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Literatur-Dauerrecherche **Multiple Sklerose**

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(= Neuaufnahmen in der Literaturdatenbank)

Inhaltsverzeichnis

1. Episodic Neurologic Symptoms.
Good DC. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 51.
Intermittent neurologic symptoms comprise a group of complaints that may be associated with dysfunction of many organ systems, including the central nervous system, cardiovascular system, and vestibular apparatus. Intermittent metabolic disturbances and psychiatric problems may also result in neurologic symptoms. Despite these diverse etiologies, all the conditions discussed here share the following features: (1) They are intermittent; (2) they are recurrent; (3) they are usually brief, lasting minutes to hours; (4) the patient is usually asymptomatic between attacks; and (5) the symptoms are usually stereotyped for an individual patient. Although intermittent neurologic symptoms often have a benign prognosis, some may be a manifestation of a serious condition. Multiple sclerosis, myasthenia gravis, and certain other neurologic illnesses may have intermittent symptoms. Most patients with these conditions have a more chronic course on which intermittent symptoms are superimposed, however; they will not be discussed further here.
PMID: 21250215 [PubMed]

2. Acta Neurol Scand. 2011 Jan 6. doi: 10.1111/j.1600-0404.2010.01475.x. [Epub ahead of print]
Elevated HSP27 levels during attacks in patients with multiple sclerosis.
Ce P, Erkizan O, Gedizlioglu M.
Department of Neurology, Izmir Bozyaka Training and Research Hospital, Bozyaka, Izmir, Turkey
Department of Biochemistry, Izmir Bozyaka Training and Research Hospital, Bozyaka, Izmir, Turkey.
Ce P, Erkizan O, Gedizlioglu M. Elevated HSP27 levels during attacks in patients with multiple sclerosis. Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2010.01475.x. © 2011 John Wiley & Sons A/S. Objectives - The small heat shock protein, HSP27, has been shown to have a more potent protective effect in the nervous system. However, there is limited information about the behavior of HSP27 in the course of multiple sclerosis (MS). Thus, we investigated the HSP27 levels during relapse and remission phases of MS. Materials and Methods - A total of 50 relapsing-remitting or secondary progressive MS patients and 45 age- and gender-matched controls without any systemic diseases were enrolled. HSP27 levels were serologically detected in serum samples of both controls and MS patients during acute attacks and after a minimum of 2 months of each individual attack. Results - The mean HSP27 level was 12.41 ± 18.21 ng/ml in the attack phase, 4.58 ± 4.75 ng/ml during remission, and 2.58 ± 3.88 ng/ml in control patients. The heat shock proteins (HSP) levels of MS patients in the attack phase were significantly higher than those obtained in the remission phase (P = 0.005). Moreover, HSP levels in the attack and remission phases of MS patients were also significantly higher when compared to controls (P = 0.001 and P = 0.03, respectively). While there was no correlation between HSP27 levels in the attack phase and age, disease duration, or expanded disability status scale scores (P = 0.69, P = 0.32, and P = 0.91, respectively), a positive correlation was observed between the HSP27 levels and the total attack number (P = 0.001). Conclusions - Our findings revealed a marked elevation in HSP27 levels during the relapse phase. Therefore, it can be suggested that elevated HSP27 levels may guide in the accurate detection of an attack in patients with MS.
PMID: 21208199 [PubMed - as supplied by publisher]

3. Acta Neurol Scand. 2011 Jan 6. doi: 10.1111/j.1600-0404.2010.01473.x. [Epub ahead of print]
Multiple sclerosis and cognitive decline: is ApoE-4 a surrogate marker?
Carmona O, Masuet C, Santiago O, Alía P, Moral E, Alonso-Magdalena L, Casado V, Arbizu T.
Multiple Sclerosis Unit, Neurology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain Preventive Medicine Department, Hospital Universitari de Bellvitge, Barcelona, Spain Biochemistry Department, Hospital Universitari de Bellvitge, Barcelona, Spain.
Carmona O, Masuet C, Santiago O, Alía P, Moral E, Alonso-Magdalena L, Casado V, Arbizu T. Multiple sclerosis and cognitive decline: is ApoE-4 a surrogate marker? Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2010.01473.x. © 2011 John Wiley & Sons A/S. Background - The role of the apolipoprotein E (ApoE) polymorphism has been well demonstrated in neurodegenerative disorders such as Alzheimer. However, its role in multiple sclerosis (MS) remains unclear. Aims - The aims of our study were as follows: (i) to assess whether ApoE-4 might be a surrogate marker of cognitive decline in MS; (ii) to confirm the presence of cognitive impairment in mildly disabled patients treated with interferon-beta; and (iii) to analyse the correlation between cognitive disturbances and clinical variables. Material and methods - Fifty relapsing-remitting MS patients underwent a battery of neuropsychological tests and were genotyped for ApoE. Their scores were compared with those of 35 controls. Results - No association was found between ApoE-4 and cognitive impairment. Significant differences in most domains were observed between MS and the control group. Cognitive decline was not related to disability progression. Conclusion - No association between cognitive impairment and ApoE-4 or clinical markers was detected in our MS patients.
PMID: 21208197 [PubMed - as supplied by publisher]

4. Acta Neurol Scand. 2011 Jan 4. doi: 10.1111/j.1600-0404.2010.01463.x. [Epub ahead of print]
Sudden sensorineural hearing loss in multiple sclerosis: clinical course and possible pathogenesis.
Hellmann MA, Steiner I, Mosberg-Galili R.
Department of Neurology, Rabin Medical Center, Beilinson Campus, Petah Tikva, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.
Hellmann MA, Steiner I, Mosberg-Galili R. Sudden sensorineural hearing loss in multiple sclerosis: clinical course and possible pathogenesis. Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2010.01463.x. © 2011 John Wiley & Sons A/S. Objective - To assess the symptom of sudden hearing loss in multiple sclerosis (MS). Method - We reviewed patient files in our MS clinic between January 2004 and November 2009 for symptoms of sudden hearing loss. Results - We were able to identify 11 of 253 patients (4.35%) with sudden hearing loss. In seven patients, the hearing decline was the presenting symptom of MS and in all 11 patients, it appeared early in the course of the disease. There was no residual hearing deficit in 9/11 patients. In no patient was the condition bilateral and in none did it recur. Conclusion - Episodes of hearing loss are not uncommon in MS and have a good chance of complete recovery.
PMID: 21198448 [PubMed - as supplied by publisher]

5. Acta Neurol Scand. 2011 Jan 4. doi: 10.1111/j.1600-0404.2010.01460.x. [Epub ahead of print]
Impaired body image in patients with multiple sclerosis.
Pfaffenberger N, Gutweniger S, Kopp M, Seeber B, Stürz K, Berger T, Günther V.
Center of Psychiatry and Psychotherapy, Department of General and Social Psychiatry, Clinical Psychology, Innsbruck Medical University Department of Sport Science, University of Innsbruck Neuroimmunology and Multiple Sclerosis Clinic & Research Unit, Clinical Department of Neurology, Innsbruck Medical University, Innsbruck, Austria.
Pfaffenberger N, Gutweniger S, Kopp M, Seeber B, Stürz K, Berger T, Günther V. Impaired body image in patients with multiple sclerosis. Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2010.01460.x. © 2011 John Wiley & Sons A/S. Objective - Despite the growing research on body image disturbances in chronically ill patients, reports of such disturbances in patients with multiple sclerosis (MS) are scarce. The aim of this study was to assess the occurrence of different aspects of body image disturbances in patients with MS, taking into account the disability status as well as depressive symptoms. Materials & methods - Forty patients with MS and 28 healthy controls were investigated with questionnaires assessing attractiveness/self-confidence, accentuation of external appearance, worries about possible physical deficits, sexual problems, vitality and depressive symptoms. In MS patients, medical parameters like the expanded disability status were assessed too. Results - In comparison with healthy controls, the MS patients, being although only mildly disabled and in a quite stable mood, reported significantly higher worries about physical deficits, described a significantly worse body appraisal and significantly more sexual problems. While female MS patients predominantly suffered from worries concerning physical deficits and feelings of being less attractive, sexual problems were of particular concern in male MS patients. Conclusions - Even mildly impaired MS patients who are not markedly depressed have to deal with problems of body image. Improvement of body image perception in MS patients taking gender-specific differences into account represents a promising area of future psychological research.
PMID: 21198446 [PubMed - as supplied by publisher]

7. Acta Neurol Taiwan. 2011 Jan 18. [Epub ahead of print]
Assessments of the Reliability of the Iranian version of the Berg Balance Scale in Patients with Multiple Sclerosis.
Azad A, Taghizadeh G, Khaneghini A.
Department of Occupational Therapy, Iran University of Medical Sciences, Tehran, Iran.
Purpose: Because of the balance limitations in many patients, balance assessment is necessary for multiple sclerosis patients in rehabilitation settings. The aim of this study was to investigate the Interrater reliability and the internal consistency of the Iranian version of the Berg Balance Scale (BBS) when applied to patients with multiple sclerosis (MS) in Tehran. Methods: Fifty MS patients (with mean age of 36.6±9.5 years) from Hospitals of the Iran University of Medical Sciences and MS Society of Iran were included. Interrater reliability was measured with the Kappa statistics and Intraclass Correlation Coefficients (ICCs). Results: The mean values of the BBS scored by the 2 evaluators were 37.7 ±12.9 and 38.l ± 12.3, respectively. Kappa scores for BBS varied from 0.7 to 1.0 Intraclass correlation coefficient for the BBS's sum score was excellent (ICC=0.99 with 95% confidence interval, 0.98-0.99). An excellent internal consistency was found within the BBS's sum score (Cronbach Alpha =0.9). The item -to -total correlations for all items were higher than 0.6. Conclusion: The Iranian version of the BBS has excellent interrater reliability and internal consistency for the assessment of MS patients when applied in clinics.
PMID: 21249592 [PubMed - as supplied by publisher]

8. Acta Neuropathol. 2011 Jan 15. [Epub ahead of print]
Sildenafil (Viagra) ameliorates clinical symptoms and neuropathology in a mouse model of multiple sclerosis.
Pifarre P, Prado J, Baltrons MA, Giralt M, Gabarro P, Feinstein DL, Hidalgo J, Garcia A.
Institute of Biotechnology and Biomedicine, Universitat Autonoma de Barcelona, 08193, Bellaterra, Spain.
Cyclic GMP (cGMP)-mediated pathways regulate inflammatory responses in immune and CNS cells. Recently, cGMP phosphodiesterase inhibitors such as sildenafil, commonly used to treat sexual dysfunction in humans including multiple sclerosis (MS) patients, have been reported to be neuroprotective in animal models of stroke, Alzheimer's disease, and focal brain lesion. In this work, we have examined if sildenafil ameliorates myelin oligodendrocyte glycoprotein peptide (MOG(35-55))-induced experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. We show for the first time that treatment with sildenafil after disease onset markedly reduces the clinical signs of EAE by preventing axonal loss and promoting remyelination. Furthermore, sildenafil decreases CD3+ leukocyte infiltration and microglial/macrophage activation in the spinal cord, while increasing forkhead box transcription factor 3-expressing T regulatory cells (Foxp3 Tregs). However, sildenafil treatment did not significantly affect MOG(35-55)-stimulated proliferation or release of Th1/Th2 cytokines in splenocytes but decreased ICAM-1 in spinal cord infiltrated cells. The presence of reactive astrocytes forming scar-like structures around infiltrates was enhanced by sildenafil suggesting a possible mechanism for restriction of leukocyte spread into healthy parenchyma. These results highlight novel actions of sildenafil that may contribute to its beneficial effects in EAE and suggest that treatment with this widely used and well-tolerated drug may be a useful therapeutic intervention to ameliorate MS neuropathology.
PMID: 21234581 [PubMed - as supplied by publisher]

9. Am J Rhinol Allergy. 2010 Sep;24(5):93-7.
Olfactory and gustatory function in patients with multiple sclerosis.
Fleiner F, Dahlslett SB, Schmidt F, Harms L, Goektas O.
BACKGROUND: The olfactory function (OF) and gustatory function in patients with multiple sclerosis (MS) can be limited. METHODS: We performed the testing of orthonasal (Threshold Discrimination Identification [TDI] score with Sniffin' Sticks) and retronasal (Taste Powder) OF and gustatory function (Taste Strips; Burghart, Wedel, Germany) in patients diagnosed with MS and healthy controls matching in age, sex, and smoking habits. RESULTS: Eight of 16 MS patients (50%) displayed hyposmia (TDI score, 28.75 ± 1.28; p = 0.06); the identification subtest significantly was restricted (12.63 ± 1.67; p = 0.001). Four of 16 MS patients (25%) had limited retronasal OF with a Taste Powder score of 4.5 ± 1.29. The gustatory function in 19% of MS patients was significantly limited (Taste Strip score, 5.33 ± 2.52; p = 0.02). Patients who estimated their ability to smell as diminished performed more poorly on retronasal OF testing (r =0.657; p = 0.046). CONCLUSION: This study confirms the incidence of olfactory disorder in MS patients that has been reported in the literature. Interestingly, a significant correlation between orthonasal and retronasal OF testing was not shown. A higher incidence of gustatory dysfunction was shown and might serve as another potential marker for this disease.
PMID: 21244723 [PubMed - in process]

10. Anal Biochem. 2011 Jan 7. [Epub ahead of print]
Measurement of serum levels of natalizumab, an immunoglobulin G4 therapeutic monoclonal antibody.
Rispens T, Leeuwen AV, Vennegoor A, Killestein J, Aalberse RC, Wolbink GJ, Aarden LA.
Sanquin Research, 1066 CX Amsterdam, The Netherlands; Landsteiner Laboratory, Academic Medical Centre, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands.
Human immunoglobulin G4 (IgG4) is a poor trigger of effector functions and, therefore, is the preferred subclass for therapeutic monoclonal antibodies that merely aim to block their in vivo targets. An example is natalizumab, a recombinant IgG4 antibody directed against α4-integrin and used for treatment of multiple sclerosis. Efficient treatment requires that the pharmacokinetics of therapeutic monoclonal antibodies can be accurately monitored. For natalizumab, this requires special precautions due to recently reported structural peculiarities of human IgG4. Here we describe the development of an assay to determine serum levels of natalizumab. Compared with other IgG subclasses, human IgG4 possesses unique structural properties that influence its interactions in both in vivo and in vitro settings. Thus, IgG4 undergoes Fab arm exchange in vivo, resulting in effectively monovalent antibodies. Furthermore, IgG4 is able to bind to other human and nonhuman IgG via Fc interactions. We demonstrate how these features can interfere with measurement of specific IgG4 and describe how we addressed these issues, resulting in an assay that is not sensitive to Fab arm exchange by natalizumab or to IgG4 Fc interactions.
PMID: 21216215 [PubMed - as supplied by publisher]

11. Ann Behav Med. 2011 Jan 7. [Epub ahead of print]
Further Evaluation of the Motivational Model of Pain Self-Management: Coping with Chronic Pain in Multiple Sclerosis.
Kratz AL, Molton IR, Jensen MP, Ehde DM, Nielson WR.
Department of Rehabilitation Medicine, University of Washington, HMC BX359612, Seattle, WA, 98104, USA, alkratz@uw.edu.
BACKGROUND: Growing evidence suggests that motivation to engage in pain-coping strategies is a key predictor of how well a person adjusts to pain. According to the Motivational Model of Pain Self-Management, readiness to engage in pain self-management behaviors is influenced by beliefs about the importance of the behavior (importance) and the ability to carry out the behavior (self-efficacy). PURPOSE: The purpose of this study was to test the Motivational Model of Pain Self-Management for exercise and task persistence pain-coping behaviors in a sample of 114 individuals with multiple sclerosis and chronic pain. METHODS: Measures included the Multidimensional Pain Readiness to Change Questionnaire-2 and measures of importance, self-efficacy, and coping behavior duration. Tests of mediation were conducted with two path analyses, one for each coping behavior. RESULTS: The effects of importance and self-efficacy beliefs on coping behaviors were mediated or partially mediated by readiness to engage in those behaviors. CONCLUSIONS: These findings provide support for the Motivational Model of Pain Self-Management and have important implications for the development of treatments for chronic pain.
PMID: 21213092 [PubMed - as supplied by publisher]

12. Ann Indian Acad Neurol. 2010 Oct;13(4):313.
Beta-interferons in multiple sclerosis.
Aggarwal S, Sharma V, Mathew JS.
University College of Medical Sciences, New Delhi, India.
PMCID: PMC3021941 PMID: 21264146 [PubMed - in process]

13. Ann Indian Acad Neurol. 2010 Oct;13(4):289-92.
Central nervous system inflammatory demyelinating disorders of childhood.
Kamate M, Chetal V, Tonape V, Mahantshetti N, Hattiholi V.
Department of Pediatrics, KLE University's J N Medical College, Belgaum, Karnataka, India.
BACKGROUND AND OBJECTIVES: Childhood Central Nervous System (CNS) inflammatory demyelinating disorders (CIDD) are being diagnosed more commonly now. There is ambiguity in the use of different terms in relation to CIDD. Recently, consensus definitions have been proposed so that there is uniformity in studies across the world. The prevalence of these disorders and the spectrum varies from place to place. This study was undertaken to study the clinico-radiological profile and outcome of children with CIDD using the recent consensus definition. STUDY DESIGN: Prospective descriptive study. MATERIALS AND METHODS: All patients admitted in pediatric ward and pediatric intensive care with neurological symptoms and signs suggestive of CNS inflammatory demyelinating disorders from July 2007-August 2008 were enrolled. The details of clinical presentation, neuroimaging findings, laboratory results, treatment, and outcome were noted and analyzed. RESULTS: Fifteen patients (11 with acute disseminated encephalomyelitis and 4 with clinically isolated syndrome) were diagnosed with CIDD. Clinical presentation was quite varied. Eight patients recovered completely; 4 cases were left with sequelae and 3 patients expired. There were no cases of multiple sclerosis or neuromyelitis optica. CONCLUSIONS: CNS inflammatory demyelinating disorders are common illnesses in developing countries because of recurrent infections. Even the spectrum of CIDD is different. Neuroimaging in the form of magnetic resonance imaging is essential for diagnosis.
PMCID: PMC3021933 PMID: 21264138 [PubMed - in process]

14. Ann Neurol. 2011 Jan 19. doi: 10.1002/ana.22302. [Epub ahead of print]
Role of CD8 regulatory T Cells in multiple sclerosis.
Correale J, Villa A.
Department of Neurology, Raúl Carrea Institute for Neurological Research (FLENI), Buenos Aires, Argentina.
PMID: 21246606 [PubMed - as supplied by publisher]

15. Ann Neurol. 2010 Dec;68(6):855-64.
Dysexecutive syndrome: diagnostic criteria and validation study.
Godefroy O, Azouvi P, Robert P, Roussel M, LeGall D, Meulemans T; Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives Study Group.
Collaborators: Godefroy O, Roussel M, Le Gall D, Bertola C, Giroire JM, Joseph PA, Seron X, Coyette F, Bretault E, Bernard I, Leclercq M, Azouvi P, Vallat-Azouvi C, Pollack P, Mosca C, Bindschadler C, Krier M, Meulemans T, Marquet V, Leys D, Roussel M, Renou P, Vercelletto M, Michel E, Robert P, Labauge P, Franconie C, Pillon B, Verny M, Lenoir H, De Rotrou J, Hannequin D, Bioux S, Fuchs J, Bellmann A, Vuadens P.
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OBJECTIVE: Disorders of executive functions are among the most frequent cognitive deficits, but they remain poorly defined and are subject to heterogeneous assessment. To address this major issue, the Groupe de Réflexion sur l'Evaluation des Fonctions Exécutives (GREFEX) group has proposed criteria for behavioral and cognitive dysexecutive syndromes and has designed a battery including a specific heteroquestionnaire and 7 cognitive tests. We investigated the frequency of behavioral and cognitive dysexecutive disorders in patients suffering from various diseases and the association of these disorders with loss of autonomy. METHODS: A total of 461 patients aged between 16 and 90 years with severe traumatic brain injury, stroke, mild cognitive impairment, Alzheimer disease, multiple sclerosis, and Parkinson disease were recruited into this prospective cohort study by 21 centers between September 2003 and June 2006. Behavioral and cognitive dysexecutive disorders were examined using the GREFEX battery. RESULTS: A dysexecutive syndrome was observed in 60% of patients, concerning both behavioral and cognitive domains in 26% and dissociated in 34%. All behavioral and cognitive dysexecutive disorders discriminated ($p = 0.001$, all) patients from controls. The pattern of cognitive syndrome differed ($p = 0.0001$) according to the disease. Finally, behavioral (odds ratio [OR], 4.6; 95% confidence interval [CI], 2. 3-9.1; $p = 0.0001$) and cognitive (OR, 3.36; 95% CI, 1.7-6.6; $p = 0.001$) dysexecutive syndromes and Mini Mental State Examination score (OR, 0.79; 95% CI, 0.68-0.91; $p = 0.002$) were independent predictors of loss of autonomy. INTERPRETATION: This study provided criteria of dysexecutive syndrome and showed that both behavioral and cognitive syndromes contribute to loss of autonomy. Profiles vary across patients and diseases, and therefore systematic assessment of behavioral and cognitive disorders in reference to diagnostic criteria is needed.
PMID: 21194155 [PubMed - indexed for MEDLINE]

16. Ann Neurol. 2010 Dec;68(6):806-15.
Evidence for acute neurotoxicity after chemotherapy.
Petzold A, Mondria T, Kuhle J, Rocca MA, Cornelissen J, te Boekhorst P, Lowenberg B, Giovannoni G, Filippi M, Kappos L, Hintzen R.
Department of Neuroimmunology, UCL Institute of Neurology, Queen Square, London, United Kingdom. a.petzold@vumc.nl
Comment in: Ann Neurol. 2010 Dec;68(6):778-9.
OBJECTIVE: Chronic neurotoxicity is a recognized long-term complication following chemotherapy in a range of diseases. Neurotoxicity adversely affects patients' quality of life. The objective of this study is to examine whether there is evidence of acute neurotoxicity. METHODS: This prospective study included patients with secondary progressive multiple sclerosis (SPMS-BMT, n = 14) and hematological malignancies (HM-BMT, n = 17) receiving chemotherapy as preconditioning for bone marrow transplant. The control groups included SPMS patients matched for demographic and clinical data (SPMS-PL, n = 14) and healthy controls (n = 14). Neurodegeneration was assessed at baseline and longitudinally (months 1, 2, 3, 6, 9, 12, 24, and 36), combining a clinical scale for disability (Expanded Disability Status Scale [EDSS]), a serum protein biomarker for neurodegeneration (neurofilaments, NfH-SMI35), and brain atrophy measures (magnetic resonance imaging). RESULTS: Disability progression was significantly more acute and severe following chemotherapy compared to placebo. Immediately after starting chemotherapy, serum NfH-SMI35 levels increased in 79% ($p < 0.0001$) of SPMS-BMT patients and 41% ($p < 0.01$) of HM-BMT patients compared to 0% of SPMS-PL patients or healthy controls. In SPMS-BMT serum NfH-SMI35 levels were > 100-fold higher 1 month after chemotherapy (29.73ng/ml) compared to baseline (0.28ng/ml, $p < 0.0001$). High serum NfH-SMI35 levels persisting for at least 3 months were associated with sustained disability progression on the EDSS ($p < 0.05$). Brain atrophy rates increased acutely in SPMS-BMT (-2.09) compared to SPMS-PL (-1.18, $p < 0.05$). INTERPRETATION: Neurotoxicity is an unwanted acute side effect of aggressive chemotherapy.
PMID: 21194151 [PubMed - indexed for MEDLINE]

17. Ann Neurol. 2010 Dec;68(6):778-9.
Cerebral pseudoatrophy or real atrophy after therapy in multiple sclerosis.
Khoury S, Bakshi R.
Comment on: Ann Neurol. 2010 Dec;68(6):806-15.
PMID: 21194148 [PubMed - indexed for MEDLINE]

18. Ann Rheum Dis. 2011 Jan 7. [Epub ahead of print]
Interleukin 1 receptor antagonist mediates the beneficial effects of systemic interferon beta in mice: implications for rheumatoid arthritis.
Corr M, Boyle DL, Ronacher LM, Lew BR, van Baarsen LG, Tak PP, Firestein GS.
1Division of Rheumatology, Allergy and Immunology, University of California at San Diego, La Jolla, California, USA.
OBJECTIVES: /st> Interferon beta (IFNβ) therapy is effective in multiple sclerosis and murine models of arthritis. Surprisingly, systemic IFNβ treatment induces only minimal improvement in rheumatoid arthritis (RA). To explain this paradox, the authors evaluated the mechanism of IFNβ benefit in passive K/BxN arthritis and the effect of IFNβ treatment on RA synovium. METHODS: /st> Interleukin 10 (IL-10) null, IL-1 receptor antagonist (IL-1Ra) null, IL-1Ra transgenic and wild-type mice were administered K/BxN serum and in some cases treated with IFNβ or normal saline. Clinical response and histological scores were assessed. Gene expression was measured by quantitative PCR. Serum IL-1Ra and IL-6 were measured by ELISA. Paired synovial biopsy specimens from RA patients pre-IFNβ and post-IFNβ treatment (purified natural fibroblast IFNβ (Frone) subcutaneously three times weekly 6 million IU, 12 million IU or 18 million IU) were immunostained for IL-1Ra and IL-10. RESULTS: /st> Il1rn transgenic mice had an attenuated course of arthritis, whereas Il1rn(-/-) and Il10(-/-) mice had more severe serum transfer arthritis than wild-type mice. Daily IFNβ treatment significantly decreased arthritis severity in Il10(-/-) but not Il1rn(-/-) mice. IFNβ treatment did not reduce the histological scores in Il1rn(-/-) mice or gene expression of articular cytokines and chemokines. Paired synovial biopsy specimens from RA patients treated with IFNβ demonstrated a trend towards increased IL-1Ra and reduced IL-10 expression on day 85 levels compared with pretreatment specimens. CONCLUSIONS: /st> The anti-inflammatory effects of IFNβ in passive K/BxN arthritis are dependent on IL-1Ra, but not IL-10. Systemic IFNβ treatment in RA increases synovial IL-1Ra production, but also decreases IL-10 production.
PMID: 21216819 [PubMed - as supplied by publisher]

19. Arch Clin Neuropsychol. 2011 Jan 6. [Epub ahead of print]
Deficits in Processing Speed in Patients with Multiple Sclerosis: Evidence from Explicit and Covert Measures.
Denney DR, Gallagher KS, Lynch SG.
Department of Psychology, University of Kansas Medical Center, Kansas City, KS, USA.
Cognitive slowing in individuals with multiple sclerosis (MS) has been documented by numerous studies employing explicitly timed measures in which speed of responding is an obvious focus of task performance. The present study examined information processing speed in MS patients and controls with a computerized battery of covertly timed as well as explicitly timed measures. The explicit measures were derived from two tests requiring rapid serial processing of visual stimuli, the Stroop Test and a Picture Naming Test. Covert measures were derived from the Rotated Figures Test, Remote Associates Test, and Tower of London, all tasks in which participants' attention was drawn toward arriving at an accurate solution, and the latency with which they arrived at these solutions was timed by the computer "behind the scenes." Significant differences in processing speed for patients and controls occurred on both types of measures, although the effect sizes were notably larger on the explicit measures.
PMID: 21216726 [PubMed - as supplied by publisher]

20. Arch Immunol Ther Exp (Warsz). 2011 Jan 26. [Epub ahead of print]
CD46 Plasticity and Its Inflammatory Bias in Multiple Sclerosis.
Ni Choileain S, Astier AL.
Institute for Immunology and Infection Research, University of Edinburgh, Edinburgh, UK.
Known as a link to the adaptive immune system, a complement regulator, a "pathogen magnet" and more recently as an inducer of autophagy, CD46 is the human receptor that refuses to be put in a box. This review summarizes the current roles of CD46 during immune responses and highlights the role of CD46 as both a promoter and attenuator of the immune response. In patients with multiple sclerosis (MS), CD46 responses are overwhelmingly pro-inflammatory with notable defects in cytokine and chemokine production. Understanding the role of CD46 as an inflammatory regulator is a distant goal considering the darkness in which its regulatory mechanisms reside. Further research into the regulation of CD46 expression through its internalization and processing will undoubtedly extend our knowledge of how the balance is tipped in favor of inflammation in MS patients.
PMID: 21267793 [PubMed - as supplied by publisher]

21. Arq Neuropsiquiatr. 2010 Dec;68(6):914-7.
The effect of multiple sclerosis on the professional life of a group of Brazilian patients.
Fragoso YD, Finkelsztejn A, Giacomo MC, Russo L, Cruz WS.
Department of Neurology, Medical School, Universidade Metropolitana de Santos, Santos, SP, Brazil.
OBJECTIVE: To assess the impact of multiple sclerosis (MS) on the professional life of Brazilian patients. METHOD: One hundred MS patients were randomly selected from the database of the Brazilian Multiple Sclerosis Association (ABEM). An individual interview was carried out by telephone by a member of ABEM, who collected data on the patients' clinical status, educational level and professional lives. RESULTS: Complete data were obtained from 96 patients (27 males and 69 females) aged 55.0±14.1 years, with average disease duration of 4.6±4.0 years). Eighty percent had eleven or more years of schooling. Among the whole group, 66% did not present limitations on walking. The longer the disease duration and the older the patient were, the higher the chances were that the patient was retired or receiving workers' compensation benefits. However, even among patients with MS for less than five years, the rate of non-participation in the workforce was 47.7%. Fatigue, paresthesia, cognitive dysfunction and pain were often cited as the motives for not working. CONCLUSION: MS patients presented high levels of unemployment, retirement and receipt of workers' compensation benefits, despite their high schooling levels. Age, disease duration and disability influenced these results for the whole group. However, even among younger patients with shorter disease duration and low disability, this finding remained.
PMID: 21243252 [PubMed - in process]

22. Autoimmun Rev. 2010 Dec 30. [Epub ahead of print]
γδ T cells and multiple sclerosis: Friends, foes, or both?
Chen Z, Freedman MS.
Department of Microbiology and Immunology, University of Ottawa, Ottawa, ON, Canada; Ottawa Hospital Research Institute, Ottawa, ON, Canada.
Multiple sclerosis (MS) is a debilitating CNS disease characterized by demyelination and neuro-axonal loss. Though the exact etiology is still unknown, accumulated evidence points to the immune system being involved in the MS disease-process. Both ill-fated adaptive and innate immune responses can potentially contribute to the etiopathogenesis. We have been interested in deciphering how innate immunity might be involved; in particular, the role of γδ T cells. In this review, we discuss the current understanding about γδ T cells and describe the evidence implicating them in myelin injury, neurotoxicity, and immunoregulation in the development of MS.
PMID: 21195807 [PubMed - as supplied by publisher]

23. Autoimmune Dis. 2010 Dec 9;2011:932351.
Heterogeneity in multiple sclerosis: scratching the surface of a complex disease.
Disanto G, Berlanga AJ, Handel AE, Para AE, Burrell AM, Fries A, Handunnetthi L, De Luca GC, Morahan JM.
Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Headington, Oxford, OX3 7BN, UK.
Multiple Sclerosis (MS) is the most common demyelinating disease of the central nervous system. Although the etiology and the pathogenesis of MS has been extensively investigated, no single pathway, reliable biomarker, diagnostic test, or specific treatment have yet been identified for all MS patients. One of the reasons behind this failure is likely to be the wide heterogeneity observed within the MS population. The clinical course of MS is highly variable and includes several subcategories and variants. Moreover, apart from the well-established association with the HLA-class II DRB1*15:01 allele, other genetic variants have been shown to vary significantly across different populations and individuals. Finally both pathological and immunological studies suggest that different pathways may be active in different MS patients. We conclude that these "MS subtypes" should still be considered as part of the same disease but hypothesize that spatiotemporal effects of genetic and environmental agents differentially influence MS course. These considerations are extremely relevant, as outcome prediction and personalised medicine represent the central aim of modern research.
PMCID: PMC3005811 PMID: 21197462 [PubMed - in process]

24. Autoimmune Dis. 2010 Dec 28;2011:485752.
Effects of IFN-B on TRAIL and Decoy Receptor Expression in Different Immune Cell Populations from MS Patients with Distinct Disease Subtypes.
Hebb AL, Moore CS, Bhan V, Robertson GS.
Department of Pharmacology, Dalhousie University, Halifax, NS, Canada B3H 1X5.
Using quantitative RT-PCR, we compared mRNA levels for TRAIL [tumor necrosis factor (TNF)-related apoptosis-inducing ligand] and its receptors in various immune cell subsets derived from the peripheral blood of untreated normal subjects (NS) and patients with distinct subtypes of multiple sclerosis (MS): active relapsing-remitting MS (RRA), quiescent relapsing-remitting MS (RRQ), secondary-progressive MS (SPMS) or primary-progressive MS (PPMS). Consistent with a role for TRAIL in the mechanism of action of interferon-β (IFN-β), TRAIL mRNA levels were increased in monocytes from patients clinically responsive to IFN-β (RRQ) but not those unresponsive to this therapeutic (RRA). TRAIL-R3 (decoy receptor) expression was elevated in T cells from untreated RRMS patients while IFN-β therapy reversed this increase suggesting that IFN-β may promote the apoptotic elimination of autoreactive T cells by increasing the amount of TRAIL available to activate TRAIL death receptors. Serum concentrations of soluble TRAIL were increased to a similar extent by IFN-β therapy in RRQ, RRA and SPMS patients that had not generated neutralizing antibodies against this cytokine. Although our findings suggest altered TRAIL signaling may play a role in MS pathogenesis and IFN-β therapy, they do not support use of TRAIL as a surrogate marker for clinical responsiveness to this therapeutic.
PMCID: PMC3022173 PMID: 21253524 [PubMed - in process]

25. Autoimmune Dis. 2010 Dec 20;2011:708750.
Multiple sclerosis: are protective immune mechanisms compromised by a complex infectious background?
Krone B, Grange JM.
Institute of Virology, Centre for Hygiene and Human Genetics, University of Göttingen, Kreuzbergring 57, 37075 Göttingen, Germany.
The immunological background of multiple sclerosis (MS) manifests as an altered reactivity against a diverse range of infections, particularly with the Epstein-Barr virus. Although this could be only an epiphenomenon of a more generalised dysfunction of the immune system in MS, it is also possible that a complex infectious background forms the basis of a specific immune dysregulation finally causing the disease. It is thus suggested that the complex infectious background bears the key for an understanding of the immune pathogenesis of the disease. It appears probable that improved standards of hygiene cause regulatory defects in the immune system, allowing the abnormal expression of human endogenous retroviral (HERV) genes. On the basis of epidemiological observations we describe how a failure of expansion or an eclipse of a subfraction of self-antigen-specific CD8(+) T cells mediating immune repair, and a deleterious mode of action of HERV gene products, could underlie the pathogenesis of MS.
PMCID: PMC3010623 PMID: 21197482 [PubMed - in process]

26. Autoimmune Dis. 2010 Dec 15;2011:164608.
Mechanisms of oxidative damage in multiple sclerosis and a cell therapy approach to treatment.
Witherick J, Wilkins A, Scolding N, Kemp K.

Multiple Sclerosis and Stem Cell Group, Institute of Clinical Neurosciences, School of Clinical Sciences, University of Bristol, Bristol BS16 1LE, UK.

Although significant advances have recently been made in the understanding and treatment of multiple sclerosis, reduction of long-term disability remains a key goal. Evidence suggests that inflammation and oxidative stress within the central nervous system are major causes of ongoing tissue damage in the disease. Invading inflammatory cells, as well as resident central nervous system cells, release a number of reactive oxygen and nitrogen species which cause demyelination and axonal destruction, the pathological hallmarks of multiple sclerosis. Reduction in oxidative damage is an important therapeutic strategy to slow or halt disease processes. Many drugs in clinical practice or currently in trial target this mechanism. Cell-based therapies offer an alternative source of antioxidant capability. Classically thought of as being important for myelin or cell replacement in multiple sclerosis, stem cells may, however, have a more important role as providers of supporting factors or direct attenuators of the disease. In this paper we focus on the antioxidant properties of mesenchymal stem cells and discuss their potential importance as a cell-based therapy for multiple sclerosis.

