTS. Methods: 21 patients (5 men, 16 women) with MS and LUTS unresponsive to anticholinergics were treated with 12 sessions of PTNS. Assessment of LUTS was by validated, self-administered chart and questionnaires, testing the subjective and objective relevance of LUTS for patients and their impact on QoL before and after treatment; the mean postmicturition residual was assessed by trans-abdominal ultrasound scanning. Analysis was by intention to treat. Results: There was a significant reduction of daytime frequency (from 9 to 6, p = 0.04), nocturia (from 3 to 1, p = 0.002) and mean post-micturition residual (from 98 ± 124 ml to 43 ± 45 ml, p = 0.02). The mean voided volume increased from 182 ± 50 ml to 225 ± 50 ml (p = 0.003). Eighty-nine percent of patients reported a treatment satisfaction of 70%. Significant improvement in QoL was seen in most domains of the King's Health QoL questionnaire (p<0.05). No adverse events were reported. Conclusions: PTNS is an effective, safe and well-tolerated treatment for LUTS in patients with MS.
PMID: 21757534 [PubMed - as supplied by publisher]

Death receptor 6 negatively regulates oligodendrocyte survival, maturation and myelination.
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Survival and differentiation of oligodendrocytes are important for the myelination of central nervous system (CNS) axons during development and crucial for myelin repair in CNS demyelinating diseases such as multiple sclerosis. Here we show that death receptor 6 (DR6) is a negative regulator of oligodendrocyte maturation. DR6 is expressed strongly in immature oligodendrocytes and weakly in mature myelin basic protein (MBP)-positive oligodendrocytes. Overexpression of DR6 in oligodendrocytes leads to caspase 3 (casp3) activation and cell death. Attenuation of DR6 function leads to enhanced oligodendrocyte maturation, myelination and downregulation of casp3. Treatment with a DR6 antagonist antibody promotes remyelination in both lysolceithin-induced demyelination and experimental autoimmune encephalomyelitis (EAE) models. Consistent with the DR6 antagonist antibody studies, DR6-null mice show enhanced remyelination in both demyelination models. These studies reveal a pivotal role for DR6 signaling in immature oligodendrocyte maturation and myelination that may provide new therapeutic avenues for the treatment of demyelination disorders such as multiple sclerosis.
PMID: 21725297 [PubMed - in process]

Multiple sclerosis: MS treatment adherence-how to keep patients on medication?
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PMID: 21727393 [PubMed - as supplied by publisher]

Multiple sclerosis: Cladribine-a contentious therapeutic contender for MS.
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PMID: 21750524 [PubMed - as supplied by publisher]

Control of TH17 cells occurs in the small intestine.

Esplugues E, Huber S, Gagliani N, Hauser AE, Town T, Wan YY, O'Connor W Jr, Rongvaux A, Van Rooijen N, Haberman AM, Iwakura Y, Kuchroo VK, Kolls JK, Bluestone JA, Herold KC, Flavell RA. Department of Immunobiology, Yale University School of Medicine, New Haven, Connecticut 06520, USA. enric.esplugues@yale.edu

Interleukin (IL)-17-producing T helper cells (T(H)17) are a recently identified CD4(+) T cell subset distinct from T helper type 1 (T(H)1) and T helper type 2 (T(H)2) cells. T(H)17 cells can drive antigen-specific autoimmune diseases and are considered the main population of pathogenic T cells driving experimental autoimmune encephalomyelitis (EAE), the mouse model for multiple sclerosis. The factors that are needed for the generation of T(H)17 cells have been well characterized. However, where and how the immune system controls T(H)17 cells in vivo remains unclear. Here, by using a model of tolerance induced by CD3-specific antibody, a model of sepsis and influenza A viral infection (H1N1), we show that pro-inflammatory T(H)17 cells can be redirected to and controlled in the small intestine. T(H)17-specific IL-17A secretion induced expression of the chemokine CCL20 in the small intestine, facilitating the migration of these cells specifically to the small intestine via the CCR6/CCL20 axis. Moreover, we found that T(H)17 cells are controlled by two different mechanisms in the small intestine: first, they are eliminated via the intestinal lumen; second, pro-inflammatory T(H)17 cells simultaneously acquire a regulatory phenotype with in vitro and in vivo immune-suppressive properties (rT(H)17). These results identify mechanisms limiting T(H)17 cell pathogenicity and implicate the gastrointestinal tract as a site for control of T(H)17 cells.


[Neuroprotection in the treatment of multiple sclerosis.]
[Article in German]

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Atrophy, the wasting or shrinkage of tissue, of the nervous system is the main feature of neurodegeneration, i.e. the umbrella term for the progressive loss of structure or function of neurons. Loss of neurons due to cell death and axonal degeneration characterize neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis. In these illnesses, it still has to be elucidated to which extent inflammation is part of the pathology. Conversely, in chronic inflammation of the central nervous system (CNS), atrophy has previously also been described and neurodegeneration is discussed as a pathologic feature. The most frequent chronic inflammatory disease of the CNS is multiple sclerosis (MS), which leads to devastating relapsing-remitting symptoms and disability during the relapses, increasingly during the course of disease in patients. Meanwhile it became clear that axons already reveal pathology early in the disease and neurons are affected in the cortex and the spinal cord, albeit to a different extent. The broadening of understanding neurodegenerative aspects of MS pathology demands and creates new therapeutic strategies. Current medication used in MS treatment as well as medications about to be approved are primarily anti-inflammatory therapies. By modulating the immune system and thereby blocking key steps of the pathology, the immunomodulation therapies in MS have a slight impact on disability progression. There is, however, clinical and experimental data concerning the potential neuroprotective properties of novel therapies. Combining anti-inflammatory and direct neuroprotective or even neuroregenerative therapy strategies would be a step forward in the treatment of multiple sclerosis.

PMID: 21761185 [PubMed - as supplied by publisher]
TGF-β/BMPs: Crucial crossroad in neural autoimmune disorders.
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Transforming growth factor beta (TGF-β) has a crucial role in the differentiation of ectodermal cells to neural or epidermal precursors. TGF-β and bone morphogenetic protein molecules (BMPs) are involved in many developmental processes, including cell proliferation and differentiation, apoptosis, mitotic arrest and intercellular interactions during morphogenesis. Additionally, the failure of central thymic tolerance mechanisms, leading to T cells with a skewed autoreactive response, is being described as a contributor in inflammatory processes in autoimmune diseases such as multiple sclerosis. Since TGF-β and BMP proteins are crucial for the development of the neural system and the thymus, as well as for the differentiation of T cells, it is essential to further investigate their role in the pathophysiology of this disorder by using references from embryonic experimental research. Available literature in the TGF/BMP signalling cascade, mostly during embryonic development of the nervous system is being reviewed. An attempt is made to further elucidate a potential role of TGF/BMP signalling in the pathophysiology of MS. During demyelination, BMP signaling, through various molecular mechanisms, directs the development of the adult neural stem cell in the astrocyte rather than the oligodendrocyte direction, therefore inhibiting the repair process. Further understanding of the above relationships could lead to the development of potentially efficient therapies for MS in the future.
PMID: 21718734 [PubMed - as supplied by publisher]