PMCID: PMC3010615 PMID: 21197107 [PubMed - in process]

27. Autoimmunity. 2011 Jan 20. [Epub ahead of print]
Heterologous immunity: Immunopathology, autoimmunity and protection during viral infections.
Selin LK, Wlodarczyk MF, Kraft AR, Nie S, Kenney LL, Puzone R, Celada F.
Department of Pathology, University of Massachusetts Medical School, Worcester, MA, 01655, USA.
Heterologous immunity is a common phenomenon present in all infections. Most of the time it is beneficial, mediating protective immunity, but in some individuals that have the wrong crossreactive response it leads to a cascade of events that result in severe immunopathology. Infections have been associated with autoimmune diseases such as diabetes, multiple sclerosis and lupus erythematosis, but also with unusual autoimmune like pathologies where the immune system appears dysregulated, such as, sarcoidosis, colitis, panniculitis, bronchiolitis obliterans, infectious mononucleosis and even chronic fatigue syndrome. Here we review the evidence that to better understand these autoreactive pathologies it requires an evaluation of how T cells are regulated and evolve during sequential infections with different pathogens under the influence of heterologous immunity.
PMID: 21250837 [PubMed - as supplied by publisher]

28. Aviat Space Environ Med. 2011 Jan;82(1):61-4.
Return to flight with multiple sclerosis: aeromedical considerations.
Zinger H, Grossman A, Assa A, Barel O, Barenboim E, Levite R.
Israel Air Force Aeromedical Center, Tel Hashomer, Ramat Gan, Israel.
Multiple sclerosis (MS) is the most frequent demyelinating disease of the central nervous system, with versatile manifestations--relapsing-remitting or progressive--and an unpredictable course, with prognoses ranging from minimal neurological impairment to severely disabled. Disease modifying agents can minimize relapse rate and slow disease progression. Yet most patients suffer relapses and progression despite use of these agents. Several of the manifestations of MS may cause overall decrease in the performance of the aviator. These include cognitive impairment, fatigue, and depression. Episodes of spasms, dysarthria, ataxia, parasthesias, diplopia, and hemiplegia, as well as drug side effects may also affect flight. Seizures and episodes of vertigo may occur suddenly and result in in-flight incapacitation. We present our experience with two aviators with definite MS and a navigator with probable MS. The various manifestations of MS are specifically addressed with an emphasis on the aeromedical implications.
PMID: 21235109 [PubMed - in process]

29. Behav Brain Res. 2011 Jan 19. [Epub ahead of print]
Inflammation modulates anxiety in an animal model of multiple sclerosis.
Peruga I, Hartwig S, Thöne J, Hovemann B, Gold R, Juckel G, Linker RA.
Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, 44791 Bochum, Germany.
Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by inflammation, but also degenerative changes. Besides neurological deficits, the rate of affective disorders such as depression and anxiety is at least six fold increased. Many aspects of MS can be mimicked in the animal model of myelin oligodendrocyte glycoprotein experimental autoimmune encephalomyelitis (MOG-EAE). Here we investigate behavioral changes in C57BL/6 mice suffering from mild MOG-EAE. In the later phase of the disease, mice were subjected to behavioral tests including the light-dark-box (LD Box), the acoustic startle response (SR) with a pre-pulse inhibition protocol as well as the learned helplessness (LH) paradigm. Behavioral data were correlated with the motor performance in an open field and rotarod test (RR). In the RR and open field, there was no significant difference in the motor performance between controls and mice suffering from mild MOG-EAE. Yet EAE mice displayed an increased anxiety-like behavior with a 23% reduction of the time spent in the bright compartment of the LD Box as well as an increased SR. In the LH paradigm, mice suffering from MOG-EAE were twice as much prone to depressive-like behavior. These changes correlate with an increase of hippocampal tissue tumor necrosis factor alpha levels and neuronal loss in the hippocampus. Modulation of monoaminergic transmission by chronic application of the antidepressant amitriptyline resulted in a decreased startle reaction and increased hippocampal norepinephrine levels. These data imply that chronic inflammation in the CNS may impact on emotional responses in rodent models of anxiety.
PMID: 21255614 [PubMed - as supplied by publisher]

30. Biochem Pharmacol. 2011 Jan 15. [Epub ahead of print]
Evaluating the role of Toll-like receptors in diseases of the central nervous system.
Carty M, Bowie AG.
School of Biochemistry and Immunology, Trinity College Dublin, Dublin 2, Ireland.
A key part of the innate immune system is a network of pattern recognition receptors (PRRs) and their associated intracellular signalling pathways. Toll-like receptors (TLRs) are one such group of PRRs that detect pathogen associated molecular patterns (PAMPs). Activation of the TLRs with their respective agonists results in the activation of intracellular signalling pathways leading to the expression of proinflammatory mediators and anti-microbial effector molecules. Activation of the innate immune system through TLRs also triggers the adaptive immune response, resulting in a comprehensive immune program to eradicate invading pathogens. It is now known that immune surveillance and inflammatory responses occur in the central nervous system (CNS). Furthermore it is becoming increasingly clear that TLRs have a role in such CNS responses and are also implicated in the pathogenesis of a number of conditions in the CNS, such as Alzheimer's, stroke and multiple sclerosis. This is likely due to the generation of endogenous TLR agonists in these conditions which amplifies a detrimental neurotoxic inflammatory response. However TLRs in some situations can be neuroprotective, if triggered in a favourable context. This review aims to examine the recent literature on TLRs in the CNS thus demonstrating their importance in a range of infectious and non-infectious diseases of the brain.
PMID: 21241665 [PubMed - as supplied by publisher]

31. Bioconjug Chem. 2011 Jan 21. [Epub ahead of print]
Production of a PEGylated Fab' of the anti-LINGO-1 Li33 Antibody and Assessment of Its Biochemical and Functional Properties in Vitro and in a Rat Model of Remyelination.
Pepinsky RB, Walus L, Shao Z, Ji B, Gu S, Sun Y, Wen D, Lee X, Wang Q, Garber E, Mi S.
Departments of Drug and Molecular Discovery, Biogen Idec, Inc. , 14 Cambridge Center, Cambridge, Massachusetts 02142, United States.
The use of LINGO-1 antagonists to promote repair of damaged myelin is an emerging therapeutic opportunity for treatment of CNS diseases caused by demyelination such as multiple sclerosis. The Li33 anti-LINGO-1 antibody is a potent inducer of myelination in vitro and in vivo, but aggregation issues prevented the engineering of an optimal development candidate. PEGylated Li33 Fab' is one of several versions of the Li33 antibody that is being investigated in an attempt to identify the most favorable anti-LINGO-1 antibody design. For targeted PEGylation, a Li33 Fab' construct was engineered with a single unpaired cysteine in the heavy-chain hinge sequence. The Fab' was expressed in CHO cells, purified, and PEGylated with 20 kDa methoxy-poly(ethylene glycol) maleimide using a reaction strategy optimized to improve the yield of the PEG-Fab'. Biochemical analysis of the Li33 PEG-Fab' verified the selectivity of the PEGylation reaction. The in vitro and in vivo attributes of the PEG-Fab' were benchmarked against a Li33 full antibody. Both the Li33 PEG-Fab' and intact antibody bound LINGO-1 with nanomolar affinity, promoted myelination in an in vitro signaling assay, and promoted the repair of damaged myelin in the rat lysolecithin model. These studies extend our understanding of the biological activity of the Li33 mAb and validate the use of an anti-LINGO-1 PEG-Fab' for treatment of CNS diseases caused by demyelination.
PMID: 21254764 [PubMed - as supplied by publisher]

32. Biol Chem. 2011 Jan 2. [Epub ahead of print]
PETIR-001, a dual inhibitor of dipeptidyl peptidase IV (DP IV) and aminopeptidase N (APN), ameliorates experimental autoimmune encephalomyelitis in SJL/J mice.
Reinhold D, Bank U, Entz D, Goihl A, Stoye D, Wrenger S, Brocke S, Thielitz A, Stefin S, Nordhoff K, Heimburg A, Täger M, Ansorge S.
Institute of Molecular and Clinical Immunology, Otto von Guericke University Magdeburg, D-39120 Magdeburg, Germany.
Abstract Cellular dipeptidyl peptidase IV (DP IV, CD26) and aminopeptidase N (APN, CD13) play regulatory roles in T cell activation and represent potential targets for treatment of inflammatory disorders. We have developed a novel therapeutic strategy, 'peptidase-targeted Immunoregulation' (PETIR™), which simultaneously targets both cellular DP IV and APN via selective binding sites different from the active sites with a single inhibitor. In order to prove the therapeutic concept of PETIR™ in autoimmunity of the central nervous system, we evaluated the effect of a single substance, PETIR-001, in an animal model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE) in SJL/J mice. Administration of PETIR-001 significantly delayed and decreased clinical signs of active EAE, when given in a therapeutic manner intraperitoneally from day 15 to day 24 after induction of EAE. Both the acute phase and the first relapse of EAE were markedly inhibited. Importantly, a similar therapeutic benefit was obtained after oral administration of PETIR-001 from day 12 to day 21 after disease induction. Our results demonstrate that PETIR-001 exhibits a therapeutic effect on EAE in SJL/J mice. Thus, PETIR™ represents a novel and efficient therapeutic approach for immunotherapy of CNS inflammation.
PMID: 21194377 [PubMed - as supplied by publisher]

33. Biol Sex Differ. 2011 Jan 4;2(1):1.
Sex differences in autoimmune diseases.
Voskuhl R.
Professor, UCLA Dept, of Neurology, Jack H Skirball Chair for Multiple Sclerosis Research, Director, UCLA Multiple Sclerosis Program, Neuroscience Research Building 1, Room 475D, 635 Charles Young Drive South, Los Angeles, CA 90095, USA. rvoskuhl@ucla.edu.
ABSTRACT: Women are more susceptible to a variety of autoimmune diseases including systemic lupus erythematosus (SLE), multiple sclerosis (MS), primary biliary cirrhosis, rheumatoid arthritis and Hashimoto's thyroiditis. This increased susceptibility in females compared to males is also present in animal models of autoimmune diseases such as spontaneous SLE in (NZBxNZW)F1 and NZM.2328 mice, experimental autoimmune encephalomyelitis (EAE) in SJL mice, thyroiditis, Sjogren's syndrome in MRL/Mp-lpr/lpr mice and diabetes in non-obese diabetic mice. Indeed, being female confers a greater risk of developing these diseases than any single genetic or environmental risk factor discovered to date. Understanding how the state of being female so profoundly affects autoimmune disease susceptibility would accomplish two major goals. First, it would lead to an insight into the major pathways of disease pathogenesis and, secondly, it would likely lead to novel treatments which would disrupt such pathways.
PMCID: PMC3022636 PMID: 21208397 [PubMed - in process]

34. BMC Genomics. 2011 Jan 12;12:22.
A systematic evaluation of expression of HERV-W elements; influence of genomic context, viral structure and orientation.
Li F, Nellåker C, Yolken RH, Karlsson H.
Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden. hakkar@ki.se.
ABSTRACT:BACKGROUND: One member of the W family of human endogenous retroviruses (HERV) appears to have been functionally adopted by the human host. Nevertheless, a highly diversified and regulated transcription from a range of HERV-W elements has been observed in human tissues and cells. Aberrant expression of members of this family has also been associated with human disease such as multiple sclerosis (MS) and schizophrenia. It is not known whether this broad expression of HERV-W elements represents transcriptional leakage or specific transcription initiated from the retroviral promoter in the long terminal repeat (LTR) region. Therefore, potential influences of genomic context, structure and orientation on the expression levels of individual HERV-W elements in normal human tissues were systematically investigated. RESULTS: Whereas intronic HERV-W elements with a pseudogene structure exhibited a strong anti-sense orientation bias, intronic elements with a proviral structure and solo LTRs did not. Although a highly variable expression across tissues and elements was observed, systematic effects of context, structure and orientation were also observed. Elements located in intronic regions appeared to be expressed at higher levels than elements located in intergenic regions. Intronic elements with proviral structures were expressed at higher levels than those elements bearing hallmarks of processed pseudogenes or solo LTRs. Relative to their corresponding genes, intronic elements integrated on the sense strand appeared to be transcribed at higher levels than those integrated on the anti-sense strand. Moreover, the expression of proviral elements appeared to be independent from that of their corresponding genes. CONCLUSIONS: Intronic HERV-W provirus integrations on the sense strand appear to have elicited a weaker negative selection than pseudogene integrations of transcripts from such elements. Our current findings suggest that the previously observed diversified and tissue-specific expression of elements in the HERV-W family is the result of both directed transcription (involving both the LTR and internal sequence) and leaky transcription of HERV-W elements in normal human tissues.
PMCID: PMC3031232 PMID: 21226900 [PubMed - in process]

35. BMC Med. 2011 Jan 10;9:1.
Risk of venous thromboembolism in people admitted to hospital with selected immune-mediated diseases: record-linkage study.
Ramagopalan SV, Wotton CJ, Handel AE, Yeates D, Goldacre MJ.
Unit of Health-Care Epidemiology, Department of Public Health, University of Oxford, Oxford, UK. michael.goldacre@dphpc.ox.ac.uk.
ABSTRACT:BACKGROUND: Venous thromboembolism (VTE) is a common complication during and after a hospital admission. Although it is mainly considered a complication of surgery, it often occurs in people who have not undergone surgery, with recent evidence suggesting that immune-mediated diseases may play a role in VTE risk. We, therefore, decided to study the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in people admitted to hospital with a range of immune-mediated diseases. METHODS: We analysed databases of linked statistical records of hospital admissions and death certificates for the Oxford Record Linkage Study area (ORLS1:1968 to 1998 and ORLS2:1999 to 2008) and the whole of England (1999 to 2008). Rate ratios for VTE were determined, comparing immune-mediated disease cohorts with comparison cohorts. RESULTS: Significantly elevated risks of VTE were found, in all three populations studied, in people with a hospital record of admission for autoimmune haemolytic anaemia, chronic active hepatitis, dermatomyositis/polymyositis, type 1 diabetes mellitus, multiple sclerosis, myasthenia gravis, myxoedema, pemphigus/pemphigoid, polyarteritis nodosa, psoriasis, rheumatoid arthritis, Sjogren's syndrome, and systemic lupus erythematosus. Rate ratios were considerably higher for some of these diseases than others: for example, for systemic lupus erythematosus the rate ratios were 3.61 (2.36 to 5.31) in the ORLS1 population, 4.60 (3.19 to 6.43) in ORLS2 and 3.71 (3.43 to 4.02) in the England dataset. CONCLUSIONS: People admitted to hospital with immune-mediated diseases may be at an increased risk of subsequent VTE. Our findings need independent confirmation or refutation; but, if confirmed, there may be a role for thromboprophylaxis in some patients with these diseases.
PMCID: PMC3025873 PMID: 21219637 [PubMed - in process]

36. Bone Marrow Transplant. 2011 Jan 17. [Epub ahead of print]
CD49d blockade by Natalizumab therapy in patients with multiple sclerosis increases immature B-lymphocytes.
Lesesve JF, Debouverie M, Decarvalho Bittencourt M, Béné MC.
Laboratory of Hematology, University Hospital, Nancy, France.
PMID: 21243032 [PubMed - as supplied by publisher]

37. Brain. 2011 Jan 11. [Epub ahead of print]
Retinal pathology in multiple sclerosis: insight into the mechanisms of neuronal pathology.
Gundogan FC, Tas A, Erdem U, Sobaci G.
1 Etimesgut Military Hospital, Department of Ophthalmology, Ankara, Turkey.
PMID: 21224308 [PubMed - as supplied by publisher]

38. Brain. 2011 Feb;134(Pt 2):518-33. Epub 2011 Jan 20.
Primary retinal pathology in multiple sclerosis as detected by optical coherence tomography.
Saidha S, Syc SB, Ibrahim MA, Eckstein C, Warner CV, Farrell SK, Oakley JD, Durbin MK, Meyer SA, Balcer LJ, Frohman EM, Rosenzweig JM, Newsome SD, Ratchford JN, Nguyen QD, Calabresi PA.
Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Pathology 627, Baltimore, MD 21287, USA. calabresi@jhmi.edu.
Optical coherence tomography studies in multiple sclerosis have primarily focused on evaluation of the retinal nerve fibre layer. The aetiology of retinal changes in multiple sclerosis is thought to be secondary to optic nerve demyelination. The objective of this study was to use optical coherence tomography to determine if a subset of patients with multiple sclerosis exhibit primary retinal neuronopathy, in the absence of retrograde degeneration of the retinal nerve fibre layer and to ascertain if such patients may have any distinguishing clinical characteristics. We identified 50 patients with multiple sclerosis with predominantly macular thinning (normal retinal nerve fibre-layer thickness with average macular thickness <5th percentile), a previously undescribed optical coherence tomography defined phenotype in multiple sclerosis, and compared them with 48 patients with multiple sclerosis with normal optical coherence tomography findings, 48 patients with multiple sclerosis with abnormal optical coherence tomography findings (typical for multiple sclerosis) and 86 healthy controls. Utilizing a novel retinal segmentation protocol, we found that those with predominant macular thinning had significant thinning of both the inner and outer nuclear layers, when compared with other patients with multiple sclerosis ($P < 0.001$ for both), with relative sparing of the ganglion cell layer. Inner and outer nuclear layer thicknesses in patients with non-macular thinning predominant multiple sclerosis were not different from healthy controls. Segmentation analyses thereby demonstrated extensive deeper disruption of retinal architecture in this subtype than may be expected due to retrograde degeneration from either typical clinical or sub-clinical optic neuropathy. Functional corroboration of retinal dysfunction was provided through multi-focal electroretinography in a subset of such patients. These findings support the possibility of primary retinal pathology in a subset of patients with multiple sclerosis. Multiple sclerosis-severity scores were also significantly increased in patients with the macular thinning predominant phenotype, compared with those without this phenotype ($n = 96$, $P = 0.006$). We have identified a unique subset of patients with multiple sclerosis in whom there appears to be disproportionate thinning of the inner and outer nuclear layers, which may be occurring as a primary process independent of optic nerve pathology. In vivo analyses of retinal layers in multiple sclerosis have not been previously performed, and structural demonstration of pathology in the deeper retinal layers, such as the outer nuclear layer, has not been previously described in multiple sclerosis. Patients with inner and outer nuclear layer pathology have more rapid disability progression and thus retinal neuronal pathology may be a harbinger of a more aggressive form of multiple sclerosis.
PMID: 21252110 [PubMed - in process]

39. Brain. 2011 Feb;134(Pt 2):571-84. Epub 2011 Jan 13.
Acid-sensing ion channel 1 is involved in both axonal injury and demyelination in multiple sclerosis and its animal model.
Vergo S, Craner MJ, Etzensperger R, Attfield K, Friese MA, Newcombe J, Esiri M, Fugger L.
Department of Clinical Neurology, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DS, UK. lars.fugger@imm.ox.ac.uk.
Although there is growing evidence for a role of excess intracellular cations, particularly calcium ions, in neuronal and glial cell injury in multiple sclerosis, as well as in non-inflammatory neurological conditions, the molecular mechanisms involved are not fully determined. We previously showed that the acid-sensing ion channel 1 which, when activated under the acidotic tissue conditions found in inflammatory lesions opens to allow influx of sodium and calcium ions, contributes to axonal injury in experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis. However, the extent and cellular distribution of acid-sensing ion channel 1 expression in neurons and glia in inflammatory lesions is unknown and, crucially, acid-sensing ion channel 1 expression has not been determined in multiple sclerosis lesions. Here we studied acute and chronic experimental autoimmune encephalomyelitis and multiple sclerosis spinal cord and optic nerve tissues to describe in detail the distribution of acid-sensing ion channel 1 and its relationship with neuronal and glial damage. We also tested the effects of amiloride treatment on tissue damage in the mouse models. We found that acid-sensing ion channel 1 was upregulated in axons and oligodendrocytes within lesions from mice with acute experimental autoimmune encephalomyelitis and from patients with active multiple sclerosis. The expression of acid-sensing ion channel 1 was associated with axonal damage as indicated by co-localization with the axonal injury marker beta amyloid precursor protein. Moreover, blocking acid-sensing ion channel 1 with amiloride protected both myelin and neurons from damage in the acute model, and when given either at disease onset or, more clinically relevant, at first relapse, ameliorated disability in mice with chronic-relapsing experimental autoimmune encephalomyelitis. Together these findings suggest that blockade of acid-sensing ion channel 1 has the potential to provide both neuro- and myelo-protective benefits in multiple sclerosis.
PMID: 21233144 [PubMed - in process]

40. Brain. 2011 Feb;134(Pt 2):542-54. Epub 2011 Jan 7.
CD161highCD8+T cells bear pathogenetic potential in multiple sclerosis.
Annibali V, Ristori G, Angelini DF, Serafini B, Mechelli R, Cannoni S, Romano S, Paolillo A, Abderrahim H, Diamantini A, Borsellino G, Aloisi F, Battistini L, Salvetti M.
Neurologia, Ospedale S. Andrea, Via di Grottarossa 1035, 00189-Rome, Italy. marco.salvetti@uniroma1.it.
To identify differentially expressed genes in multiple sclerosis, microarrays were used in a stringent experimental setting-leukapheresis from disease-discordant monozygotic twins and gene expression profiling in CD4(+) and CD8(+) T-cell subsets. Disease-related differences emerged only in the CD8(+) T-cell subset. The five differentially expressed genes identified included killer cell lectin-like receptor subfamily B, member 1, also known as natural killer receptor protein 1a/CD161, presented by the International Multiple Sclerosis Genetics Consortium as one of the non-MHC candidate loci. Flow cytometric analysis on peripheral blood of healthy donors and patients with multiple sclerosis and rheumatoid arthritis confirmed an upregulation of CD161 at the protein level, showing also a significant excess of CD161(high)CD8(+) T cells in multiple sclerosis. This subset prevalently included chemokine (C-C motif) receptor 6(+), cytokine-producing, effector-memory T cells with proinflammatory profiles. It also included all circulating interleukin-17(+)CD8(+) T cells. In the CD161(high)CD8(+) subset, interleukin-12 facilitated proliferation and interferon-γ production, with CD161 acting as a co-stimulatory receptor. CD161(+)CD8(+)CD3(+) T cells producing interferon-γ were part of intralesional immune infiltrates and ectopic B cell follicles in autopsy multiple sclerosis brains. Variations of CD161 expression on CD8(+) T cells identify a subset of lymphocytes with proinflammatory characteristics that have not been previously reported in multiple sclerosis and are likely to contribute to disease immunopathology.
PMID: 21216829 [PubMed - in process]

41. Brain. 2011 Feb;134(Pt 2):534-41. Epub 2011 Jan 7.
Related B cell clones populate the meninges and parenchyma of patients with multiple sclerosis.
Lovato L, Willis SN, Rodig SJ, Caron T, Almendinger SE, Howell OW, Reynolds R, O'Connor KC, Hafler DA.
Yale School of Medicine, 15 York Street, PO Box 208018, New Haven, CT 06520, USA.
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In the central nervous system of patients with multiple sclerosis, B cell aggregates populate the meninges, raising the central question as to whether these structures relate to the B cell infiltrates found in parenchymal lesions or instead, represent a separate central nervous system immune compartment. We characterized the repertoires derived from meningeal B cell aggregates and the corresponding parenchymal infiltrates from brain tissue derived primarily from patients with progressive multiple sclerosis. The majority of expanded antigen-experienced B cell clones derived from meningeal aggregates were also present in the parenchyma. We extended this investigation to include 20 grey matter specimens containing meninges, 26 inflammatory plaques, 19 areas of normal appearing white matter and cerebral spinal fluid. Analysis of 1833 B cell receptor heavy chain variable region sequences demonstrated that antigen-experienced clones were consistently shared among these distinct compartments. This study establishes a relationship between extraparenchymal lymphoid tissue and parenchymal infiltrates and defines the arrangement of B cell clones that populate the central nervous system of patients with multiple sclerosis.
PMCID: PMC3030766 [Available on 2012/2/1] PMID: 21216828 [PubMed - in process]

42. Brain Pathol. 2011 Jan 19. doi: 10.1111/j.1750-3639.2011.00477.x. [Epub ahead of print]
Cannabinoid receptor and N-acyl phosphatidylethanolamine phospholipase D - evidence for altered expression in multiple sclerosis.
Zhang H, Hilton DA, Hanemann CO, Zajicek J.
Clinical Neurobiology, Peninsula College of Medicine and Dentistry, Plymouth, UK. PL6 8BU Cellular and Anatomical Department, Derriford Hospital, Plymouth, UK. PL6 8DH.
Cannabinoids have been shown to have a beneficial effect in both animal models of MS and human disease, although the mechanisms of action are unclear. We examined expression of the major cannabinoid receptors (CB1 and CB2) and a key enzyme involved in synthesis of the endocannabinoid anandamide (N-acyl phosphatidylethanolamine phospholipase D, NAPE-PLD) in autopsy brain samples from patients with multiple sclerosis. CB1 was expressed in neurons, injured axons, oligodendrocytes, macrophages/microglia, some astrocytes, endothelial cells, smooth muscle cells and pericytes. CB2 and NAPE-PLD were localized to cerebral endothelial cells, pericytes, smooth muscle cells, astrocytes and macrophages/microglia. NAPE-PLD immunoreactivity was also seen in neurons. Endothelial CB2 expression was greatest in chronic inactive plaques, and in areas was seen in segments of endothelium where the endothelial expression of adhesion molecules (VCAM-1 and ICAM-1) was focally undetectable, and was often expressed in areas of blood-brain-barrier damage. Vascular density was increased in chronic active plaques and normal appearing white matter compared with controls. These data support findings from animal models which suggest a role for the endocannabinoid system in the MS, particularly in the regulation of endothelial leukocyte adhesion and the cellular response to injury.
PMID: 21251115 [PubMed - as supplied by publisher]

43. Brain Pathol. 2011 Jan 17. doi: 10.1111/j.1750-3639.2011.00475.x. [Epub ahead of print]
Reappraisal of Aquaporin-4 Astrocytopathy in Asian Neuromyelitis Optica and Multiple Sclerosis Patients.
Matsuoka T, Suzuki SO, Suenaga T, Iwaki T, Kira JI.
Departments of Neurology and Neuropathology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Japan Department of Neurology, Tenri Hospital, Japan.
Selective aquaporin-4 (AQP4) loss and vasculocentric complement and immunoglobulin deposition are characteristic of neuromyelitis optica (NMO). We recently reported extensive AQP4 loss in demyelinated and myelinated layers of Baló's lesions without perivascular immunoglobulin and complement deposition. We aimed to reappraise AQP4 expression patterns in NMO and multiple sclerosis (MS). We evaluated AQP4 expression relative to glial fibrillary acidic protein, extent of demyelination, lesion staging (CD68 staining for macrophages), and perivascular deposition of complement and immunoglobulin in 11 cases with NMO and NMO spectrum disorders (NMOSD), five with MS, and 30 with other neurological diseases. The lesions were classified as actively demyelinating (n= 66), chronic active (n= 86), chronic inactive (n= 48) and unclassified (n= 12). Six NMO/NMOSD and two MS cases showed preferential AQP4 loss beyond the demyelinated areas, irrespective of lesion staging. Five NMO and three MS cases showed AQP4 preservation even in actively demyelinating lesions, despite grave tissue destruction. Vasculocentric deposition of complement and immunoglobulin was detected only in NMO/NMOSD patients, with less than 30% of actively demyelinating lesions showing AQP4 loss. Our present and previous findings suggest that antibody-independent AQP4 loss can occur in heterogeneous demyelinating conditions, including NMO, Baló's disease, and MS.
PMID: 21241398 [PubMed - as supplied by publisher]

44. Brain Res. 2011 Jan 19. [Epub ahead of print]
Prevention and Diminished Expression of Experimental Autoimmune Encephalomyelitis by Low Dose Naltrexone (LDN) or Opioid Growth Factor (OGF) for an Extended Period: Therapeutic Implications for Multiple Sclerosis.
Rahn KA, McLaughlin PJ, Zagon IS.
Endogenous opioids inhibit the onset and progression of experimental autoimmune encephalomyelitis (EAE) with 30 days of treatment. This study examined the long term effects of the opioid growth factor (OGF, [Met(5)]-enkephalin) and a low dose of the opioid antagonist naltrexone (LDN) on expression of myelin oligodendrocyte glycoprotein (MOG)-induced EAE. C57BL/6 mice began receiving daily injections of 10 mg/kg OGF (MOG+OGF), 0.1 mg/kg naltrexone (MOG+LDN), or saline (MOG+Vehicle) at the time of EAE induction and continuing for 60 days. In contrast to 100% of the MOG+Vehicle group with behavioral symptoms of EAE, 63% and 68% of the MOG+OGF and MOG+LDN mice expressing disease. Both severity and disease indices of EAE in OGF- and LDN-treated mice were notably decreased from MOG+Vehicle cohorts. By day 60, 6- and 3-fold more animals in the MOG+OGF and MOG+LDN groups, respectively, had a remission, compared to MOG+Vehicle mice. Neuropathological studies revealed i) astrocyte activation and neuronal damage as early as day 10 (prior to behavioral symptoms) in all MOG-injected groups, ii) a significant reduction of activated astrocytes in MOG+OGF and MOG+LDN groups compared to MOG+Vehicle mice at day 30, and iii) no demyelination on day 60 in mice treated with OGF or LDN and not displaying disease symptoms. These results indicate that treatment with OGF or LDN had no deleterious long-term repercussions and did not exacerbate EAE, but i) halted progression of disease, ii) reversed neurological deficits, and iii) prevented the onset of neurological disorders across a considerable span of time. RESEARCH HIGHLIGHTS: OGF and LDN have long-term effects on EAE OGF and LDN prevent the onset of neurological behavioral symptoms of EAE OGF and LD can halt the expression of EAE OGF and LDN can reverse neurological deficits of EAE OGF and LDN may be utilized in translational studies for multiple sclerosis.
PMID: 21256121 [PubMed - as supplied by publisher]

45. Brain Res. 2010 Dec 28. [Epub ahead of print]
PPARδ deficient mice develop elevated Th1/Th17 responses and prolonged experimental autoimmune encephalomyelitis.
Kanakasabai S, Walline CC, Chakraborty S, Bright JJ.
Neuroscience Research Laboratory, Methodist Research Institute, Indianapolis, IN, USA.
Multiple sclerosis (MS) is a neurological disorder that affects more than a million people worldwide. The etiology of MS is not known and there is no medical treatment that can cure MS. Earlier studies have shown that peroxisome proliferator-activated receptor (PPARs) agonists ameliorate MS-like disease in experimental allergic encephalomyelitis (EAE). In this study we have used PPARδ deficient mice to determine its physiological role in the regulation of CNS EAE and MS. We found that PPARδ(-/-) mice develop EAE with similar day of onset and disease incidence compared to C57BL/6 wild type mice. Interestingly, both male and female PPARδ(-/-) mice showed prolonged EAE with resistance to remission and recovery. PPARδ(-/-) mice with EAE expressed elevated levels of IFNγ and IL-17 along with IL-12p35 and IL-12p40 in the brain and spleen. PPARδ(-/-) mice also developed augmented neural antigen-specific Th1/Th17 responses and impaired Th2/Treg responses compared to wild type mice. These findings indicate that PPARδ(-/-) mice develop prolonged EAE in association with augmented Th1/Th17 responses, suggesting a critical physiological role for PPARδ in the remission and recovery of EAE.
PMID: 21192919 [PubMed - as supplied by publisher]

46. Brain Res Rev. 2011 Jan 13. [Epub ahead of print]
Interleukin-6, a Mental Cytokine.
Spooren A, Kolmus K, Laureys G, Clinckers R, De Keyser J, Haegeman G, Gerlo S.
Laboratory of Eukaryotic Signal Transduction and Gene Expression (LEGEST), University of Ghent (UGent), K.L. Ledeganckstraat 35, 9000 Gent, Belgium.
Almost a quarter of a century ago, interleukin-6 (IL-6) was discovered as an inflammatory cytokine involved in B cell differentiation. Today, IL-6 is recognized to be a highly versatile cytokine, with pleiotropic actions not only on immune cells, but also on other cell types, such as cells of the central nervous system (CNS). The first evidence implicating IL-6 in brain-related processes originated from its dysregulated expression in several neurological disorders such as multiple sclerosis, Alzheimer's disease and Parkinson's disease. In addition, IL-6 was shown to be involved in multiple physiological CNS processes such as neuron homeostasis, astrogliogenesis and neuronal differentiation. The molecular mechanisms underlying IL-6 functions in the brain have only recently started to emerge. In this review, an overview of the latest discoveries concerning the actions of IL-6 in the nervous system is provided. The central position of IL-6 in the neuroinflammatory reaction pattern, and more specifically, the role of IL-6 in specific neurodegenerative processes, which accompany Alzheimer's disease, multiple sclerosis and excitotoxicity, is discussed. It is evident that IL-6 has a dichotomic action in the CNS, displaying neurotrophic properties on the one hand, and detrimental actions on the other. This is in agreement with its central role in neuroinflammation, which evolved as a beneficial process, aimed at maintaining tissue homeostasis, but which can become malignant when exaggerated. In this perspective, it is not surprising that 'well-meant' actions of IL-6 are often causing harm instead of leading to recovery.
PMID: 21238488 [PubMed - as supplied by publisher]

47. Can J Neurol Sci. 2010 Sep;37 Suppl 2:S49-58.
Inverse vaccination to silence immunity to myelin in multiple sclerosis.
Steinman L.
Department of Neurological Sciences and Interdepartmental Program in Immunology, Stanford University, Stanford, California, 94305, USA.
The adaptive immune response in multiple sclerosis is complex. We have devised large scale arrays to measure the antibody response to myelin proteins and lipids. Despite the widespread immune responses to myelin, we have devised an inverse vaccine aimed at turning off key drivers of this diverse response. Clinical trials in patients with multiple sclerosis show that it is possible to constrain antibody responses to myelin on a large scale with this approach.
PMID: 21246935 [PubMed - in process]

48. Can J Neurol Sci. 2010 Sep;37 Suppl 2:S42-8.
New directions in multiple sclerosis therapy: matching therapy with pathogenesis.
Antel J.
Neuroimmunnology Unit, Montreal Neurologic Institute, Montreal, Quebec, Canada.
All currently approved therapies for multiple sclerosis (MS) modulate systemic immune components prior to their entry into the central nervous system (CNS). Available data indicate they lack impact on the progressive phases of disease; the more potent systemic immune-directed agents predispose to development of infectious or neoplastic disorders. Development of new agents that enhance disease stage related efficacy and limit systemic toxicity will need to consider the underlying mechanisms related to each phase of the clinical disorder, namely relapses, remission, and progression. This report focuses on disease related mechanisms ongoing within the CNS that contribute to the different phases of MS and how these may serve as potential therapeutic targets. Such mechanisms include CNS compartment specific immunologic properties especially as related to the innate immune system and neural cell-related properties that are determinants of the extent of actual tissue injury and repair (or lack thereof).
PMID: 21246934 [PubMed - in process]

49. Can J Neurol Sci. 2010 Sep;37 Suppl 2:S24-33.
The human microbiome in multiple sclerosis: pathogenic or protective constituents?
Power C, Antony JM, Ellestad KK, Deslauriers A, Bhat R, Noorbakhsh F.
Division of Neurology, Department of Medicine, University of Alberta, Edmonton, Alberta, Canada.
The human microbiome is comprised of commensal and pathogenic microorganisms, which exert diverse effects in close proximity to the site of intection as well as in remote tissues through immune-mediated mechanisms. Multiple infectious agents have been implicated in the pathogenesis of multiple sclerosis (MS) with variable findings depending on the agent, techniques, and disease phenotype. Herein, the contributions of individual infectious agents to MS and their effects on the immune and nervous systems are reviewed, focusing on herpes viruses, coronaviruses, retroviruses, and synchronic infections. While infectious agents are often assumed to be pathogenic, their effects might also be beneficial to the host in the long-term, depending on age and the type of immunogen/pathogen exposure, as proposed by the hygiene hypothesis. The human microbiome has potential impact on future diagnostic and therapeutic issues in MS.
PMID: 21246932 [PubMed - in process]

50. Can J Neurol Sci. 2010 Sep;37 Suppl 2:S16-23.
Multiple sclerosis: autoimmune disease or autoimmune reaction?
Stys PK.
Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada. pstys@ucalgary.ca
Multiple sclerosis (MS) is traditionally considered an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) with much knowledge available to support this view. However, this characterization implies that the primary event is an aberrant immune response directed at CNS antigens, promoting inflammation and later driving progressive axo-glial degeneration. Trials with potent anti-inflammatory agents and detailed neuropathological studies raise questions about this sequence of events. This hypothetical paper argues that MS may be primarily a "cytodegenerative" disease, possibly first involving the oligodendrocyte/myelin unit. Liberation of autoantigens secondarily recruits an immune response, the force of which heavily depends on the host's immune predisposition. Thus, the spectrum of MS from highly aggressive Marburg type, to primary progressive disease with little inflammatory burden, is governed by a "convolution" between the underlying cytodegeneration and the host's immune predilection. Clinical heterogeneity may be a reflection of a variable immune response, whereas in reality, the "real MS" may be a homogeneous degenerative process analogous to well known primary neurodegenerative diseases.
PMID: 21246931 [PubMed - in process]

51. Can J Neurol Sci. 2010 Sep;37 Suppl 2:S5-15.
Current concepts in the neuropathology and pathogenesis of multiple sclerosis.
Moore GR.
Department of Pathology and Laboratory Medicine, University of British Columbia, Canada.
Multiple sclerosis (MS) has been classically regarded as an inflammatory demyelinating disease of the central nervous system. In recent years, the classification and pathogenesis of the disease have become controversial, particularly with respect to whether an individual patient demonstrates a single or multiple pathogenetic mechanisms in the establishment of the focal plaque of MS. It is also becoming increasingly apparent that there is a significant neurodegenerative component in the disease, involving not only plaques but the non-plaque parenchyma as well. Magnetic resonance imaging, together with histopathologic studies, will continue to shed light on the pathogenesis of these focal and diffuse abnormalities in MS.
PMID: 21246930 [PubMed - in process]

53. Clin Exp Immunol. 2011 Jan 14. doi: 10.1111/j.1365-2249.2010.04303.x. [Epub ahead of print]
Prevention of clinical and histological signs of proteolipid protein (PLP)-induced experimental allergic encephalomyelitis (EAE) in mice by the water-soluble carbon monoxide-releasing molecule (CORM)-A1.
Fagone P, Mangano K, Quattrocchi C, Motterlini R, Di Marco R, Magro G, Penacho N, Romao CC, Nicoletti F.
Department of Biomedical Sciences, School of Medicine Department G.F. Ingrassia, Section of Anatomic Pathology, University of Catania Drug Discovery and Development, Italian Institute of Technology, Genoa Department of Health Sciences, University of Molise, Campobasso, Italy Alfama, Lda., Taguspark, Porto Salvo Instituto de Tecnologia Química e Biológica, Universidade Nova de Lisboa, Avenida da República (EAN), Oeiras, Portugal.
We have evaluated the effects of the carbon monoxide-releasing molecule CORM-A1 [Na(2) (BH(3) CO(2)); ALF421] on the development of relapsing-remitting experimental allergic encephalomyelitis (EAE) in SJL mice, an established model of multiple sclerosis (MS). The data show that the prolonged prophylactic administration of CORM-A1 improves the clinical and histopathological signs of EAE, as shown by a reduced cumulative score, shorter duration and a lower cumulative incidence of the disease as well as milder inflammatory infiltrations of the spinal cords. This study suggests that the use of CORM-A1 might represent a novel therapeutic strategy for the treatment of multiple sclerosis.
PMID: 21235533 [PubMed - as supplied by publisher]

54. Clin Neurol Neurosurg. 2011 Jan 24. [Epub ahead of print]
Injection of interferon-beta in the morning decreases flu-like syndrome in many patients with multiple sclerosis.
Nadjar Y, Coutelas E, Prouteau P, Panzer F, Paquet D, Saint-Val C, Créange A.
Service de Neurologie, Hôpital Henri Mondor, AP-HP, Université Paris Est, Créteil, France.
BACKGROUND: Although it is recommended that interferon-beta (IFNβ) injections be administered in the evening, it is possible that morning injections could more effectively decrease interleukin 6 secretion. METHODS: This study evaluated the effects of switching from an evening injection of IFNβ to a morning injection on the intensity of flu-like syndrome in patients with multiple sclerosis (MS). We performed an intervention study that consisted of a quantitative evaluation of IFNβ-related flu-like syndrome in a cohort of 105 MS patients. Patients with persistent flu-like reactions who injected IFNβ in the evening were encouraged to switch to morning injections. After one month, we evaluated various quantitative and qualitative changes (e.g., severity of flu-like syndrome, sleep quality, antipyretic drug use). RESULTS: Of the 98 patients (93%) who injected IFNβ in the evening, 88 (85%) had a persistent flu-like syndrome (the severity score was 3.92±0.26). A total of 50 (57%) patients switched to morning injections. One month after changing the injection time, 29 patients (58%) reported that their flu-like syndrome was decreased, 11 (24%) thought that it was unchanged and 9 (18%) thought that it was increased (p=0.014). In addition, 23 patients (48%) reported improved sleep (p=0.001), and 33 (68%) patients chose to continue morning injections, whereas 17 (32%) patients switched back to evening injections (p=0.024). Quantitative measures, however, indicated that there was no change in the severity of flu-like syndrome or the number of antipyretic doses taken for its management. CONCLUSION: Morning injections qualitatively improved IFNβ-related flu-like syndrome and sleep. A change in IFNβ injection time from evening to morning could benefit a significant proportion of patients with MS.
PMID: 21269761 [PubMed - as supplied by publisher]

55. Clin Neuropharmacol. 2011 Jan-Feb;34(1):28-35. Cladribine: mode of action and implications for treatment of multiple sclerosis.
Leist TP, Weissert R.
*Thomas Jefferson University, Philadelphia, PA; †Merck Serono S.A. - Geneva; and ‡Department of Neurology, Geneva University Hospital, Geneva, Switzerland.
Multiple sclerosis (MS) is an inflammatory neurodegenerative disease of the central nervous system. The inflammation is driven significantly by autoreactive lymphocytes, which recruit cells of the innate immune system such as macrophages that contribute to subsequent tissue damage, ultimately resulting in demyelination and axonal damage that are characteristic in MS lesions. Cladribine (2-chlorodeoxyadenosine [2-CdA]) is a synthetic chlorinated deoxyadenosine analog that is biologically active in selected cell types and provides targeted and sustained reduction of circulating T and B lymphocytes implicated in the pathogenesis of MS. The biologic activity of cladribine depends on the preferential accumulation of cladribine phosphates in cell types with a high intracellular ratio of deoxycytidine kinase to 5'-nucleotidases. Cladribine-phosphates interfere with DNA synthesis and repair through incorporation into DNA and through inhibition of enzymes involved in DNA metabolism, including DNA polymerase and ribonucleotide reductase. This in turn leads to DNA strand breaks and ultimately cell death. This review explores the mechanism of action of cladribine further, in the context of recent clinical data, after completion of the phase III, 96-week, placebo-controlled CLARITY study. In this study, cladribine tablets demonstrated significant efficacy on clinical and neuroimaging outcomes in relapsing-remitting MS.
PMID: 21242742 [PubMed - in process]

56. Clin Neuropsychol. 2011 Jan 12:1-17. [Epub ahead of print]
Relationship Between Global Cognitive Decline and Depressive Symptoms in Multiple Sclerosis.
Barwick FH, Arnett PA.
Psychology Department, The Pennsylvania State University, University Park, PA, USA.
Cognitive impairment and depressed mood are common symptoms in multiple sclerosis (MS), which significantly impact patients' role functioning and quality of life. Cross-sectional studies indicate a modest association between cognitive impairment and depressive symptoms in MS. Longitudinal studies show inconsistent results but provide some data indicating a relationship between increasing global cognitive decline and increasing depressive symptoms over time. Establishing whether such a relationship exists represents an important first step in understanding the temporal nature of that relationship along with any treatment implications. The current study investigated this relationship by using the adjusted difference between a demographic estimate of premorbid intellectual functioning (Barona) and a performance measure of current intellectual functioning (Shipley Institute of Living) to capture long-term global cognitive decline in MS patients. Degree of global cognitive decline was then related to a self-report measure of mood, evaluative, and vegetative depression symptoms (Chicago Multiscale Depression Inventory). Global cognitive decline accounted for 5% of the variance in mood-evaluative symptoms but none of the variance in vegetative symptoms. When groups experiencing moderate, mild, and no global cognitive decline were compared on depression symptom subscales, MS patients experiencing moderate cognitive decline reported significantly higher mood and evaluative, but not vegetative, depressive symptoms than MS patients with stable cognitive functioning.
PMID: 21246447 [PubMed - as supplied by publisher]

57. Clin Oral Investig. 2011 Jan 6. [Epub ahead of print]
Case series: non vascular considerations in trigeminal neuralgia.
Balasundram S, Cotrufo S, Liew C.
Oral and Maxillofacial Surgery Unit, Eastman Dental Hospital, University College London Hospital, London, UK, satbala@yahoo.com.
An abnormal vascular course of the superior cerebellar artery is often cited as the cause for trigeminal neuralgia. However, among patients with TN-like symptoms, 6% to 16% are variously reported to have intracranial tumours. Aneurysms, tumours, or other lesions may impinge or irritate the trigeminal nerve along its course. Uncommonly, an area of demyelination from multiple sclerosis may be the precipitant. We would like to present a series of unusual lesions, all of which initially presented with neuralgic-like symptoms and were refractory to treatment. Collated case series with photographs and imaging are reviewed in this paper. Discussion of case presentation and management are done for evaluation. A wide range of other compressive lesions can cause trigeminal neuralgia. This paper illustrates the clinical presentation of atypical trigeminal neuralgia and emphasises the value of diagnostic imaging in trigeminal neuralgia patient. Suggested algorithm for management of trigeminal neuralgia.
PMID: 21210165 [PubMed - as supplied by publisher]

58. Clin Rev Allergy Immunol. 2011 Jan 14. [Epub ahead of print]
The Strategies Used for Treatment of Experimental Autoimmune Neuritis (EAN): A Beneficial Effect of Glatiramer Acetate Administered Intraperitoneally.
Aronovich R, Katzav A, Chapman J.
Department of Physiology and Pharmacology, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, 69978, Israel.
Glatiramer acetate (GA) significantly ameliorates multiple sclerosis and was initially discovered through its effects on the animal model experimental autoimmune encephalomyelitis (EAE). Guillain-Barré syndrome (GBS) is a relatively common demyelinating disease of peripheral nerves for which there is a parallel animal model, experimental autoimmune neuritis (EAN). We review the treatments found useful in EAN with special emphasis on the need for quick onset of action and the relevance of treatments used for EAE and multiple sclerosis. We evaluated the effect of GA administered by a novel intraperitoneal route in EAN. GA significantly ameliorated the severity of disease in rats (F□=□6.3, p□=□0.01 by analysis of variance (ANOVA)) and course of disease (F□=□4.9, p□=□0.02 by repeated-measures ANOVA with a day□×□treatment interaction term). Neurophysiology data supported the trend for the beneficial effect of GA. Myelin-induced immune cell proliferation was significantly modulated by GA (p□<□0.025). This report describes a novel route of administration of GA and a rapid beneficial effect of GA in EAN. GA may be useful in human diseases, such as GBS, where the intravenous route may offer a rapid onset of drug action.
PMID: 21234710 [PubMed - as supplied by publisher]

59. Contemp Clin Trials. 2011 Jan 1. [Epub ahead of print]
Bayesian sample size determination under hypothesis tests. Zhang X, Cutter G, Belin T.
Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, AL 35294, United States.
We develop a Bayesian approach for calculating sample sizes for clinical trials under the framework of hypothesis tests. We extend the work of Weiss (The Statistician 1997; 46: 185-191) to include composite distributions for the treatment effect and the variance of the data within the null and alternative hypotheses. We select sample sizes using the Bayes factor and the averaged type I error and type II error defined by Weiss (The Statistician 1997; 46: 185-191). Our approach allows the uncertainty inherent in eliciting prior information for both the treatment effect and the variance and permits informative prior information for unknown quantities through the hypothesis specification. We illustrate our method through a real data example from a clinical trial for treatment of multiple sclerosis and from the cerclage trial for preterm birth prevention in high-risk women.
PMID: 21199689 [PubMed - as supplied by publisher]

60. Curr Med Chem. 2011 Jan 24. [Epub ahead of print]
Cannabinoids: Occurrence and Medicinal Chemistry.
Appendino G, Chianese G, Taglialatela-Scafati O.
Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università del Piemonte Orientale, Viale Ferrucci 33, 28100 Novara, Italy. appendino@pharm.unipmn.it.
With an inventory of several hundreds secondary metabolites identified, Cannabis sativa L. (hemp) is one of the phytochemically best characterized plant species. The biomedical relevance of hemp undoubtedly underlies the wealth of data on its constituents and their biological activities, and cannabinoids, a class of unique meroterpenoids derived from the alkylation of an olivetollike alkyl resorcinol with a monoterpene unit, are the most typical constituents of Cannabis. In addition to the well-known psychotropic properties of Δ(9)-THC, cannabinoids have been reported to show potential in various fields of medicine, with the capacity to address unmet needs like the relief of chemotherapy-derived nausea and anorexia, and symptomatic mitigation of multiple sclerosis. Many of the potential therapeutic uses of cannabinoids are related to the interaction with (at least) two cannabinoid G-protein coupled receptors (CB1 and CB2). However, a number of activities, like the antibacterial or the antitumor properties are non totally dependent or fully independent from the interaction with these proteins. These pharmacological activities are particularly interesting since, in principle, they could be easily dissociated by the unwanted psychotropic effects. This review aims at giving readers a survey of the more recent advances in both phytochemistry of C. sativa, the medicinal chemistry of cannabinoids, and their distribution in plants, highlighting the impact that research in these hot fields could have for modern medicinal chemistry and pharmacology.
PMID: 21254969 [PubMed - as supplied by publisher]

61. Curr Opin Genet Dev. 2011 Jan 17. [Epub ahead of print]
Revealing the genetic basis of multiple sclerosis: are we there yet?
Baranzini SE.
Department of Neurology, School of Medicine, University of California San Francisco, 513 Parnassus Ave., Room S-256, San Francisco, CA 94143-0435, United States.
For more than 30 years the only genetic factor associated with susceptibility to multiple sclerosis (MS) was the human leukocyte antigen (HLA) region. Recent advancements in genotyping platforms and the development of more effective statistical methods resulted in the identification of 16 more genes by genome-wide association studies (GWAS) in the last three years alone. While the effect of each of these genes is modest compared to that of HLA, this list is expected to grow significantly in the near future, thus defining a complex landscape in which susceptibility may be determined by a combination of allelic variants in different pathways according to ethnic background, disease sub-type, and specific environmental triggers. A considerable overlap of susceptibility genes among multiple autoimmune diseases is becoming evident and integration of these genetic variants with our current knowledge of affected biological pathways will greatly improve our understanding of mechanisms of general autoimmunity and of tissue specificity.
PMID: 21247752 [PubMed - as supplied by publisher]

62. Curr Protoc Neurosci. 2011 Jan;Chapter 10:Unit10.4.
Clinical and neuroimaging assessments for research studies (including drug trials) in multiple sclerosis.
Apperson ML, Agius MA.
Department of Neurology, University of California Davis and VA Northern California Health System (VANCHS), Sacramento, California, USA.
Multiple sclerosis (MS) is an immune-mediated disorder causing inflammation and demyelination in the central nervous system. As the onset of multiple sclerosis is at a young age, it is one of the leading neurological causes of disability. Disease activity and disability can be measured by neurological assessments and by magnetic resonance imaging. The development of standardized assessments has been a very important step in clinical research in MS. Clinical research in MS has led to a better understanding of the disease itself and has resulted in exciting new therapies. The protocols provided in this unit are four basic clinical and neuroimaging assessments commonly used as outcome measures in clinical research studies of MS subjects. These step-by-step instructions may be used by researchers and neurologists in clinical practice to obtain objective measures of MS disease progression and response to treatments.
PMID: 21207365 [PubMed - in process]

63. Curr Top Med Chem. 2011 Jan 25. [Epub ahead of print]
Synthetic Sphingosine 1-phosphate Receptor Modulators - Opportunities and Potential Pitfalls.
Bolli MH, Lescop C, Nayler O.
Sphingosine 1-phosphate (S1P) evokes a plethora of physiological responses by stimulating members of a G protein-coupled receptor family, known as S1P receptors. Currently five different mammalian S1P receptor subtypes, S1P(1-5), each with a different cellular expression pattern, were identified. The S1P(1) receptor in particular has attracted major interest throughout the pharmaceutical industry following the breakthrough discovery that this S1P receptor subtype is critically involved in the regulation of lymphocyte trafficking through secondary lymphoid organs. Since then, examples of synthetic S1P(1) agonists with lymphocyte reducing and immunomodulating activity demonstrated efficacy in numerous preclinical models of autoimmune disease and transplantation. Notably FTY720 (fingolimod), a pro-drug that is phosphorylated in vivo and converted into a non-selective S1P(1,3,4,5) receptor agonist, has been widely used to increase the understanding of S1P(1) receptor biology. Results from recently completed phase III clinical trials using FTY720 (fingolimod) suggest that this non-selective S1P(1) receptor agonist may become the first oral therapy in multiple sclerosis, with potential expansion into many other autoimmune diseases. This review briefly outlines the field of S1P(1) receptor biology and summarizes recent approaches in medicinal chemistry to discover potent and selective S1P(1) receptor agonists. In particular, the complexity of discovering a molecule akin to FTY720 but with an improved side-effect profile will be discussed.
PMID: 21261590 [PubMed - as supplied by publisher]

64. Disabil Rehabil. 2011 Jan 13. [Epub ahead of print]
Hydration and independence in activities of daily living in people with multiple sclerosis: a pilot investigation.
Collett J, Dawes H, Cavey A, Meaney A, Sackley C, Wade D, Howells K.
Movement Science Group, Oxford Brookes University, Oxford OX3 0BP, UK.
Purpose. Bladder dysfunction and disability may cause people with multiple sclerosis (pwMS) to limit fluid intake. However, hydration is rarely considered in the multiple sclerosis literature. We investigated the hydration status of people with pwMS and its association with independence in activities of daily living. Methods. Twenty-six (six men) pwMS over 18 years old and able to walk with or without an aid took part in the study. Hydration status was measured via urine osmolality, with adequate hydration defined as an osmolality□≤500 (mOsm kg(-1)). Independence in daily activities was measured using the Barthel index. Results. Mean urine osmolality was 470□±□209 mOsm kg(-1) and indicated 11 (42%) participants were not adequately hydrated. Independence in daily activities could partly explain hydration status (R(2)□=□0.209, p□<□0.05). Additionally there was a trend for men to be less well hydrated than women. Conclusions. The results indicate that some pwMS were not adequately hydrated and that this could be partly explained by disability. Implications of reducing and maintaining fluid levels on function and quality of life in relation to bladder dysfunction and disability in pwMS should be investigated.
PMID: 21231820 [PubMed - as supplied by publisher]

65. Drug Saf. 2011 Feb 1;34(2):117-23. doi: 10.2165/11585960-000000000-00000.
Incidence of Infusion-Associated Reactions with Rituximab for Treating Multiple Sclerosis: A Retrospective Analysis of Patients Treated at a US Centre.
Brown BA, Torabi M.
Department of Pharmacy, Brigham and Women's Hospital, Boston, Massachusetts, USA.
Background: Rituximab is a monoclonal antibody approved for treating CD20-positive B-cell non-Hodgkin's lymphoma and rheumatoid arthritis but is used off-label for treating many autoimmune disorders, including multiple sclerosis (MS). Similarly to other monoclonal antibodies, the incidence of infusion-related reactions to rituximab is high. Reactions to monoclonal antibodies, including rituximab, vary widely in type and severity, but may include mild pruritis and rash to more severe complications such as Stevens-Johnson syndrome and anaphylactic reactions. Objective: To assess the incidence of infusion-associated reactions in our MS patients receiving rituximab infusions and compare it to previous trials investigating rituximab for treating MS. Methods: From 1 to 30 November 2009, we retrospectively reviewed medical charts from Partners Multiple Sclerosis Centre, Brookline, MA, USA, of patients being treated with rituximab for MS between 20 November 2007 and 24 November 2009 for evidence of infusion-associated reactions and further classified reactions on a grading scale. Results: During the period studied, 70 patients were infused with rituximab. Infusion-associated events occurred in 25.7% of our patients. Reactions were mild to moderate and most commonly occurred during the first infusion. Most patients were able to complete the infusion after appropriate treatment of the reaction was administered, and most patients went on to receive subsequent doses without any further reactions. Conclusions: The occurrence of infusion-associated reactions to rituximab in patients with MS is fairly common. However, premedication that includes corticosteroids may reduce the incidence of reactions dramatically. Should they occur, proper treatment of reactions with histamine H(1) or H(2) receptor antagonists and infusion rate reduction is an effective management strategy in this situation.
PMID: 21247220 [PubMed - in process]

66. Duodecim. 2010;126(24):2845-52.
[The possibilities of neuropsychological rehabilitation in multiple sclerosis].
[Article in Finnish]
Rosti-Otajärvi E, Hämäläinen P.
TAYS, neuroalojen ja kuntoutuksen vastuualue PL 2000, 33521 Tampere.
Cognitive deficits are common in multiple sclerosis (MS) occurring in over half of the patients. Deficits may have a multidimensional impact on patients' quality of life. The preliminary research evidence on the effectiveness of neuropsychological rehabilitation in MS so far is positive: rehabilitation may have favourable effects on patient's cognitive performance, mood, and fatigue symptoms. The patient's ability to manage with disease-related cognitive symptoms can be promoted by individually planned neuropsychological rehabilitation. In clinical work, the diagnostics and treatment of cognitive problems should be improved in patients with MS. Neuropsychological rehabilitation should be an important part of rehabilitation regimen in MS.
PMID: 21268907 [PubMed - in process]

67. Eur J Neurol. 2011 Jan 11. doi: 10.1111/j.1468-1331.2010.03332.x. [Epub ahead of print]
Carnitine serum levels and levocarnitine administration in multiple sclerosis patients treated with natalizumab.
Laffon-Pioger M, Rocher F, Caruba C, Cohen M, Thomas P, Lebrun C.
Neurology, Hôpital Pasteur, Nice Pharmacovigilance, Hôpital Cimiez 4, Nice Cedex 1 Biology, Hôpital Pasteur, Nice, France.
PMID: 21219544 [PubMed - as supplied by publisher]

68. Eur J Neurol. 2010 Dec 29. doi: 10.1111/j.1468-1331.2010.03313.x. [Epub ahead of print]
Health care situation of patients with relapsing-remitting multiple sclerosis receiving immunomodulatory therapy: a retrospective survey of more than 9000 German patients with MS.
Mäurer M, Dachsel R, Domke S, Ries S, Reifschneider G, Friedrich A, Knorn P, Landefeld H, Niemczyk G, Schicklmaier P, Wernsdörfer C, Windhagen S, Albrecht H, Schwab S; for the TYPIC Study Investigators.
Department of Neurology, Caritas Hospital Bad Mergentheim, Bad Mergentheim MS-Schwerpunktpraxis Dachsel/Domke, Chemnitz Neurocenter Odenwald, Erbach Zentrum für ambulante Neurologie Biogen Idec GmbH, Ismaning Department of Neurology, Clinic Osnabrück, Osnabrück Neurozentrum-Riem, Munich Department of Neurology, University Hospital Erlangen, Erlangen, Germany.
Background and purpose: First-line immunomodulatory treatment with interferon-beta or glatiramer acetate is accepted as effective basic therapy in patients with relapsing-remitting multiple sclerosis (RRMS). However, a considerable portion of patients does not benefit from treatment. Method: To test basic immunomodulatory treatment under real-life conditions, we retrospectively analyzed clinical and subclinical disease activity within the last 12 months in a cohort of 9916 patients with RRMS, of which 7896 patients were receiving immunomodulatory treatment. In addition, factors associated with treating physicians' consideration of a switch of current treatment were assessed. Results: The majority of treated patients (approximately 66%) experienced no relapse during the last 12 months. However, in line with common clinical study findings, about one-third (approximately 34%) of patients had relapses. When MRI data were taken into account, approximately one-quarter (24%) of patients would qualify for therapy escalation to monoclonal antibody natalizumab. Relapse rate in the preceding year (the year directly prior to the start of retrospective data collection) was strongly associated with considering a switch of current treatment. In addition, therapy switch was more often considered in younger patients. The relationship between MRI findings in the absence of clinical symptoms and consideration of a treatment switch was not as clear. Conclusions: This analysis confirms that disease progression occurs in a considerable proportion of patients with RRMS. These patients should be considered for therapy escalation.
PMID: 21199183 [PubMed - as supplied by publisher]

69. Eur J Neurol. 2010 Dec 29. doi: 10.1111/j.1468-1331.2010.03304.x. [Epub ahead of print]
Answer to: The possible risk of cancer in multiple sclerosis patients: a controversial issue.
Ragonese P, Aridon P, Salemi G, D'Amelio M, Savettieri G.
Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche (BioNeC), Università di Palermo, Palermo, Italy.
PMID: 21199178 [PubMed - as supplied by publisher]

70. Eur J Pain. 2011 Jan 7. [Epub ahead of print]
Frequency of chronic pain descriptors: Implications for assessment of pain quality.
Lin CP, Kupper AE, Gammaitoni AR, Galer BS, Jensen MP.
Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA.
The current study interviewed patients with chronic pain to: (1) identify the most common words used by patients in the samples to describe the "quality" of their pain (i.e. sharp, dull) and (2) evaluate the validity of existing pain quality measures. Two-hundred and thirteen individuals with pain associated with spinal cord injury (SCI) or multiple sclerosis (MS) were asked to describe their pain. Consistent with previous research that has shown that patients with different types of pain problems describe their pain using different pain quality descriptors, there was variability in the frequency of pain descriptors used by the study participants. For example, patients with SCI and below injury level pain used "burning" more often than patients with SCI and shoulder, arm, or neck pain or patients with MS. Regarding the validity of existing pain measures, only one pain quality measure assessed all 14 of the most common pain descriptors volunteered by the sample. Also, although a number of pain quality measures have been developed to discriminate neuropathic from nociceptive pain, there was surprisingly little overlap in descriptors between these measures. The results of the current study and other studies using similar procedures would be useful for evaluating and developing existing and future pain quality measures.
PMID: 21216641 [PubMed - as supplied by publisher]

71. Eur Neurol. 2011 Jan 4;65(2):59-67. [Epub ahead of print]
Adherence to Disease-Modifying Therapies in Spanish Patients with Relapsing Multiple Sclerosis: Two-Year Interim Results of the Global Adherence Project.
Arroyo E, Grau C, Ramo-Tello C, Parra J, Sánchez-Soliño O.
Biogen Idec Iberia SL, Madrid, Spain.
The post-marketing international Global Adherence Project investigated adherence to disease-modifying therapy for relapsing-remitting multiple sclerosis. We report adherence data from the first 2 years in the Spanish subset of patients (n = 254 at baseline). The overall adherence rate was 85.4%. Patients taking intramuscular (IM) interferon-β (IFNβ)-1a were significantly more adherent (96.4%) compared with patients taking subcutaneous (SC) IFNβ-1a 22 μg (79.1%; p = 0.0064), SC IFNβ-1a 44 μg (79.6%; p = 0.0064) and glatiramer acetate (82.7%; p = 0.0184). At year 1 (n = 142), the overall adherence rate was 86.6%. Patients on IM IFNβ-1a were significantly more adherent than patients on SC IFNβ-1a 22 μg (93.9 vs. 66.7%; p = 0.0251). At year 2 (n = 131), the overall adherence rate was 82% (87.5% for IM IFNβ-1a, 80.0% for SC IFNβ-1a 22 μg, 77.8% for SC IFNβ-1a 44 μg, 85.2% for IFNβ-1b, and 80.0% for glatiramer acetate). In conclusion, adherence remained high among all disease-modifying therapies over the first 2 years of the study and was significantly higher for IM IFNβ-1a, at visit 1, compared with SC IFNβ-1a.
PMID: 21212677 [PubMed - as supplied by publisher]

72. Eur Neurol. 2011 Jan 27;65(2):99-104. [Epub ahead of print]
The Prevalence of Long Spinal Cord Lesions and Anti-Aquaporin 4 Antibodies in Neuromyelitis Optica Patients in Taiwan.
Wang KC, Tsai CP, Lee CL, Chen SY, Chen SJ.
Graduate Institute of Medical Sciences, National Defense Medical Center, Cheng Hsin General Hospital, Neurological Institute, Taipei-Veterans General Hospital, Taipei, Taiwan, ROC.
Background and Objective: It was the aim of this study to determine the prevalence of anti-aquaporin 4 antibody (anti-AQP4 Ab) and long spinal cord lesions in neuromyelitis optica (NMO) and multiple sclerosis (MS) patients in Taiwan. Asia has a relatively high rate of NMO compared with MS patients. Anti-AQP4 Ab is an important marker for NMO worldwide, but serological data and clinical profiles of NMO patients in Taiwan have not been reported. Methods: This retrospective study compared the clinical symptoms, demographics, spinal cord lesion length and AQP4 Ab status of 34 patients with NMO with 34 patients diagnosed with conventional MS. Results: Our NMO patients were predominantly middle-aged women (median age 45 years), exhibited many relapses (1.0/year) and displayed a higher Expanded Disability Status Scale score (4.75) than conventional MS patients. NMO patients exhibited long spinal cord lesions as detected by MRI. Forty-one percent of the NMO patients had detectable anti-AQP4 Ab. The Expanded Disability Status Scale score was significantly higher in AQP4 Ab- NMO patients. Conclusion: The prevalence of AQP4 Ab in a Taiwanese NMO group was 41%. Long spinal cord lesions and detection of AQP4 Ab helped to differentiate NMO patients from MS patients. Long spinal cord lesions with the anti-AQP4 Ab test may allow for an earlier diagnosis of NMO and improve therapeutic decisions.
PMID: 21273778 [PubMed - as supplied by publisher]

73. Eur Neurol. 2011;65(1):40-5. Epub 2010 Dec 22.
Tolerability and acceptance of prolonged low/delayed mitoxantrone regimens in patients with worsening multiple sclerosis.
Zecca C, Petrini L, Limoni C, Staedler C, Gobbi C.
Neurocenter of Southern Switzerland, Ospedale Civico, Lugano, Switzerland.
Background: Severe side effects such as cardiotoxicity and leukemia limit long-term use of mitoxantrone (MTX) despite its recommendation in patients with malignant forms of relapsing remitting (RR) and secondary progressive (SP) multiple sclerosis (MS). Methods: We analyzed data on tolerability, measured as compliance with the treatment, and patients' acceptance of an alternative MTX treatment schedule in 12 patients with aggressive RRMS or SPMS treated for at least 3 years with low/delayed dose MTX. Results: Twelve patients received 9-17 cycles of MTX treatment, with individual median doses of 7.6-12.16 mg/m(2)/course during 36 to 114 (median 49.5) months resulting in cumulative doses of 101.9-143.0 mg/m(2) per patient. The overall follow-up period was 37-122 (median 69.5) months. Treatment was well tolerated and appreciated by patients according to the Treatment Satisfaction-Visual Analogue Scale. No significant safety findings were seen concerning cardiological, hematological and oncological follow-up. The patients showed a stabilization of disease progression and a reduced annual relapse rate. Conclusions: Delayed, and/or dose-reduced, long-term MTX regimens over several years might represent a feasible alternative treatment for MS patients without any other therapeutic options.
PMID: 21196739 [PubMed - in process]

74. FASEB J. 2011 Jan 19. [Epub ahead of print]
Neurobiological effects of sphingosine 1-phosphate receptor modulation in the cuprizone model.
Kim HJ, Miron VE, Dukala D, Proia RL, Ludwin SK, Traka M, Antel JP, Soliven B.
*Department of Neurology, University of Chicago, Chicago, Illinois, USA;
Fingolimod (FTY720) is a sphingosine 1-phosphate (S1P) receptor modulator that regulates lymphocyte trafficking and exerts pleiotropic actions on oligodendrocytes (OLGs) and other neural cells. The purpose of this study was to investigate the role of S1P receptors in a non-T-cell model of demyelination, the cuprizone (cupr) model in C57BL/6 mice. Treatment with FTY720 (1 mg/kg) led to attenuated injury to OLGs, myelin, and axons in the corpus callosum (percentage of myelinated fibers was 44.7% in cupr-water and 63% in cupr-FTY720). Reactive astrogliosis and microgliosis were ameliorated when FTY720 was given from d 1, but astrogliosis was augmented when FTY720 was given from wk 4-9. FTY720 did not promote remyelination in this model. The protective effect of FTY720 was associated with decreased interleukin-1β and CCL2 transcripts in the corpus callosum, as well as altered S1P1 expression. Targeted deletion of S1P1 in OLG lineage cells did not lead to obvious clinical phenotype, but resulted in subtle abnormalities in myelin and an increased susceptibility to cupr-induced demyelination. We conclude that S1P receptors expressed by neuroglia are involved in regulating the response to injury, and CNS effects of FTY720 could contribute to its favorable therapeutic response in multiple sclerosis.-Kim, H. J., Miron, V. E., Dukala, D., Proia, R. L., Ludwin, S. K., Traka, M., Antel, J. P., Soliven, B. Neurobiological effects of sphingosine 1-phosphate receptor modulation in the cuprizone model.
PMID: 21248243 [PubMed - as supplied by publisher]

75. Folia Neuropathol. 2010;48(4):246-57.
Calf thymus extract attenuates severity of experimental encephalomyelitis in Lewis rats.
Zimecki M, Artym J, Kocięba M, Kuryszko J, Kaleta-Kuratewicz K, Marycz K.
Department of Experimental Therapy, Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Weigla 12, Wrocław, Poland. zimecki@iitd.pan.wroc.pl
The aim of this study was to evaluate the efficacy of treatment of Lewis rats with calf thymus extract (TFX®) and its six-peptide fraction on the course of experimental allergic encephalomyelitis (EAE). Interferon- ß served as a reference drug. We found that intramuscular administration of the thymus extract fraction significantly reduced clinical, immunological, histological, and ultrastructural alterations inherent in the disease. We suggest that TFX® or TFX®-derived fractions have potential as therapeutics in treatment of neurodegenerative diseases such as multiple sclerosis.
PMID: 21225507 [PubMed - in process]

76. Fortschr Neurol Psychiatr. 2011 Jan 20. [Epub ahead of print]
[The Significance of a B Cell-Dependent Immunopathology in Multiple Sclerosis.]
[Article in German]
Kuerten S, Pauly R, Blaschke S, Rottlaender A, Kaiser CC, Schroeter M, Fink GR, Addicks K.
Anatomie I, Universität zu Köln.
In spite of keen clinical and neuroscientific interest, the aetiology and immunopathology of multiple sclerosis (MS) remain to be elucidated. The present work seeks to give insight into the important, but thus far underestimated contribution of B cells to the disease. Emphasis will be placed on the role of B cells as producers of autoantibodies and as antigen presenting cells. In addition, the development of ectopic B cell follicles in the CNS and their potential correlation with the course of the disease and MS severity will be discussed. Finally, regulatory functions of a B cell-dependent immunopathology should be mentioned. A better understanding of the complex pathomechanisms of MS will allow for therapeutic options that are causative. Potential targets of a B cell-oriented therapy will be delineated in the following review. We hereby aim at triggering a critical re-evaluation of traditional paradigms assigned to MS, appreciating the importance of B cells in the disease.
PMID: 21253995 [PubMed - as supplied by publisher]

77. Front Biosci. 2011 Jan 1;16:1157-71.
Antigen presentation in EAE: role of microglia, macrophages and dendritic cells.
Almolda B, Gonzalez B, Castellano B.
Unit of Histology, Department of Cell Biology, Physiology and Immunology, Institute of Neuroscience. Universitat Autonoma de Barcelona, Bellaterra 08193, Spain.
Experimental autoimmune encephalomyelitis (EAE), a well-established model of multiple sclerosis, is characterised by microglial activation and lymphocytic infiltration. Lymphocytic activation through the antigen presentation process involves three main signals, the first provided by the engagement of major histocompatibility complex molecules (MHC) with the receptor of T-cells (TCR), the second by the binding of co-stimulatory molecules and the third by the secretion or expression of T-cell polarising molecules in specific populations of antigen presenting cells (APC). Microglial cells are considered to be the main APC population in the central nervous system (CNS). Specifically in EAE an increase in MHCs, co-stimulatory molecules and different T-cell polarising factors have been reported in microglia. However, a growing number of evidences suggest that dendritic cells (DCs), the main APC in the peripheral immune system, may also participate in the regulation of T-cell responses within the CNS. In this review we summarize the principal knowledge regarding microglial/macrophage function in EAE and their role in T-cell modulation, as well as the participation of DCs in the immune response associated to this disease.
PMID: 21196224 [PubMed - in process]

78. Gend Med. 2010 Dec;7(6):637-46.
Burden among male caregivers assisting people with multiple sclerosis.
Buchanan RJ, Radin D, Huang C.
Department of Political Science and Public Administration, Mississippi State University, Mississippi 39762, USA. rjb161@ps.msstate.edu
BACKGROUND: Caregiver burden is a multidimensional response to many factors associated with providing assistance to people with multiple sclerosis (MS), including physical, psychological, emotional, and social stressors. OBJECTIVE: The aim of this analysis was to identify the characteristics of male informal caregivers, the assistance provided, and the people receiving assistance who were associated with the burden of care. METHODS: Data were collected from a national survey (which included the Mental Component Summary of the SF-8 Health Survey) of informal caregivers and analyzed using an ordered logistic regression model to identify characteristics associated with burden among male informal caregivers. RESULTS: Greater burden among male caregivers was associated with significantly greater hours per week providing assistance ($P = 0.009$) and significantly greater restriction on the caregiver's ability to perform daily activities ($P < 0.001$) due to assisting the person with MS. We found a strong association between the perception of burden and the mental health status of the male caregiver ($P < 0.001$). CONCLUSIONS: Our findings highlight the strong association of caregiver burden and the Mental Component Summary of the SF-8. Reducing burden may improve the mental health of informal caregivers. Health professionals treating either male caregivers or people with MS should be sensitive to the impact that providing assistance has on the mental health of informal caregivers.
PMID: 21195363 [PubMed - in process]

79. Genes Immun. 2011 Jan 27. [Epub ahead of print]
Revisiting the T-cell receptor alpha/delta locus and possible associations with multiple sclerosis.
Watson CT, Para AE, Lincoln MR, Ramagopalan SV, Orton SM, Morrison KM, Handunnetthi L, Handel AE, Chao MJ, Morahan J, Sadovnick AD, Breden F, Ebers GC.
Department of Biological Sciences, Simon Fraser University, Burnaby, British Columbia, Canada.
A role for T cells in the pathogenesis of multiple sclerosis (MS) is well supported, evidenced by myriad immunological studies, as well as the unequivocal genetic influence of the major histocompatibility complex (MHC). Despite many attempts, no convincing genetic associations have been made between T-cell receptor (TCR) gene loci and MS. However, these studies may not be definitive because of small sample sizes and under-representative marker coverage of the chromosomal regions being investigated. To explore potential roles between the TCR alpha locus and MS, we have genotyped a large family-based cohort, including 1360 affected individuals and 1659 of their unaffected first-degree relatives, at 40 single-nucleotide polymorphism (SNP) markers within the TCR alpha/delta locus. This represents the largest TCR alpha-MS study to date. From this screen, we identified three potential loci of interest in TCR alpha variable and constant gene regions using the transmission disequilibrium test. Although SNPs implicating each of these regions of interest will require genotyping in independent replication cohorts, these findings suggest a role for TCR gene polymorphisms in MS susceptibility. In the context of these findings we review the evidence.Genes and Immunity advance online publication, 27 January 2011; doi:10.1038/gene.2010.65.
PMID: 21270827 [PubMed - as supplied by publisher]

80. Genome Med. 2011 Jan 18;3(1):3. [Epub ahead of print]
Modeling the Cumulative Genetic Risk for Multiple Sclerosis from Genome Wide Association Data.
Wang JH, Pappas D, De Jager PL, Pelletier D, de Bakker PI, Kappos L, Polman CH, Multiple Sclerosis Genetics Consortium AA, Chibnik LB, Hafler DA, Matthews PM, Hauser SL, Baranzini SE, Oksenberg JR.
ABSTRACT: BACKGROUND: Multiple Sclerosis (MS) is the most common cause of chronic neurologic disability beginning in early to middle adult life. Results from recent genome-wide association studies (GWAS) have substantially lengthened the list of disease loci and provide convincing evidence supporting a multifactorial and polygenic model of inheritance. Nevertheless, the knowledge of MS genetics remains incomplete, with many risk alleles still to be revealed. METHODS: We used a discovery GWAS dataset (8,844 samples, 2,124 cases and 6,720 controls) and a multi-step logistic regression protocol to identify novel genetic associations. The emerging genetic profile included 350 independent markers and was used to calculate and estimate the cumulative genetic risk in an independent validation dataset (3,606 samples). Analysis of Covariance (ANCOVA) was implemented to compare clinical characteristics of individuals with various degree of genetic risk. Gene ontology and pathway enrichment analysis was done using the DAVID functional annotation tool, the GO Tree Machine, and the Pathway-Express profiling tool. RESULTS: In the discovery dataset, the median cumulative genetic risk (P-Hat) was 0.903 and 0.007 in the case and control groups, together with 79.9% classification sensitivity and 95.8% specificity. The identified profile shows a significant enrichment of genes involved in the immune response, cell adhesion, cell communication/signaling, nervous system development, and neuronal signaling, including ionotropic glutamate receptors, which have been implicated in the pathological mechanism driving neurodegeneration. In the validation dataset, the median cumulative genetic risk was 0.59 and 0.32 in the case and control groups, with classification sensitivity 62.3%, and the specificity 75.9%. No differences in disease progression or T2-lesion volumes were observed among four levels of predicted genetic risk groups (High, Medium, Low, Misclassified). On the other hand, a significant difference (F=2.75, p=0.04) was detected for age of disease onset between the affected misclassified as controls (mean=36 yrs.) and the other three groups (High: 33.5 yrs.; Medium: 33.4 yrs.; Low: 33.1 yrs.). CONCLUSION: The results are consistent with the polygenic model of inheritance. The cumulative genetic risk established using currently available genome-wide association data provides important insights into disease heterogeneity and completeness of current knowledge in MS genetics.
PMID: 21244703 [PubMed - as supplied by publisher]