The generation and validation of white matter connectivity importance maps.
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Both the size and location of injury in the brain influences the type and severity of cognitive or sensorimotor dysfunction. However, even with advances in MR imaging and analysis, the correspondence between lesion location and clinical deficit remains poorly understood. Here, structural and diffusion images from 14 healthy subjects are used to create spatially unbiased white matter connectivity importance maps that quantify the amount of disruption to the overall brain network that would be incurred if that region were compromised. Some regions in the white matter that were identified as highly important by such maps have been implicated in strategic infarct dementia and linked to various attention tasks in previous studies. Validation of the maps is performed by investigating the correlations of the importance maps' predicted cognitive deficits in a group of 15 traumatic brain injury patients with their cognitive test scores measuring attention and memory. While no correlation was found between amount of white matter injury and cognitive test scores, significant correlations (r>0.68, p<0.006) were found when including location information contained in the importance maps. These tools could be used by physicians to improve surgical planning, diagnosis, and assessment of disease severity in a variety of pathologies like multiple sclerosis, trauma, and stroke.
Evidence linking the ε4 allele of APOE to more severe brain MRI abnormalities in multiple sclerosis (MS) has been conflicting and limited to studies of lesion load and whole brain atrophy. The purpose of the present study was to determine whether the ε4 allele of APOE is associated with more extensive brain pathology in MS using structural and diffusion tensor MRI. Using a case-control design, 43 MS patients with the ε4 allele and 47 ε4 negative MS patients underwent structural and diffusion tensor imaging (DTI) at 3T. Hypo- and hyperintense lesion volumes, whole brain and medial temporal volumes, and DTI parameters (fractional anisotropy (FA) and mean diffusivity (MD)) in normal-appearing brain tissue and lesions were compared between the groups. ε4+ and ε4- MS patients were well-matched on demographic characteristics, disease variables, and proportions receiving disease-modifying therapy. ε4+ and ε4- patients did not differ on any MRI or DTI measure. This study refutes a role for the ε4 allele in MRI abnormalities in MS, particularly those linking ε4 to greater T1 hypointense lesion volume and brain atrophy. Previous work on this putative gene-MRI relationship is extended by comparing DTI measures within lesions and normal-appearing brain tissue. A lack of differences in medial temporal regions, areas that have been linked to ε4-associated changes in health and disease, further supports the conclusion that that ε4 is not associated with more subtle MRI markers of brain pathology in MS.

PMID: 21723395 [PubMed - as supplied by publisher]
Autoimmune disease after alemtuzumab treatment for multiple sclerosis in a multicenter cohort.
From the Department of Psychological Medicine and Neurology (M.C., G.I., K.B., C.H., T.P., N.P.R.), Cardiff University, University Hospital of Wales, Heath Park, Cardiff, UK; Department of Neurology (A.A.P., J.Z.), Penninsula Medical School, Tamar Science Park, Derriford, Plymouth; Neurology Unit (J.J., A.C.), Department of Clinical Neurosciences, Cambridge University, Addenbrooke's Hospital, Cambridge; Department of Neurology (R.A., M.B.), The Walton Centre NHS Foundation Trust, Fazakerley, Liverpool; Institute of Clinical Neurology (N.S.), University of Bristol, Frenchay Hospital, Bristol; and Department of Social and Community Medicine University of Bristol (Y.B.-S.), Canynge Hall, Bristol, UK.
OBJECTIVE: To define the rate, timing, and clinical risk factors for the development of autoimmune disease (AID) after alemtuzumab treatment for multiple sclerosis (MS). METHODS: We analyzed prospective clinical and serologic data from 248 patients with MS treated with alemtuzumab, with median follow-up of 34.3 months (range 6.7-107.3). RESULTS: Novel AID developed in 22.2%. Thyroid AID was most frequent (15.7%). A range of hematologic, renal, and dermatologic AID were also observed as was asymptomatic development of novel autoantibodies. AID was seen from 2 weeks after initial treatment and was most frequent 12-18 months after first treatment. No new cases of AID were identified 60 months or more after initial treatment and risk of AID was independent of total alemtuzumab dose or interval of dosage. While established risk factors for AID including sex and age had no impact on AID frequency, both family history (odds ratio=7.31, 95% confidence interval 3.02-17.68) of AID and a personal smoking history (odds ratio=3.05, 95% confidence interval 1.50-6.19) were predictive of AID expression. CONCLUSIONS: Cumulative risk for AID in MS following alemtuzumab is 22.2%, most frequent between 12 and 18 months following first dose and evident for up to 5 years. Individual risk is modified by smoking and family history, which should be incorporated within the counseling process prior to treatment. Classification of evidence: This study provides Class IV evidence that the risk of AID after alemtuzumab treatment for MS is time-limited and modified by external factors.
PMID: 21795656 [PubMed - as supplied by publisher]
Antibodies to MOG are transient in childhood acute disseminated encephalomyelitis.


From the Max Planck Institute of Neurobiology (A.K.P., K.D., R.B., P.S., D.J., M.K., R.H., E.M., T.D.), Department of Neuroimmunology, Martinsried; Institute of Clinical Neuroimmunology (A.K.P., K.D., R.B., P.S., M.K., T.K., R.H., E.M., T.D.), Department of Pediatric Neurology and Developmental Medicine, Dr von Haunersches Kinderspital (A.B.), and Munich Centre of Integrated Protein Science and Adolf Butenandt Institute (I.F.), Ludwig-Maximilians-University, Munich, Germany; Department of Neurology and Neurosurgery (S.M., A.V., A.B.-O.) and Experimental Therapeutics Program (A.B.-O.), Montreal Neurological Institute, McGill University, Montreal, Canada; Institute of Biochemistry and Biotechnology (C.B.), Martin-Luther-University Halle-Wittenberg, Halle, Germany; Department of Neurology (R.W.), University of Geneva Hospital, Geneva, Switzerland; Westend-Innovation (U.J.), Biotech Consulting, Munich; Department of Pediatrics and Pediatric Neurology (W.S., J.G.), Georg August University, Göttingen, Germany; Children's Hospital of Eastern Ontario (D.P.), Ottawa, Canada; Division of Neuropediatrics and Inherited Metabolic Disorders (K.R.), Department of Pediatrics, Innsbruck Medical University, Innsbruck, Austria; RG Inflammatory Disorders of the Central Nervous System (F.W.), Max Planck Institute of Psychiatry, Munich, Germany; Neuroimmunology Unit (M.K., T.O.), Department of Clinical Neuroscience, Karolinska University Hospital, Stockholm, Sweden; Neuroimmunology Group (F.B., E.T., R.C.D.), Institute of Neuroscience and Muscle Research, the Kids Research Institute at the Children's Hospital at Westmead, University of Sydney, Sydney, Australia; Division of Neurology (B.B.), Department of Pediatrics, The Hospital for Sick Children, Toronto, Canada; and Department of Neurology (T.D.), University Hospital Basel, Basel, Switzerland.

OBJECTIVE: To study the longitudinal dynamics of anti-myelin oligodendrocyte glycoprotein (MOG) autoantibodies in childhood demyelinating diseases. METHODS: We addressed the kinetics of anti-MOG immunoglobulins in a prospective study comprising 77 pediatric patients. This was supplemented by a cross-sectional study analyzing 126 pediatric patients with acute demyelination and 62 adult patients with multiple sclerosis (MS). MOG-transfected cells were used for detection of antibodies by flow cytometry.

RESULTS: Twenty-five children who were anti-MOG immunoglobulin (Ig) positive at disease onset were followed for up to 5 years. Anti-MOG antibodies rapidly and continuously declined in all 16 monophasic patients with acute disseminated encephalomyelitis and in one patient with clinically isolated syndrome. In contrast, in 6 of 8 patients (75%) eventually diagnosed with childhood MS, the antibodies to MOG persisted with fluctuations showing a second increase during an observation period of up to 5 years. Antibodies to MOG were mainly IgG 1 and their binding was largely blocked by pathogenic anti-MOG antibodies derived from a spontaneous animal model of autoimmune encephalitis. The cross-sectional part of our study elaborated that anti-MOG Ig was present in about 25% of children with acute demyelination, but in none of the pediatric or adult controls. Sera from 4/62 (6%) adult patients with MS had anti-MOG IgG at low levels.

CONCLUSIONS: The persistence or disappearance of antibodies to MOG may have prognostic relevance for acute childhood demyelination.

PMID: 21795651 [PubMed - as supplied by publisher]

Evaluation of soluble HLA-G as a biomarker for multiple sclerosis.


From the Department of Neurology (A.W., S.S.), Friedrich-Alexander University of Erlangen, Erlangen; Bayer Health Care (R.S., C.P.), Berlin; Department of Neurology (R.S., H.-P.H.), Heinrich Heine University, Duesseldorf, Germany; Neurology and Clinical Neuroimmunology (L.K.), University Hospital, Basel, Switzerland; Department of Neurology (C.P.), University Hospital of Bonn, Bonn; and Department of Neurology, Neuroimmunology and Neuro-Oncology (H.W.), University of Muenster, Muenster, Germany.

PMID: 21795647 [PubMed - as supplied by publisher]

Multiple sclerosis and disease-modifying therapies.

Minen MT, Karceski S.

PMID: 21788616 [PubMed - in process]
Cost-effectiveness analyses of treatments for multiple sclerosis: Are they clinically relevant?
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PMID: 21775745 [PubMed - in process]

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OBJECTIVE: To evaluate the cost-effectiveness of disease-modifying therapies (DMTs) in the United States
compared to basic supportive therapy without DMT for patients with relapsing multiple sclerosis (MS).
METHODS: Using data from a longitudinal MS survey, we generated 10-year disease progression paths for
an MS cohort. We used first-order annual Markov models to estimate transitional probabilities. Costs
associated with losses of employment were obtained from the Bureau of Labor Statistics. Medical costs
were estimated using the Centers for Medicare and Medicaid Services reimbursement rates and other
sources. Outcomes were measured as gains in quality-adjusted life-years (QALY) and relapse-free years.
Monte Carlo simulations, resampling methods, and sensitivity analyses were conducted to evaluate model
uncertainty. RESULTS: Using DMT for 10 years resulted in modest health gains for all DMTs compared to
treatment without DMT (0.082 QALY or <1 quality-adjusted month gain for glatiramer acetate, and 0.126-
0.192 QALY gain for interferons). The cost-effectiveness of all DMTs far exceeded $800,000/QALY.
Reducing the cost of DMTs had by far the greatest impact on the cost-effectiveness of these treatments
(e.g., cost reduction by 67% would improve the probability of Avonex being cost-effective at $164,000/QALY
to 50%). Compared to treating patients with all levels of disease, starting DMT earlier was associated with
a lower (more favorable) incremental cost-effectiveness ratio compared to initiating treatment at any disease
state. CONCLUSION: Use of DMT in MS results in health gains that come at a very high cost.

Low bone mass in newly diagnosed multiple sclerosis and clinically isolated syndrome.
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OBJECTIVE: Osteoporosis is common in patients with multiple sclerosis (MS) with long-standing disease.
Hypovitaminosis D is a candidate risk factor for MS, and vitamin D also mediates bone mineralization. If
vitamin D exerts a major effect on MS risk, skeletal consequences of hypovitaminosis D could be apparent
shortly after the onset of MS. In order to test this hypothesis, we assessed bone mineral density (BMD) at
eye stages of disease in patients with no or minor disability. METHODS: A population-based case-control
study was conducted on 99 consecutive and newly diagnosed patients with clinically isolated syndrome or
MS, and on 159 age-, sex-, and ethnicity-matched controls. BMD was measured by dual-energy x-ray
absorptiometry of the femoral neck, total hip, anterior-posterior lumbar spine, total body, and nondominant
ultradistal radius. RESULTS: A total of 50.5% of the patients exhibited either osteopenia (–2.5 < T score < –
1.0) or osteoporosis (T score ≤ –2.5) in at least one skeletal site, compared to 37.1% of controls (p = 0.034).
After adjusting for possible confounders, left femoral total hip T score and lumbar spine BMD and T score
were significantly lower in patients than in controls (p = 0.023, 0.039, and 0.026, respectively).
CONCLUSIONS: Low bone mass appears to occur early in MS. This is compatible with shared etiologic or
pathogenic factors in MS and osteoporosis, and calls for an active approach to optimize bone health in early
stages of MS.
PMID: 21747073 [PubMed - in process]
Breastfeeding is not related to postpartum relapses in multiple sclerosis.


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OBJECTIVE: To assess the relationship between breastfeeding and risk of puerperal relapses in a large cohort of patients with multiple sclerosis (MS). METHODS: We prospectively followed-up pregnancies occurring between 2002 and 2008 in women with MS, recruited from 21 Italian MS centers, and gathered data on breastfeeding through a standardized interview. The risk of relapses after delivery was assessed using the Cox regression analysis. RESULTS: A total of 302 out of 423 pregnancies in 298 women resulted in full-term deliveries. Patients were followed up for at least 1 year after delivery. The time-dependent profile of the relapse rate before, during, and after pregnancy did not differ between patients who breastfed and patients who did not. In the multivariate analysis, adjusting for age at onset, age at pregnancy, disease duration, disability level, and relapses in the year prior to pregnancy and during pregnancy, treatment with disease-modifying drugs (DMDs), and exposure to toxins, the only significant predictors of postpartum relapses were relapses in the year before pregnancy (hazard ratio [HR] = 1.5; 95% confidence interval [CI] 1.3-1.9; p < 0.001) and during pregnancy (HR = 2.2; 95% CI 1.5-3.3; p < 0.001). CONCLUSIONS: In our sample, postpartum relapses were predicted only by relapses before and during pregnancy. Therefore, the reported association between breastfeeding and a lower risk of postpartum relapses may simply reflect different patient behavior, biased by the disease activity. Our results can assist neurologists facing the breastfeeding issue in mother counseling and shared decision-making. Especially, among patients with high risk of postpartum relapses, breastfeeding may not be feasible and early postpartum treatment should be an option.

PMID: 21734184 [PubMed - as supplied by publisher]

Immune thrombocytopenic purpura in a patient with multiple sclerosis treated with natalizumab.

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PMID: 21775738 [PubMed - in process]

Diffusion-weighted imaging in acute demyelinating myelopathy.

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INTRODUCTION: Diffusion-weighted imaging (DWI) has become a reference MRI technique for the evaluation of neurological disorders. Few publications have investigated the application of DWI for inflammatory demyelinating lesions. The purpose of the study was to describe diffusion-weighted imaging characteristics of acute, spinal demyelinating lesions. METHODS: Six consecutive patients (two males, four females; aged 28-64 years) with acute spinal cord demyelinating lesions were studied in a prospective case series design from June 2009 to October 2010. We performed magnetic resonance imaging studies from 2 to 14 days from symptom onset on the patients with relapsing remitting multiple sclerosis (n=3) or clinically isolated syndrome (n=3). Main outcome measures were diffusion-weighted imaging and apparent diffusion coefficient pattern (ADC) of acute spinal cord demyelinating lesions. RESULTS: All spinal lesions showed a restricted diffusion pattern (DWI+/ADC-) with a 24% median ADC signal decrease. A good correlation between clinical presentation and lesion site was observed. CONCLUSION: Acute demyelinating spinal cord lesions show a uniform restricted diffusion pattern. Clinicians and neuro-radiologists should be aware that this pattern is not necessarily confirmatory for an ischaemic aetiology.