81. Georgian Med News. 2010 Dec;(189):69-75.
Treatment of experimental autoimmune encephalomyelitis by vitamin in animal model.
Davitashvili D, Beridze M, Sanikidze T, Pavliashvili N, McHedlishvili T.
Tbilisi State Medical University, Department of Neuromedicine, Department of Medical Biophysics, Department of Pathophysiology, Tbilisi, Georgia.
Study purposed to determine the effectivness of vitamin treatment in experimental autoimmune encephalomyelitis (EAE) animal model of multiple sclerosis (MS) by comparing several blood serum inflammatory markers, neurological deficiensy and histopathological changes in untreated and treated EAE animals. Eighteen, 9-13 week old, male Wistar rats were immunised by 100 µl MOG injection. Clinical signs of EAE scored by a masked investigator. After EAE exposition all rats were divided equally as untreated control and experimental group treated by vitamins (E, C, D3). Blood was obtained from all rats before and after immunization and on 7th day of treatment. ELISA method was used to detect the serum cytokine contents of IL-6, IFN-γ, IL-10. On 10th day of disease the rats were euthanized and transverse sections of spinal cord were divided in 16 areas with score of 1 for each area showing lymphocyte infiltration or demyelination. Mann-Whitney U-test was used for determining the level of significance of differences between sample means. On 7th day of treatment neurological deficiency stayed unchanged in control and was ameliorated in experimental group ($p<0.05$). Significant histopathological differences were found between control and experimental groups on 10th day of EAE. Serum levels of IFN-γ, IL-6 and IL-10 were elevated after exposition of EAE against healthy rats, while on 7th day of treatment the experimental group revealed the significant differences as compared to untreated control. Positive correlation was found between IL-6 and IFN-γ serum contents and neurological deficiency on 7th day of disease ($r=+0.53$, $p<0.02$ and $r=+0.49$; $p<0.01$).
PMID: 21252412 [PubMed - in process]

82. Haematologica. 2010 Dec 29. [Epub ahead of print]
Presenting features and treatment outcome of acute promyelocytic leukemia arising after multiple sclerosis.
Ammatuna E, Montesinos P, Hasan SK, Ramadan SM, Esteve J, Hubmann M, Pagoni M, Grimwade D, Sanz MA, Lo-Coco F.
University of Tor Vergata, Rome, Italy;
We report the clinical features and treatment outcome of 33 patients with multiple sclerosis who developed acute promyelocytic leukemia. Thirty patients were previously exposed to mitoxantrone. The median latency period between treatment initiation and acute promyelocytic leukemia diagnosis was 32 months. The PML-RARA bcr1 isoform was identified in 87% of cases. Twenty-nine (90%) patients achieved hematologic remission after all-trans retinoic acid and chemotherapy (n=31) or arsenic trioxide and all-trans retinoic acid. Consolidation included modified chemotherapy or arsenic trioxide. At a median follow-up of 26 months, 23 patients are in complete remission, 4 relapsed and one developed secondary leukemia. The 5 years cumulative incidence of relapse and overall survival were 23% and 68% respectively. Although treatment heterogeneity and suboptimal post-remission therapy must be taken into account, overall results and development of secondary leukemia in one patient suggest that effective and less toxic agents like arsenic trioxide warrants further investigation in this context.
PMID: 21193421 [PubMed - as supplied by publisher]

83. Harv Womens Health Watch. 2010 Dec;18(4):5.
FDA approves the first oral drug for reducing multiple sclerosis relapses.
[No authors listed]
PMID: 21268796 [PubMed - in process]

84. Immunity. 2011 Jan 28;34(1):75-84. Epub 2011 Jan 13.
Signaling via the RIP2 Adaptor Protein in Central Nervous System-Infiltrating Dendritic Cells Promotes Inflammation and Autoimmunity.
Shaw PJ, Barr MJ, Lukens JR, McGargill MA, Chi H, Mak TW, Kanneganti TD.
Department of Immunology, St. Jude Children's Research Hospital, Memphis, TN 38104, USA.
Peripheral peptidolgycan (PGN) is present within antigen-presenting cells in the central nervous system (CNS) of multiple sclerosis (MS) patients, possibly playing a role in neuroinflammation. Accordingly, PGN is linked with disease progression in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), but the role of specific PGN-sensing proteins is unknown. Here we report that the progression of EAE was dependent on the intracellular PGN sensors NOD1 and NOD2 and their common downstream adaptor molecule, receptor interacting protein 2 (RIP2; also known as RIPK2 and RICK). We found that RIP2, but not toll-like receptor 2 (TLR2), played a critical role in the activation of CNS-infiltrating dendritic cells. Our results suggest that PGN in the CNS is involved in the pathogenesis of EAE through the activation of infiltrating dendritic cells via NOD1-, NOD2-, and RIP2-mediated pathways.
PMID: 21236705 [PubMed - in process]

85. Immunology. 2011 Jan 24. doi: 10.1111/j.1365-2567.2010.03384.x. [Epub ahead of print]
Expression and agonist responsiveness of CXCR3 variants in human T lymphocytes.
Korniejewska A, McKnight AJ, Johnson Z, Watson ML, Ward SG.
Department of Pharmacy and Pharmacology, University of Bath, Claverton Down, Bath UCB, Slough, UK.
The chemokine receptor CXCR3 and its ligands CXCL9, CXCL10 and CXCL11 are involved in variety of inflammatory disorders including multiple sclerosis, rheumatoid arthritis, psoriasis and sarcoidosis. Two alternatively spliced variants of the human CXCR3-A receptor have been described, termed CXCR3-B and CXCR3-alt. Human CXCR3-B binds CXCL9, CXCL10, CXCL11 as well as an additional ligand CXCL4. In contrast, CXCR3-alt only binds CXCL11. We report that CXCL4 induces intracellular calcium mobilization as well as Akt and p44/p42 extracellular signal-regulated kinase phosphorylation, in activated human T lymphocytes. These responses have similar concentration dependence and time-courses to those induced by established CXCR3 agonists. Moreover, phosphorylation of Akt and p44/p42 is inhibited by pertussis toxin, suggesting coupling to Gα(i) protein. Surprisingly, and in contrast with the other CXCR3 agonists, stimulation of T lymphocytes with CXCL4 failed to elicit migratory responses and did not lead to loss of surface CXCR3 expression. Taken together, our findings show that, although CXCL4 is coupled to downstream biochemical machinery, its role in T cells is probably distinct from that of CXCR3-A agonists.
PMID: 21255008 [PubMed - as supplied by publisher]

86. Indian J Palliat Care. 2010 Sep;16(3):138-46.
Physical therapy in palliative care: from symptom control to quality of life: a critical review.
Kumar SP, Jim A.
Department of Physiotherapy, Kasturba Medical College, Manipal University, Mangalore, India.
Physiotherapy is concerned with identifying and maximizing movement potential, within the spheres of promotion, prevention, treatment and rehabilitation. Physical therapists practice in a broad range of inpatient, outpatient, and community-based settings such as hospice and palliative care centers where as part of a multidisciplinary team of care, they address the physical and functional dimensions of the patients' suffering. Physiotherapy treatment methods like therapeutic exercise, electrical modalities, thermal modalities, actinotherapy, mechanical modalities, manual physical therapy and assistive devices are useful for a range of life-threatening and life-limiting conditions like cancer and cancer-associated conditions; HIV; neurodegenerative disorders like amyotrophic lateral sclerosis, multiple sclerosis; respiratory disorders like idiopathic pulmonary fibrosis; and altered mental states. The professional armamentarium is still expanding with inclusion of other miscellaneous techniques which were also proven to be effective in improving quality of life in these patients. Considering the scope of physiotherapy in India, and in palliative care, professionals in a multidisciplinary palliative care team need to understand and mutually involve toward policy changes to successfully implement physical therapeutic palliative care delivery.
PMCID: PMC3012236 PMID: 21218003 [PubMed - in process]

87. Infect Immun. 2011 Jan 18. [Epub ahead of print]
Interferon-{beta} Suppresses the Development of Experimental Cerebral Malaria.
Morrell CN, Srivastava K, Swaim A, Lee MT, Chen J, Nagineni C, Hooks JJ, Detrick B.
Aab Cardiovascular Research Institute, University of Rochester School of Medicine and Dentistry, Rochester, NY, 14642; Department of Molecular and Comparative Pathobiology, The Johns Hopkins University, School of Medicine; Department of Pathology, The Johns Hopkins University, School of Medicine; Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD.
Cerebral malaria (CM) is a major complication of Plasmodium falciparum infection particularly in children. The pathogenesis of cerebral malaria involves parasitized red blood cell mediated vascular inflammation, immune stimulation, loss of blood brain barrier integrity, and obstruction of cerebral capillaries. Therefore, blunting vascular inflammation and immune cell recruitment is crucial in limiting the disease course. Interferon beta (IFN-β) has been used in the treatment of diseases, such as, multiple sclerosis (MS) but has not yet been explored in the treatment of CM. Therefore, we sought to determine whether IFN-β also limits disease progression in experimental cerebral malaria (ECM). Plasmodium berghei (P. berghei) infected mice treated with IFN-β have greatly delayed death and increased survival, with improved blood brain barrier function. IFN-β did not alter systemic parasitemia. However, we identified multiple action sites that were modified by IFN-β administration. P. berghei infection resulted in increase expression of CXCL9 on brain vascular endothelial cells that attract T cells to the brain, as well as increased T cell CXCR3 expression. The infection also increased the cellular content of ICAM-1, a molecule important for attachment of parasitized RBC to the endothelial cell. In this report we describe that IFN-β treatment leads to reduction of CXCL9 and ICAM-1 in the brain, reduction of T-cell CXCR3 expression and down-regulation of serum TNF-α. In addition, IFN-β treated P. berghei infected mice also had fewer brain T-cell infiltrates further demonstrating its protective effects. Hence, IFN-β has important anti-inflammatory properties that ameliorate the severity of ECM and prolong mouse survival.
PMID: 21245265 [PubMed - as supplied by publisher]

88. Int Immunol. 2011 Feb;23(2):139-48. Epub 2011 Jan 6.
Impaired IFN-{gamma} production and proliferation of NK cells in Multiple Sclerosis.
Lünemann A, Tackenberg B, Deangelis T, Barreira da Silva R, Messmer B, Vanoaica LD, Miller A, Apatoff B, Lublin FD, Lünemann JD, Münz C.
Christopher H. Browne Center for Immunology and Immune Diseases, The Rockefeller University, New York, NY 10065, USA.
NK cells are multicompetent lymphocytes of the innate immune system with a central role in host defense and immune regulation. Studies in experimental animal models of multiple sclerosis (MS) provided evidence for both pathologic and protective effects of NK cells. Humans harbor two functionally distinct NK-cell subsets exerting either predominantly cytotoxic (CD56(dim)CD16(+)) or immunoregulatory (CD56(bright)CD16(-)) functions. We analyzed these two subsets and their functions in the peripheral blood of untreated patients with relapsing-remitting MS compared with healthy blood donors. While ex vivo frequencies of CD56(bright)CD16(-) and CD56(dim)CD16(+) NK cells were similar in patients and controls, we found that cytokine-driven in vitro accumulation and IFN-γ production of CD56(bright)CD16(-) NK cells but not of their CD56(dim)CD16(+) counterparts were substantially diminished in MS. Impaired expansion of CD56(bright)CD16(-) NK cells was cell intrinsic because the observed effects could be reproduced with purified NK cells in an independent cohort of patients and controls. In contrast, cytolytic NK-cell activity toward the human erythromyeloblastoid leukemia cell line K562, the allogeneic CD4(+) T cell line CEM and allogeneic primary CD4(+) T-cell blasts was unchanged. Thus, characteristic functions of CD56(bright)CD16(-) NK cells, namely cytokine-induced NK cell expansion and IFN-γ production, are compromised in the NK cell compartment of MS patients.
PMCID: PMC3030728 [Available on 2012/2/1] PMID: 21212154 [PubMed - in process]

89. Int J Cell Biol. 2010;2010:529376. Epub 2011 Jan 17.
Interferonβ-1b Induces the Expression of RGS1 a Negative Regulator of G-Protein Signaling.
Tran T, Paz P, Velichko S, Cifrese J, Belur P, Yamaguchi KD, Ku K, Mirshahpanah P, Reder AT, Croze E.
Bayer HealthCare, Applied Research, Richmond, CA 94804, USA.
We present evidence of a link between interferonβ-1b (IFN-β) and G-protein signaling by demonstrating that IFN-β can induce the expression of the negative regulator of G-protein signaling 1 (RGS1). RGS1 reduces G-protein activation and immune cell migration by interacting with heterotrimeric G-proteins and enhancing their intrinsic GTPase activity. In this study, IFN-β treatment resulted in the induction of RGS1 in peripheral blood mononuclear cells (PBMCs), monocytes, T cells, and B cells. Induction of RGS1 by IFN-β was concentration dependent and observed at both the RNA and protein level. Other members of the RGS family were not induced by IFN-β, and induction of RGS1 required the activation of the IFN receptor. In addition, RGS1 induction was observed in PBMCs obtained from IFN-β-treated multiple sclerosis patients suggesting a possible, as yet unexplored, involvement of G-protein regulation in disease treatment. The upregulation of RGS1 by IFN-β has not been previously reported.
PMCID: PMC3026965 PMID: 21274427 [PubMed - in process]

90. Int J Colorectal Dis. 2010 Dec 31. [Epub ahead of print]
Modulation of the rectoanal inhibitory reflex (RAIR): qualitative and quantitative evaluation in multiple sclerosis.
Guinet A, Jousse M, Damphousse M, Hubeaux K, Le Breton F, Sheikh Ismael S, Amarenco G.
Service de Neuro-Urologie et Explorations Périnéales, Unité de Recherche Er6 UPMC, Université Pierre et Marie Curie Paris VI, Hôpital Tenon, APHP, 4, Rue de la Chine, 75970, Paris Cedex 20, France, mandineguinet@yahoo.fr.
BACKGROUND: Rectoanal inhibitory reflex (RAIR) is a physiological modulated reflex involved in anorectal continence and defined by a relaxation of internal anal sphincter following rectal distension. Its existence depends on intramural autonomic ganglions and its modulation on the integrity of the autonomic nervous system (ANS). AIMS: The aim of this study was to analyse RAIR modulation in terms of amplitude and duration in multiple sclerosis (MS) patients. METHODS: Twenty-one patients with MS and 40 control patients had anorectal manometry. Qualitative assessment (presence or absence) of RAIR was evaluated together with its modulation in amplitude and in duration. RESULTS: All patients had present RAIR for each volume of rectal distension (10-50 ml). Seven patients (33.3%) in the MS group had abnormal RAIR modulation in amplitude (odds ratio (OR) = 2.78, compared to control group, p□=□0.11). Nine patients (42.9%) in the MS group had abnormal RAIR modulation in duration (p□=□0.14, OR = 2.54, compared to control group). Alteration of RAIR modulation was not correlated with Expanded Disability Status Scale, faecal incontinence and constipation (p□>□0.05). Course of MS (relapsing-remitting MS or secondary progressive form) seems to be correlated to alteration of modulation in amplitude and in duration (OR = 1.31 and 1.07). CONCLUSION: Even if our results do not have the required statistical significance (p□>□0.05), they are interesting. If RAIR is always present in MS, its modulation seems to be altered. A hypothesis for this lack of RAIR modulation could be the alteration of ANS, often involved in MS besides somatic nervous system lesions.
PMID: 21193913 [PubMed - as supplied by publisher]

91. Int J Pharm. 2011 Jan 14. [Epub ahead of print]
Macrophages and liposomes in inflammatory disease: Friends or foes?
Crielaard BJ, Lammers T, Morgan ME, Chaabane L, Carboni S, Greco B, Zaratin P, Kraneveld AD, Storm G.
Department of Pharmaceutics, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands.
Liposome-encapsulated corticosteroids have shown to exert strong beneficial effects in inflammatory diseases, such as arthritis and cancer. To extend the clinical applicability of these potent nanomedicines, the therapeutic effect of dexamethasone phosphate loaded long-circulating liposomes (LCL-DXP) was evaluated in animal models of multiple sclerosis (MS) and Crohn's disease (CD). In mice with experimental autoimmune encephalitis (EAE), a model for MS, treatment with LCL-DXP, but not free DXP, resulted in a decrease in disease activity when compared to PBS treated mice. In contrast, in mice with chronic DSS-induced colitis, a model for CD, treatment with LCL-DXP did not induce an improvement, but in fact worsened the fecal blood loss after treatment, indicating an aggravation of the disease. It is hypothesized that modulation of macrophage polarization towards a M2 phenotype underlies the efficacy of corticosteroid-based drug delivery systems, which is supported by the presented data. On the one hand, M1 polarized macrophages are part of the pathogenesis of MS; the modulation to M2-polarization by LCL-DXP is therefore beneficial. On the other hand, M1-polarized intestinal macrophages fulfill a protective and inflammation-suppressing role in intestinal homeostasis; changing their phenotype to M2 causes reduced protection to invading microorganisms, leading to a more severe intestinal inflammation. These findings therefore indicate that the interplay between the specific phenotype of macrophages and the specific inflammatory context of the inflammatory disease in question may be an important determining factor in the therapeutic applicability of liposomal corticosteroids in inflammatory disease.
PMID: 21238559 [PubMed - as supplied by publisher]

92. Invest Ophthalmol Vis Sci. 2011 Jan 12. [Epub ahead of print]
Spermidine alleviates severity of murine experimental autoimmune encephalomyelitis.
Guo X, Harada C, Namekata K, Kimura A, Mitamura Y, Yoshida H, Matsumoto Y, Harada T.
Department of Molecular Neurobiology, Tokyo Metropolitan Institute for Neuroscience, Fuchu, Tokyo.
Purpose. To assess the effects of spermidine on the severity of experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS), with a focus on optic neuritis often associated with MS and EAE. Methods. Myelin oligodendrocyte glycoprotein-induced EAE mice were administered with or without spermidine at 30 mM in drinking water for 25 days. Clinical signs of EAE were scored daily and visual functions were measured by multifocal electroretinograms. Histopathology analysis of the spinal cord and optic nerve were performed after mice were sacrificed on day 25. Hydrogen peroxide (H(2)O(2)) was detected using the probe 2'-7' dichlorofluorescein diacetate (DCFDA) in the optic nerve. The effect of spermidine on H(2)O(2)-induced retinal ganglion cell apoptosis was investigated by lactate dehydrogenase assay. Results. Everyday clinical scoring revealed that the severity of EAE was significantly attenuated in spermidine-treated group, which was confirmed by milder demyelination and improved axon survival in the spinal cord of spermidine-treated mice. Visual functions were significantly improved in spermidine-treated mice compared with vehicle-treated mice. Spermidine treatment ameliorated the extent of demyelination in the optic nerve and prevented cell loss in the retinal ganglion cell layer. Furthermore, fewer DCFDA-labeled cells were found in the optic nerve in the spermidine-treated EAE mice, and in vitro analysis revealed that spermidine reduced H(2)O(2)-induced retinal ganglion cell apoptosis, suggesting that spermidine alleviated the severities of EAE, particularly of optic neuritis, by acting as an antioxidant. Conclusions. The results from this study suggest that oral spermidine administration could be a useful treatment for MS.
PMID: 21228387 [PubMed - as supplied by publisher]

93. Invest Ophthalmol Vis Sci. 2011 Jan 12. [Epub ahead of print]
Evaluation of a transgenic mice model of multiple sclerosis with non invasive methods.
Enriquez-Algeciras M, Ding D, Chou TH, Wang J, Padgett KR, Porciatti V, Bhattacharya SK.
Bascom Palmer Eye Institute, University of Miami, Miami, Florida, 33136;
Purpose: To evaluate the ND4 transgenic mice model of multiple sclerosis using non-invasive METHODS: Methods: Assessment of neurological/behavioral abnormalities, Pattern electroretinogram (PERG), Magnetic resonance imaging (MRI), Optic coherence tomography (OCT), and endpoint histological analysis. Results: Electrophysiological (PERG) recordings demonstrate functional deficits in vision commensurate with neurological/behavioral abnormalities. In ND4 mice we found PERG abnormalities preceded neurologic/gait abnormalities. MRI demonstrates subtle structural changes that progress over time in correlation with behavioral abnormalities. Conclusion: The ND4 mice model have been evaluated using well defined parameters of non-invasive methods (PERG, MRI and OCT) enabling objective identification of functional and structural deficits and their correlation with neurologic/gait abnormality.
PMID: 21228378 [PubMed - as supplied by publisher]

94. J Am Chem Soc. 2011 Jan 25. [Epub ahead of print]
A Myelin-Specific Contrast Agent for Magnetic Resonance Imaging of Myelination.
Frullano L, Wang C, Miller RH, Wang Y.
Division of Radiopharmaceutical Science, Case Center for Imaging Research, Department of Radiology, and ‡Department of Neuroscience, Case Western Reserve University , Cleveland, Ohio 44106, United States.
Myelination is one of the most fundamental biological processes in the development of vertebrate nervous systems. Abnormal or disrupted myelination occurs in many acquired or inherited neurodegenerative diseases, including multiple sclerosis (MS) and various leukodystrophies. To date, magnetic resonance imaging (MRI) has been the primary tool for diagnosing and monitoring the progression of MS and related diseases; however, any change in signal intensity of conventional MRI reflects a change only in tissue water content, which is a nonspecific measure of the overall changes in macroscopic tissue injury. Thus, the use of MRI as a primary measure of disease activity was shown to be disassociated from the clinical outcome due to the lack of specificity for myelination. In order to increase the MRI specificity for myelin pathologies, we designed and synthesized the first Gd-based T(1) MR contrast agent (MIC) that binds to myelin with high specificity. In this Communication, we demonstrate that MIC localizes in brain regions in proportion to the extent of myelination. In addition, MIC possesses promising MR contrast properties, which allow for direct detection of myelin distribution through T(1) mapping in the mouse brain.
PMID: 21265506 [PubMed - as supplied by publisher]

95. J Anat. 2011 Jan 20. doi: 10.1111/j.1469-7580.2010.01339.x. [Epub ahead of print]
Glutamate and ATP signalling in white matter pathology.
Matute C.
Departamento de Neurociencias and CIBERNED, Universidad del País Vasco, Leioa, Vizcaya, Spain Neurotek-UPV/EHU, Parque Tecnológico de Bizkaia, Zamudio, Spain.
Excessive signalling by excitatory neurotransmitters like glutamate and ATP can be deleterious to neurons and oligodendroglia, and cause disease. In particular, sustained activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate and N-methyl-d-aspartate (NMDA) receptors damages oligodendrocytes, a feature that depends entirely on Ca(2+) overload of the cytoplasm and that can be initiated by disruption of glutamate homeostasis. Thus, inhibition of glutamate uptake by activated microglia can compromise glutamate homeostasis and induce oligodendrocyte excitotoxicity. Moreover, non-lethal, brief activation of kainate receptors in oligodendrocytes rapidly sensitizes these cells to complement attack as a consequence of oxidative stress. In addition to glutamate, ATP signalling can directly trigger oligodendrocyte excitotoxicity via activation of Ca(2+) -permeable P2X7 purinergic receptors, which mediates ischaemic damage to white matter (WM) and causes lesions that are reminiscent of multiple sclerosis (MS) plaques. Conversely, blockade of P2X7 receptors attenuates post-ischaemic injury to WM and ameliorates chronic experimental autoimmune encephalomyelitis, a model of MS. Importantly, P2X7 expression is elevated in normal-appearing WM in patients with MS, suggesting that signalling through this receptor in oligodendrocytes may be enhanced in this disease. Altogether, these observations reveal novel mechanisms by which altered glutamate and ATP homeostasis can trigger oligodendrocyte death. This review aims at summarizing current knowledge about the mechanisms leading to WM damage as a consequence of altered neurotransmitter signalling, and their relevance to disease. This knowledge will generate new therapeutic avenues to treat more efficiently acute and chronic WM pathology.
PMID: 21250988 [PubMed - as supplied by publisher]

96. J Autoimmun. 2011 Jan 7. [Epub ahead of print]
Blockade of the kinin receptor B1 protects from autoimmune CNS disease by reducing leukocyte trafficking.
Göbel K, Pankratz S, Schneider-Hohendorf T, Bittner S, Schuhmann MK, Langer HF, Stoll G, Wiendl H, Kleinschnitz C, Meuth SG.
Department of Neurology, University of Wuerzburg, Josef-Schneider-Strasse 11, 97080 Wuerzburg, Germany; University of Muenster, Department of Neurology - Inflammatory Disorders of the Nervous System and Neurooncology, Domagkstr. 13, 48149 Muenster, Germany.
Disruption of the blood brain barrier (BBB) and transendothelial trafficking of immune cells into the central nervous system (CNS) are pathophysiological hallmarks of Multiple Sclerosis (MS) and its animal model, Experimental Autoimmune Encephalomyelitis (EAE). Kinins are proinflammatory peptides which are released during tissue injury including EAE. They increase vascular permeability and enhance inflammation by acting on distinct bradykinin receptors, B1R and B2R. We studied the expression of B1R and B2R and the effect of their inhibition on the disease course, BBB integrity and T cell migration following myelin oligodendrocyte glycoprotein (MOG(35-55))-induced EAE. B1R, but not B2R expression was markedly enhanced in inflammatory CNS lesions in mice and humans. Brain endothelial cells could be identified as major source of B1R protein. The severity of EAE was significantly alleviated in B1R(-/-) mice compared with wild-type (WT) controls ($P < 0.05$). Treatment of WT mice with the B1R antagonist R715 before and after disease onset was equally effective ($P < 0.05$) while B1R activation by R838 promoted EAE ($P < 0.05$). B1R inhibition was accompanied by a remarkable reduction of BBB disruption and tissue inflammation. In vitro analyses revealed that B1R suppression reverses the upregulation of ICAM-I and VCAM-I at the inflamed BBB thereby limiting T cell transmigration. In contrast, blocking B2R had no significant impact on EAE. We conclude that B1R inhibition can reduce BBB damage and cell invasion during autoimmune CNS disease and may offer a novel anti-inflammatory strategy for the treatment of MS.
PMID: 21216565 [PubMed - as supplied by publisher]

97. J Autoimmun. 2011 Jan 25. [Epub ahead of print]
Virus expanded regulatory T cells control disease severity in the Theiler's virus mouse model of MS.
Richards MH, Getts MT, Podojil JR, Jin YH, Kim BS, Miller SD.
Department of Microbiology-immunology and Interdepartmental Immunobiology Center, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA.
Theiler's murine encephalomyelitis virus (TMEV)-induced demyelinating disease (TMEV-IDD) serves as virus-induced model of chronic progressive multiple sclerosis. Infection of susceptible SJL/J mice leads to life-long CNS virus persistence and a progressive autoimmune demyelinating disease mediated by myelin-specific T cells activated via epitope spreading. In contrast, virus is rapidly cleared by a robust CTL response in TMEV-IDD-resistant C57BL/6 mice. We investigated whether differential induction of regulatory T cells (Tregs) controls susceptibility to TMEV-IDD. Infection of disease-susceptible SJL/J, but not B6 mice, leads to rapid activation and expansion of Tregs resulting in an unfavorable CNS ratio of Treg:Teffector cells. In addition, anti-CD25-induced inactivation of Tregs in susceptible SJL/J, but not resistant B6, mice results in significantly decreased clinical disease concomitant with enhanced anti-viral CD4(+), CD8(+) and antibody responses resulting in decreased CNS viral titers. This is the first demonstration that virus-induced Treg activation regulates susceptibility to autoimmune disease differentially in susceptible and resistant strains of mice and provides a new mechanistic explanation for the etiology of infection-induced autoimmunity.
PMID: 21273044 [PubMed - as supplied by publisher]

98. J Autoimmun. 2011 Jan 21. [Epub ahead of print]
Neuroantigen-specific CD8+ regulatory T-cell function is deficient during acute exacerbation of multiple sclerosis.
Baughman EJ, Mendoza JP, Ortega SB, Ayers CL, Greenberg BM, Frohman EM, Karandikar NJ.
Department of Pathology, UT Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390, USA.
Multiple sclerosis (MS) is an inflammatory, demyelinating disease of the central nervous system (CNS). MS is thought to be T-cell-mediated, with prior research predominantly focusing on CD4+ T-cells. There is a high prevalence of CNS-specific CD8+ T-cell responses in MS patients and healthy subjects. However, the role of neuroantigen-specific CD8+ T-cells in MS is poorly understood, with the prevalent notion that these may represent pathogenic T-cells. We show here that healthy subjects and MS patients demonstrate similar magnitudes of CD8+ and CD4+ T-cell responses to various antigenic stimuli. Interestingly, CD8+ T-cells specific for CNS autoantigens, but not those specific for control foreign antigens, exhibit immune regulatory ability, suppressing proliferation of CD4+CD25- T-cells when stimulated by their cognate antigen. While CD8+ T-cell-mediated immune suppression is similar between healthy subjects and clinically quiescent treatment-naïve MS patients, it is significantly deficient during acute exacerbation of MS. Of note, the recovery of neuroantigen-specific CD8+ T-cell suppression correlates with disease recovery post-relapse. These studies reveal a novel immune suppressor function for neuroantigen-specific CD8+ T-cells that is clinically relevant in the maintenance of peripheral tolerance and the intrinsic regulation of MS immune pathology.
PMID: 21257291 [PubMed - as supplied by publisher]

99. J Behav Med. 2011 Jan 23. [Epub ahead of print]
Exacerbation history is associated with medication and appointment adherence in MS.
Hancock LM, Bruce JM, Lynch SG.
Department of Psychology, University of Missouri-Kansas City, 4825 Troost Ave., Suite 124, Kansas City, MO, 64110, USA.
Disease-modifying treatments are designed to prevent exacerbations in multiple sclerosis (MS). To date, few studies have examined the relationship between disease activity and treatment adherence in MS. The primary aim of this study was to examine the association between disease activity (e.g., annualized relapse rates), medication adherence, and appointment adherence in relapsing-remitting MS. Retrospective exacerbation and appointment data were collected and used to predict prospective medication adherence. Results indicated that patients with higher annualized relapse rates missed fewer doses of medication and were less likely to miss appointments. Conversely, patients with relatively stable disease were more likely to demonstrate poor medication adherence and poor appointment adherence. Patients who missed more appointments also missed more doses of their disease modifying medication. Future studies may wish to examine clinical methods designed to improve immunotherapy adherence among patients who are in relatively symptom-free stages of relapsing-remitting MS.
PMID: 21259038 [PubMed - as supplied by publisher]

100. J Biol Chem. 2011 Jan 18. [Epub ahead of print]
Identification of the synthetic cannabinoid R(+)WIN55,212-2 as a novel regulator of IFN regulatory factor 3 (IRF3) activation and IFN-{beta} expression: relevance to therapeutic effects in models of multiple sclerosis.
Downer EJ, Clifford E, Gran B, Nel HJ, Fallon PG, Moynagh PN.
National Univ of Ireland Maynooth, Ireland;
Beta Interferons (IFN-βs) represent one of the first line treatments for relapsing-remitting multiple sclerosis (RRMS), slowing disease progression whilst reducing the frequency of relapses. Despite this, more effective, well tolerated therapeutic strategies are needed. Cannabinoids palliate experimental autoimmune encephalomyelitis (EAE) symptoms and have therapeutic potential in MS patients although the precise molecular mechanism for these effects is not understood. Toll-like receptor (TLR) signaling controls innate immune responses and TLRs are implicated in MS. Here we demonstrate that the synthetic cannabinoid R(+)WIN55,212-2 is a novel regulator of TLR3 and TLR4 signaling by inhibiting the pro-inflammatory signaling axis triggered by TLR3 and TLR4 whilst selectively augmenting TLR3-induced activation of IFN regulatory factor 3 (IRF3) and expression of IFN-β. We present evidence that R(+)WIN55,212-2 strongly promotes the nuclear localization of IRF3. The potentiation of IFN-β expression by R(+)WIN55,212-2 is critical for manifesting its protective effects in the murine MS model EAE as evidenced by its reduced therapeutic efficacy in the presence of an anti-IFN-β antibody. R(+)WIN55,212-2 also induces IFN-β expression in MS patient peripheral blood mononuclear cells (PBMCs), whilst downregulating inflammatory signaling in these cells. These findings identify R(+)WIN55,212-2 as a novel regulator of TLR3 signaling to IRF3 activation and IFN-β expression and highlights a new mechanism that may be open to exploitation in the development of new therapeutics for the treatment of MS.
PMID: 21245146 [PubMed - as supplied by publisher]

101. J Clin Exp Neuropsychol. 2011 Jan 10:1-7. [Epub ahead of print]
The relative contributions of processing speed and cognitive load to working memory accuracy in multiple sclerosis.
Leavitt VM, Lengenfelder J, Moore NB, Chiaravalloti ND, Deluca J.
Kessler Foundation Research Center, West Orange, NJ, USA.
Cognitive symptoms of multiple sclerosis (MS) include processing-speed deficits and working memory impairment. The precise manner in which these deficits interact in individuals with MS remains to be explicated. We hypothesized that providing more time on a complex working memory task would result in performance benefits for individuals with MS relative to healthy controls. Fifty-three individuals with clinically definite MS and 36 matched healthy controls performed a computerized task that systematically manipulated cognitive load. The interval between stimuli presentations was manipulated to provide increasing processing time. The results confirmed that individuals with MS who have processing-speed deficits significantly improve in performance accuracy when given additional time to process the information in working memory. Implications of these findings for developing appropriate cognitive rehabilitation interventions are discussed.
PMID: 21229437 [PubMed - as supplied by publisher]

102. J Clin Invest. 2011 Feb 1;121(2):658-70. doi: 10.1172/JCI42974. Epub 2011 Jan 25.
Liver X receptor (LXR) mediates negative regulation of mouse and human Th17 differentiation.
Cui G, Qin X, Wu L, Zhang Y, Sheng X, Yu Q, Sheng H, Xi B, Zhang JZ, Zang YQ.
Th17 cells are a subset of CD4+ T cells with an important role in clearing certain bacterial and fungal pathogens. However, they have also been implicated in autoimmune diseases such as multiple sclerosis. Exposure of naive CD4+ T cells to IL-6 and TGF-β leads to Th17 cell differentiation through a process in which many proteins have been implicated. We report here that ectopic expression of liver X receptor (LXR) inhibits Th17 polarization of mouse CD4+ T cells, while LXR deficiency promotes Th17 differentiation in vitro. LXR activation in mice ameliorated disease in the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis, whereas LXR deficiency exacerbated disease. Further analysis revealed that Srebp-1, which is encoded by an LXR target gene, mediated the suppression of Th17 differentiation by binding to the E-box element on the Il17 promoter, physically interacting with aryl hydrocarbon receptor (Ahr) and inhibiting Ahr-controlled Il17 transcription. The putative active site (PAS) domain of Ahr and the N-terminal acidic region of Srebp-1 were essential for this interaction. Additional analyses suggested that similar LXR-dependent mechanisms were operational during human Th17 differentiation in vitro. This study reports what we believe to be a novel signaling pathway underlying LXR-mediated regulation of Th17 cell differentiation and autoimmunity.
PMCID: PMC3026720 PMID: 21266776 [PubMed - in process]

103. J Clin Res Pediatr Endocrinol. 2010 Dec;2(4):137-43. Epub 2010 Nov 1.
Nutritional rickets.
Ozkan B.
Atatürk University, Faculty of Medicine, Department of Pediatric Endocrinology, Erzurum, Turkey.
Nutritional rickets (NR) is still the most common form of growing bone disease despite the efforts of health care providers to reduce the incidence of the disease. Today, it is well known that the etiology of NR ranges from isolated vitamin D deficiency (VDD) to isolated calcium deficiency. In Turkey, almost all NR cases result from VDD. Recent evidence suggests that in addition to its short- or long-term effects on skeletal development, VDD during infancy may predispose the patient to diseases such as diabetes mellitus, cancer and multiple sclerosis. Among the factors responsible for the high prevalence of VDD in developing countries and its resurgence in developed countries is limited sunshine exposure due to individuals' spending more time indoors (watching television and working on computer) or avoiding sun exposure intentionally for fear of skin cancer. Traditional clothing (covering the entire body except the face and hands) further limits the exposure time to sunlight and, thus, decreases the endogenous synthesis of vitamin D. In Turkey, maternal VDD and exclusive breastfeeding without supplementation were reported to be the most prominent reasons leading to NR. The diagnosis of NR is established by a thorough history and physical examination and confirmed by laboratory evaluation. Recent reports draw attention to the supplemental doses of vitamin D required to achieve a serum 25-hydroxyvitamin D level of at least 20 ng/ml (50 nmol/l) - the serum concentration that is needed to optimize absorption of dietary calcium and to suppress excessive secretion of parathyroid hormone. This type of prevention will also reduce fracture risk as well as prevent long-term negative effect of vitamin D insufficiency.Conflict of interest:None declared.
PMCID: PMC3005686 PMID: 21274312 [PubMed - in process]

104. J Craniofac Surg. 2011 Jan;22(1):376.
Face, brain, and veins: a new perspective for multiple sclerosis onset.
Zamboni P, Carinci F.
PMID: 21239945 [PubMed - in process]

105. J Crohns Colitis. 2011 Feb;5(1):75-6. Epub 2010 Nov 26.
Rapid onset of ulcerative colitis after treatment with interferon β1a in a patient with multiple sclerosis.
Tuna Y, Başar O, Dikici H, Köklü S.
Department of Gastroenterology, Akdeniz University of Faculty of Medicine, Antalya, Turkey.
PMID: 21272812 [PubMed - in process]