PMID: 21743997 [PubMed - as supplied by publisher]
173. NeuroRehabilitation. 2011 Jan 1;28(4):373-82. Improvement in strength following resistance training in MS patients despite varied disability levels. Filippi ML, Kucera DL, Filippi EO, Ridpath AC, Leuschen MP. University of Nebraska Medical Center, College of Nursing, Omaha, NE, USA Neurology Associates, PC., Lincoln, NE, USA.

Strength and endurance data from 67 participants with multiple sclerosis (MS) were compared before, during and after a 6-month program of standardized resistance training. The hypothesis was that a standardized, structured resistance training exercise program improves strength in MS patients with different levels of disability. The range of EDSS scores was 1-8: (40% - EDSS of 1-4.5), (35% - EDSS of 5-7) (25% - EDSS of 7.5 or higher). This unique study evaluated patients with differing levels of disability for a change in strength and endurance following a 6-month training program. Data were analyzed by repeat measures and analysis of variables using Proc GLM in SAS to account for variability between subjects, and within subjects, due to repeated measures at 3 time points. Each treatment was blocked by disability class. Every within-treatment analysis was significant. Each exercise showed significant improvement in strength for participants, despite disability levels. Increases in strength followed parallel improvement pathways, at all disability levels. All but one treatment displayed highly significant improvement (p-value < 0.0001). The results demonstrated that all individuals with MS, despite disability levels, show parallel improvement in strength and endurance. This study supports the use of exercise, including resistance programs, for all MS patients.

PMID: 21725171 [PubMed - in process]


Objective: The aim of this study was to assess the effect of Kinesio Taping on body stability in subjects with MS. Study design: Non controlled intervention study in a Rehabilitation Unit. Intervention: A consecutive convenience sample of 15 individuals with multiple sclerosis was assessed. Kinesio Tex Tape was applied directly to the skin of both calves and kept for the next two days. Main outcome measures: Clinical and stabilometric assessments were performed at baseline, immediately after application of the tape and the day after its removal. To control for learning effect 10 subject with multiple sclerosis were tested repeatedly under the same conditions without tape. Results: No statistically or clinically relevant differences were observed among conditions in the mediolateral plane. In the AP plane Friedman's ANOVA showed statistically significant differences between baseline and taping condition with respect to length of sway. A trend towards statistically relevant differences were found also with respect to mean sway and velocity of sway. No learning effect was found for repeated testing within the no treated group. Conclusions: These preliminary results suggest that the use of ankle taping may be useful in immediately stabilising body posture.

PMID: 21725170 [PubMed - in process]

Unilateral Thalamic Deep Brain Stimulation for Disabling Kinetic Tremor in Multiple Sclerosis.

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BACKGROUND:: Surgical options of multiple sclerosis (MS) tremor treatment are limited and narrowed to thalamotomy or deep brain stimulation (DBS) of the thalamic nucleus ventralis intermedius (Vim). Lack of qualification protocol frequently results in poor outcome. OBJECTIVE:: To determine prospectively the efficacy and safety of unilateral Vim DBS as a tool to control disabling kinetic arm tremor related to MS. METHODS:: Neurological and neuropsychological evaluations were performed one month and one day before surgery, and 1, 3 and 6 months after surgery. The evaluation included measurement of tremor, dexterity, EDSS, MMSE and Quality of Life (QOL). Nine consecutive patients were enrolled in the group. Mean age at the time of surgery was 38.9±9 years, median EDSS at baseline was 7.1. Mean MS duration was 11.7 years and mean tremor duration was 6.11 years. Mean postural and kinetic scores and hand capacity was measured. RESULTS:: One month after surgery, median scores OFF and ON were respectively 12 and 6 for postural tremor; 12 and 10.5 for kinetic tremor score; 12 and 7.5 for manual capacity; 22 and 20 for functional handicap. Similar results were respectively 10 and 4 at three months follow-up. Six months after surgery, median scores OFF and ON were respectively 10.4 and 4 for postural tremor, 12 and 7.8 for kinetic tremor. CONCLUSION:: This prospective study confirms the value and safety of Vim DBS for treatment of kinetic tremor related to MS. Accurate and precise presurgical qualification plays the key role in successful treatment.

PMID: 21768914 [PubMed - as supplied by publisher]


Fast radio-frequency enforced steady state (FRESS) spin echo MRI for quantitative T(2) mapping: minimizing the apparent repetition time (TR) dependence for fast T(2) measurement.
Cheung JS, Wang E, Zhang X, Mandeville E, Lo EH, Sorensen AG, Sun PZ.
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Transverse relaxation time (T(2)) is a basic but very informative MRI parameter, widely used in imaging to examine a host of diseases, including multiple sclerosis, stroke, and tumor. However, short repetition time (TR) is often used to minimize scan time, which may introduce non-negligible errors in T(2) measurement. Specifically, due to the use of refocusing pulse, the steady state magnetization depends not only on TR but also on the TE. Hence, if the TE dependence is not properly accounted for, it may be mistaken as T(2) - induced signal attenuation, leading to non-negligible T(2) underestimation. Our study proposed a fast radio-frequency enforced steady state (FRESS) spin echo (SE) MRI sequence, which saturates the magnetization after the echo and ensures a TE-independent steady state. The proposed FRESS-SE MRI was evaluated with numerical simulation, implemented with echo planar imaging readout, and validated by both phantom and in vivo experiments. In summary, FRESS-SE T(2) MRI technique was developed for fast and accurate T(2) imaging, suitable for in vivo applications. Copyright © 2011 John Wiley & Sons, Ltd.

PMID: 21755552 [PubMed - as supplied by publisher]
Towards resolving the transcription factor network controlling myelin gene expression. Fulton DL, Denarier E, Friedman HC, Wasserman WW, Peterson AC.
Department of Medical Genetics, Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, University of British Columbia, Vancouver, V5Z 4H4, Department of Oncology, Department of Human Genetics and Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec H3A 2B4, Canada.
In the central nervous system (CNS), myelin is produced from spirally-wrapped oligodendrocyte plasma membrane and, as exemplified by the debilitating effects of inherited or acquired myelin abnormalities in diseases such as multiple sclerosis, it plays a critical role in nervous system function. Myelin sheath production coincides with rapid up-regulation of numerous genes. The complexity of their subsequent expression patterns, along with recently recognized heterogeneity within the oligodendrocyte lineage, suggest that the regulatory networks controlling such genes drive multiple context-specific transcriptional programs. Confering this nuanced level of control likely involves a large repertoire of interacting transcription factors (TFs). Here, we combined novel strategies of computational sequence analyses with in vivo functional analysis to establish a TF network model of coordinate myelin-associated gene transcription. Notably, the network model captures regulatory DNA elements and TFs known to regulate oligodendrocyte myelin gene transcription and/or oligodendrocyte development, thereby validating our approach. Further, it links to numerous TFs with previously unsuspected roles in CNS myelination and suggests collaborative relationships amongst both known and novel TFs, thus providing deeper insight into the myelin gene transcriptional network.
PMID: 21729871 [PubMed - as supplied by publisher]

A survey on managing multiple sclerosis: the managed care perspective. Edlin M, Sonnenreich P.
PMCID: PMC3138380 PMID: 21785554 [PubMed - in process]

Adolescent and adult children of parents with Parkinson’s disease: incorporating their needs in clinical guidelines. Morley D, Selai C, Schrag A, Jahanshahi M, Thompson A.
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Purpose. To compare the quality of life (QoL) and emotional well-being of the offspring of parents with Parkinson’s disease (PD) and multiple sclerosis (MS) and to consider results in light of current UK clinical guidelines. Methods. 143 adolescent and adult children of parents with PD and MS were postally administered the Parental Illness Impact Scale and a measure of emotional well-being. Results. Minimal differences were observed between the two groups in both QoL and emotional well-being. Levels of mild to moderate depression were substantially greater than those of the general population. Conclusions. The nonsignificant differences reported indicate a similar degree of impact across the two conditions assessed. A significant body of evidence demonstrates the considerable impact of parental MS, with the needs of children being acknowledged in current clinical guidelines. There is a need to similarly acknowledge the potential impact of parental Parkinson’s in UK guidelines for PD.
PMCID: PMC3135087 PMID: 21766002 [PubMed - in process]
Impact of walking impairment in multiple sclerosis: perspectives of patients and care partners. Larocca NG.
National Multiple Sclerosis Society, New York, NY, USA.
Background: Multiple sclerosis (MS) is a chronic neurologic disease associated with gait impairment that adversely affects quality of life (QOL). Data are lacking on the impact of these impairments from the perspectives of people with MS and care partners of a person with MS, defined as individuals caring for a friend or family member with MS. Methods: In January and February 2008, online surveys were conducted by Harris Interactive® (HI) on behalf of Acorda Therapeutics, Inc. and the National MS Society (USA) to explore the impact of difficulty walking (defined as trouble walking at least twice a week and/or an inability to walk at least twice a week due to MS) from the perspectives of people with MS and care partners of a person with MS. The study population was drawn from pre-existing panels, generated by HI and eRewards market research, of self-reported people with MS, care partners of a person with MS, or adults living in the same household as a person with MS. Panel members were invited to participate by e-mail, and their status/eligibility was verified with screening questions. Survey results were weighted for demographic factors and propensity to be online. Percentages were adjusted to account for acceptance of multiple responses and exclusion of non-responses. Results: The respondents included 1011 people with MS and 317 care partners. Demographic and MS disease characteristics in the people with MS sample were similar to those of people with MS in the general population. Among people with MS, 41% reported having difficulty walking, including 13% with inability to walk at least twice a week. Of those with difficulty walking, 70% said it was the most challenging aspect of having MS. Of those with inability to walk at least twice a week, 74% said it disrupted their daily lives. Only 34% of people with MS with difficulty walking were employed. Communication between people with MS and physicians regarding difficulty walking was suboptimal; 39% of all people with MS said they never or rarely discussed it with their doctor. Significant percentages of all care partners experienced reduced QOL and socioeconomic status in association with caring for a person with MS. Conclusions: Difficulty walking is a common impairment in people with MS, with adverse effects on the QOL of people with MS and care partners of a person with MS.
PMID: 21766914 [PubMed - in process]

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Over a century ago, hyperplasia and hypertrophy of the astrocyte population was noted as a histopathological hallmark of multiple sclerosis and was hypothesized to play an important role in the development and course of this disease. However until today, the factual contribution of astrocytes to multiple sclerosis is elusive. Astrocytes may play an active role during degeneration and demyelination by controlling local inflammation in the CNS, provoking damage of oligodendrocytes and axons, and glial scarring but might also be beneficial by creating a permissive environment for remyelination and oligodendrocyte precursor migration, proliferation, and differentiation. Recent findings from our lab suggest that brain lipid binding protein (FABP7) is implicated in the course of multiple sclerosis and the regulation of astrocyte function. The relevance of our findings and data from other groups are highlighted and discussed in this paper in the context of myelin repair.
PMID: 21777034 [PubMed - as supplied by publisher]
We tested effects of RTL therapy on expression of pathogenic and effector T-cell maturation markers, CD226, T-bet and CD44, by CD4+ Th1 cells early after treatment of MOG-35-55 peptide-induced EAE in C57BL/6 mice. We showed that 1-5 daily injections of RTL551 (two-domain I-A(b) covalently linked to MOG-35-55 peptide), but not the control RTL550 ("empty" two-domain I-A(b) without a bound peptide) or Vehicle, reduced clinical signs of EAE, prevented trafficking of cells outside the spleen, significantly reduced the frequency of CD226 and T-bet expressing CD4+ T-cells in blood and inhibited expansion of CD44 expressing CD4+ T-cells in blood and spleen. Concomitantly, RTL551 selectively reduced CNS inflammatory lesions, absolute numbers of CNS infiltrating T-bet expressing CD4+ T-cells and IL-17 and IFN-γ secretion by CNS derived MOG-35-55 reactive cells cultured ex vivo. These novel results demonstrate that a major effect of RTL therapy is to attenuate Th1 specific changes in CD4+ T-cells during EAE and prevent expansion of effector T-cells that mediate clinical signs and CNS inflammation in EAE.

PMCID: PMC3130056 PMID: 21750737 [PubMed - in process]

Physiological Induction of Regulatory Qa-1-Restricted CD8+ T Cells Triggered by Endogenous CD4+ T Cell Responses.


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T cell-dependent autoimmune diseases are characterized by the expansion of T cell clones that recognize immunodominant epitopes on the target antigen. As a consequence, for a given autoimmune disorder, pathogenic T cell clones express T cell receptors with a limited number of variable regions that define antigenic specificity. Qa-1, a MHC class I-like molecule, presents peptides from the variable region of TCRs to Qa-1-restricted CD8+ T cells. The induction of V8-specific CD8+ T cells has been harnessed in an immunotherapeutic strategy known as the "T cell vaccination" (TCV) that comprises the injection of activated and attenuated CD4+ T cell clones so as to induce protective CD8+ T cells. We hypothesized that Qa-1-restricted CD8+ regulatory T cells could also constitute a physiologic regulatory arm of lymphocyte responses upon expansion of endogenous CD4+ T cells, in the absence of deliberate exogenous T cell vaccination. We immunized mice with two types of antigenic challenges in order to sequentially expand antigen-specific endogenous CD4+ T cells with distinct antigenic specificities but characterized by a common V8 chain in their TCR. The first immunization was performed with a non-self antigen while the second challenge was performed with a myelin-derived peptide known to drive experimental autoimmune encephalomyelitis (EAE), a mouse model of multiple sclerosis. We show that regulatory V8-specific Qa-1-restricted CD8+ T cells induced during the first endogenous CD4+ T cell responses are able to control the expansion of subsequently mobilized pathogenic autoreactive CD4+ T cells. In conclusion, apart from the immunotherapeutic TCV, Qa-1-restricted specialized CD8+ regulatory T cells can also be induced during endogenous CD4+ T cell responses. At variance with other regulatory T cell subsets, the action of these Qa-1-restricted T cells seems to be restricted to the immediate re-activation of CD4+ T cells.

PMCID: PMC3124544 PMID: 21738737 [PubMed - in process]

T regulatory cells are markers of disease activity in multiple sclerosis patients.


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FoxP3(+) Treg cells are believed to play a role in the occurrence of autoimmunity and in the determination of clinical recurrences. Contradictory reports are, however, available describing frequency and function of Treg cells during autoimmune diseases. We examined, by both polychromatic flow cytometry, and real-time RT-PCR, several Treg markers in peripheral blood mononuclear cells from patients with multiple sclerosis (MS), an autoimmune disease affecting the central nervous system. We found that Tregs, as defined by CD25, CD39, FoxP3, CTLA4, and GITR expression, were significantly decreased in stable MS patients as compared to healthy donors, but, surprisingly, restored to normal levels during an acute clinical attack. We conclude that Treg cells are not involved in causing clinical relapses, but rather react to inflammation in the attempt to restore homeostasis.