106. J Exp Med. 2011 Jan 17;208(1):91-102. Epub 2011 Jan 3.
A highly tilted binding mode by a self-reactive T cell receptor results in altered engagement of peptide and MHC.
Sethi DK, Schubert DA, Anders AK, Heroux A, Bonsor DA, Thomas CP, Sundberg EJ, Pyrdol J, Wucherpfennig KW.
Department of Cancer Immunology and AIDS, Dana-Farber Cancer Institute, and 2 Program in Immunology, Harvard Medical School, Boston, MA 02115.
Self-reactive T cells that escape elimination in the thymus can cause autoimmune pathology, and it is therefore important to understand the structural mechanisms of self-antigen recognition. We report the crystal structure of a T cell receptor (TCR) from a patient with relapsing-remitting multiple sclerosis that engages its self-peptide-major histocompatibility complex (pMHC) ligand in an unusual manner. The TCR is bound in a highly tilted orientation that prevents interaction of the TCR-α chain with the MHC class II β chain helix. In this structure, only a single germline-encoded TCR loop engages the MHC protein, whereas in most other TCR-pMHC structures all four germline-encoded TCR loops bind to the MHC helices. The tilted binding mode also prevents peptide contacts by the short complementarity-determining region (CDR) 3β loop, and interactions that contribute to peptide side chain specificity are focused on the CDR3α loop. This structure is the first example in which only a single germline-encoded TCR loop contacts the MHC helices. Furthermore, the reduced interaction surface with the peptide may facilitate TCR cross-reactivity. The structural alterations in the trimolecular complex are distinct from previously characterized self-reactive TCRs, indicating that there are multiple unusual ways for self-reactive TCRs to bind their pMHC ligand.
PMCID: PMC3023130 [Available on 2011/7/17] PMID: 21199956 [PubMed - in process]

107. J Immunol. 2011 Jan 26. [Epub ahead of print]
Anaphylaxis and Mortality Induced by Treatment of Mice with Anti-VLA-4 Antibody and Pertussis Toxin.
Ji N, Rao N, Guentzel NM, Arulanandam BP, Forsthuber TG.
Department of Biology, University of Texas at San Antonio, San Antonio, TX 78249.
Ab-mediated blockade of the adhesion molecule VLA-4 has been shown to ameliorate disease in human multiple sclerosis patients and experimental autoimmune encephalomyelitis (EAE) animal models. We wanted to determine whether anti-VLA-4 Ab treatment affected the function and persistence of autoreactive T cells in mice with EAE. Unexpectedly, we observed a high level of mortality in anti-VLA-4 mAb (PS/2)-treated mice with actively induced EAE despite decreased disease severity. Investigation of the underlying mechanism showed that injection of PS/2 mAb in combination with pertussis toxin resulted in anaphylaxis and mortality. Furthermore, the data showed that CD4(+) T cells were required for this effect and suggested a role for IL-1β and TNF-α in the underlying pathology. The results reveal a previously not appreciated deleterious effect of anti-VLA-4 Ab treatment in combination with exposure to pertussis toxin.
PMID: 21270409 [PubMed - as supplied by publisher]

108. J Immunol. 2011 Jan 15;186(2):647; author reply 648.
Comment on "Gender differences in 1,25 dihydroxyvitamin D3 immunomodulatory effects in multiple sclerosis patients and healthy subjects".
Handel AE, De Luca GC, Ramagopalan SV.
Comment on: J Immunol. 2010 Oct 15;185(8):4948-58.
PMID: 21209286 [PubMed - in process]

109. J Immunol Methods. 2010 Dec 31. [Epub ahead of print]
Active immunization with proteolipid protein (190-209) induces ascending paralysing experimental autoimmune encephalomyelitis in C3H/HeJ mice.
Göbel K, Bittner S, Ruck T, Budde T, Wischmeyer E, Döring F, Wiendl H, Meuth SG.
University of Muenster, Department of neurology-Inflammatory disorders of the nervous system and neurooncology, Domagkstr, 13, 48149 Muenster, Germany.
Experimental autoimmune encephalomyelitis (EAE) is a demyelinating disease of the central nervous system (CNS) that shares clinical and pathophysiological feature with multiple sclerosis (MS) and is commonly used as an animal model for the human disease. Upon active immunization, different myelin proteins and other neuronal antigens are known to induce EAE in susceptible mouse strains. However, there are rodent strains reputed to be resistant to actively-induced EAE and the correct combination of animal strains and their respective autoantigen is absolutely critical as some antigens are encephalitogenic in one animal strain, but not in another. Here we describe actively-induced EAE in C3H/HeJ mice with different myelin peptides. Whereas no clinical signs could be found by immunization with myelin oligodendrocyte glycoprotein 35-55, significant weight loss as well as rapidly occurring severe ascending paralysis was found in animals immunized with proteolipid protein 190-209 (PLP(190-209)). Histologically, this form of EAE was characterized by predominant involvement of the spinal cord. As PLP is one of the major lipid antigens putatively involved in the pathogenesis of MS, this model may be useful for further studies of the disease.
PMID: 21199659 [PubMed - as supplied by publisher]

110. J Interferon Cytokine Res. 2011 Jan 12. [Epub ahead of print]
Frequency and Magnitude of Interferon β Neutralizing Antibodies in the Evaluation of Interferon β Immunogenicity in Patients with Multiple Sclerosis.
Grossberg SE, Oger J, Grossberg LD, Gehchan A, Klein JP.
1 Department of Microbiology and Molecular Genetics, Medical College of Wisconsin , Milwaukee, Wisconsin.
Patients with multiple sclerosis (MS) treated with interferon β (IFNβ) preparations develop varying levels of antibodies that neutralize the biological effects of IFNβ, reduce its in vivo bioavailability, and diminish its therapeutic efficacy. The aim was to determine as distinct measures of immunogenicity the occurrence (frequency) and the magnitude (level) of IFNβ neutralizing antibody (NAb) formation in a large Canadian population as a cross-sectional study of patients with MS treated in a clinical practice setting with different, equally available IFNβ products: Avonex(®) (intramuscular IFNβ-1a), Rebif(®) (subcutaneous (SC) IFNβ-1a) at 22 and 44□µg, and Betaseron(®) (SC IFNβ-1b). Over a 3-year period 3,124 serum samples from 2,711 patients with MS were submitted by neurologists in MS clinics distributed across Canada and tested for NAbs in a single independent laboratory, utilizing a quantitative, standardized NAb bioassay. NAb frequency was greatest (35%) with Rebif (SC IFNβ-1a) 44□µg and least (7.5%) with Avonex (intramuscular IFNβ-1a), whereas Betaseron (IFNβ-1b) and Rebif 22□µg were in between (22%). NAb serum levels at magnitudes considered high, ≥100 tenfold reduction units (TRU)/mL, were found in 65%-83% of patients with detectable NAbs. Nearly half (42%-47%) of NAb-positive patients given IFNβ-1a preparations had very high titers (≥1,000 TRU/mL), whereas only 22% of NAb-positive patients on Betaseron had titers >1,000 TRU/mL. Differences in patterns of NAb formation among the four IFNβ product-dose combinations became more evident in patients with MS when both NAb frequency and the full range of NAb titer magnitude were measured.
PMID: 21226608 [PubMed - as supplied by publisher]

111. J Investig Allergol Clin Immunol. 2010;20(6):521-3.
Allergy workup in immediate-type local reactions to glatiramer acetate.
Sánchez-López J, Rodríguez del Rio P, Cases-Ortega B, Martínez-Cócera C, Fernández-Rivas M.
Department of Allergy, Hospital Clinico San Carlos, Madrid, Spain.
Local reactions to glatiramer acetate are common, but few cases of hypersensitivity reaction have been reported. We present 3 patients with multiple sclerosis who suffered immediate-type local reactions after subcutaneous injection of glatiramer acetate. Skin prick test (SPT), intradermal test (IDT), and determination of immunoglobulin (Ig) E to glatiramer acetate were performed in patients and controls (enzyme-linked immunosorbent assay). The results of SPT were all negative. Those of IDT in controls were negative at concentrations below 200 microg/mL, but positive for patients 1, 2, and 3 at 2, 20, and 200 microg/mL, respectively. Serum IgE to glatiramer acetate in patient 1 was 2.1 times higher than in the controls, whereas no differences were found between controls and patients 2 and 3. Glatiramer acetate was safely reintroduced in patients 2 and 3. The results obtained for patient 1 suggest that an IgE-mediated mechanism was probably involved. In conclusion, IDT and serum IgE determination to glatiramer acetate seem useful for identifying allergic reactions among the common local reactions induced by this drug.
PMID: 21243937 [PubMed - indexed for MEDLINE]

112. J Med Internet Res. 2011 Jan 24;13(1):e12.
Use of an Online Community to Develop Patient-Reported Outcome Instruments: The Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ).
Wicks P, Massagli M, Kulkarni A, Dastani H.
PatientsLikeMe, Research & Development, Cambridge, MA, United States. pwicks@patientslikeme.com.
BACKGROUND: Patients with multiple sclerosis (MS) may face barriers, such as treatment fatigue, memory problems, or side effects, that may influence their adherence to medication. OBJECTIVE: The objective of our study was to use an online community to develop a self-report questionnaire to quantify adherence and barriers to achieving adherence, that is specific to MS disease-modifying treatments (DMTs) and predictive of missed doses. METHODS: A review of the scientific literature and analysis of discussions between MS patients on PatientsLikeMe.com were used to generate survey items salient to patients. Cognitive debriefing was used to refine the items. The Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ) contains 30 questions in three subscales: Barriers, Side Effects, and Coping Strategies. RESULTS: MS patients completed an online survey (response rate: 431 of 1209 invited, 35.7%). Between 16% (14/86) and 51% (51/100) of MS patients missed at least 1 dose of their DMT in the previous 28 days, with significant between-treatment differences. The MS-TAQ Barriers scale was positively correlated with the proportion of doses missed (r = .5), demonstrating a stronger relationship between adherence and perceived barriers than was found with clinical or demographic variables (r ≈ .3). The Coping Strategies subscale was negatively correlated with missed doses (r = -.3), suggesting that use of more coping strategies is associated with higher adherence. CONCLUSIONS: Online communities can provide domains of interest and psychometric data to more rapidly develop and prototype patient-reported outcome instruments. The MS-TAQ offers patients and clinicians a simple method for identifying barriers to adherence, which may then be targeted through interventions.
PMID: 21266318 [PubMed - in process]

114. J Med Life. 2010 Oct-Dec;3(4):352-8.
Quality of life in multiple sclerosis.
Opara JA, Jaracz K, Brola W.
Academy of Physical Education, Katowice, Poland. jozefopara@wp.pl
An overall aim of treatment in multiple sclerosis is to lower the negative impact of the disease on functioning and quality of life of patients. Therefore, a measurement of functioning and quality of life should be included in the evaluation of the effectiveness of treatment. The most commonly used quality of life questionnaires, either generic or specific, were presented in this paper,. Information about clinical and functional status is useful in the interpretation of the quality of life assessment results. Because of that, instruments for the assessment of depression, cognitive functions, functional ability and fatigue in multiple sclerosis were also described.
PMID: 21254730 [PubMed - in process]

115. J Mol Neurosci. 2011 Jan 19. [Epub ahead of print]
Amelioration of Experimental Autoimmune Encephalomyelitis by β-elemene Treatment is Associated with Th17 and Treg Cell Balance.
Zhang R, Tian A, Zhang H, Zhou Z, Yu H, Chen L.
Department of Geriatrics, The First Affiliated Hospital of China Medical University, No.155 Nanjing Bei Street, Heping, 110001, Shenyang, Liaoning, People's Republic of China.
Experimental autoimmune encephalomyelitis (EAE), an animal mode of multiple sclerosis (MS), was previously considered that is mediated by Th1 cells. However, a number of recent studies provided strong evidence that T helper cells that produce interleukin (IL)-17 (Th17) and anti-inflammatory CD4+ Foxp3+ regulatory T cells (Tregs) play a dominant role in the pathogenesis of EAE. β-elemene is a natural antitumor plant drug with the role of multiple target, and it has been found to pass through the blood-brain barrier easily. It also has been strongly implicated as an immune modulatory agent, but the precise mechanisms of its action are largely unknown. In the present study, we mainly investigated the efficacy and mechanism of β-elemene against EAE in vivo and vitro. The treatment of C57 mice with β-elemene significantly delayed the onset of EAE, markedly suppressed MOG-specific T cell proliferation in a dose-dependent manner, dramatically reduced the IL-17, IL-6, IL-23, and RORγt production and induced the Foxp3 expression in both the periphery and the inflamed spinal cord. These findings indicated that β-elemene amelioration EAE was, to a large extent, due to inhibit differentiation and development of Th17 cells depends on down-regulating expression of IL-6, IL-23, RORγt signaling, and promoting expansion in Treg cells. Suggesting it is useful in the control of MS and other Th17 cell-mediated inflammatory diseases.
PMID: 21246417 [PubMed - as supplied by publisher]

116. J Neural Eng. 2011 Jan 19;8(1):016005. [Epub ahead of print]
Nerve lesioning with direct current.
Ravid EN, Gan LS, Todd K, Prochazka A.
Spastic hypertonus (muscle over-activity due to exaggerated stretch reflexes) often develops in people with stroke, cerebral palsy, multiple sclerosis and spinal cord injury. Lesioning of nerves, e.g. with phenol or botulinum toxin is widely performed to reduce spastic hypertonus. We have explored the use of direct electrical current (DC) to lesion peripheral nerves. In a series of animal experiments, DC reduced muscle force by controlled amounts and the reduction could last several months. We conclude that in some cases controlled DC lesioning
may□provide□an□effective□alternative□to□the□less□controllable□molecular□treatment
s□available□today.
PMID: 21248380 [PubMed - as supplied by publisher]

117. J Neurochem. 2011 Jan 7. doi: 10.1111/j.1471-4159.2010.07025.x. [Epub ahead of print]
Purinergic signalling at the plasma membrane: a multipurpose and multidirectional mode to deal with amyotrophic lateral sclerosis and multiple sclerosis.
Amadio S, Apolloni S, D'Ambrosi N, Volonté C.
CNR, Institute of Neurobiology and Molecular Medicine/Santa Lucia Foundation, Rome, Italy.
J. Neurochem. (2011) 10.1111/j.1471-4159.2010.07025.x ABSTRACT: ATP is a widespread and multipurpose signalling molecule copiously released in the extracellular environment of the whole nervous system upon cell activation, stress, or damage. Extracellular ATP is also a multidirectional information molecule, given the concurrent presence at the plasma membrane of various targets for ATP. These include ectonucleotidases (metabolizing ATP down to adenosine), ATP/adenosine transporters, P2 receptors for purine/pyrimidine nucleotides (ligand-gated ion channels P2X receptors and G-protein-coupled P2Y receptors), in addition to metabotropic P1 receptors for nucleosides. All these targets rarely operate as single units, rather they associate with each other at the plasma membrane as multi-protein complexes. Altogether, they control the duration, magnitude and/or direction of the signals triggered and propagated by purine/pyrimidine ligands, and the impact that each single ligand has on a variety of short- and long-term functions. A strict control system allows assorted, even divergent, biological outcomes. Among these, we enumerate cell-to-cell communication, tropic, trophic, but also noxious actions causing the insurgence/progression of pathological conditions. Here, we show that purinergic signalling in the nervous system can be instrumental for instance to neurodegenerative and neuroinflammatory diseases such as amyotrophic lateral sclerosis and multiple sclerosis.
PMID: 21214557 [PubMed - as supplied by publisher]

118. J Neurochem. 2011 Jan 14. doi: 10.1111/j.1471-4159.2011.07182.x. [Epub ahead of print]
Decreased activity of the 20S proteasome in the brain white matter and gray matter of patients with multiple sclerosis.
Zheng J, Bizzozero OA.
Dept. of Cell Biology and Physiology, University of New Mexico - Health Sciences Center, Albuquerque, New Mexico.
Carbonylated (oxidized) proteins are known to accumulate in the cerebral white matter (WM) and gray matter (GM) of patients with multiple sclerosis (MS). While oxidative stress is necessary for carbonyl generation, it is the failure of the degradation systems that ultimately leads to the build-up of carbonylated proteins within tissues. In this study, we measured the activity of the 20S proteasome and other proteolytic systems in the cerebral WM and GM of 13 MS patients and 13 controls. We report that the activities of the three peptidases of the 20S proteasome (i.e. chymotrypsin-like, caspase-like and trypsin-like) in both MS-WM and MS-GM are greatly reduced. Interestingly, neither the amount of proteasome nor the levels of the catalytic subunits (β1, β2, and β5) are diminished in this disease. Proteins containing Lys-48 poly-ubiquitin also accumulate in MS tissues, indicating failure of the 26S proteasome as well. Levels of the regulatory caps PA28α and PA700 are also lower in MS than in controls, suggesting that the activity of the more complex proteasomes may be reduced further. Finally, the activities of other proteases that might also remove oxidized proteins (calpain, cathepsin B, mitochondrial LonP) are not lessened in MS. Together, these studies suggest that direct inactivation of proteolytic centers in the 20S particle and/or the presence of specific inhibitors is the underlying cause of proteasomal dysfunction in MS.
PMID: 21235577 [PubMed - as supplied by publisher]

119. J Neuroeng Rehabil. 2011 Jan 24;8(1):5. [Epub ahead of print]
The Armeo Spring as training tool to improve upper limb functionality in multiple sclerosis: a pilot study.
Gijbels D, Lamers I, Kerkhofs L, Alders G, Knippenberg E, Feys P.
ABSTRACT: BACKGROUND: Few research in multiple sclerosis (MS) has focused on physical rehabilitation of upper limb dysfunction, though the latter strongly influences independent performance of activities of daily living. Upper limb rehabilitation technology could hold promise for complementing traditional MS therapy. Consequently, this pilot study aimed to examine the feasibility of an 8-week mechanical-assisted training program for improving upper limb muscle strength and functional capacity in MS patients with evident paresis. METHODS: A case series was applied, with provision of a training program (3x/week, 30 minutes/session), supplementary on the customary maintaining care, by employing a gravity-supporting exoskeleton apparatus (Armeo Spring). Ten high-level disability MS patients (Expanded Disability Status Scale 7.0-8.5) actively performed task-oriented movements in a virtual real-life-like learning environment with the affected upper limb. Tests were administered before and after training, and at 2-month follow-up. Muscle strength was determined through the Motricity Index and Jamar hand-held dynamometer. Functional capacity was assessed using the TEMPA, Action Research Arm Test (ARAT) and 9-Hole Peg Test (9HPT). RESULTS: Muscle strength did not change significantly. Significant gains were particularly found in functional capacity tests. After training completion, TEMPA scores improved (p=0.02), while a trend towards significance was found for the 9HPT (p=0.05). At follow-up, the TEMPA as well as ARAT showed greater improvement relative to baseline than after the 8-week intervention period (p=0.01, p=0.02 respectively). CONCLUSIONS: The results of present pilot study suggest that upper limb functionality of high-level disability MS patients can be positively influenced by means of a technology-enhanced physical rehabilitation program.
PMID: 21261965 [PubMed - as supplied by publisher]

120. J Neuroimmunol. 2011 Jan 5. [Epub ahead of print]
Enhanced complement consumption in neuromyelitis optica and Behçet's disease patients.
Tüzün E, Kürtüncü M, Türkoğlu R, Içöz S, Pehlivan M, Birişik O, Eraksoy M, Akman-Demir G.
Istanbul University, Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey.
The complement system is essential in the pathogenesis of inflammatory central nervous system disorders. To investigate the involvement of complement pathways in neuromyelitis optica (NMO), levels of breakdown products for classical (C4d), alternative (FBb) and common (sC5b-9) pathways were measured in the sera of 28 NMO and control patients (30 Behçet's disease (BD), 29 multiple sclerosis (MS)) and 31 healthy controls by ELISA. Classical and/or alternative pathway consumption was enhanced in NMO and BD patients as compared to MS patients and healthy controls. Our results suggest that NBD and NMO differ from MS by the predominance of complement system involvement.
PMID: 21215465 [PubMed - as supplied by publisher]

121. J Neuroimmunol. 2011 Jan 5. [Epub ahead of print]
IgG and IgM antibodies to the refolded MOG(1-125) extracellular domain in humans.
Gori F, Mulinacci B, Massai L, Avolio C, Caragnano M, Peroni E, Lori S, Chelli M, Papini AM, Rovero P, Lolli F.
Laboratorio Interdipartimentale di Chimica e Biologia di Peptidi e Proteine, Dipartimento di Scienze Farmaceutiche, Università degli Studi di Firenze, Via Ugo Schiff 6, 50019, Sesto Fiorentino, Firenze, Italy.
Antibodies to MOG in serum have a dubious prognostic value in multiple sclerosis. The MOG recombinant protein conformational properties relevant to the antigenic activity are unknown. We employed a solid-phase ELISA based on a product (rMOG(ED)(His)(6)) expressed in E. coli after subcloning the cDNA of the extracellular domain of rat MOG, performing a refolding procedure on column and affinity purification. The far-UV Circular Dichroism (CD) spectra of rMOG(ED)(His)(6) showed a β-sheet, a characteristic feature of the Ig-fold. However, in MS sera and controls we failed to detected IgM or IgG antibodies.
PMID: 21215463 [PubMed - as supplied by publisher]

122. J Neuroimmunol. 2011 Jan 5. [Epub ahead of print]
Lipoic acid decreases inflammation and confers neuroprotection in experimental autoimmune optic neuritis.
Chaudhary P, Marracci G, Yu X, Galipeau D, Morris B, Bourdette D.
Department of Neurology, L226, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA.
Lipoic acid (LA) is an antioxidant that is effective in treating experimental autoimmune encephalomyelitis (EAE), a model for multiple sclerosis (MS). C57BL/6 mice with EAE develop experimental autoimmune optic neuritis (EAON), which models acute optic neuritis in humans. Here we determined whether LA is therapeutically effective in EAON. We immunized C57BL/6 mice with MOG 35-55 peptide. Mice received either daily subcutaneous injections of LA (100mg/kg) or saline in early or late suppression paradigms. In the early suppression paradigm, optic nerve cross-sections showed 14.9±3.8% (mean±SEM) damage in mice receiving saline (n=7) and 2.0±0.4% damage in mice given LA (n=7, p=0.001). In the late suppression paradigm, optic nerve sections showed 24.6±3.5% damage in mice treated with saline (n=7) and 8.4±2.5% in mice treated with LA (n=7, p=0.004). Thus a dramatic reduction in axonal injury was seen after LA administration in both experimental paradigms. Compared with saline treated mice with EAON, optic nerves from mice receiving LA had significantly fewer CD4+ and CD11b+ cells in both paradigms. This study provides a rationale for investigating the therapeutic efficacy of LA in acute optic neuritis in humans.
PMID: 21215462 [PubMed - as supplied by publisher]

123. J Neuroimmunol. 2011 Jan 25. [Epub ahead of print]
Reduced thymic output and peripheral naïve CD4 T-cell alterations in primary progressive multiple sclerosis (PPMS).
Haegert DG, Hackenbroch JD, Duszczyszyn D, Fitz-Gerald L, Zastepa E, Mason H, Lapierre Y, Antel J, Bar-Or A.
Department of Pathology, McGill University, 3775 rue University, Montreal, QC, Canada H3A 2B4.
We compared naïve CD4 and CD8 T-cell homeostasis in primary progressive multiple sclerosis (PPMS), relapsing-remitting MS (RRMS) and controls. Quantitation of signal joint T-cell receptor (TCR) excision circles (sjTRECs) and quantitative estimates of daily thymic export confirm our previous report of reduced thymic output in RRMS and demonstrate reduced thymic output in PPMS. In PPMS, the decreasing % CD31+ naïve CD4 T-cells but constant sjTRECs and constant naïve CD4 T-cell numbers with age, together with increased Bcl-2 expression suggest increased TCR signaling with increased naïve T-cell survival. We conclude PPMS patients have peripheral immune alterations related to reduced thymic output.
PMID: 21272945 [PubMed - as supplied by publisher]

124. J Neuroimmunol. 2011 Jan 21. [Epub ahead of print]
IRF-1 signaling in central nervous system glial cells regulates inflammatory demyelination.
Ren Z, Wang Y, Liebenson D, Liggett T, Goswami R, Stefoski D, Balabanov R.
The present study provides evidence that interferon regulatory factor 1 (IRF-1) signaling in glial cells is involved in the pathogenesis of multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE). Using a bone marrow chimera model of EAE, we demonstrated that CNS IRF-1 regulates inflammatory demyelination and disease severity independently of the peripheral immune cells. In addition, we identified Caspase 1, a pro-inflammatory and pro-apoptotic molecule, as an important transcriptional target of IRF-1. The findings of our study indicate that IRF-1 signaling in glial cells serves as a final common pathway of inflammatory demyelination and may have important clinical implications in MS.
PMID: 21257209 [PubMed - as supplied by publisher]

125. J Neuroimmunol. 2011 Jan 13. [Epub ahead of print]
Acute disseminated encephalomyelitis (ADEM).
Wender M.
ADEM is a disease that is characterized by an inflammatory reaction and demyelination in the central nervous system, with a distinct tendency to a peripheral localization of pathological changes. ADEM happens to occur with a temporal, and probably also with a causative relationship to viral, exanthematous diseases, as well as to preventive vaccinations. However, there are still many unresolved problems with respect to the relationship of ADEM to multiple sclerosis (MS), especially in instances with a multiphasic course of the disease. Many question marks can also be raised in cases, in which the examinations were unable to determine the exact preceding or causative factor. A lot of studies on cytokines and chemokines in blood plasma and CSR from patients with ADEM have enabled investigators to get a better insight into some stages of immunopathological processes, leading to an evolvement of the disease, without a more important impact on the clinical diagnosis.
PMID: 21237518 [PubMed - as supplied by publisher]

126. J Neuroinflammation. 2011 Jan 7;8(1):2.
Plasmacytoid dendritic cells are increased in cerebrospinal fluid of untreated patients during multiple sclerosis relapse.
Longhini AL, von Glehn F, Brandão CO, de Paula RF, Pradella F, Moraes AS, Farias AS, Oliveira EC, Quispe-Cabanillas JG, Abreu CH, Damasceno A, Damasceno BP, Balashov KE, Santos LM.
Neuroimmunology Unit, Dept Genetics, Evolution and Bioagents, Biology Institute University of Campinas - UNICAMP. leonilda@unicamp.br.
ABSTRACT: The plasmacytoid dendritic cells (pDCs) express a high level of Toll-like receptor 9 (TLR-9), which recognizes viral DNA. Activated via TLR-9, pDCs also secrete large amounts of type I interferon which are involved either in stimulation or down regulation of immune response in multiple sclerosis (MS). In the present study, we determinate pDCs levels by flow cytometry in Cerebrospinal Fluid (CSF) and Peripheral Blood from MS patients in relapsing and in remitting phases of the disease, comparing with other non-inflammatory diseases (OND). We provide evidence that MS patients in relapse without any treatment have a significantly ($p < 0.01$) higher percentage of pDCs in CSF than do patients in remission or those with OND. No change in the percentage of pDCs was observed in the peripheral blood of any of these patients. The increase of pDCs in central nervous system during relapse may be explained either by a virus infection or a down regulatory process.
PMCID: PMC3022734 PMID: 21214939 [PubMed - in process]

127. J Neuroinflammation. 2011 Jan 24;8(1):8. [Epub ahead of print]
Cooperative contributions of Interferon regulatory factor 1 (IRF1) and IRF8 to interferon-gamma-mediated cytotoxic effects on oligodendroglial progenitor cells.
Horiuchi M, Itoh A, Pleasure D, Ozato K, Itoh T.
ABSTRACT: BACKGROUND: Administration of exogenous interferon-gamma (IFNgamma) aggravates the symptoms of multiple sclerosis (MS), whereas interferon-beta (IFNbeta) is used for treatment of MS patients. We previously demonstrated that IFNgamma induces apoptosis of oligodendroglial progenitor cells (OPCs), suggesting that IFNgamma is more toxic to OPCs than IFNbeta. Thus we hypothesized that a difference in expression profiles between IFNgamma-inducible and IFNbeta-inducible genes in OPCs would predict the genes responsible for IFNgamma-mediated cytotoxic effects on OPCs. We have tested this hypothesis particularly focusing on the interferon regulatory factors (IRFs) well-known transcription factors up-regulated by IFNs. METHODS: Highly pure primary rat OPC cultures were treated with IFNgamma and IFNbeta. Cell death and proliferation were assessed by MTT reduction, caspse-3-like proteinase activity, Annexin-V binding, mitochondrial membrane potential, and BrdU-incorporation. Induction of all nine IRFs was comprehensively compared by quantitative PCR between IFNgamma-treated and IFNbeta-treated OPCs. IRFs more strongly induced by IFNgamma than by IFNbeta were selected, and tested for their ability to induce OPC apoptosis by overexpression and by inhibition by dominant-negative proteins or small interference RNA either in the presence or absence of IFNgamma. RESULTS: Unlike IFNgamma, IFNbeta did not induce apoptosis of OPCs. Among nine IRFs, IRF1 and IRF8 were preferentially up-regulated by IFNgamma. In contrast, IRF7 was more robustly induced by IFNbeta than by IFNgamma. Overexpressed IRF1 elicited apoptosis of OPCs, and a dominant negative IRF1 protein partially protected OPCs from IFNgamma-induced apoptosis, indicating a substantial contribution of IRF1 to IFNgamma-induced OPC apoptosis. On the other hand, overexpression of IRF8 itself had only marginal proapoptotic effects. However, overexpressed IRF8 enhanced the IFNgamma-induced cytotoxicity and the proapoptotic effect of overexpressed IRF1, and down-regulation of IRF8 by siRNA partially but significantly reduced preapoptotic cells after treatment with IFNgamma, suggesting that IRF8 cooperatively enhances IFNgamma-induced OPC apoptosis. CONCLUSIONS: This study has identified that IRF1 and IRF8 mediate IFNgamma-signaling leading to OPC apoptosis. Therapies targeting at these transcription factors and their target genes could reduce IFNgamma-induced OPC loss and thereby enhance remyelination in MS patients.
PMID: 21261980 [PubMed - as supplied by publisher]

128. J Neurol. 2011 Jan 7. [Epub ahead of print]
Religiosity and its relation to quality of life in primary caregivers of patients with multiple sclerosis: a case study in Greece.
Argyriou AA, Iconomou G, Ifanti AA, Karanasios P, Assimakopoulos K, Makridou A, Giannakopoulou F, Makris N.
Department of Neurology, "Saint Andrew's" State General Hospital of Patras, 26335, Patras, Greece, andargyriou@yahoo.gr.
The first objective of the current observational study was to assess the degree of religiosity in Greek Christian Orthodox primary caregivers of patients with multiple sclerosis (MS). The second objective was to evaluate the interrelations between religiosity and quality of life (QOL) and to identify the determinants of QOL, an endpoint of considerable importance in clinical research and practice. Twenty-two male and 13 female primary caregivers (mean age 47.3 ± 12.4 years) of an equal number of patients with MS, who consented to participate, completed the Systems of the Greek version of the Belief Inventory (SBI-15R) and the Greek validated version of EuroQOL (EQ-5D). The analysis revealed high scores on religiosity, especially among females. Caregivers scored in the religious beliefs and practices subscale of SBI-15R with a mean score of 22.8 ± 7.8 (range 0-30) and with 7.1 ± 4.8 (range 0-14) in the social support subscale. However, both of the SBI-15R domains were almost unrelated to the degree of overall QOL. There was only a reliable (but with little clinical value) association between the pain/discomfort domain of the EQ-5D with the SBI-15R beliefs and practices subscale ($r = -0.38$, $p = 0.03$). Although high levels of religiosity among Greek Christian Orthodox primary caregivers of MS patients were evident, this study did not demonstrate any beneficial effect of religious beliefs and practices on their QOL. Further prospective studies with a population with the same and/or diverse religious and cultural backgrounds are needed to better elucidate the complex association between religiosity and QOL in primary caregivers of MS patients.
PMID: 21212972 [PubMed - as supplied by publisher]

129. J Neurol. 2011 Jan 25. [Epub ahead of print]
Migration and multiple sclerosis in immigrants to Australia from United Kingdom and Ireland: a reassessment. I. Risk of MS by age at immigration.
McLeod JG, Hammond SR, Kurtzke JF.
Department of Medicine, University of Sydney, Camperdown, NSW 2006, Australia, james.mcleod@sydney.edu.au.
A previous study of the prevalence of multiple sclerosis (MS) in 1981 among immigrants from the United Kingdom and Ireland to Australia found that the prevalence for those with age at immigration (AAI) under 15 years of age did not differ from the older immigrants. We have reanalysed the original materials as well as census data for 1901-1981 for UKI and other high MS risk country immigrants. There was a highly significant trend in the prevalence rates of all Australians from New South Wales (NSW) to South Australia (SA) to Western Australia (WA) to Queensland (QLD). Rates by state among the Australian-born were almost identical to these, but there was no prevalence gradient for the UKI-born. The denominator population at risk of MS by AAI was calculated from special census tables of length of residence in Australia by age 0-79 in 1981 for UKI immigrants 1947-1981. The numerator was limited to the subset of 258 MS (Group II) also immigrating in 1947 and later, and age 0-79 in 1981. The absolute risk of MS for these migrants to the four states entering at age 0-14 was 22/100,000, significantly less than for all older age groups; age 15-39 immigrants had a risk of 54/100,000. Similar risk ratios for 0-14 versus 15-39 by state were 31 versus 61 (NSW), 29 versus 44 (QLD), 11 versus 50 (SA), 15 versus 51 (WA).
PMID: 21264474 [PubMed - as supplied by publisher]

130. J Neurol. 2011 Jan 25. [Epub ahead of print]
Lamotrigine therapy for paroxysmal dysarthria caused by multiple sclerosis: a case report.
Valentino P, Nisticò R, Pirritano D, Bilotti G, Del Giudice F, Sturniolo M, Quattrone A.
Institute of Neurology, University Magna Græcia, Catanzaro, Italy.
PMID: 21264473 [PubMed - as supplied by publisher]

131. J Neurol. 2011 Jan 15. [Epub ahead of print]
Impact of fatigue on the efficacy of rehabilitation in multiple sclerosis.
Judica E, Martinelli Boneschi F, Ungaro D, Comola M, Gatti R, Comi G, Rossi P.
Neurorehabilitation Unit, Department of Neurology, Institute of Experimental Neurology, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy.
Fatigue is considered to be one of the most common and disabling symptoms among individuals with multiple sclerosis (MS). The aim of this study is to investigate if an intensive, short-term inpatient rehabilitation program is able to improve fatigue in MS, and if fatigue is able to negatively influence the clinical and functional outcome of rehabilitation in MS. One-hundred eighty six consecutively recruited MS patients underwent an intensive, short-term inpatient rehabilitation program. Sixty-four of them were selected for this study according to our inclusion criteria and compared to a control group of 22 MS patients who did not follow a rehabilitation program. We measured fatigue symptoms with the Fatigue Severity Scale (FSS) before and after rehabilitation, and classified patients into fatigued (FMS) in the case of an FSS score ≥36 and into non-fatigued MS (NFMS) in the case of an FSS <36. Expanded Disability Status Scale (EDSS) and Functional Independence Measure (FIM) were used as clinical outcome measures of the efficacy of the rehabilitation program. In our sample, an intensive, short-term rehabilitation treatment is able to determine a significant reduction of fatigue symptoms compared to untreated MS patients ($p < 0.0001$); however, the presence of fatigue at the beginning of the rehab program seems not to have any impact on the clinical and functional outcome of rehabilitation. An intensive inpatient rehabilitation trial decreases symptom of fatigue in MS patients; furthermore fatigue seems not to modify the amelioration of disability and impairment determined by a rehabilitation program.
PMID: 21240518 [PubMed - as supplied by publisher]

132. J Neurol. 2011 Jan 1. [Epub ahead of print]
Glial fibrillary acidic protein: a potential biomarker for progression in multiple sclerosis.
Axelsson M, Malmeström C, Nilsson S, Haghighi S, Rosengren L, Lycke J.
Department of Neurosciences, Sahlgrenska Academy, Institute of Neuroscience and Physiology, Gothenburg University, 413 45, Gothenburg, Sweden, markus.axelsson@vgregion.se.
The major intermediate cytoskeletal protein of astrocytes, glial fibrillary acidic protein (GFAP), and that of axons, neurofilament light protein (NFL), may both be released into the cerebrospinal fluid (CSF) during pathological processes in the central nervous system (CNS). We investigated GFAP and NFL levels in CSF as possible biomarkers for progression in multiple sclerosis (MS). Patients with relapsing-remitting MS (RRMS, n = 15) or secondary progressive MS (SPMS, n = 10) and healthy control subjects (n = 28) were examined twice with an interval of 8-10 years apart. Neurological deficits were scored with the Expanded Disability Status Scale (EDSS). GFAP and NFL levels were determined in CSF by enzyme-linked immunosorbent assay (ELISA). GFAP levels and NFL levels correlated with age (r and r (s) = 0.50, $p = 0.006$). Adjusting for age, MS patients had increased GFAP levels compared with controls ($p = 0.03$) and GFAP levels correlated with neurological disability (EDSS, $r = 0.51$, $p < 0.05$) and disease progression [Multiple Sclerosis Severity Score (MSSS), $r = 0.47$, $p < 0.05$]. The mean annual increase of GFAP was 6.5 ng/L for controls, 8.1 ng/L for RRMS patients, and 18.9 ng/L for SPMS patients. GFAP level at the first examination had predictive value for neurological disability 8-10 years later (EDSS, $r = 0.45$, $p < 0.05$) but not for EDSS increase between the examinations. NFL levels were not significantly increased in MS patients compared with controls and had no relationship to disability or progression and no prognostic value for disability development. GFAP, a marker for astrogliosis, is a potential biomarker for MS progression and may have a role in clinical trials for assessing the impact of therapies on MS progression.
PMID: 21197541 [PubMed - as supplied by publisher]

133. J Neurol Neurosurg Psychiatry. 2011 Jan 8. [Epub ahead of print]
CADASIL with cord involvement associated with a novel and atypical NOTCH3 mutation.
Bentley P, Wang T, Malik O, Nicholas R, Ban M, Sawcer S, Sharma P.
Imperial College Cerebrovascular Research Unit, Imperial College London, Charing Cross Campus, London, UK.
Background Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a hereditary cause of cerebral small-vessel disease associated with one of many recognised mutations of the NOTCH3 gene. Spinal cord involvement is not a recognised feature. The authors describe a unique CADASIL pedigree that manifested a stereotypical pattern of cord lesions, in association with a novel and atypical NOTCH3 mutation. Methods Clinical, radiological, laboratory and genetic characterisation of three affected family members. The associated NOTCH3 mutation was further evaluated by site-directed mutagenesis, immunohistochemistry, CBF1-transcription reporter assay, and screened for in 100 unrelated pathologically confirmed multiple sclerosis (MS) patients. Results Three members of a family presented with CADASIL caused by a novel NOTCH3 missense mutation, C212Y. Two daughters of the proband also manifested a distinctive pattern of cord lesions confined to the posterocentral zone, cerebral lesions showing both a demyelinating and a typical CADASIL topography, positive antinuclear antibodies and intrathecally derived oligoclonal bands. The mutation occurred in exon 4-that is, outside the Notch3 ligand-binding domain-yet unusually for this location impaired Notch function as assessed by Jagged1 signal transduction. The C212Y mutation did not occur in 100 separate MS cases. Conclusions This is the first description of an inherited pattern of cord lesions in association with CADASIL. The fact that certain features of dysregulated immunity also occurred, in association with a novel and atypical loss-of-function NOTCH3 mutation, supports evidence for functional interactions of Notch3 with the immune system, in addition to its vascular support role.
PMID: 21217157 [PubMed - as supplied by publisher]

134. J Neurol Neurosurg Psychiatry. 2011 Jan 6. [Epub ahead of print]
Geography of hospital admissions for multiple sclerosis in England and comparison with the geography of hospital admissions for infectious mononucleosis: a descriptive study.
Ramagopalan SV, Hoang U, Seagroatt V, Handel A, Ebers GC, Giovannoni G, Goldacre MJ.
Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, UK.
Objective It is well recognised that variation in the geographical distribution of multiple sclerosis (MS) exists. Early studies in England have shown the disease to have been more common in the North than the South. However, this could be an artefact of inaccurate diagnosis and ascertainment, and recent data on MS prevalence are lacking. In the present study, data were analysed to provide a more contemporary map of the distribution of MS in England and, as infectious mononucleosis (IM) has been shown to be associated with the risk of MS, the geographical distribution of IM with that of MS was compared. Methods Analysis of linked statistical abstracts of hospital data for England between 1999 and 2005. Results There were 56 681 MS patients. The admission rate for MS was higher in females (22/10(5); 95% CI 21.8 to 22.3) than males (10.4/10(5); 95% CI 10.2 to 10.5). The highest admission rate for MS was seen for residents of Cumbria and Lancashire (North of England) (20.1/10(5); 95% CI 19.3 to 20.8) and the lowest admission rate was for North West London residents (South of England) (12.4/10(5); 95% CI 11.8 to 13.1). The geographical distributions of IM and MS were significantly correlated (weighted regression coefficient (r (w))=0.70, $p<0.0001$). Admission rates for MS were lowest in the area quintile with the highest level of deprivation and they were also lowest in the area quintile with the highest percentage of population born outside the UK. A significant association between northernliness and MS remained after adjustment for deprivation and UK birthplace. Conclusions The results show the continued existence of a latitude gradient for MS in England and show a correlation with the distribution of IM. The data have implications for healthcare provision, because lifetime costs of MS exceed £1 million per case in the UK, as well as for studies of disease causality and prevention.
PMID: 21212107 [PubMed - as supplied by publisher]

135. J Neurol Neurosurg Psychiatry. 2011 Jan 19. [Epub ahead of print]
Multiple sclerosis prevalence in Ireland: relationship to vitamin D status and HLA genotype.
Lonergan R, Kinsella K, Fitzpatrick P, Brady J, Murray B, Dunne C, Hagan R, Duggan M, Jordan S, McKenna M, Hutchinson M, Tubridy N.
Department of Neurology, St Vincent's University Hospital and University College Dublin, Ireland.
Background The relationship between prevalence of multiple sclerosis (MS) and latitude may be due to both genetic and environmental factors. The hypothesis that, in Ireland, MS prevalence is increasing and that north-south differences relate to variation in serum 25-hydroxyvitamin D (25(OH)D) levels was tested in this study. Patients and methods Patients and matched control subjects were identified in counties Donegal, Wexford and South Dublin through multiple sources. Prevalence was determined. Blood samples were taken for serum 25(OH)D and serum intact parathyroid hormone measurement, and DNA was extracted. Results Prevalence in 2007 was significantly greater in Donegal (northwest) (290.3/105, 95% CI 262.3 to 321.7) compared with 2001 (184.6/105; 162 to 209.5). In Wexford (southeast), there was a non-significant increase in prevalence in 2007 compared with 2001. Prevalence was significantly higher in Donegal than in Wexford (144.8/105; 126.7 to 167.8, p<0.0001) and South Dublin (127.8/105; 111.3 to 148.2, p<0.0001). Overall, mean 25(OH)D levels were low and did not differ between patients (38.6 nmol/l) and controls (36.4 nmol/l) However, significantly more patients than controls had 25(OH)D levels <25 nmol/l (deficiency) (p=0.004). Levels of 25(OH)D (mean 50.74 nmol/l) were significantly higher in South Dublin (area with lowest prevalence) (p<0.0001) than in Donegal or Wexford. HLA DRB1*15 occurred most frequently in Donegal (greatest MS prevalence) and least frequently in South Dublin. Conclusion Vitamin D deficiency is common in Ireland. Latitudinal variation in MS probably relates to an interaction between genetic factors and environment (25(OH)D levels), and MS risk may be modified by vitamin D in genetically susceptible individuals.
PMID: 21248317 [PubMed - as supplied by publisher]

136. J Neurol Sci. 2011 Jan 18. [Epub ahead of print]
Accounting for disease modifying therapy in models of clinical progression in multiple sclerosis.
Healy BC, Engler D, Gholipour T, Weiner H, Bakshi R, Chitnis T.
Department of Neurology, Partners Multiple Sclerosis Center, Brigham and Women's Hospital, Harvard Medical School, USA; Biostatistics Center, Massachusetts General Hospital, USA.
Identifying predictors of clinical progression in patients with relapsing-remitting multiple sclerosis (RRMS) is complicated in the era of disease modifying therapy (DMT) because patients follow many different DMT regimens. To investigate predictors of progression in a treated RRMS sample, a cohort of RRMS patients was prospectively followed in the Comprehensive Longitudinal Investigation of Multiple Sclerosis at the Brigham and Women's Hospital (CLIMB). Enrollment criteria were exposure to either interferon-β (IFN-β, n=164) or glatiramer acetate (GA, n=114) for at least 6months prior to study entry. Baseline demographic and clinical features were used as candidate predictors of longitudinal clinical change on the Expanded Disability Status Scale (EDSS). We compared three approaches to account for DMT effects in statistical modeling. In all approaches, we analyzed all patients together and stratified based on baseline DMT. Model 1 used all available longitudinal EDSS scores, even those after on-study DMT changes. Model 2 used only clinical observations prior to changing DMT. Model 3 used causal statistical models to identify predictors of clinical change. When all patients were considered using Model 1, patients with a motor symptom as the first relapse had significantly larger change in EDSS scores during follow-up (p=0.04); none of the other clinical or demographic variables significantly predicted change. In Models 2 and 3, results were generally unchanged. DMT modeling choice had a modest impact on the variables classified as predictors of EDSS score change. Importantly, however, interpretation of these predictors is dependent upon modeling choice.
PMID: 21251671 [PubMed - as supplied by publisher]

137. J Neurol Sci. 2011 Jan 15. [Epub ahead of print]
Sleep disorders and fatigue in multiple sclerosis: Evidence for association and interaction.
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Fatigue is highly prevalent in multiple sclerosis (MS). It appears to be multifactorial, with "primary" or disease-related factors involved, as well as "secondary" factors, including comorbidities. Sleep disturbances are frequent in MS as well, and often result from disease-related factors. Subjective sleep disturbances in MS have been extensively studied and have been associated with fatigue. Sleep disorders in the general population have been associated with fatigue as well. However, data on objectively diagnosed sleep disorders in MS are less conclusive. Studies of sleep in MS have often suffered from low numbers of study subjects and suboptimal methodology. We review the current knowledge on sleep disturbances in MS and the relationship to fatigue. Data from neuroimaging studies and studies of molecular consequences of sleep disorders in the general population, with particular attention to sleep-disordered breathing (SDB), are briefly reviewed. Potential biologic interactions with MS are discussed in this context. We conclude that further studies of sleep disorders in MS are needed, to objectively establish their significance in this disease, and also to document any impact of treatment of sleep disorders on biologic and clinical outcomes such as fatigue.
PMID: 21241993 [PubMed - as supplied by publisher]

138. J Neurol Sci. 2011 Jan 12. [Epub ahead of print]
Brain abnormalities in neuromyelitis optica.
Kim JE, Kim SM, Ahn SW, Lim BC, Chae JH, Hong YH, Park KS, Sung JJ, Lee KW.
Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea.
BACKGROUND: Differentiating neuromyelitis optica (NMO) from multiple sclerosis (MS) is a real challenge in the clinical field. In the past, NMO (not MS), was inferred when abnormality was not detected in the brain magnetic resonance imaging (MRI). Recently, some studies have reported abnormalities in the brain MRIs of NMO, but only few among the Asian population. The aim of this study was to evaluate the frequency of brain MRI among Korean NMO patients and characterize findings that might be helpful to distinguish NMO from MS. METHODS: Medical records, NMO-IgG, and brain MRI of 17 patients diagnosed with NMO by the revised diagnostic criteria of Wingerchuk et al. (2006) [6] from 2008 to 2010, were reviewed. RESULTS: 11 out of 17 patients (64.7%) had abnormal MRI findings. More than two lesions were detected in most patients. The majority of patients with brain MRI abnormality showed nonspecific (5 patients) or atypical (6 patients) findings. Cerebral white matter was most frequently involved (58.8%). 3 patients (17.6%) involved corpus callosum, 4 (23.5%) with internal capsule, 2 (11.8%) with cerebellum, and 3 (17.6%) with brainstem. There were 5 (29.4%) patients who met the Paty et al. criteria (1988) [15] and 3 patients (35.3%) who met the multiple sclerosis (MS) spatial distribution diagnostic criteria of Barkhof et al. (1997) [14] in their brain MRI. CONCLUSIONS: Brain abnormalities have been frequently found among Korean NMO patients and the frequencies have been reported to be higher than that of Caucasians. Current MS spatial distribution criteria, such as Paty et al. (1988) [15] or Barkhof et al. (1997) [14], are not sufficient to discriminate NMO from MS in brain MRI findings. Our results will provide valuable information that would be useful in establishing future revising criteria for NMO.
PMID: 21236446 [PubMed - as supplied by publisher]

139. J Neurol Sci. 2011 Jan 10. [Epub ahead of print]

Cup to disc ratio by optical coherence tomography is abnormal in multiple sclerosis.

Syc SB, Warner CV, Saidha S, Farrell SK, Conger A, Bisker ER, Wilson J, Frohman TC, Frohman EM, Balcer LJ, Calabresi PA.

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OBJECTIVE: To identify and characterize cup to disc ratio (CDR) and related optic nerve head abnormalities in multiple sclerosis (MS) using spectral domain optical coherence tomography (OCT). BACKGROUND: While CDR is routinely assessed by ophthalmologists in the evaluation of glaucoma, CDR and related optic nerve head metrics remain largely unexplored in MS. DESIGN/METHODS: Cirrus-HD (high density) OCT was used to evaluate average CDR, vertical CDR, optic disc area, optic cup volume, and neuro-retinal rim area in 105 MS patients and 88 age-matched healthy individuals. High-contrast (100%) visual acuity, 2.5% low-contrast letter acuity and 1.25% low-contrast letter acuity were assessed in 77 MS patients. Two-sample t-tests were used in the analysis of OCT-derived optic nerve head measures between healthy controls and MS patients. Multivariate regression (accounting for age and gender) was used to assess relationships between optic nerve head measures and visual function. RESULTS: Average CDR (p=0.007) and vertical CDR (p=0.005) were greater in MS patients compared to healthy controls, while neuro-retinal rim area was decreased in MS patients (p=0.001). CDR increased with retinal nerve fiber layer (RNFL) thinning (r=-0.29, p=0.001). 2.5% low-contrast (p=0.005) and 1.25% low-contrast letter acuity (p=0.03) were lower in MS patients with higher vertical CDR. CONCLUSIONS/RELEVANCE: CDR (as determined by spectral domain OCT) is abnormal in MS and correlates with visual function. OCT-derived CDR and related optic nerve head metrics may represent an objective measure by which to monitor disease progression, and potentially neuroprotection, in therapeutic MS trials.

PMID: 21227470 [PubMed - as supplied by publisher]

140. J Neurosci. 2011 Jan 19;31(3):1069-1080.

Genetically Induced Adult Oligodendrocyte Cell Death Is Associated with Poor Myelin Clearance, Reduced Remyelination, and Axonal Damage.

Pohl HB, Porcheri C, Mueggler T, Bachmann LC, Martino G, Riethmacher D, Franklin RJ, Rudin M, Suter U.

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Loss of oligodendrocytes is a feature of many demyelinating diseases including multiple sclerosis. Here, we have established and characterized a novel model of genetically induced adult oligodendrocyte death. Specific primary loss of adult oligodendrocytes leads to a well defined and highly reproducible course of disease development that can be followed longitudinally by magnetic resonance imaging. Histological and ultrastructural analyses revealed progressive myelin vacuolation, in parallel to disease development that includes motor deficits, tremor, and ataxia. Myelin damage and clearance were associated with induction of oligodendrocyte precursor cell proliferation, albeit with some regional differences. Remyelination was present in the mildly affected corpus callosum. Consequences of acutely induced cell death of adult oligodendrocytes included secondary axonal damage. Microglia were activated in affected areas but without significant influx of B-cells, T-helper cells, or T-cytotoxic cells. Analysis of the model on a RAG-1 (recombination activating gene-1)-deficient background, lacking functional lymphocytes, did not change the observed disease and pathology compared with immune-competent mice. We conclude that this model provides the opportunity to study the consequences of adult oligodendrocyte death in the absence of primary axonal injury and reactive cells of the adaptive immune system. Our results indicate that if the blood-brain barrier is not disrupted, myelin debris is not removed efficiently, remyelination is impaired, and axonal integrity is compromised, likely as the result of myelin detachment. This model will allow the evaluation of strategies aimed at improving remyelination to foster axon protection.

PMID: 21248132 [PubMed - as supplied by publisher]

141. J Neurosci. 2011 Jan 12;31(2):669-77.
EMMPRIN: a novel regulator of leukocyte transmigration into the CNS in multiple sclerosis and experimental autoimmune encephalomyelitis.
Agrawal SM, Silva C, Tourtellotte WW, Yong VW.
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Extracellular matrix metalloproteinase inducer (EMMPRIN, CD147) is a member of the Ig superfamily, with various physiological roles including the induction of matrix metalloproteinases (MMPs), leukocyte activation, and tumor progression. In this study, we illustrate a novel involvement of EMMPRIN in multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). We found EMMPRIN levels to be upregulated on peripheral leukocytes before onset of EAE clinical signs and on infiltrating leukocytes and resident cells within the CNS in symptomatic mice. In EAE brain sections, EMMPRIN expression was localized with MMP-9 protein and activity. The increased EMMPRIN level was also characteristic of brain samples from MS subjects, particularly in plaque-containing areas. To evaluate the implications of elevated EMMPRIN levels, we treated EAE mice with an EMMPRIN function-blocking antibody and found reduced EAE clinical severity accompanied by decreased CNS parenchymal infiltration of leukocytes. Amelioration of EAE clinical signs by the anti-EMMPRIN antibody was critically dependent on its administration around the period of onset of clinical signs, which is typically associated with significant influx of leukocytes into the CNS. Moreover, the reduction in disease severity in anti-EMMPRIN-treated mice was associated with diminished MMP proteolytic activity at the glia limitans, the final barrier before parenchymal infiltration of leukocytes. Together, our results are the first to emphasize a role for EMMPRIN in MS and EAE, whereby EMMPRIN regulates leukocyte trafficking through increasing MMP activity. These results identify EMMPRIN as a novel therapeutic target in MS.
PMID: 21228176 [PubMed - in process]

142. J Neurosci Nurs. 2010 Dec;42(6):342-53.
Recent developments in the early diagnosis and management of multiple sclerosis.
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The management paradigm for multiple sclerosis (MS) is moving toward earlier diagnosis (on the basis of clinical, paraclinical, and laboratory findings), differentiation of patients with varying prognoses, and earlier implementation of treatment in selected individuals. On the basis of a survey conducted at the American Association of Neuroscience Nurses Annual Conference in 2009, several topics were identified for which nurses indicated a need for new and updated information, including current diagnostic methods for MS, optimal time to initiate treatment of MS, and emerging therapies for MS. This article was designed to address these issues.
PMID: 21207772 [PubMed - indexed for MEDLINE]

143. J Neurosci Nurs. 2010 Dec;42(6):331-41.
Quality of life in spite of an unpredictable future: the next of kin of patients with multiple sclerosis.
Liedström E, Isaksson AK, Ahlström G.
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The aim of the study was to describe the quality of life of the next of kin of patients diagnosed as having multiple sclerosis (MS). Forty-four next of kin were interviewed and thereafter answered the Subjective Quality of Life questionnaire. The next of kin's quality of life emerged as good in terms of both external conditions and interpersonal relationships in both the interviews and the Subjective Quality of Life. In the interviews, most of the next of kin indicated a trusting and secure relationship with the cohabiting partner, but others described a strained situation with an unsatisfactory married/cohabiting life. There was worry about a worsening of the relationship in the future. In addition, the next of kin spoke of a decrease in freedom, self-actualization, and security, also of a more negative general mood and negative emotional experiences. The results of the questionnaire showed that a sense of engagement in life, having energy, self-actualization, self-assuredness, self-acceptance, security, and general mood were significantly correlated with quality of life as a whole. The study confirms that MS is a disease affecting the whole family, and the next of kin were living in uncertainty, facing an unpredictable future. The nurses could start family support groups and help the next of kin to look after their own health, giving advice on health-promoting behavior to make it possible for the person with MS to live at home even if the illness becomes worse.
PMID: 21207771 [PubMed - indexed for MEDLINE]

144. J Nucl Med. 2011 Feb;52(2):257-62. Epub 2011 Jan 13.
11C-(R)-PK11195 PET Imaging of Microglial Activation and Response to Minocycline in Zymosan-Treated Rats.
Converse AK, Larsen EC, Engle JW, Barnhart TE, Nickles RJ, Duncan ID.
Waisman Center, University of Wisconsin-Madison, Madison, Wisconsin.
We sought to advance methodology for studying microglial activation and putative therapeutic downregulation in response to minocycline by means of noninvasive in vivo imaging. A reproducible focal white matter lesion was used to reliably compare treatment conditions.METHODS: The corpus callosum of female Sprague Dawley rats was injected with zymosan to promote microglial activation as confirmed by hematoxylin and eosin staining, (3)H-PK11195 autoradiography, and CD11b immunohistochemistry. A subset of subjects was treated systemically with minocycline to potentially alter microglial activation. Seven days after zymosan injection, subjects were imaged with PET using the radiotracer (11)C-(R)-PK11195. In vivo binding was evaluated using the distribution volume ratio (DVR) with respect to a reference region. RESULTS: At the lesion site, the observed (11)C-(R)-PK11195 DVR for each treatment was as follows: mean saline DVR ± SD, 1.17 ± 0.05 (n = 5); zymosan-only DVR, 1.96 ± 0.33 (n = 10); and zymosan with minocycline DVR, 1.58 ± 0.12 (n = 9). Therefore, compared with controls, zymosan increased binding (P = 0.0001, 2-tailed t test) and minocycline treatment reduced zymosan-induced binding by 46% (P = 0.004, 2-tailed t test). CONCLUSION: Zymosan-induced microglial activation and its response to minocycline can be quantitatively imaged in the rat brain using (11)C-(R)-PK11195 PET. The ability to detect a treatment effect in a focal white-matter lesion may be of use in studying therapies for multiple sclerosis (MS).
PMID: 21233178 [PubMed - in process]

145. J Radiol. 2010 Dec;91(12-C2):1387-1397.
[Spasticity: clinical and imaging features.]
[Article in French]
Mokhtari S, Hugeron C, Thibaut JB, Le Breton C, Mompoint D, Vallée C, Carlier R.
Service d'imagerie médicale du Pr Vallée, Hôpital Raymond Poincaré, 104 boulevard Raymond Poincaré, 92380 Garches, France.
Spasticity, a component of the pyramidal syndrome, characterized by increased tonic stretch reflexes and hyperactive deep tendon reflexes, occurs in patients with central nervous system lesions (stroke, brain or cord injury, multiple sclerosis, cerebral motor impairment). The implementation of standard procedures (patient positioning, increased examination time, turning off certain devices before MR imaging) allows the acquisition of high quality examinations in spastic patients. Worsening spasticity in a handicaped patients is due to an irritative process (deep seated infection, fracture, syrinx...) usually detectable with imaging. Ultrasound or CT guided injections of botulinum agents provides radiologists with the opportunity to further participate in the management of spastic patients.
PMID: 21242936 [PubMed - as supplied by publisher]

146. J Sex Med. 2011 Jan 6. doi: 10.1111/j.1743-6109.2010.02161.x. [Epub ahead of print]
Female Sexual Dysfunction and Hormonal Status in Multiple Sclerosis Patients.
Lombardi G, Celso M, Bartelli M, Cilotti A, Del Popolo G.
Careggi University, Hospital of Florence-Neuro-urology Spinal Unit Department, Florence, Italy University of Florence-Department of Neurological Sciences, Florence, Italy University of Florence-Andrology Unit, Department of Clinical Physiopathology, Florence, Italy.
Introduction. Literature holds no information on a correlation between blood hormonal levels, in particular sex hormones and the sexual response of women with multiple sclerosis (MS). Aim. To investigate a possible correlation between hormonal status and the sexual response of females with MS. Main Outcome Measures. The Female Sexual Function Index (FSFI) questionnaire was used to determine sexual dysfunctions (SDs). Methods for measuring blood hormones were chemiluminescence immunoassay, electrochemiluminescence immunoassay, enzyme immunoassay, and radioimmunoassay. Methods. During the screening phase, 55 women of reproductive age were recruited and completed the FSFI. In the first phase of the study females underwent a hematic hormonal evaluation on the third day of their menstrual cycle. Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), thyroid stimulating hormone (TSH), cortisol, dehydroepiandrosterone sulphate (DHEA-S), androstenedione, 17[alpha]-hydroxyprogesterone, total and free testosterone, 17 beta estradiol, inhibin and sex hormone binding globulin (SHBG), and thyroid hormones (fT3 and fT4) were checked. On the day 20-21 into their menstrual cycle the progesterone hematic value was noted. Patients with amenorrhea had all hormones tested once with a random blood drawing. After a 3-month period patients began phase 2, completing the FSFI again. The same blood hormones were investigated. Results. Fifty-four females completed the study. Thirty-one continued to manifest at least one SD: desire (57.4%) was the most common. Overall, 36.4% showed abnormal hormonal alterations. The most frequent was 40% for 17 beta-estradiol. None of the FSFI domains, including the total score, revealed any statistically significant correlation to the hormones investigated. No statistically significant clinical predictive factors for blood hormone abnormalities were detected; comparing females with and without SD, P = 0.250 using chi-squared test was reached. Conclusions. Notable percentages of blood hormonal alterations and SD were documented, but no significant statistical correlations were detected between hormonal status and sexual function. Lombardi G, Celso M, Bartelli M, Cilotti A, and Del Popolo G. Female sexual dysfunction and hormonal status in multiple sclerosis patients. J Sex Med **;**:**-**.
PMID: 21210956 [PubMed - as supplied by publisher]

147. Mayo Clin Proc. 2011 Jan;86(1):50-60.
Vitamin D insufficiency.
Thacher TD, Clarke BL.
Department of Family Medicine, Mayo Clinic, Rochester, MN 55905, USA. thacher.thomas@mayo.edu
Vitamin D deficiency, which classically manifests as bone disease (either rickets or osteomalacia), is characterized by impaired bone mineralization. More recently, the term vitamin D insufficiency has been used to describe low levels of serum 25-hydroxyvitamin D that may be associated with other disease outcomes. Reliance on a single cutoff value to define vitamin D deficiency or insufficiency is problematic because of the wide individual variability of the functional effects of vitamin D and interaction with calcium intakes. In adults, vitamin D supplementation reduces the risk of fractures and falls. The evidence for other purported beneficial effects of vitamin D is primarily based on observational studies. We selected studies with the strongest level of evidence for clinical decision making related to vitamin D and health outcomes from our personal libraries of the vitamin D literature and from a search of the PubMed database using the term vitamin D in combination with the following terms related to the potential nonskeletal benefits of vitamin D: mortality, cardiovascular, diabetes mellitus, cancer, multiple sclerosis, allergy, asthma, infection, depression, psychiatric, and pain. Conclusive demonstration of these benefits awaits the outcome of controlled clinical trials.
PMCID: PMC3012634 PMID: 21193656 [PubMed - in process]

148. Med Glas Ljek komore Zenicko-doboj kantona. 2011 Feb;8(1):56-60.
[Epidemiology of multiple sclerosis in Bosnia and Herzegovina.]
[Article in Bosnian]
Alajbegovic A, Alajbegovic S, Vranic JD.
Clinic of Neurology, Clinical Center of Sarajevo University[1], Cantonal Hospital Zenica[2]
In order to examine precipitating factors for occurrence of multiple sclerosis or inception of a relapse in patients suffering from multiple sclerosis a specially designed questionnaire was used, including history records of patients with multiple sclerosis treated at the Clinic of Neurology of the Clinical Center of Sarajevo in the period between January 1st and December 31st 2006. The number of patients with MS was 71 (48 women and 23 men). An infection as a precipitating factor was noted in 21 (29.57%) cases, stress was noted in 12 patients (16.9%) whereas 43 patients (60,12%) had the RR type of the disease. Nine patients were treated with interferon therapy (12.67%) and 47 patients (66.1%) with high doses of metilpredinisolone . Depression disorder was noted in 23 (32.9%) patients whereas 7 patients had cognitive dysfunction (9.86%). Results of this study, which have shown epidemiological characteristics of multiple sclerosis for the first time in Bosnia and Herzegovina, indicate that there is a need to create a unified register of patients and to request compliance with therapeutic guidelines.
PMID: 21263396 [PubMed - as supplied by publisher]

149. Med Image Anal. 2010 Dec 25. [Epub ahead of print]
Evaluating intensity normalization on MRIs of human brain with multiple sclerosis.
Shah M, Xiao Y, Subbanna N, Francis S, Arnold DL, Collins DL, Arbel T.
Centre for Intelligent Machines, McGill University, Montreal, Canada; NeuroRx Research, Montreal, Canada.
Intensity normalization is an important pre-processing step in the study and analysis of Magnetic Resonance Images (MRI) of human brains. As most parametric supervised automatic image segmentation and classification methods base their assumptions regarding the intensity distributions on a standardized intensity range, intensity normalization takes on a very significant role. One of the fast and accurate approaches proposed for intensity normalization is that of Nyul and colleagues. In this work, we present, for the first time, an extensive validation of this approach in real clinical domain where even after intensity inhomogeneity correction that accounts for scanner-specific artifacts, the MRI volumes can be affected from variations such as data heterogeneity resulting from multi-site multi-scanner acquisitions, the presence of multiple sclerosis (MS) lesions and the stage of disease progression in the brain. Using the distributional divergence criteria, we evaluate the effectiveness of the normalization in rendering, under the distributional assumptions of segmentation approaches, intensities that are more homogenous for the same tissue type while simultaneously resulting in better tissue type separation. We also demonstrate the advantage of the decile based piece-wise linear approach on the task of MS lesion segmentation against a linear normalization approach over three image segmentation algorithms: a standard Bayesian classifier, an outlier detection based approach and a Bayesian classifier with Markov Random Field (MRF) based post-processing. Finally, to demonstrate the independence of the effectiveness of normalization from the complexity of segmentation algorithm, we evaluate the Nyul method against the linear normalization on Bayesian algorithms of increasing complexity including a standard Bayesian classifier with Maximum Likelihood parameter estimation and a Bayesian classifier with integrated data priors, in addition to the above Bayesian classifier with MRF based post-processing to smooth the posteriors. In all relevant cases, the observed results are verified for statistical relevance using significance tests.
PMID: 21233004 [PubMed - as supplied by publisher]

150. Mol Med. 2011 Jan 4. [Epub ahead of print]
Novel aspects of fibrin(ogen) fragments in the course of inflammation.
Jennewein C, Tran N, Paulus P, Ellinghaus P, Eble JA, Zacharowski K.
Clinic of Anesthesiology, Intensive Care Medicine and Pain Therapy, Goethe-University Hospital Frankfurt, Frankfurt am Main, Germany.
Coagulation is a constant attendant of inflammation and is fundamental for the confinement of infection and/or the inflammatory response to a limited area. Under pathological inflammatory conditions such as arthritis, multiple sclerosis or sepsis an uncontrolled activation of the coagulation system contributes to inflammation, microvascular failure and organ dysfunction. Coagulation is initiated by the activation of thrombin which in turn by the release of fibrinopeptides, triggers fibrin formation. Fibrin is cleaved by plasmin resulting in clot lysis and accompanied generation of fibrin fragments such as D and E fragments. Various coagulation factors including fibrin(ogen) and also fibrin degradation products modulate the inflammatory response by affecting leukocyte migration and cytokine production. Fibrin fragments are mostly pro-inflammatory, however, Bβ15-42 in particular possesses potential anti-inflammatory effects. Bβ15-42 inhibits Rho kinase activation by dissociating Fyn from Rho and, hence prevents stress-induced loss of endothelial barrier function and also leukocyte migration. This article summarizes state of the art of inflammatory modulation by fibrin(ogen) and fibrin fragments. However, further research is required to gain better understanding of the entire role, fibrin fragments play during inflammation and possibly disease development.
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151. Mol Neurobiol. 2011 Jan 28. [Epub ahead of print]
Evolution of the VEGF-Regulated Vascular Network from a Neural Guidance System.
Ponnambalam S, Alberghina M.
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The vascular network is closely linked to the neural system, and an interdependence is displayed in healthy and in pathophysiological responses. How has close apposition of two such functionally different systems occurred? Here, we present a hypothesis for the evolution of the vascular network from an ancestral neural guidance system. Biological cornerstones of this hypothesis are the vascular endothelial growth factor (VEGF) protein family and cognate receptors. The primary sequences of such proteins are conserved from invertebrates, such as worms and flies that lack discernible vascular systems compared to mammals, but all these systems have sophisticated neuronal wiring involving such molecules. Ancestral VEGFs and receptors (VEGFRs) could have been used to develop and maintain the nervous system in primitive eukaryotes. During evolution, the demands of increased morphological complexity required systems for transporting molecules and cells, i.e., biological conductive tubes. We propose that the VEGF-VEGFR axis was subverted by evolution to mediate the formation of biological tubes necessary for transport of fluids, e.g., blood. Increasingly, there is evidence that aberrant VEGF-mediated responses are also linked to neuronal dysfunctions ranging from motor neuron disease, stroke, Parkinson's disease, Alzheimer's disease, ischemic brain disease, epilepsy, multiple sclerosis, and neuronal repair after injury, as well as common vascular diseases (e.g., retinal disease). Manipulation and correction of the VEGF response in different neural tissues could be an effective strategy to treat different neurological diseases.
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152. Mult Scler. 2011 Jan 6. [Epub ahead of print]
Staphylococcus aureus harbouring Enterotoxin A as a possible risk factor for multiple sclerosis exacerbations.
Mulvey MR, Doupe M, Prout M, Leong C, Hizon R, Grossberndt A, Klowak M, Gupta A, Melanson M, Gomori A, Esfahani F, Klassen L, Frost EE, Namaka M.
National Microbiology Laboratory, Antimicrobial Resistance & Nosocomial Infections/Dept. of Medical Microbiology & Infectious Diseases, Uni. of Manitoba, Canada.
Background: Staphylococcus aureus may produce superantigens that can non-specifically activate CD4(+) cells to potentially target the myelin basic protein. Objective: This study examined the association between individuals with multiple sclerosis (MS) and colonization with S. aureus harbouring superantigens. Methods: Nasal swabs were collected from non-MS subjects and patients with MS who had not experienced a relapse in the past six months (MS stable group) and who had suffered a relapse within 30 days of study recruitment (MS exacerbation group). S. aureus was isolated from the anterior nares of participants following standard procedures and staphylococcal superantigen genes (sea, seb, and tsst-1) were detected using standard laboratory PCR techniques. Results: The study enrolled 204 patients, 80 in the non-MS and MS stable groups and 44 patients in the MS exacerbation group. Overall, 27.0% of patients were colonized with S. aureus with no significant differences identified between study groups. Amongst individuals colonized with S. aureus, the prevalence of sea was significantly greater in the MS exacerbation versus non-MS study group ($p < 0.05$; odds ratio 7.9; 95% confidence interval 1.2-49.5). Conclusions: The ability to rapidly screen patients for the presence of S. aureus producing sea may serve as a useful marker of a potential MS exacerbation.
PMID: 21212089 [PubMed - as supplied by publisher]

153. Mult Scler. 2011 Jan 6. [Epub ahead of print]
Temporal relationship between environmental Influenza A and Epstein-Barr viral infections and high multiple sclerosis relapse occurrence.
Oikonen M, Laaksonen M, Aalto V, Ilonen J, Salonen R, Erälinna JP, Panelius M, Salmi A.
University of Turku, Finland.
Background: Multiple sclerosis (MS) relapses have been associated with viral and bacterial infection epidemics in MS patients who have not used interferon. Objectives: We studied whether environmental viral infections in the general population can be associated with increased MS relapse occurrence using retrospective data from 1986 to 1995 when interferons were not yet available. Methods: Logistic regression modelling was used to compare retrospectively the monthly relapse occurrence from 407 MS patients in Turku University hospital archives and data on ten different specifically diagnosed viral infection epidemics in the general population of Southwestern Finland from 1986 to 1995. The outcome was the odds ratio (OR) of very high relapse occurrence versus low relapse occurrence, or moderate versus low relapse occurrence. Results: After a peak in diagnosed influenza A cases in the general population, the MS relapse occurrence was 6.5 times more likely to be very high (95% CI 1.8-24.0) and 7.1 times more likely to be moderately high (95% CI 1.5-33.2). An increase in MS relapse counts also followed Epstein-Barr virus (EBV) infections (OR 4.4, 95% CI 1.3-15.1), but we found no significant association with adenovirus infections and MS relapses. The MS relapse occurrence was lowest in the summer months July-August (Chi-square test, $p < 0.01$). Conclusions: Our findings suggest that influenza A and EBV viral infections in the general population are associated with a higher occurrence of exacerbations in MS patients, and thus environmental infection data should be included in epidemiological models on MS relapses.
PMID: 21212088 [PubMed - as supplied by publisher]

154. Mult Scler. 2011 Jan 6. [Epub ahead of print]
Towards molecular imaging of multiple sclerosis.
Owen DR, Piccini P, Matthews PM.
Division of Experimental Medicine, Imperial College, Hammersmith Hospital/GSK Clinical Imaging Centre, Hammersmith Hospital, London, UK.
Magnetic resonance imaging (MRI) has had a profound impact on both research and clinical management of multiple sclerosis (MS), but signal changes reflect underlying neuropathology only indirectly and often non-specifically. Positron emission tomography (PET) offers the potential to complement MRI with quantitative measures of molecularly specific markers of cellular and metabolic processes. PET radiotracers already available promise new insights into the dynamics of the innate immune response, neuronal function, neurodegeneration and remyelination. Because PET is an exquisitely sensitive technique (able to image even picomolar concentrations), only microdoses of radioligand (<10 µg) are needed for imaging. This facilitates rapid implementation of novel radioligands because extensive toxicology data is not required. In the future, molecular imaging could assist clinical decision-making with patient stratification for optimization of treatment selection.
PMID: 21212087 [PubMed - as supplied by publisher]

155. Mult Scler. 2011 Jan 6. [Epub ahead of print]
Vitamin D status and antibody levels to common viruses in pediatric-onset multiple sclerosis.
Mowry EM, James JA, Krupp LB, Waubant E.
MS Center, Department of Neurology, University of California, San Francisco, CA, USA.
Background: The relative contribution and interaction of risk factors for multiple sclerosis (MS) have not been evaluated. Objectives: To determine whether vitamin D status is associated with antibody levels to common viruses in pediatric-onset MS or clinically isolated syndrome (CIS) patients and controls. Methods: We assessed whether vitamin D status was associated with viral antibody levels to Epstein-Barr virus, cytomegalovirus (CMV), and herpes simplex virus (HSV)-1 or -2 in subjects who demonstrated evidence of remote infection with these viruses and whether these associations differed depending on disease status. Results: In 140 subjects, vitamin D status was weakly associated with antibody levels to CMV but not to the other viruses. However, there were some interactions between vitamin D status and disease state. Among those with vitamin D sufficiency (≥30 ng/ml), MS/CIS patients had higher antibody levels to Epstein-Barr nuclear antigen-1 than controls. Vitamin D sufficiency was associated with higher CMV antibody levels in MS/CIS subjects but lower CMV antibody levels in controls. Higher vitamin D levels appeared to be associated with higher titers to HSV-2 in MS/CIS patients but not controls. Conclusions: Vitamin D status may be differentially associated with antibody levels to common childhood viruses among seropositive subjects.
PMID: 21212086 [PubMed - as supplied by publisher]

156. Mult Scler. 2011 Jan 27. [Epub ahead of print]
Trend for decreasing Multiple Sclerosis Severity Scores (MSSS) with increasing calendar year of enrollment into the New York State Multiple Sclerosis Consortium.
Kister I, Chamot E, Bacon JH, Cutter G, Herbert J; on behalf of the New York State Multiple Sclerosis Consortium.
Multiple Sclerosis Care Center, Department of Neurology, NYU School of Medicine, USA.
Background: Although the natural history of multiple sclerosis has been charted extensively, it is still not known whether the trajectory of disability accumulation has changed in the era of disease-modifying therapies (DMTs). Objective: The objective of this study was to examine trends in Multiple Sclerosis Severity Score (MSSS) with regard to calendar year of enrollment into the New York State MS Consortium (NYSMSC). Methods: Distributions of MSSS were calculated for each year of enrollment, from 1996 to 2007. Quantile regression was used in a multivariable analysis to model for conditional distribution of MSSS quantiles as functions of potential confounders. Results: The cohort consisted of 6238 patients. Mean age at enrollment was 38 years (SD = 10) and mean disease duration was 10.1 years (SD = 7.3); 57% were on DMTs. The quantile regression model of trends in MSSS between 1996 and 2007 controlled for age, sex, ethnicity, diagnostic delay, and disease duration and demonstrated a robust trend toward lower MSSS with increasing year of enrollment. The model-predicted median MSSS at enrollment in 1996 was 5.04 (95% CI, 4.86-5.21), and in 2007 was 3.78 (95%CI, 3.36-4.20; $p < 0.001$). The downward trend in MSSS during the enrollment period was confirmed by analysis of Expanded Disability Status Scale (EDSS) distributions, adjusted for disease duration, in successive years of enrollment. Conclusions: The recent enrollees into the NYSMSC had lower MSSSs compared to the earlier enrollees. The apparent slowing in disability accumulation is likely due to a complex combination of factors: advent of DMTs and improvements in MS care, as well as selection, migration, and recall biases.
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157. Mult Scler. 2011 Jan 26. [Epub ahead of print]

Texture analysis differentiates persistent and transient T1 black holes at acute onset in multiple sclerosis: A preliminary study.