PMCID: PMC3123332 PMID: 21731726 [PubMed - in process]
**Falls in multiple sclerosis.**

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OBJECTIVE: To examine incidence, associated factors, and health care provider (HCP) response to falls in persons with multiple sclerosis (MS). DESIGN: Cross-sectional retrospective design. SETTING: Community setting. PARTICIPANTS: Four hundred seventy-four persons with MS. METHODS: Mailed survey questionnaire examined incidence, risk factors, and HCP response to falls in persons with MS who were dwelling in the community. Univariate and multiple ordinal regression analysis identified variables associated with single and multiple falls. MAIN OUTCOME MEASUREMENTS: Falls, causes and perceived reasons for falls, and HCP response. RESULTS: A total of 265 participants (58.2%) reported one or more falls in the previous 6 months, and 58.5% of falls were medically injurious. Trips/slips while walking accounted for 48% of falls. Factors associated with falls included use of a cane or walker (odds ratio [OR] 2.62; 95% confidence interval [CI] 1.66-4.14), income <$25,000 (OR 1.85; 95% CI 1.13-3.04), balance problems (OR 1.28; 95% CI 1.11-1.49), and leg weakness (OR 1.26; 95% CI 1.09-1.46). Fifty-one percent of those who fell (135/265) reported speaking to an HCP about their falls; recommended strategies included safety strategies (53.2%), use of gait assistive devices (42.1%), exercise/balance training (22.2%), and home modifications (16.6%). CONCLUSIONS: Factors associated with falls in persons with MS are similar to those in other populations with neurologic diseases. Despite the high incidence of falls, fewer than 50% of people with MS receive information about prevention of falls from an HCP.  
PMID: 21777861 [PubMed - in process]

**Cladribine: limited evaluation in multiple sclerosis.**  
[No authors listed]  
PMID: 21751748 [PubMed - in process]

**Fingolimod.**  
[No authors listed]  
In the absence of a better alternative, subcutaneous interferon beta is the standard first-line treatment for relapsing-remitting multiple sclerosis. Fingolimod, an oral immunosuppressant that reduces the circulating lymphocyte count, is in the process of receiving marketing authorisation for this use in the European Union. Initial clinical evaluation is based on 2 trials. In a 12-month, comparative, double-blind, randomised trial including 1292 patients daily treatment with oral fingolimod (0.5 mg or 1.25 mg) modestly prolonged the interval between exacerbations compared to weekly intramuscular injections of interferon beta-1a: about one exacerbation prevented every 6 years. No tangible impact on progression of disability was observed. A double-blind placebo-controlled trial that lasted 2 years also showed a statistically significant reduction in the annual frequency of exacerbations. There was no firm evidence that fingolimod had a tangible effect on progression of disability. An indirect comparison suggests that the impact of fingolimod on exacerbations is roughly similar to that of cladribine, another oral immunosuppressant that received a negative opinion in this indication from the European Medicines Agency. Several short-term adverse effects consistent with the pharmacological action of fingolimod and the results of animal pharmacology studies were observed in clinical trials, including infections (especially herpetic), pulmonary disorders, cardiac conduction disorders and macular oedema. A risk of lymphoma and heart failure is possible in the longer term. Given the modest gain in efficacy compared with interferon beta (based on weak supporting evidence) and the major adverse effects of fingolimod, it is better to continue to use interferon beta for initial treatment of relapsing-remitting multiple sclerosis, and to reserve fingolimod for use in clinical trials in which patients are closely monitored.  
PMID: 21751747 [PubMed - in process]
188. Psychol Health Med. 2011 Jul 25. [Epub ahead of print]

**Physical activity, social support, and depression: Possible independent and indirect associations in persons with multiple sclerosis.**

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The present study examined the pattern of associations among physical activity, social support, mobility disability, perceived stress, and depressive symptoms in relapsing-remitting MS (RRMS). Persons (N = 218) with RRMS completed a battery of questionnaires that was sent and returned through the United States Postal Service (USPS). Bivariate correlation analysis indicated that physical activity and social support were both inversely associated with depressive symptoms (r's = -0.288 and -0.386, p ≤ 0.05, respectively). Multiple linear regression analysis indicated that physical activity (β = -0.21, p = 0.002) and social support (β = -0.37, p = 0.0001) were independently associated with depressive symptoms. Path analysis confirmed that the associations between physical activity and social support with depressive symptoms were indirect via mobility disability and perceived stress. Collectively, the evidence indicates that physical activity and social support are independently and indirectly associated with depression via mobility disability and perceived stress in relapsing-remitting MS. This supports the design of interventions and programs that target physical activity and social support for reducing depressive symptoms among persons with MS.

PMID: 21781021 [PubMed - as supplied by publisher]

189. Purinergic Signal. 2011 Jul 27. [Epub ahead of print]

**Emerging role of extracellular nucleotides and adenosine in multiple sclerosis.**

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Extracellular nucleotides and adenosine play important roles in inflammation. These signaling molecules interact with the cell-surface-located P2 and P1 receptors, respectively, that are widely distributed in the central nervous system and generally exert opposite effects on immune responses. Indeed, extracellular ATP, ADP, UTP, and UDP serve as alarmins or damage-associated molecular patterns that activate mainly proinflammatory mechanisms, whereas adenosine has potent anti-inflammatory and immunosuppressive effects. This review discusses the actual and potential role of extracellular nucleotides and adenosine in multiple sclerosis (MS).

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190. QJM. 2011 Jun 29. [Epub ahead of print]

**Vitamin D and multiple sclerosis hospital admissions in Scotland.**


From the Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Headington, Oxford, OX3 7BN, UK, Nuffield Department of Clinical Neurosciences (Clinical Neurology), University of Oxford, The West Wing, John Radcliffe Hospital, Oxford, OX3 9DU, UK, Centre for Paediatric Epidemiology and Biostatistics and MRC Centre of Epidemiology for Child Health, UCL Institute of Child Health, London WC1N 1EH, UK, Blizard Institute, Queen Mary University of London, Barts and The London School of Medicine and Dentistry, London, E1 2AT, UK.

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192. Rehabil Psychol. 2011 Jul 18. [Epub ahead of print]
The health action process approach as a motivational model for physical activity self-management for people with multiple sclerosis: A path analysis.
Chiu CY, Lynch RT, Chan F, Berven NL.
Objective: To evaluate the Health Action Process Approach (HAPA) as a motivational model for physical activity self-management for people with multiple sclerosis (MS). Design: Quantitative descriptive research design using path analysis. Participants: One hundred ninety-five individuals with MS were recruited from the National Multiple Sclerosis Society and a neurology clinic at a university teaching hospital in the Midwest. Outcome Measures: Outcome was measured by the Physical Activity Stages of Change Instrument, along with measures for nine predictors (severity, action self-efficacy, outcome expectancy, risk perception, perceived barriers, intention, maintenance self-efficacy, action and coping planning, and recovery self-efficacy). Results: The respecified HAPA physical activity model fit the data relatively well (goodness-of-fit index = .92, normed fit index = .91, and comparative fit index = .93) explaining 38% of the variance in physical activity. Recovery self-efficacy, action and coping planning, and perceived barriers directly contributed to the prediction of physical activity. Outcome expectancy significantly influenced intention and the relationship between intention and physical activity is mediated by action and coping planning. Action self-efficacy, maintenance self-efficacy, and recovery self-efficacy, directly or indirectly affected physical activity. Severity of MS and action self-efficacy had an inverse relationship with perceived barriers and perceived barriers influenced physical activity. Conclusions: Empirical support was found for the proposed HAPA model of physical activity for people with MS. The HAPA model appears to provide useful information for clinical rehabilitation and health promotion interventions. (PsycINFO Database Record (c) 2011 APA, all rights reserved).
PMID: 21767037 [PubMed - as supplied by publisher]

Telangiectasias bleeding in patient with multiple sclerosis.
Martínez Caselles A, Martínez Pascual C, Moreno Martínez MJ, Sánchez Torres A, Carballo Álvarez LF.
PMID: 21736400 [PubMed - as supplied by publisher]

[HLA-DRB1 typing in Caucasians patients with neuromyelitis optica.]
[Article in Spanish]
INTRODUCTION. The existence of antibodies to aquaporin-4 (AQP-4-ab) has identified neuromyelitis optica (NMO) and multiple sclerosis (MS) as different diseases. Although HLA-DRB1 alleles contribute to MS risk, recent studies suggest that HLA back-ground differs between patients with NMO or MS in non-Caucasians populations. Our study was aimed to analyze HLA-DRB1 distribution in Caucasians NMO patients.
SUBJECTS AND METHODS. We recruited a cohort of 22 NMO patients (73% were AQP-4-ab positive), 228 MS patients and 225 healthy controls from Spain and we genotyped the HLA-DRB1 locus. Then, we performed a pool analysis using reported data from 45 NMO patients (53% were AQP-4-ab positive), 156 MS patients and 310 controls from Caucasian French population. RESULTS. In the Spanish cohort, NMO was associated with increased frequency of DRB1*10 allele compared with MS (odds ratio, OR = 15.1; 95% confidence interval, 95% CI = 3.26-69.84; p = 0.012). In the pooled analysis, by comparison with healthy controls, NMO was associated with increased frequency of DRB1*03 allele (OR = 2.27; 95% CI = 1.44-3.58; p < 0.0008) which was related to AQP-4-ab seropositivity (OR = 2.74; 95% CI = 1.58-4.77; p < 0.0008). By contrast, MS was associated with increased frequency of DRB1*15 allele (OR = 2.09; 95% CI = 1.62-2.68; p < 0.0008) and decreased frequency of DRB1*07 allele (OR = 0.58; 95% CI = 0.44-0.78; p < 0.0008). CONCLUSIONS. Caucasian patients with NMO and MS have a different HLA-DRB1 allelic distribution. DRB1*03 allele seems to contribute to NMO seropositivity. Multicenter collaborative efforts are needed to adequately address the genetic contribution to NMO susceptibility.
PMID: 21748712 [PubMed - as supplied by publisher]
[Budget impact analysis of the first-line treatment of relapsing remitting multiple sclerosis in Spain.]  
[Article in Spanish] 
Sanchez-De la Rosa R, Sabater E, Casado MA.  
Pharmacoeconomics and Outcomes Research Iberia, Pozuelo de Alarcon, Espana.  
AIM. To assess the budget impact of the treatment for relapsing remitting multiple sclerosis (RRMS), interferons, and glatiramer acetate, from the National Health System perspective in Spain. PATIENTS AND METHODS. A budget impact model was designed to compare the cost of RRMS treatment in different settings, using a five year time-horizon, considering different percentages of administration of each medication. A reference setting or base case using all the available first line treatments (interferons and glatiramer acetate) was compared with five alternatives scenarios excluding each one of these treatments. The cost analysis (euros, year 2010) includes direct medical resources (drugs, administration, visits, disease management, diagnostic tests). Unitary cost data was obtained from the health costs database e-Salud and drugs catalogue. RESULTS. Considering a cohort of 22 255 patients with RRMS, the mean global budget impact per year would be 260 775 470 euros in the base case. The setting that excluded glatiramer acetate increases the budget impact in a 3.23% (372 euros per patient per year). Pharmacological costs were the key drivers of total cost (90%). CONCLUSION. The use of glatiramer acetate in the first-line-treatment of RRMS patients is a cost-saving strategy, which may decrease the budget impact from the National Health System perspective in Spain. 
PMID: 21748710 [PubMed - as supplied by publisher]  

Olfactory bulb volume and olfactory function in patients with multiple sclerosis.  
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BACKGROUND: Some studies reported olfactory dysfunction in patients with multiple sclerosis (MS). There is no agreement about the most suitable testing method for measuring olfactory function (OF) in MS patients. Recent studies showed that olfactory bulb volume changes with the degree of olfactory dysfunction. We assessed olfactory bulb volume of MS patients with magnetic resonance imaging (MRI) and related it to the OF. MATERIAL AND METHODS: Volumetric measurements of the right and left olfactory bulb (OB) were performed by manual segmentation within 36 MS patients. Psychophysical testing of the orthonasal OF was performed using threshold-discrimination-identification (TDI) score in MS patients. RESULTS: Of all MS patients, 44.4% displayed olfactory dysfunction. The TDI score of all 36 MS patients, especially the score of the Identification subtest correlated strongly with neurological scores typical of MS. In patients with a decreased OB volume, there was a positive correlation between volumetry of the OB and OF. CONCLUSION: OB volumes may provide valuable information about MS patients with olfactory dysfunction. The TDI test and Identification subtest were very sensitive in detecting olfactory dysfunction in MS patients. 
PMID: 21743881 [PubMed - in process]  

[Evaluation of blood flow and the cross-sectional area of internal jugular vein in Japanese multiple sclerosis and neuromyelitis optica patients].  
[Article in Japanese] 
Tanaka M, Uchizumi H, Tanaka K.  
MS Center, Utano National Hospital.  
Zamboni et al proposed a new hypothesis for the pathomechanisms of multiple sclerosis (MS): chronic cerebrospinal venous insufficiency (CCSVI). Using Doppler ultrasound and venograms, they found severe extracranial venous stenosis in MS patients. They suggested that a venous obstruction in the neck caused a reflux back into the brain, which led to edema and demyelination. We examined the blood flow and the cross-sectional area of the internal jugular veins using Doppler ultrasound (Vivid 7 PRO, GE Health Japan, Tokyo) in 17 MS (8 males and 9 females; 20-58 years of age, median 38 years) and 11 neuromyelitis optica (NMO) Japanese patients (1 male and 10 females; 23-60 years of age, median 44 years). Nine of the 11 NMO patients were seropositive for anti-aquaporin4 antibodies. We did not find any obstruction or stenosis of the internal jugular veins in any patient. Other disorders such as bilateral internal and external jugular venous ligation or radical neck dissection, which result in venous stasis, are not known causes of demyelination in the central nervous system. Our data also does not support the hypothesis of CCSVI theory, despite the fact that our study was limited to a small group of patients and the examination was performed only using Doppler ultrasound. 
PMID: 21735737 [PubMed - in process]
IL-7 Promotes Th1 Development and Serum IL-7 Predicts Clinical Response to Interferon-β in Multiple Sclerosis.