Zhang Y, Traboulsee A, Zhao Y, Metz LM, Li DK.
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Background and Objective: The persistence of new enhancing T1 hypointense lesions (acute black holes, ABHs) in multiple sclerosis (MS) cannot be predicted visually at lesion onset. Texture analysis using the polar Stockwell transform (PST) applied to conventional MR images however shows promise in quantifying tissue injury early. The objective of this study was to explore whether ABHs that persist (pABHs) differ from those that are transient (tABHs) using PST texture analysis. Methods: Fifteen ABHs (8 pABHs; 7 tABHs) from 9 patients were analyzed on 3T images obtained during a clinical trial. Persistence was defined as remaining T1 hypointense 5-8 months later. NAWM regions were examined to control for changes unrelated to ABHs. Results: At first appearance, there was higher coarse texture indicating greater tissue damage in the pABHs than in the tABHs ($p < 0.01$). Both had greater coarse texture than the contralateral and general NAWM ($p \leq 0.01$). No difference was identified in normalized signal intensity between pABHs and tABHs and neither demonstrated location preference. While tABHs tended to be smaller than pABHs there was no correlation between lesion size and texture ($r = 0.44$, $p > 0.05$). Furthermore, coarse texture content appeared to predict persistence of individual lesions. Conclusions: This preliminary study suggests that PST texture could predict persistence of tissue injury based on the severity of structural disorganization within acute lesions. While confirmation of this data is required texture analysis may prove to be a valuable tool to quantify tissue damage and predict recovery in proof-of-concept neuroprotection and repair trials.

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158. Mult Scler. 2011 Jan 19. [Epub ahead of print]

Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities.

Collett J, Dawes H, Meaney A, Sackley C, Barker K, Wade D, Izardi H, Bateman J, Duda J, Buckingham E.
Movement Science Group, School of Life Sciences, Oxford Brookes University, UK.

Background: The most effective exercise dose has yet to be established for multiple sclerosis (MS). Objective: The aim of this study was to investigate the effect of different exercise intensities in people with MS. Methods: We completed a randomized comparator study of three cycling exercise intensities, with blinded assessment, was carried out in Oxford. Sixty-one adults with MS who fulfilled inclusion criteria were randomized at entry into the study, using a computer-generated list held by an exercise professional, into either: continuous (at 45% peak power, n = 20), intermittent (30 sec on, 30 sec off at 90% peak power, n = 21) or combined (10 min intermittent at 90% peak power then 10 min continuous at 45% peak power, n = 20) exercise for 20 min twice a week for 12 weeks in a leisure facility. Groups were assessed at: baseline, halfway (6 weeks), end intervention (12 weeks) and follow-up (24 weeks). Primary outcome measure was 2 min walk. Results: Fifty-five participants were included in the analysis (n = continuous 20, intermittent 18, combined 17). No differences were found between groups. After 6 weeks, considering all participants, 2 min walk distance increased by 6.96 ± 2.56 m (95% CI: 1.81 to 12.10, effect size (es): 0.25, $p < 0.01$). The continuous group increased by 4.71 ± 4.24 m (95% CI: -3.80 to 13.22, es: 0.06), intermittent by 12.94 ± 4.71 m (95% CI: 3.97 to 21.92, es: 0.28) and combined by 3.22 ± 4.60 m (95% CI: -6.01 to 12.46, es: 0.04). Two minute walk did not significantly change between further assessments. Between 6 and 12 weeks there was a drop in attendance that seemed to be associated with the intermittent and combined groups; these groups also had a greater number of adverse events (leg pain during cycling most common) and dropouts (n = continuous 1, intermittent 5, combined 10). Considering all participants, 6 weeks of cycling exercise produced benefits in mobility that were maintained with further sessions. Conclusion: While no differences were found between groups, greater benefit may be associated with higher-intensity exercise, but this may be less well tolerated.CONSORT - trial registration number (ISRCTN89009719).

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159. Mult Scler. 2011 Jan 14. [Epub ahead of print]
Distributed changes in default-mode resting-state connectivity in multiple sclerosis.
Bonavita S, Gallo A, Sacco R, Della Corte M, Bisecco A, Docimo R, Lavorgna L, Corbo D, Di Costanzo A, Tortora F, Cirillo M, Esposito F, Tedeschi G.
Dept of Neurological Sciences, Second Uni. of Naples/Neurological Institute for Diagnosis and Care "Hermitage Capodimonte", Naples, Italy.
Background: The default-mode network (DMN) has been increasingly recognized as relevant to cognitive status. Objectives: To explore DMN changes in patients with relapsing-remitting (RR) multiple sclerosis (MS) and to relate these to the cognitive status. Methods: Eighteen cognitively impaired (CI) and eighteen cognitively preserved (CP) RRMS patients and eighteen healthy controls (HCs), matched for age, sex and education, underwent neuropsychological evaluation and anatomical and resting-state functional MRI (rs-fMRI). DMN functional connectivity was evaluated from rs-fMRI data via independent component analysis. T2 lesion load (LL) was computed by a semi-automatic method and global and local atrophy was estimated by SIENAX and SPM8 voxel-based morphometry analyses from 3D-T1 images. Results: When the whole group of RRMS patients was compared with HCs, DMN connectivity was significantly weaker in the anterior cingulate cortex, whereas it was significantly weaker in the core but stronger at the periphery of the posterior cingulate cortex. These findings were more evident in CP than CI patients. Observed DMN changes did not correlate with global atrophy or T2-LL, but were locally associated with regional grey matter loss. Conclusion: Relapsing-remitting multiple sclerosis patients show a consistent dysfunction of DMN at the level of the anterior node. DMN distribution changes in the posterior node may reflect a possible compensatory effect on cognitive performance.
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160. Mult Scler. 2011 Jan 14. [Epub ahead of print]
Association of IL2RA polymorphisms with susceptibility to multiple sclerosis is not explained by missense mutations in IL2RA.
Matiello M, Weinshenker BG, Atkinson EJ, Schaefer-Klein J, Kantarci OH.
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Genome-wide association studies have identified an association between two intronic single nucleotide polymorphisms (SNPs), rs12722489 and rs2104286, in the interleukin-2 receptor alpha-chain gene (IL2RA) and susceptibility to multiple sclerosis (MS). We studied these SNPs in association with susceptibility to and severity of MS in a population-based cohort of 220 patients from Olmsted County, Minnesota, compared with 442 matched controls. We sequenced the exons, splice sites and 5' and 3' untranslated regions in 27 randomly selected MS patients (powered for allele frequency ≥0.04) to search for mutations. No novel missense mutation was identified. Two patients (7.5%) had an exon 2 SNP (rs4308625) and two patients had an exon 4 SNP (rs2228149), both synonymous.
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161. Mult Scler. 2011 Jan 12. [Epub ahead of print]
Safety and tolerability of cladribine tablets in multiple sclerosis: the CLARITY (CLAdRIbine Tablets treating multiple sclerosis orallY) study.
Cook S, Vermersch P, Comi G, Giovannoni G, Rammohan K, Rieckmann P, Sørensen PS, Hamlett A, Miret M, Weiner J, Viglietta V, Musch B, Greenberg S.
University of Medicine and Dentistry, New Jersey Medical School, Newark, NJ, USA.
Background: Cladribine is a synthetic deoxyadenosine analogue in development as an oral multiple sclerosis (MS) therapy. Objective: To report in detail the safety findings from the 96-week, phase III, double-blind CLARITY study, which evaluated treatment with cladribine tablets in relapsing-remitting MS. Methods: A total of 1,326 patients were randomized 1 : 1 : 1 to two short-course regimens of cladribine tablets (3.5 or 5.25 mg/kg cumulative dose over 96 weeks) or placebo. Safety assessments included monitoring for adverse events (AEs), routine physical and neurologic examinations and frequent laboratory parameter assessments. Results: Of the randomized patients, 88.6% completed treatment with cladribine tablets versus 86.3% with placebo. Lymphopenia was the most commonly reported AE in patients treated with cladribine tablets and was anticipated based on the mechanism of action. The incidence of infections was 48.3% with cladribine tablets and 42.5% with placebo, with 99.1% and 99.0% rated mild-to-moderate by investigators. Herpes zoster infections developed in 20 (2.3%) cladribine-treated patients; all cases were dermatomal. There were no herpes zoster infections in the placebo group. Nine (1.0%) patients experienced events related to uterine leiomyomas in the cladribine tablets groups versus one (0.2%) with placebo. Three isolated cases of malignancy were reported in cladribine-treated patients during the study; a fourth was reported during post-study surveillance. A pre-malignant cervical carcinoma in situ was also reported. The incidence of malignancies during the study did not exceed the expected rate in a population standardized for country, gender and age. Conclusion: The safety and tolerability profile observed in the CLARITY study together with the reported efficacy support the potential for cladribine tablets as an MS therapy.
PMID: 21228029 [PubMed - as supplied by publisher]

162. Mult Scler. 2011 Jan 12. [Epub ahead of print]
Predicting the severity of relapsing-remitting MS: The contribution of cross-sectional and short-term follow-up MRI data.
Enzinger C, Fuchs S, Pichler A, Wallner-Blazek M, Khalil M, Langkammer C, Ropele S, Fazekas F.
Department of Neurology, Medical University of Graz/ Division of Neuroradiology, Department of Radiology, Medical University of Graz, Graz, Austria.
Background and objective: Predicting the long-term clinical course of multiple sclerosis (MS) is difficult on clinical grounds. Recent studies have suggested magnetic resonance imaging (MRI) metrics to be helpful. We wanted to confirm this. Methods: Contactable individuals (N = 84) from an initial 99 patients with relapsing-remitting MS (RRMS) who had undergone careful baseline and 2-year follow-up examinations including MRI were reassessed after a mean of 10.8 ± 2.7 years. We investigated using multivariate linear regression analyses if clinical and MRI data obtained at the prior time-points and the rates of change in morphologic variables over a mean observational period of 2.5 years could have served to predict a patient's MS severity score (MSSS) 11 years later. Conversion to secondary progressive MS (SPMS) was a further outcome variable. Results: In univariate analyses, the 'black hole ratio' (BHR) at baseline ($p = 0.017$, beta = 0.148) and at first follow-up ($p = 0.007$, beta = -0.154) was the only MRI parameter showing a significant correlation with the MSSS. In a multiple regression model, the independent predictive value of imaging variables became statistically non-significant and the latest MSSS was predicted primarily by the baseline EDSS ($r (2)= 0.28$; $p < 0.001$). The BHR at baseline explained 9.4% of variance of conversion to SPMS ($p = 0.033$). Over the observational period the MSSS remained stable in patients remaining RRMS, but increased in converters to SPMS from 4.0 to 6.4. Conclusions: We failed to confirm a clear independent contribution of cross-sectional and short-term follow-up MRI data for the prediction of the long-term clinical course of MS. The MSSS is not a stable indicator of disease severity but may increase in converters to SPMS.
PMID: 21228028 [PubMed - as supplied by publisher]

163. Mult Scler. 2011 Jan 12. [Epub ahead of print]
A Swedish national post-marketing surveillance study of natalizumab treatment in multiple sclerosis.
Holmén C, Piehl F, Hillert J, Fogdell-Hahn A, Lundkvist M, Karlberg E, Nilsson P, Dahle C, Feltelius N, Svenningsson A, Lycke J, Olsson T.
Karolinska Institutet, Department of Clinical Neuroscience, Stockholm, Sweden.
Background: A post marketing surveillance study was conducted to evaluate safety and efficacy of natalizumab in Swedish multiple sclerosis (MS) patients since its introduction in August 2006 until March 2010. Methods: Patients were registered in the web-based Swedish MS-registry at 40 locations and evaluated every 6 months. Adverse events and clinical outcomes were recorded. Results: One thousand one hundred and fifty-two patients were included (71.4% female) and 149 patients stopped treatment; the main reason was planned pregnancy. Anti-natalizumab antibodies were found in 4.5% (52 patients) of which 1.6% displayed persistent antibodies. Serious adverse events were rare, but included three cases with progressive multifocal leukoencephalopathy (PML). There were seven fatal cases, probably unrelated to the natalizumab treatment. For relapsing-remitting MS patients (n = 901), mean Expanded Disability Status Scale (EDSS, -10.7%), Multiple Sclerosis Severity Scale (MSSS, -20.4%), Multiple Sclerosis Impact Scale (MSIS-29, physical -9.9%, psychological -13.3%) and Symbol Digit Modalities Test (SDMT, +10.7%) all showed significant improvements during 24 months of treatment with natalizumab. The Swedish web-based MS quality registry proved to function as a platform for post-marketing MS drug surveillance, providing long-term data regarding drug effects and adverse events beyond clinical trials. Conclusions: Our results indicate that natalizumab is generally well tolerated and has sustained efficacy for patients with active MS, though the risk of PML is still an important concern.
PMID: 21228027 [PubMed - as supplied by publisher]

164. Mult Scler. 2011 Jan 12. [Epub ahead of print]
Intracranial venous pressure is normal in patients with multiple sclerosis.
Meyer-Schwickerath R, Haug C, Hacker A, Fink F, Seidel D, Hartung HP, Haupts MR.
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Chronic cerebrospinal venous insufficiency (CCSVI) has been postulated as a cause for multiple sclerosis (MS). Venous pressure assessments have not been made. Intracranial venous pressure was assessed using ophthalmodynamometry in 29 MS patients and compared with 28 healthy controls and 19 cases with elevated intracranial pressure (ICP). MS and control subjects had normal venous pressures (mean 15.5 resp. 15.1 cmHg). Only cases with intracranial pressure pathology had elevated venous pressures (mean 28.8 cmHg). There is no evidence of an increased intracranial venous pressure in MS patients.
PMID: 21228026 [PubMed - as supplied by publisher]

165. Mult Scler. 2011 Jan 12. [Epub ahead of print]
Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis.
Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F, Perini P, Gallo P.
The Multiple Sclerosis Centre of the Veneto Region, Department of Neurology, University Hospital of Padova, Padova, Italy.
Objective: To measure the effects of disease-modifying drugs (DMDs) on the development of cortical lesions (CL) and cortical atrophy in patients with relapsing-remitting multiple sclerosis (RRMS). Methods: RRMS patients (n = 165) were randomized to subcutaneous (sc) interferon (IFN) beta-1a (44 mcg three times weekly), intramuscular (im) IFN beta-1a (30 mcg weekly) or glatiramer acetate (GA; 20 mg daily). The reference population comprised 50 untreated patients. Clinical and MRI examinations were performed at baseline, 12 months and 24 months. Results: One hundred and forty-one treated patients completed the study. After 12 months, 37/50 (74%) of untreated patients developed ≥1 new CL (mean 1.6), compared with 30/47 (64%) of im IFN beta-1a-treated patients (mean 1.2, p = 0.021), 24/48 (50%) of GA-treated patients (mean 0.8, p = 0.001) and 12/46 (26%) of sc IFN beta-1a-treated patients (mean 0.4, p < 0.001). After 24 months, ≥1 new CL was observed in 41/50 (82%) of untreated (mean 3.0), 34/47 (72%) of im IFN beta-1a-treated (mean 1.6, p < 0.001), 30/48 (62%) of GA-treated (mean 1.3, p < 0.001) and 24/46 (52%) of sc IFN beta-1a-treated patients (mean 0.8, p < 0.001). Mean grey matter fraction decrease in DMD-treated patients at 24 months ranged from 0.7 to 0.8 versus 1.0 in untreated patients (p = 0.023). Conclusions: Disease-modifying drugs significantly decreased new CL development and cortical atrophy progression compared with untreated patients, with faster and more pronounced effects seen with sc IFN beta-1a than with im IFN beta-1a or GA.
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166. Mult Scler. 2011 Jan 12. [Epub ahead of print]
Deep grey matter T2 hypo-intensity in patients with paediatric multiple sclerosis.
Ceccarelli A, Rocca MA, Perego E, Moiola L, Ghezzi A, Martinelli V, Comi G, Filippi M.
Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, Scientific Institute/University Ospedale San Raffaele, Milan Italy.
Objective: T2 hypo-intensity on magnetic resonance imaging scans is thought to reflect pathological iron deposition in the presence of disease. In this pilot study, we evaluated the utility of the quantification of T2 hypo-intensities in paediatric patients by estimating deep grey matter (DGM) T2 hypo-intensities in paediatric patients with multiple sclerosis (MS) or clinically isolated syndromes (CIS), and their changes over 1 year. Methods: A dual-echo sequence was obtained from 45 paediatric patients (10 with CIS, 35 with relapsing-remitting MS, 8 with an onset of the disease before the age of 10 and 37 during adolescence) and 14 age-matched healthy controls (HC). Eleven patients were reassessed both clinically and with MRI after 1 year. Normalized T2 intensity in the basal ganglia and thalamus was quantified. Results: At baseline, DGM T2 intensity was similar between paediatric patients and HC in all the structures analysed, except for the head of the left caudate nucleus ($p = 0.001$). DGM T2 intensity of the head of the left caudate nucleus was similar between paediatric CIS and RRMS patients, but it was reduced in adolescent-onset paediatric patients versus HC ($p = 0.002$). In all patients, DGM T2 intensity of the head of the left caudate nucleus was correlated with T2 lesion volume ($r = -0.39$, $p = 0.007$). DGM T2 intensity in all the structures analysed with longitudinal assessment remained stable over the follow-up in the cohort of patients. Conclusions: The quantification of DGM T2 intensity in paediatric patients may provide surrogate markers of neurodegeneration. In paediatric MS, DGM is likely to be affected by iron-related changes, which are likely to be, at least partially, secondary to WM damage.
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167. Mult Scler. 2011 Jan 10. [Epub ahead of print]
Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a Therapy.
Sandberg-Wollheim M, Alteri E, Stam Moraga M, Kornmann G.
Department of Neurology, University Hospital, Lund, Sweden.
Background: Women with multiple sclerosis (MS) are advised to discontinue interferon-beta therapy before trying to conceive. Unplanned pregnancies occur and risks related to exposure remain unclear. Methods: To determine pregnancy outcomes following interferon-beta therapy, we examined pregnancies from a global drug safety database containing individual case safety reports received in the post-marketing setting and safety data from clinical trials of subcutaneous interferon beta-1a in MS. Results: One thousand and twenty-two cases of exposure to subcutaneous interferon beta-1a during pregnancy were retrieved; 679 had a documented outcome. In cases for which exposure duration was available (n = 231), mean time of foetal exposure to subcutaneous interferon beta-1a before treatment discontinuation was 28 days; most pregnancies (199/231; 86.1%) were exposed for ≤45 days. To avoid bias, only outcomes for prospective data (n = 425) in pregnancies exposed to interferon beta-1a in utero were analysed further. Of these, 324 (76.2%) resulted in normal live births and four (0.9%) in live births with congenital anomalies (3 [0.7%] were 'major'). Four (0.9%) pregnancies resulted in stillbirths (1 [0.2%] with foetal defects). There were 5 (1.2%) ectopic pregnancies, 49 (11.5%) spontaneous abortions and 39 (9.2%) elective terminations. Most pregnancies exposed to subcutaneous interferon beta-1a in utero were associated with normal live births. The rates of spontaneous abortion and major congenital anomalies in live births were in line with those observed in the general population. Conclusions: These data should be taken into account when considering options for women with MS who become pregnant or who are planning pregnancy while on treatment with subcutaneous interferon beta-1a.
PMID: 21220368 [PubMed - as supplied by publisher]

168. Nat Rev Neurol. 2011 Jan 25. [Epub ahead of print]
Monoclonal antibody therapy-associated neurological disorders.
Bosch X, Saiz A, Ramos-Casals M; the BIOGEAS Study Group.
Department of Internal Medicine, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, University of Barcelona, Villarroel 170, 08036-Barcelona, Spain.
Several neurological disorders have been associated with the use of monoclonal antibodies (mAbs), especially those targeting tumor necrosis factor (TNF) and its receptors. These disorders include, among others, multiple sclerosis, optic neuritis, and various forms of peripheral demyelinating neuropathy. Progressive multifocal leukoencephalopathy, the natural course of which is lethal within months, has been mainly associated with the anti-α4-integrin mAb natalizumab and, to a lesser extent, with rituximab, alemtuzumab and efalizumab. The prevalence of demyelinating disease induced by biological therapies, as reported in randomized controlled trials and postmarketing studies, has been estimated to range from 0.02-0.20%. Peripheral neuropathies can occur early or late after initiation of therapy. Short-term follow-up indicates relatively good outcomes, sometimes after mAb discontinuation alone, although corticosteroids or intravenous immunoglobulin may be necessary to reverse and stabilize the condition. Definitive cessation of the biological therapy should be discussed on a case-by-case basis. Prospective postmarketing studies in which the control group includes patients with rheumatic autoimmune diseases-most notably rheumatoid arthritis-treated with conventional therapies could help us to evaluate the real risks and outcomes in patients receiving mAbs who develop neurological diseases.
PMID: 21263460 [PubMed - as supplied by publisher]

169. Nat Rev Neurol. 2011 Jan 11. [Epub ahead of print]
Therapies for multiple sclerosis: considerations in the pediatric patient. Banwell B, Bar-Or A, Giovannoni G, Dale RC, Tardieu M.
Department of Pediatrics, Division of Neurology, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, ON M5G 1X8, Canada.
Current and emerging therapies for multiple sclerosis (MS) offer promise for improved disease control and long-term clinical outcome. To date, these therapies have been evaluated solely in the context of adult MS. However, onset of MS in children is being increasingly recognized, and recent studies have identified a significant impact of MS onset during childhood on cognitive and physical functioning. Optimization of pediatric MS care requires that promising new therapies be made available to children and adolescents, but also that safety and tolerability and potential influence of therapies on the developing immune and neural networks of pediatric patients be closely considered. We propose care algorithms illustrating models for therapy that detail careful monitoring of pediatric patients with MS, provide definitions for inadequate treatment response and treatment escalation, and foster multinational collaboration in future therapeutic trials.
PMID: 21224883 [PubMed - as supplied by publisher]

170. Nervenarzt. 2011 Jan 16. [Epub ahead of print]
[Progressive multifocal leukoencephalopathy under natalizumab : Initial possibilities for risk stratification?]
[Article in German]
Warnke C, Adams O, Gold R, Hartung HP, Hohlfeld R, Wiendl H, Kieseier BC.
Neurologische Klinik, Heinrich-Heine-Universität, Moorenstr. 5, 40225, Düsseldorf, Deutschland.
Natalizumab (Tysabri®) is the first monoclonal antibody approved for the treatment of relapsing forms of multiple sclerosis (MS) but while treatment is highly efficient, it carries the risk of progressive multifocal leukoencephalopathy (PML). Based on reports of confirmed cases of PML, the risk of PML might increase beyond 24 months of treatment. Thus, attempts to stratify patients treated with natalizumab into those carrying higher or lower risk for developing PML are currently being undertaken. Among these strategies JC virus serology might potentially be the first tool available. As a large variety of methods have been published resulting in controversial results for JC virus seroprevalence, standardized testing will be mandatory when applying this method in clinical practice. In addition, risk management strategies for the seropositive majority of patients need to be redefined and optimized further.
PMID: 21240604 [PubMed - as supplied by publisher]

171. Neurochem Res. 2011 Jan 5. [Epub ahead of print]

Structure-Dependent Inhibition of Gelatinases by Dietary Antioxidants in Rat Astrocytes and Sera of Multiple Sclerosis Patients.

Liuzzi GM, Latronico T, Branà MT, Gramegna P, Coniglio MG, Rossano R, Larocca M, Riccio P.
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We investigated whether polyphenols modulate the expression and activity of the enzymes gelatinases A (MMP-2) and B (MMP-9), involved in the pathogenesis of multiple sclerosis (MS). LPS-activated primary rat astrocytes were treated with the flavonoids quercetin (QRC) and cathechins [green tea extract (GTE)] and the non-flavonoids resveratrol (RSV) and tyrosol/hydroxytyrosol (Oliplus). As assessed by zymography and RT-PCR, RSV and Oliplus, but not QRC and GTE, dose-dependently inhibited the LPS-induced levels and mRNA expression of MMP-2 and MMP-9. By contrast, in cell-free systems direct inhibition of gelatinase activity in MS sera was determined by QRC and GTE, but not by RSV. Oliplus was only partially effective. Our results indicate that the flavonoids and non-flavonoids tested exert their inhibitory effect on MMPs, displaying different mechanisms of action, possibly related to their structure. Therefore, their combined use may represent a powerful tool for the down-regulation of MMPs in the course of MS.

PMID: 21207142 [PubMed - as supplied by publisher]

172. Neurogenetics. 2011 Feb;12(1):65-72. Epub 2011 Jan 12.

Genomic duplications mediate overexpression of lamin B1 in adult-onset autosomal dominant leukodystrophy (ADLD) with autonomic symptoms.

Schuster J, Sundblom J, Thuresson AC, Hassin-Baer S, Klopstock T, Dichgans M, Cohen OS, Raininko R, Melberg A, Dahl N.
Department of Genetics and Pathology, The Rudbeck Laboratory and Science for Life Laboratory, Uppsala University and University Hospital, SE-751 85, Uppsala, Sweden.

Adult-onset autosomal dominant leukodystrophy (ADLD) with autonomic symptoms features micturition urgency, constipation, erectile dysfunction, and orthostatic hypotension, usually followed by pyramidal signs and ataxia. Peripheral nerve conduction is normal. The disease is often mistaken for multiple sclerosis in the initial phase. There is a characteristic pattern of white matter changes in the brain and spinal cord on magnetic resonance imaging (MRI), mild atrophy of the brain, and a more marked atrophy of the spinal cord. ADLD is associated with duplications of the lamin B1 (LMNB1) gene but the mechanism by which the rearrangement conveys the phenotype is not fully defined. We analyzed four unrelated families segregating ADLD with autonomic symptoms for duplications of the LMNB1 gene. A single nucleotide polymorphism (SNP) array analysis revealed novel duplications spanning the entire LMNB1 gene in probands from each of the four families. We then analyzed the expression of lamin B1 in peripheral leukocytes by Western blot analysis in five patients from two available families. The protein levels of lamin B1 were found significantly increased. These results indicate that the ADLD phenotype associated with LMNB1 duplications is mediated by increased levels of the lamin B1 protein. Furthermore, we show that a molecular diagnosis for ADLD with autonomic symptoms can be obtained by a direct analysis of lamin B1 in peripheral leukocytes.

PMID: 21225301 [PubMed - in process]

173. Neuroimage. 2011 Jan 13. [Epub ahead of print]
Radial diffusivity predicts demyelination in ex vivo multiple sclerosis spinal cords.
Klawiter EC, Schmidt RE, Trinkaus K, Liang HF, Budde MD, Naismith RT, Song SK, Cross AH, Benzinger TL.
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OBJECTIVE: Correlation of diffusion tensor imaging (DTI) with histochemical staining for demyelination and axonal damage in multiple sclerosis (MS) ex vivo human cervical spinal cords. BACKGROUND: In MS, demyelination, axonal degeneration, and inflammation contribute to disease pathogenesis to variable degrees. Based upon in vivo animal studies with acute injury and histopathologic correlation, we hypothesized that DTI can differentiate between axonal and myelin pathologies within humans. METHODS: DTI was performed at 4.7 T on 9 MS and 5 normal control fixed cervical spinal cord blocks following autopsy. Sections were then stained for Luxol fast blue (LFB), Bielschowsky silver, and hematoxylin and eosin (H&E). Regions of interest (ROIs) were graded semi-quantitatively as normal myelination, mild (<50%) demyelination, or moderate-severe (>50%) demyelination. Corresponding axonal counts were manually determined on Bielschowsky silver. ROIs were mapped to co-registered DTI parameter slices. DTI parameters evaluated included standard quantitative assessments of apparent diffusion coefficient (ADC), relative anisotropy (RA), axial diffusivity and radial diffusivity. Statistical correlations were made between histochemical gradings and DTI parameters using linear mixed models. RESULTS: Within ROIs in MS subjects, increased radial diffusivity distinguished worsening severities of demyelination. Relative anisotropy was decreased in the setting of moderate-severe demyelination compared to normal areas and areas of mild demyelination. Radial diffusivity, ADC, and RA became increasingly altered within quartiles of worsening axonal counts. Axial diffusivity did not correlate with axonal density (p=0.091). CONCLUSIONS: Increased radial diffusivity can serve as a surrogate for demyelination. However, radial diffusivity was also altered with axon injury, suggesting that this measure is not pathologically specific within chronic human MS tissue. We propose that radial diffusivity can serve as a marker of overall tissue integrity within chronic MS lesions. This study provides pathologic foundation for on-going in vivo DTI studies in MS.
PMID: 21238597 [PubMed - as supplied by publisher]

174. Neurol Med Chir (Tokyo). 2011;51(1):8-14.
Efficacy of Motor Cortex Stimulation for Intractable Central Neuropathic Pain: Comparison of Stimulation Parameters Between Post-stroke Pain and Other Central Pain.
Tanei T, Kajita Y, Noda H, Takebayashi S, Nakatsubo D, Maesawa S, Wakabayashi T.
Department of Neurosurgery, Nagoya Central Hospital.
Motor cortex stimulation (MCS) has now become the preferred option for neurosurgical management of intractable central neuropathic pain such as post-stroke pain and trigeminal neuropathic pain. However, the efficacy of MCS for other central neuropathic pain such as pain resulting from spinal cord or brainstem lesions is unclear. We retrospectively reviewed 11 consecutive patients with intractable central neuropathic pain who underwent MCS in our institution. Eight patients had poststroke pain caused by thalamic hemorrhage (n = 5) or infarction (n = 3) (thalamic group). Two patients had postoperative neuropathic pain caused by spinal cord lesions, and one patient had facial pain caused by a brainstem lesion associated with multiple sclerosis (brainstem-spinal group). Visual analog scale and stimulation parameters were evaluated at 1 and 6 months postoperatively. MCS was effective for six of eight patients in the thalamic group, and all three patients in the brainstem-spinal group. These efficacies continued for 6 months after surgery without significant change in the stimulation parameters compared with the parameters at 1 month in both groups. The mean amplitude at 1 month and frequency at 6 months after surgery were significantly higher in the brainstem-spinal group than the thalamic group, although the patient number was small. MCS is effective for other central neuropathic pain, but higher intensity stimulation parameters may be necessary to gain adequate pain reduction.
PMID: 21273738 [PubMed - in process]

175. Neurol Neurochir Pol. 2010 November-December;44(6):542-545.
Thalamic deep brain stimulation for tremor among multiple sclerosis patients.
Mandat T, Koziara H, Tutaj M, Rola R, Bonicki W, Nauman P.
dr Tomasz Mandat, Klinika Nowotworów Układu Nerwowego, Centrum Onkologii - Instytut im. Marii Skłodowskiej-Curie, ul. Roentgena 5, 02-781 Warszawa, e-mail: tomaszmandat@yahoo.co.
Background and purpose : Disabling tremor might be the main cause of disability of multiple sclerosis (MS) patients. Neuromodulation with deep brain stimulation of the thalamic nucleus ventralis intermedius (Vim DBS) is a well accepted method of neurosurgical treatment of tremor related to essential tremor or Parkinson disease. Vim DBS is not widely used to control MS tremor. Material and methods : Five MS patients with tremor (3 females and 2 males) were treated with Vim DBS. Age at implantation was 37 ± 5 years. MS lasted from 5 to 12 years (mean 6) and tremor was the main cause of disability of those patients from 2 to 5 years (mean 3) before surgery. Clinical condition of the group was evaluated with spirography, the modified Fahn scale and the modified Activity of Daily Living (ADL) scale. Evaluations were performed before surgery and 3 months after surgery. MRI exclusion criteria were the presence of a thalamic hyperintense signal in T2-weight-ed images or ventricular enlargement. The procedures of implantation were performed under local and general anaesthesia. Results : Intensity of contralateral limb tremor during intraoperative macrostimulation was reduced in the whole group. The therapeutic effect of DBS was maintained at three-month follow-up. Mean contralateral limb tremor reduction was 40%. Mean ADL score improved by 18%. No mortality or morbidity was reported in the group. Conclusions : The study confirms the value and safety of Vim DBS for treatment of MS-related tremor. Further study on a larger population and introduction of a qualification protocol might increase efficacy of the treatment.
PMID: 21225515 [PubMed - as supplied by publisher]

176. Neurol Sci. 2011 Jan 26. [Epub ahead of print]
The cohort of the multiple sclerosis center of Cagliari.
Marrosu MG, Lorefice L, Frau J, Coghe G, Fenu G, Piras R, Melis M, Cocco E.
Centro Sclerosi Multipla, Dipartimento di Scienze Cardiovascolari e Neurologiche, Università di Cagliari, Cagliari, Italy, gmarrosu@unica.it.
We report our experience in long-term treatment of relapsing remitting multiple sclerosis patients with natalizumab (N). In November 2009 we evaluated 141 patients (126 AIFA criterion A, 15 AIFA criterion B). We paid particular attention to the treatment period and the patients follow-up; during the whole therapeutic program, they undergone to clinical and radiological evaluation for every 3 months. The compliance was optimal and we found no significant side effects. 26 patients completed the 24 monthly doses. After 24 months 51% of patients were free from disease activity. We found a reduction in relapses and EDSS, moreover the clinical improvement was also confirmed by radiological examinations. Our results show that the best therapeutic results are achieved by early initiation of treatment.
PMID: 21267619 [PubMed - as supplied by publisher]

177. Neurol Sci. 2011 Jan 14. [Epub ahead of print]
Medulloblastoma and gliomatosis cerebri: rare brain tumors in multiple sclerosis patients.
da Silva AA, Dos Santos Cavaco SM, Taipa RJ, Pinto PR, Pires MJ.
Serviço de Neurologia, Largo do Prof Abel Salazar, Centro Hospitalar do Porto/Hospital de Santo António, 4099-001, Porto, Portugal, anadmsilva@yahoo.com.
The simultaneous appearance of both multiple sclerosis (MS) and central nervous system (CNS) tumors is relatively uncommon. Whether the co-existence of two diseases is due to chance alone or the result of a causal relationship is still a matter of debate. There is also controversy about the effect of long-term exposure of MS patients to immunomodulatory drugs on the incidence of cancer. This paper reports two cases of rare CNS tumors (i.e., medulloblastoma and gliomatosis cerebri) in adult MS patients. Our cases emphasize that when uncommon neurological features appear in patients with MS, brain magnetic resonance imaging (MRI) ought to be done and brain biopsy should be considered to exclude a concomitant CNS disorder. These procedures are essential for the differential diagnosis and early treatment.
PMID: 21234776 [PubMed - as supplied by publisher]

178. Neurol Sci. 2011 Jan 14. [Epub ahead of print]
Natalizumab therapy of multiple sclerosis: recommendations of the Multiple Sclerosis Study Group-Italian Neurological Society.
Ghezzi A, Grimaldi LM, Marrosu MG, Pozzilli C, Comi G, Bertolotto A, Trojano M, Gallo P, Capra R, Centonze D, Millefiorini E, Sotgiu S, Brescia Morra V, Amato MP, Lugaresi A, Mancardi G, Caputo D, Montanari E, Provinciali L, Durelli L, Bergamaschi R, Bellantonio P, Tola MR, Cottone S, Savettieri G, Tedeschi G; MS-SIN Study Group.
U.O. Neurologia II, Centro Studi Sclerosi Multipla, Ospedale di Gallarate, Gallarate, Italy, angelo.ghezzi@aogallarate.it.
Three years after the introduction of natalizumab (NA) therapy for the second line treatment of relapsing-remitting multiple sclerosis (MS), Italian MS centers critically reviewed the scientific literature and their own clinical experience. Natalizumab was shown to be highly efficaciuos in the treatment of MS. However, the risk of progressive multifocal leukoencephalopathy was confirmed and defined better. This article summarizes the MS-SIN Study Group recommendations on the use of NA in MS, with particular reference to the appropriate selection and monitoring of patients as well as to the management of adverse events.
PMID: 21234775 [PubMed - as supplied by publisher]

179. Neurologia. 2010 Dec 28. [Epub ahead of print]
[Natalizumab for relapsing-remitting multiple sclerosis.]
[Article in Spanish]
Horga A, Tintoré M.
Centro de Esclerosis Múltiple de Cataluña, Hospital Universitario Vall d'Hebron, Barcelona, España.
INTRODUCTION: Natalizumab is a monoclonal antibody that inhibits leukocyte migration across the blood-brain barrier and has been approved for the treatment of relapsing-remitting multiple sclerosis. OBJECTIVE: To provide a review and update of the pharmacological and therapeutic characteristics of natalizumab, with special emphasis on the most recently published data on the efficacy, effectiveness and safety of this drug. DEVELOPMENT: Several randomized clinical trials in patients with relapsing forms of multiple sclerosis have demonstrated that natalizumab substantially reduces clinical and radiological disease activity. Post hoc analysis of phase III clinical trials and the results of post-approval observational studies indicate that natalizumab significantly increases the proportion of patients with complete clinical and radiological response and is effective in patients with highly active forms of multiple sclerosis and suboptimal response to other treatments. Like other monoclonal antibodies, natalizumab can cause hypersensitivity reactions, which are severe in 1% of patients. Other adverse effects are generally mild or infrequent. Nevertheless, several cases of progressive multifocal leukoencephalopathy have been detected in patients treated with natalizumab monotherapy. The risk of this severe complication seems to increase with the number of doses administered. CONCLUSION: Natalizumab has a favorable risk-benefit ratio in the treatment of relapsing - remitting multiple sclerosis. However, because of the potential risk of progressive multifocal leukoencephalopathy, patients must be carefully selected and specific protocols must be followed during the drug's administration.
PMID: 21193250 [PubMed - as supplied by publisher]