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The interleukin-7 receptor α chain (IL-7Rα) gene was identified as a top non-major histocompatibility complex-linked risk locus for multiple sclerosis (MS). Recently, we showed that a T helper 1 (T(H)1)-driven, but not a T(H)17-driven, form of MS exhibited a good clinical response to interferon-β (IFN-β) therapy. We now demonstrate that high serum levels of IL-7, particularly when paired with low levels of IL-17F, predict responsiveness to IFN-β and hence a T(H)1-driven subtype of MS. We also show that although IL-7 signaling is neither necessary nor sufficient for the induction or expansion of T(H)17 cells, IL-7 can greatly enhance both human and mouse T(H)1 cell differentiation. IL-7 alone is sufficient to induce human T(H)1 differentiation in the absence of IL-12 or other cytokines. Furthermore, targeting IL-7/IL-7Rα is beneficial in experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. Mice treated with IL-7Rα-blocking antibodies before or after onset of paralysis exhibited reduced clinical signs of EAE, with reduction in peripheral naïve and activated T cells, whereas central memory T, regulatory T, B, and natural killer cell populations were largely spared. IL-7Rα antibody treatment markedly reduced lymphocyte infiltration into the central nervous system in mice with EAE. Thus, a serum profile of high IL-7 may signify a T(H)1-driven form of MS and may predict outcome in MS patients undergoing IFN-β therapy. Blockade of IL-7 and the IL-7Rα pathway may have therapeutic potential in MS and other autoimmune diseases.

PMID: 21795588 [PubMed - in process]

A role of IL-1R1 signaling in the differentiation of Th17 cells and the development of autoimmune diseases.

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IL-1 cytokine family plays a key role in the innate immune response against pathogen- and danger-associated molecular patterns. More recently, IL-1 receptor type 1 (IL-R1) signaling has been identified as a critical step in the differentiation and commitment of Th17 cells, which mediate the development of autoimmune diseases. Given its significance in the induction of the adoptive immune response, this complex signaling pathway is tightly regulated. Upon binding of IL-1 to IL-1R1, IL-1R accessory protein (AcP) is recruited to form a high affinity IL-1R1-IL-1RAcP heterodimeric receptor, which initiates the downstream signaling cascade. Multiple negative regulators of this pathway, including inhibitory membrane-bound IL-RII, secreted soluble (s)IL-1R, sIL-Rll and sIL-1RAcP, the regulatory IL-1R1 antagonist (IL-1R1a) and the IL-1R1-signalin-induced single Ig-IL-1R-related (SIGIRR), provide a negative feedback control of this pathway, and suppress excessive IL-1 signaling and Th17 cell differentiation. IL-1R1 signaling induces human Th17 cell differentiation, leading to the expression of IL-1R-associated protein kinase (IRAK)4 and retinoic acid-related orphan nuclear hormone receptor (ROR), Th17 cell lineage transcription factors, which together with signal transducer and activator of the transcription (STAT)3, activate this cell lineage’s specific cytokine expression profile, including IL-17A, IL-17F, IL-21 and IL-22. Given the role of IL-1 signaling and Th17 cells in the development of the autoinflammatory and autoimmune diseases, therapeutic strategies inhibiting IL-1R1 signaling are discussed as a novel approach for the treatment of autoimmune diseases and particularly multiple sclerosis (MS).

PMCID: PMC3136902 PMID: 21776333 [PubMed]
Neuropathic itch.
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Chronic itch can be caused by dysfunctions of itch-sensing neurons that produce sensory hallucinations of pruritogenic stimuli. The cellular and molecular mechanisms are still unknown. All neurological disease categories have been implicated, and neurological causes should be considered for patients with otherwise-unexplained itch. The same neurological illnesses that cause neuropathic pain can also or instead cause itch. These include shingles (particularly of the head or neck), small-fiber polyneuropathies, radiculopathies (eg, natalgia paresthetica and brachioradial pruritis), and diverse lesions of the trigeminal nerve, root, and central tracts. Central nervous system lesions affecting sensory pathways, including strokes, multiple sclerosis, and cavernous hemangiomas, can cause central itch. Neuropathic itch is a potent trigger of reflex and volitional scratching although this provides only fleeting relief. Rare patients whose lesion causes sensory loss as well as neuropathic itch can scratch deeply enough to cause painless self-injury. The most common location is on the face (trigeminal trophic syndrome). Treating neuropathic itch is difficult; antihistamines, corticosteroids, and most pain medications are largely ineffective. Current treatment recommendations include local or systemic administration of inhibitors of neuronal excitability (especially local anesthetics) and barriers to reduce scratching.

Multiple sclerosis and chronic cerebrospinal venous insufficiency: a critical review.
Awad AM, Marder E, Milo R, Stüve O.
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Chronic cerebrospinal venous insufficiency (CCSVI) was recently proposed as a contributing factor in the pathology of multiple sclerosis. This concept has gained remarkable attention, partly because endovascular neurointervention has been suggested as a treatment strategy. This review summarizes available evidence and provides a critical analysis of the published data. Currently, there is inconclusive evidence to support CCSVI as an etiological factor in patients with multiple sclerosis. Endovascular procedures should not be undertaken outside of controlled clinical trials.
PMCID: PMC3131174 PMID: 21765873 [PubMed - in process]

Biological outcome measurements for behavioral interventions in multiple sclerosis.
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Behavioral interventions including exercise, stress management, patient education, psychotherapy and multidisciplinary neurorehabilitation in general are receiving increasing recognition in multiple sclerosis (MS) clinical practice and research. Most scientific evaluations of these approaches have focused on psychosocial outcome measures such as quality of life, fatigue or depression. However, it is becoming increasingly clear that neuropsychiatric symptoms of MS are at least partially mediated by biological processes such as inflammation, neuroendocrine dysfunction or regional brain damage. Thus, successful treatment of these symptoms with behavioral approaches could potentially also affect the underlying biology. Rigidly designed scientific studies are needed to explore the potential of such interventions to affect MS pathology and biological pathways linked to psychological and neuropsychiatric symptoms of MS. Such studies need to carefully select outcome measures on the behavioral level that are likely to be influenced by the specific intervention strategy and should include biomarkers with evidence for an association with the outcome parameter in question. In this overview, we illustrate how biological and psychological outcome parameters can be combined to evaluate behavioral interventions. We focus on two areas of interest as potential targets for behavioral interventions: depression and fatigue.
PMCID: PMC3131172 PMID: 21765872 [PubMed - in process]

**No evidence of IL21 association with multiple sclerosis in a Swedish population.**


Department of Clinical Neuroscience, Neuroimmunology Unit, Karolinska Institutet, Stockholm, Sweden
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Multiple sclerosis (MS) patients, with a second autoimmune disease after lymphocyte depletion, had elevated serum IL-21 before and after treatment which correlated to IL21 genotypes. In addition, the IL21 gene has been associated to several other autoimmune diseases. However, in a Spanish population there was no association to MS. Here, in a Swedish cohort (2090 MS cases and 1732 controls) 12 single nucleotide polymorphisms (SNPs) tagging IL21 were not associated to disease. There was no interaction with risk alleles of IL21R and HLA-DRB1*15. Lack of genetic association was confirmed in a meta-analysis with pooled data from the present study and the Spanish study. In conclusion, IL21 has not been shown to be a major risk gene for MS.

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**Central nervous system myelin: structure, synthesis and assembly.**

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The wrapping of multiple layers of myelin membrane sheets around an axon is of fundamental importance for the function of the nervous system. In the central nervous system (CNS) oligodendrocytes synthesize tremendous amounts of cellular membrane to form multiple myelin internodes of highly stable membranes with a specific set of tightly packed lipids and proteins. In recent years, mouse mutants have allowed great advances in our understanding of the functional and structural role of many of the major components of myelin. The challenge now is to extend this knowledge to unravel the molecular machinery and mechanisms required to synthesize, assemble and wrap myelin multiple times around an axon at the appropriate developmental time. Such insight will be essential in designing new therapeutic strategies to promote remyelination in demyelinating disorders such as multiple sclerosis.

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