180. Neurology. 2011 Jan 4;76(1 Suppl 1):S1-2.
Long-term outcomes in patients with multiple sclerosis. Introduction.
Bates D.
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PMID: 21249753 [PubMed - indexed for MEDLINE]

181. Neurology. 2011 Jan 4;76(1 Suppl 1):S7-13.
Analysis of current multiple sclerosis registries.
Hurwitz BJ.
Department of Medicine Neurology, Box 3184, Duke University Medical Center, Durham, NC 27710, USA. hurwi003@mc.duke.edu
BACKGROUND: Patient registries are valuable because they provide data that cannot be captured in any other way. Observations from registry studies are particularly informative if multiple registries confirm similar findings. A selection of multiple sclerosis (MS) registry studies were reviewed, and results and consistency of those studies are presented. METHODS: A panel of experts analyzed the study findings of established MS registries and presented their conclusions on the overall results and consistency of those studies. RESULTS: A review of evidence from MS registry studies reveals similar findings with respect to patterns of disability progression, predictors of disability progression, and changes in lifespan. Several registries show that progression after Expanded Disability Status Scale (EDSS) 4 occurs at a predictable rate, and once EDSS 4 is reached, subsequent progression rates are similar regardless of the type of MS at onset. Clinicians, payers, and patients need to understand that MS may shorten life expectancy. The mortality data derived from registries reveal higher death rates in patients with MS compared with the general population, indicating that MS is an important public health issue. CONCLUSIONS: The key findings in registries should be utilized in conjunction with data from clinical trials to optimize treatment and improve long-term outcomes.
PMID: 21205683 [PubMed - indexed for MEDLINE]

182. Neurology. 2011 Jan 4;76(1 Suppl 1):S39-41.
Summary: Registry data.
Bates D.
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PMID: 21205682 [PubMed - indexed for MEDLINE]

183. Neurology. 2011 Jan 4;76(1 Suppl 1):S35-8.
Improving long-term follow-up studies of immunomodulatory therapies.
Freedman MS.
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Goals in the treatment of multiple sclerosis (MS) focus on reducing symptoms and disease progression. Registry data indicate that the accumulation of significant disability can take decades. Therefore, long-term follow-up (LTFU) studies are needed to understand the impact of disease-modifying therapy (DMT) in MS. Based on analyses of available LTFU study data, recommendations for future LTFU studies can be made. A disability milestone may be considered because exploratory data show that DMT may slow the progression of disability. Achievement of the EDSS steps 4 or 6 may be sufficient milestones because, once reached, MS progresses inevitably. Since a placebo control cannot be ethically used in LTFU studies, a standard-of-care comparator could be considered. The ideal LTFU study should be performed according to the highest possible standards. A high-quality LTFU study would achieve high retention rates, capture complete data at prespecified assessment intervals, and be powered to the key outcome measure. In addition, propensity scoring is an approach used to reduce bias in treatment comparisons in observational studies and might be a suitable approach for analyzing LTFU studies. With careful consideration of LTFU limitations and study design, it is possible to attain a high degree of rigor in future studies.
PMID: 21205681 [PubMed - indexed for MEDLINE]

184. Neurology. 2011 Jan 4;76(1 Suppl 1):S3-6.
Registry studies of long-term multiple sclerosis outcomes: description of key registries.
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BACKGROUND: Multiple sclerosis (MS) registries can provide valuable insights into the natural history of MS. Key observational findings of the registries include MS patient disability progression rate, predictors of increased disability, and changes in lifespan. MS registries have been established in Canada, the United States, and Europe, some of which have existed for decades. Recommendations for registry use and improvement based on a review of a selection of MS registries from these countries are presented. METHODS: A panel of experts analyzed the current status of a number of the established MS registries and made recommendations on their usefulness and on improvements for the creation of future MS registries. RESULTS: Improved inter-registry consistency in order to better compare and contrast the results of different registries was advocated. To follow the course of MS, the initiation of a prospective, complete, verifiable database of patients with clinically isolated syndrome was also recommended. Time to Expanded Disability Status Scale 6 was supported over mortality as the central endpoint of a registry study, because it can be detected earlier in the course of the disease than mortality. CONCLUSIONS: The data collected from registries are considered valuable in understanding MS, despite difficulties with registries such as a lack of consistency between their databases.
PMID: 21205680 [PubMed - indexed for MEDLINE]

185. Neurology. 2011 Jan 4;76(1 Suppl 1):S26-34.
Long-term follow-up of clinical trials of multiple sclerosis therapies.
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Results from registry studies can provide valuable information about the prevalence and clinical course of different forms of multiple sclerosis (MS). Such studies can also help identify medical practice patterns in a real-world setting and important risk factors that may affect long-term outcomes in patients with MS. To date, however, these observational studies have provided less information than well-planned, randomized, controlled trials on the long-term treatment effects of disease-modifying therapies (DMTs). Short-term clinical trial results have indicated that currently available DMTs are effective in reducing disease activity, manifested by relapse or MRI change, and may slow disease progression. Because MS is a chronic disease that evolves over a period of 30 to 40 years, determining the long-term effects of treatment is of critical importance to both patients and providers. This article discusses long-term studies of DMTs in patients with MS. Exploratory data provided thus far support the hypothesis that early optimal treatment aimed at reducing disease activity can improve longer-term outcomes by delaying disease progression.
PMID: 21205679 [PubMed - indexed for MEDLINE]

186. Neurology. 2011 Jan 4;76(1 Suppl 1):S14-25.
Treatment effects of immunomodulatory therapies at different stages of multiple sclerosis in short-term trials.
Bates D.
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Intervention with interferon-β (IFNβ) therapy counters early inflammatory damage to myelin and protects axons; such therapy might demonstrate greater efficacy earlier in the disease course compared with later when permanent damage has already occurred. Clinical trials conducted in patients with clinically isolated syndrome (CIS) show clinical benefits of early treatment of multiple sclerosis (MS), as evidenced by delayed conversion to clinically definite multiple sclerosis and reduced disability 3 years later; however, statistical significance is lost at 5 years. Moreover, in the CIS trials, patients who began treatment later in the course of MS did not benefit as much as those who began treatment earlier. In the treatment of relapsing-remitting multiple sclerosis (RRMS), immunomodulatory drug (IMD) therapy markedly reduced relapse rates and the burden of disease, as assessed by MRI. IFNβ therapy has demonstrated greater benefits in RRMS than in secondary progressive multiple sclerosis (SPMS). The SPMS trials consistently show reduction in relapse rates and accumulation of new MRI lesions, but have conflicting results for time to disability progression, which is the primary outcome measure in SPMS trials. Current evidence suggests that IFNβ therapy may be more effective in the early stages of SPMS, characterized by relapsing episodes and MRI evidence of greater brain lesion disease activity. Thus, intervention with IFNβ therapy is appropriate for all stages of MS except PPMS or non-relapsing SPMS. Intervention with glatiramer acetate is appropriate for RRMS. The balance of evidence indicates that early therapy is essential to delay the accumulation of irreversible neurologic damage and consequent disability.
PMID: 21205678 [PubMed - indexed for MEDLINE]

187. Neurology. 2011 Jan 26. [Epub ahead of print] Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome.
Okuda DT, Mowry EM, Cree BA, Crabtree EC, Goodin DS, Waubant E, Pelletier D.
From the Department of Neurology, UCSF Multiple Sclerosis Center, University of California, San Francisco, San Francisco.
BACKGROUND: Technological advancements in neuroimaging and the increased use of these diagnostic modalities are responsible for the discovery of incidentally identified anomalies within the CNS. In addition to the identification of unanticipated brain MRI abnormalities suggestive of demyelinating disease in patients undergoing neuroimaging for a medical reason other than evaluation for multiple sclerosis (MS), asymptomatic spinal cord lesions are periodically identified. OBJECTIVE: To determine if asymptomatic spinal cord lesions are associated with clinical progression in subjects with radiologically isolated syndrome (RIS). METHODS: A retrospective review of RIS cases at the University of California, San Francisco Multiple Sclerosis Center was performed. The presence of asymptomatic cervical spinal cord MRI lesions was analyzed as a potential predictor for clinical progression. RESULTS: Twenty-five of 71 subjects with RIS possessed findings within the cervical spine that were highly suggestive of demyelinating disease. Of these subjects, 21 (84%) progressed clinically to clinically isolated syndrome (n = 19) or primary progressive multiple sclerosis (n = 2) over a median time of 1.6 years from the date of RIS identification (interquartile range 0.8-3.8). The sensitivity, specificity, and positive predictive value of an asymptomatic spinal cord lesion for subsequent development of either a first demyelinating attack or primary progressive MS were 87.5%, 91.5%, and 84%, respectively. The odds ratio of clinical progression was 75.3 (95% confidence interval 16.1-350.0, $p < 0.0001$). This association remained significant after adjusting for potential confounders. CONCLUSION: These findings suggest that the presence of asymptomatic spinal cord lesions place subjects with RIS at substantial risk for clinical conversion to either an acute or progressive event, a risk that is independent of brain lesions on MRI.
PMID: 21270417 [PubMed - as supplied by publisher]

188. Neurology. 2011 Jan 26. [Epub ahead of print]
The radiologically isolated syndrome revisited: When is it presymptomatic multiple sclerosis?
Bourdette D, Yadav V.
From the Department of Neurology (D.B., V.Y.), Oregon Health & Science University, Portland; and the VA Multiple Sclerosis Center of Excellence-West (D.B.), Portland Veterans Affairs Medical Center, Portland, OR.
PMID: 21270414 [PubMed - as supplied by publisher]

189. Neurology. 2011 Jan 25;76(4):397-404.
White matter synapses: Form, function, and dysfunction.
Alix JJ, de Jesus Domingues AM.
Sheffield Institute for Translational Neuroscience, University of Sheffield, 385A Glossop Road, Sheffield S10 2HQ, UK j.alix@sheffield.ac.uk.
Synaptic transmission in the CNS represents the classic mechanism through which neural cells communicate. While vesicular neurotransmitter release has been known to be the preserve of gray matter, it is now known that synaptic-style release of glutamate, the brain's major excitatory neurotransmitter, occurs deep in white matter. Here it permits communication between axons and glial cells, enabling axon activity to couple with high fidelity to glial physiology. As white matter is increasingly well-recognized as a substrate for disease, dysregulation of white matter synaptic transmission will play an important role in the development of pathologies as diverse as stroke, multiple sclerosis, Alzheimer disease, and schizophrenia. This review highlights progress in this new and important field.
PMID: 21263141 [PubMed - in process]

190. Neurology. 2011 Jan 18;76(3):294-300.
Evidence-based guideline update: Plasmapheresis in neurologic disorders: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.
Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A.
1080 Montreal Avenue, St. Paul, MN 55116 guidelines@aan.com.
OBJECTIVE: To reassess the role of plasmapheresis in the treatment of neurologic disorders. METHODS: We evaluated the available evidence based on a structured literature review for relevant articles from 1995 through September 2009. In addition, due to revision of the definitions of classification of evidence since the publication of the previous American Academy of Neurology assessment in 1996, the evidence cited in that manuscript was reviewed and reclassified. Results and Recommendations: Plasmapheresis is established as effective and should be offered in severe acute inflammatory demyelinating polyneuropathy (AIDP)/Guillain-Barré syndrome (GBS) and in the short-term management of chronic inflammatory demyelinating polyneuropathy (Class I studies, Level A). Plasmapheresis is established as ineffective and should not be offered for chronic or secondary progressive multiple sclerosis (MS) (Class I studies, Level A). Plasmapheresis is probably effective and should be considered for mild AIDP/GBS, as second-line treatment of steroid-resistant exacerbations in relapsing forms of MS, and for neuropathy associated with immunoglobulin A or immunoglobulin G gammopathy, based on at least one Class I or 2 Class II studies (Level B). Plasmapheresis is probably not effective and should not be considered for neuropathy associated with immunoglobulin M gammopathy, based on one Class I study (Level B). Plasmapheresis is possibly effective and may be considered for acute fulminant demyelinating CNS disease (Level C). There is insufficient evidence to support or refute the use of plasmapheresis for myasthenia gravis, pediatric autoimmune neuropsychiatric disorders associated with streptococcus infection, and Sydenham chorea (Class III evidence, Level U).
PMID: 21242498 [PubMed - in process]

191. Neurology. 2011 Jan 18;76(3):242-6. Epub 2011 Jan 5.
MHC transmission: Insights into gender bias in MS susceptibility.
Chao MJ, Ramagopalan SV, Herrera BM, Orton SM, Handunnetthi L, Lincoln MR, Dyment DA, Sadovnick AD, Ebers GC.
Department of Clinical Neurology, University of Oxford, Level 3 West Wing, John Radcliffe Hospital, Headley Way, Oxford, OX3 9DU, UK george.ebers@clneuro.ox.ac.uk.
OBJECTIVE: Major histocompatibility complex (MHC) genes dominate genetic susceptibility factors in multiple sclerosis (MS). Given the general consensus that incidence and prevalence of MS has been rising and specifically in women, we evaluated MHC-gender interactions. METHODS: In a large family-based cohort consisting of 7,093 individuals (2,127 affected individuals) from 1,055 MS families, we examined MHC transmission by family structure and gender stratified by genetic distance of affected relatives from the MS proband. RESULTS: We found that affected individuals with HLA-DRB1*15-positive genotypes have higher female-to-male ratios as compared with affected individuals with HLA-DRB1*15-negative genotypes ($\chi(2) = 9.97$, $p = 0.0015$) with the exception of multiplex families with 3 or more affected across 2 generations. Transmission disequilibrium test results show that HLA-DRB1*15 transmission was more distorted in collateral families vs nuclear families ($\chi(2) = 8.030$, $p = 0.0046$), exclusively in affected female-female pairs ($\chi(2) = 7.81$, $p = 0.0051$), but not in mixed gender pairs ($\chi(2) = 1.58$, $p = 0.21$) or matched male pairs (Fisher $p = 0.21$). CONCLUSIONS: These observations implicate the MHC as the site of interactions and modifications mediating the female-to-male gender ratio in MS and its progressive increase. They further suggest this occurs via gene-environment interactions and epigenetic modifications in this region. The difference between collateral and nuclear families provides some insight into the inheritance, decay, and gender specificity of putative epigenetic marks.
PMID: 21209377 [PubMed - in process]

192. Neurology. 2011 Jan 11;76(2):179-86.
Longitudinal changes in diffusion tensor-based quantitative MRI in multiple sclerosis.
Harrison DM, Caffo BS, Shiee N, Farrell JA, Bazin PL, Farrell SK, Ratchford JN, Calabresi PA, Reich DS.
Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA. dharri90@jhmi.edu
OBJECTIVE: To estimate longitudinal changes in a quantitative whole-brain and tract-specific MRI study of multiple sclerosis (MS), with the intent of assessing the feasibility of this approach in clinical trials. METHODS: A total of 78 individuals with MS underwent a median of 3 scans over 2 years. Diffusion tensor imaging indices, magnetization transfer ratio, and T2 relaxation time were analyzed in supratentorial brain, corpus callosum, optic radiations, and corticospinal tracts by atlas-based tractography. Linear mixed-effect models estimated annualized rates of change for each index, and sample size estimates for potential clinical trials were determined. RESULTS: There were significant changes over time in fractional anisotropy and perpendicular diffusivity in the supratentorial brain and corpus callosum, mean diffusivity in the supratentorial brain, and magnetization transfer ratio in all areas studied. Changes were most rapid in the corpus callosum, where fractional anisotropy decreased 1.7% per year, perpendicular diffusivity increased 1.2% per year, and magnetization transfer ratio decreased 0.9% per year. The T2 relaxation time changed more rapidly than diffusion tensor imaging indices and magnetization transfer ratio but had higher within-participant variability. Magnetization transfer ratio in the corpus callosum and supratentorial brain declined at an accelerated rate in progressive MS relative to relapsing-remitting MS. Power analysis yielded reasonable sample sizes (on the order of 40 participants per arm or fewer) for 1- or 2-year trials. CONCLUSIONS: Longitudinal changes in whole-brain and tract-specific diffusion tensor imaging indices and magnetization transfer ratio can be reliably quantified, suggesting that small clinical trials using these outcome measures are feasible.
PMID: 21220722 [PubMed - in process]

193. Neurology. 2011 Feb 1;76(5):418-424. Epub 2011 Jan 5.
Consensus recommendations for MS cortical lesion scoring using double inversion recovery MRI.
Geurts JJ, Roosendaal SD, Calabrese M, Ciccarelli O, Agosta F, Chard DT, Gass A, Huerga E, Moraal B, Pareto D, Rocca MA, Wattjes MP, Yousry TA, Uitdehaag BM, Barkhof F; On behalf of the MAGNIMS Study Group.
VU University Medical Center, Department of Anatomy & Neuroscience, MF G-116, van der Boechorststraat 7, 1081 BT Amsterdam, the Netherlands j.geurts@vumc.nl.
BACKGROUND: Different double inversion recovery (DIR) sequences are currently used in multiple sclerosis (MS) research centers to visualize cortical lesions, making it difficult to compare published data. This study aimed to formulate consensus recommendations for scoring cortical lesions in patients with MS, using DIR images acquired in 6 European centers according to local protocols. METHODS: Consensus recommendations were formulated and tested in a multinational meeting. RESULTS: Cortical lesions were defined as focal abnormalities on DIR, hyperintense compared to adjacent normal-appearing gray matter, and were not scored unless ≥3 pixels in size, based on at least 1.0 mm(2) in-plane resolution. Besides these 2 obligatory criteria, additional, supportive recommendations concerned a priori artifact definition on DIR, use of additional MRI contrasts to verify suspected lesions, and a constant level of displayed image contrast. Robustness of the recommendations was tested in a small dataset of available, heterogeneous DIR images, provided by the different participating centers. An overall moderate agreement was reached when using the proposed recommendations: more than half of the readers agreed on slightly more than half (54%) of the cortical lesions scored, whereas complete agreement was reached in 19.4% of the lesions (usually larger, mixed white matter/gray matter lesions). CONCLUSIONS: Although not designed as a formal interobserver study, the current study suggests that comparing available literature data on cortical lesions may be problematic, and increased consistency in acquisition protocols may improve scoring agreement. Sensitivity and specificity of the proposed recommendations should now be studied in a more formal, prospective, multicenter setting using similar DIR protocols.
PMID: 21209373 [PubMed - as supplied by publisher]

194. Neurosci Bull. 2011 Feb;27(1):36-44.
Potassium channel blockers as an effective treatment to restore impulse conduction in injured axons.
Shi R, Sun W.
Department of Basic Medical Sciences, School of Veterinary Medicine, Weldon School of Biomedical Engineering, Purdue University, West Lafayette, Indiana 47907, USA; E-mail: riyi@purdue.edu.
Most axons in the vertebral central nervous system are myelinated by oligodendrocytes. Myelin protects and insulates neuronal processes, enabling the fast, saltatory conduction unique to myelinated axons. Myelin disruption resulting from trauma and biochemical reaction is a common pathological event in spinal cord injury and chronic neurodegenerative diseases. Myelin damage-induced axonal conduction block is considered to be a significant contributor to the devastating neurological deficits resulting from trauma and illness. Potassium channels are believed to play an important role in axonal conduction failure in spinal cord injury and multiple sclerosis. Myelin damage has been shown to unmask potassium channels, creating aberrant potassium currents that inhibit conduction. Potassium channel blockade reduces this ionic leakage and improves conduction. The present review was mainly focused on the development of this technique of restoring axonal conduction and neurological function of demyelinated axons. The drug 4-aminopyridine has recently shown clinical success in treating multiple sclerosis symptoms. Further translational research has also identified several novel potassium channel blockers that may prove effective in restoring axonal conduction.
PMID: 21270902 [PubMed - in process]

195. Neurosciences (Riyadh). 2011 Jan;16(1):24-8.
Memory impairment in multiple sclerosis and its determinant factors.
Sedighi B.
Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran. Tel. +98 (21) 66439463. Fax. +98 (21) 66423304. E-mail: behnaz.sedighi@gmail.com.
OBJECTIVE: To determine the prevalence of memory impairment and to explore the determinant factors of memory impairment severity in patients diagnosed with multiple sclerosis (MS). METHODS: A cross-sectional study was conducted in the Neurology Center of Shafa Hospital in Kerman, Iran between February and November 2008 on 100 MS patients whose diseases were confirmed by a neurologist. Patients were recruited by the convenience sampling method. Data regarding age, gender, education, and occupation were collected; medical history including co-morbidities and drug history was recorded. All the patients were examined with routine neurological examination and the Extended Disability Status Scale (EDSS), and memory impairment was assessed by standard metal status questionnaire in 7 segments. RESULTS: Generally, 71% of patients had memory impairment. Among the affected patients, 35% of patients had mild to moderate, 19% had moderate to severe, and 17% had severe memory impairment. The relationship between the severity of memory impairment and age, education, duration of disease, the duration of treatment, currently used drug, and EDSS score was statistically significance. CONCLUSION: Memory impairment is a common disability in MS patients, which worsen with age and longer duration of disease. Such patients with chronic disease should be intermittently screened for memory impairment.
PMID: 21206441 [PubMed - in process]

196. Neurotherapeutics. 2011 Jan;8(1):117-32.
Optical Coherence Tomography (OCT): Imaging the Visual Pathway as a Model for Neurodegeneration.
Galetta KM, Calabresi PA, Frohman EM, Balcer LJ.
Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA.
Axonal and neuronal degeneration are important features of multiple sclerosis (MS) and other neurologic disorders that affect the anterior visual pathway. Optical coherence tomography (OCT) is a non-invasive technique that allows imaging of the retinal nerve fiber layer (RNFL), a structure which is principally composed of ganglion cell axons that form the optic nerves, chiasm, and optic tracts. Since retinal axons are nonmyelinated until they penetrate the lamina cribrosa, the RNFL is an ideal structure (no other central nervous system tract has this unique arrangement) for visualizing the processes of neurodegeneration, neuroprotection and, potentially, even neuro-repair. OCT is capable of providing high-resolution reconstructions of retinal anatomy in a rapid and reproducible fashion and permits objective analysis of the RNFL (axons) as well as ganglion cells and other neurons in the macula. In a systematic OCT examination of multiple sclerosis (MS) patients, RNFL thickness and macular volumes are reduced when compared to disease-free controls. Conspicuously, these changes, which signify disorganization of retinal structural architecture, occur over time even in the absence of a history of acute demyelinating optic neuritis. RNFL axonal loss in MS is most severe in those eyes with a corresponding reduction in low-contrast letter acuity (a sensitive vision test involving the perception of gray letters on a white background) and in those patients who exhibit the greatest magnitude of brain atrophy, as measured by validated magnetic resonance imaging techniques. These unique structure-function correlations make the anterior visual pathway an ideal model for investigating the effects of standard and novel therapies that target axonal and neuronal degeneration. We provide an overview of the physics of OCT, its unique properties as a non-invasive imaging technique, and its potential applications toward understanding mechanisms of brain tissue injury in MS, other optic neuropathies, and neurologic disorders.
PMID: 21274691 [PubMed - in process]

197. Neurotherapeutics. 2011 Jan;8(1):54-62.
Neuroimaging in multiple sclerosis: neurotherapeutic implications.
Sicotte NL.
Multiple Sclerosis Research and Treatment Program, Division of Brain Mapping, Department of Neurology, David Geffen School of Medicine at UCLA, 710 Westwood Blvd, Rm 4-238, Los Angeles, California, 90095, USA, nsicotte@ucla.edu.
Imaging techniques, in particular magnetic resonance imaging (MRI), play an important role in the diagnosis and management of multiple sclerosis (MS) and related demyelinating diseases. Findings on MRI studies of the brain and spinal cord are critical for MS diagnosis, are used to monitor treatment response and may aid in predicting disease progression in individual patients. In addition, results of imaging studies serve as essential biomarkers in clinical trials of putative MS therapies and have led to important insights into disease pathophysiology. Although they are useful tools and provide in vivo measures of disease-related activity, there are some important limitations of MRI findings in MS, including the non-specific nature of detectable white matter changes, the poor correlation with clinical disability, the limited sensitivity and ability of standard measures of gadolinium enhancing lesions and T2 lesions to predict future clinical course, and the lack of validated biomarkers of long term outcomes. Advancements that hold promise for the future include new techniques that are sensitive to diffuse changes, the increased use of higher field scanners, measures that capture disease related changes in gray matter, and the use of combined structural and functional imaging approaches to assess the complex and evolving disease process that occurs during the course of MS.
PMID: 21274685 [PubMed - in process]

198. Nurs Health Sci. 2010 Dec;12(4):421-8. doi: 10.1111/j.1442-2018.2010.00554.x. Epub 2010 Oct 8.
Fatigue in Japanese people with multiple sclerosis.
Moriya R, Kutsumi M.
Faculty of Nursing, Senri Kinran University, Suita City, Japan. r-moriya@cs.kinran.ac.jp
The aim of this study was to obtain descriptions of the experiences of fatigue of people with multiple sclerosis, including experiences related to their interpersonal relations and social life. We used a qualitative, exploratory, and descriptive design and conducted semistructured interviews with nine participants. Seven concepts emerged from the data analysis: "fatigue as an individualized and novel sensation", "self-analysis of the factors that are associated with fatigue", "effects of fatigue on living and the self", "unique measures for handling fatigue", "insufficient coping", "living with fatigue", and "the assumption of a lack of common understanding of fatigue." Based on these findings, fatigue was found to affect the lifestyle of people with MS and their ability to be true to themself. As a result, the participants devised their own way of coping with fatigue. However, the coping measures also created other dilemmas, which led to isolation. Nevertheless, the participants made efforts to live with fatigue on their own terms.
PMID: 21210919 [PubMed - in process]

199. Open Neurol J. 2010 May 26;4:15-24.
Disease modifying agents for multiple sclerosis.
Hilas O, Patel PN, Lam S.
St. John's University College of Pharmacy and Allied Health Professions, Queens, NY, USA.
OBJECTIVE: To summarize major clinical trials which evaluate the efficacy and safety data of approved disease modifying agents for the treatment of various types of multiple sclerosis. DATA SOURCES: A MEDLINE (1966 to August 2008) search of clinical trials using the terms multiple sclerosis, interferon, glatiramer, mitoxantrone and natalizumab was performed. A manual bibliographic search was also conducted. English-language articles identified from the searches were evaluated. New agents under investigation in phase 3 clinical trials were identified using www.clinicaltrials.gov. STUDY SELECTION #ENTITYSTARTX00026; DATA EXTRACTION: Relevant information was identified and selected based on clinical relevance and evidence-based strength. Prescribing information leaflets were used to provide usual dosage, contraindications, precautions, monitoring parameters and other relevant drug-specific information. DATA SYNTHESIS: Interferon beta products are more efficacious for the treatment of relapsing-remitting multiple sclerosis. Interferon beta 1-b also delayed the time to diagnosis of definite multiple sclerosis and reduced brain lesion burden in patients with clinical isolated syndrome. Glatiramer and natalizumab have both established efficacy in relapsing forms of multiple sclerosis; whereas mitoxantrone is more commonly used in patients with advanced disease. There are limited data the comparative efficacy among different disease modifying agents. New agents currently under investigation have showed promising results and may offer more treatment options in the future. CONCLUSIONS: MS is a complex and devastating disease with challenging treatment considerations and approaches. Interferon beta products continue to be the mainstay of therapy in many patients, however, other treatments are proving to be at least as effective in the management of various types of MS. Newer compounds are being developed and studied with much anticipation and promise for the clinical management of the disease.
PMCID: PMC3024587 PMID: 21258574 [PubMed - in process]

201. PLoS One. 2011 Jan 13;6(1):e16149.
Smoking and multiple sclerosis: an updated meta-analysis.
Handel AE, Williamson AJ, Disanto G, Dobson R, Giovannoni G, Ramagopalan SV.
Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom.
BACKGROUND: Multiple sclerosis (MS) is a leading cause of disability in young adults. Susceptibility to MS is determined by environmental exposure on the background of genetic risk factors. A previous meta-analysis suggested that smoking was an important risk factor for MS but many other studies have been published since then. METHODS/PRINCIPAL FINDINGS: We performed a Medline search to identify articles published that investigated MS risk following cigarette smoking. A total of 14 articles were included in this study. This represented data on 3,052 cases and 457,619 controls. We analysed these studies in both a conservative (limiting our analysis to only those where smoking behaviour was described prior to disease onset) and non-conservative manner. Our results show that smoking is associated with MS susceptibility (conservative: risk ratio (RR) 1.48, 95% confidence interval (CI) 1.35-1.63, p<10(-15); non-conservative: RR 1.52, 95% CI 1.39-1.66, p<10(-19)). We also analysed 4 studies reporting risk of secondary progression in MS and found that this fell just short of statistical significance with considerable heterogeneity (RR 1.88, 95% CI 0.98-3.61, p□=□0.06). DISCUSSION: Our results demonstrate that cigarette smoking is important in determining MS susceptibility but the effect on the progression of disease is less certain. Further work is needed to understand the mechanism behind this association and how smoking integrates with other established risk factors.
PMCID: PMC3020969 PMID: 21249154 [PubMed - in process]

202. PLoS One. 2011 Jan 10;6(1). doi: 10.1371/annotation/b1ff1c14-fa84-40a0-b095-e5ee47c74125.
Correction: A β-Lactam Antibiotic Dampens Excitotoxic Inflammatory CNS Damage in a Mouse Model of Multiple Sclerosis.
Melzer N, Meuth SG, Torres-Salazar D, Bittner S, Zozulya AL, Weidenfeller C, Kotsiari A, Stangel M, Fahlke C, Wiendl H.
[This corrects the article on p. e3149 in vol. 3.].
PMCID: PMC3021488 PMID: 21264279 [PubMed - in process]

203. PLoS One. 2010 Dec 30;5(12):e16009.
Repetitive pertussis toxin promotes development of regulatory T cells and prevents central nervous system autoimmune disease.
Weber MS, Benkhoucha M, Lehmann-Horn K, Hertzenberg D, Sellner J, Santiago-Raber ML, Chofflon M, Hemmer B, Zamvil SS, Lalive PH.
Department of Neurology, Technische Universität München, Munich, Germany. m.weber@lrz.tu-muenchen.de
Bacterial and viral infections have long been implicated in pathogenesis and progression of multiple sclerosis (MS). Incidence and severity of its animal model experimental autoimmune encephalomyelitis (EAE) can be enhanced by concomitant administration of pertussis toxin (PTx), the major virulence factor of Bordetella pertussis. Its adjuvant effect at the time of immunization with myelin antigen is attributed to an unspecific activation and facilitated migration of immune cells across the blood brain barrier into the central nervous system (CNS). In order to evaluate whether recurring exposure to bacterial antigen may have a differential effect on development of CNS autoimmunity, we repetitively administered PTx prior to immunization. Mice weekly injected with PTx were largely protected from subsequent EAE induction which was reflected by a decreased proliferation and pro-inflammatory differentiation of myelin-reactive T cells. Splenocytes isolated from EAE-resistant mice predominantly produced IL-10 upon re-stimulation with PTx, while non-specific immune responses were unchanged. Longitudinal analyses revealed that repetitive exposure of mice to PTx gradually elevated serum levels for TGF-β and IL-10 which was associated with an expansion of peripheral CD4(+)CD25(+)FoxP3(+) regulatory T cells (Treg). Increased frequency of Treg persisted upon immunization and thereafter. Collectively, these data suggest a scenario in which repetitive PTx treatment protects mice from development of CNS autoimmune disease through upregulation of regulatory cytokines and expansion of CD4(+)CD25(+)FoxP3(+) Treg. Besides its therapeutic implication, this finding suggests that encounter of the immune system with microbial products may not only be part of CNS autoimmune disease pathogenesis but also of its regulation.
PMCID: PMC3012729 PMID: 21209857 [PubMed - in process]

204. PLoS One. 2010 Dec 22;5(12):e15632.
No evidence for XMRV in German CFS and MS patients with fatigue despite the ability of the virus to infect human blood cells in vitro.
Hohn O, Strohschein K, Brandt AU, Seeher S, Klein S, Kurth R, Paul F, Meisel C, Scheibenbogen C, Bannert N.
Centre for Biological Security 4, Robert Koch-Institute, Berlin, Germany.
BACKGROUND: Xenotropic murine leukemia virus-related virus (XMRV), a novel human retrovirus originally identified in prostate cancer tissues, has recently been associated with chronic fatigue syndrome (CFS), a disabling disease of unknown etiology affecting millions of people worldwide. However, several subsequent studies failed to detect the virus in patients suffering from these illnesses or in healthy subjects. Here we report the results of efforts to detect antibody responses and viral sequences in samples from a cohort of German CFS and relapsing remitting multiple sclerosis (MS) patients with fatigue symptoms.
METHODOLOGY: Blood samples were taken from a cohort of 39 patients fulfilling the Fukuda/CDC criteria (CFS), from 112 patients with an established MS diagnosis and from 40 healthy donors. Fatigue severity in MS patients was assessed using the Fatigue Severity Scale (FSS). Validated Gag- and Env-ELISA assays were used to screen sera for XMRV antibodies. PHA-activated PBMC were cultured for seven days in the presence of IL-2 and DNA isolated from these cultures as well as from co-cultures of PBMC and highly permissive LNCaP cells was analyzed by nested PCR for the presence of the XMRV gag gene. In addition, PBMC cultures were exposed to 22Rv1-derived XMRV to assess infectivity and virus production.
CONCLUSION: None of the screened sera from CFS and MS patients or healthy blood donors tested positive for XMRV specific antibodies and all PBMC (and PBMC plus LNCaP) cultures remained negative for XMRV sequences by nested PCR. These results argue against an association between XMRV infection and CFS and MS in Germany. However, we could confirm that PBMC cultures from healthy donors and from CFS patients can be experimentally infected by XMRV, resulting in the release of low levels of transmittable virus.
PMCID: PMC3008728 PMID: 21203514 [PubMed - in process]

205. Proc Natl Acad Sci U S A. 2011 Feb 1;108(5):2040-5. Epub 2011 Jan 18.
Neuropilin-1 attenuates autoreactivity in experimental autoimmune encephalomyelitis.
Solomon BD, Mueller C, Chae WJ, Alabanza LM, Bynoe MS.
Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853.
Neuropilin-1 (Nrp1) is a cell surface molecule originally identified for its role in neuronal development. Recently, Nrp1 has been implicated in several aspects of immune function including maintenance of the immune synapse and development of regulatory T (T(reg)) cells. In this study, we provide evidence for a central role of Nrp1 in the regulation of CD4 T-cell immune responses in experimental autoimmune encephalitis (EAE). EAE serves as an animal model for the central nervous system (CNS) inflammatory disorder multiple sclerosis (MS). EAE is mediated primarily by CD4(+) T cells that migrate to the CNS and mount an inflammatory attack against myelin components, resulting in CNS pathology. Using a tissue-specific deletion system, we observed that the lack of Nrp1 on CD4(+) T cells results in increased EAE severity. These conditional knockout mice exhibit preferential T(H)-17 lineage commitment and decreased T(reg)-cell functionality. Conversely, CD4(+) T cells expressing Nrp1 suppress effector T-cell proliferation and cytokine production both in vivo and in vitro independent of T(reg) cells. Nrp1-mediated suppression can be inhibited by TGF-β blockade but not by IL-10 blockade. These results suggest that Nrp1 is essential for proper maintenance of peripheral tolerance and its absence can result in unchecked autoreactive responses, leading to diseases like EAE and potentially MS.
PMID: 21245328 [PubMed - in process]

206. Psychol Health Med. 2011 Jan;16(1):1-11.
Effects of change in fatigue and depression on physical activity over time in relapsing-remitting multiple sclerosis.
Motl RW, McAuley E, Wynn D, Suh Y, Weikert M.
Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, Urbana, IL, USA. robmotl@uiuc.edu
This prospective, observational study examined the effects of change in the symptoms of fatigue and depression on physical activity over time in persons with relapsing-remitting multiple sclerosis (RRMS). Adults with a confirmed diagnosis of RRMS completed a battery of questionnaires at baseline (n = 269) and six-month follow-up (n = 263). The data were analyzed using linear panel analysis and covariance modeling in Mplus 3.0. The panel model fit the data ($\chi(2) = 24.00$, df = 15, $p = 0.07$, SRMR = 0.04, CFI = 0.98) and demonstrated that changes in both fatigue (path coefficient = -0.09) and depressive symptoms (path coefficient = -0.12) were significantly associated with residual change in physical activity. Such findings support the importance of fatigue and depression for predicting longitudinal changes in physical activity in adults with RRMS.
PMID: 21218359 [PubMed - in process]

207. Qual Life Res. 2011 Jan 19. [Epub ahead of print]
Using structural equation modeling to detect response shift in performance and health-related quality of life scores of multiple sclerosis patients.
King-Kallimanis BL, Oort FJ, Nolte S, Schwartz CE, Sprangers MA.
Department of Medical Psychology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.
PURPOSE: To illustrate how structural equation modeling (SEM) can be used for response shift detection with random measurement occasions and health state operationalized as fixed group membership (Study 1) or with fixed measurement occasions and health state operationalized as time-varying covariates (Study 2). METHODS: In Study 1, we explored seven items of the Performance Scales measuring physical and mental aspects of perceived disability of 771 stable, 629 progressive, and 1,552 relapsing MS patients. Time lags between the three measurements varied and were accounted for by introducing time since diagnosis as an exogenous variable. In Study 2, we considered the SF-12 scales measuring physical and mental components of HRQoL of 1,767 patients. Health state was accounted for by exogenous variables relapse (yes/no) and symptoms (worse/same/better). RESULTS: In Study 1, progressive and relapsing patients reported greater disability than stable patients but little longitudinal change. Some response shift was found with stable and relapsing patients. In Study 2, relapse and symptoms were associated with HRQoL, but no change and only little response shift was found. CONCLUSIONS: While small response shifts were found, they had little impact on the evaluation of true change in performance and HRQoL.
PMID: 21246289 [PubMed - as supplied by publisher]

208. Radiol Med. 2011 Jan 12. [Epub ahead of print]
Videourodynamics in patients with neurogenic bladder due to multiple sclerosis: our experience.
Caramella D, Donatelli G, Armillotta N, Manassero F, Traversi C, Frumento P, Pistolesi D, Selli C.
Radiologia Diagnostica e Interventistica, Università di Pisa, Pisa, Italy.
PURPOSE: The aims of this study were to: (a) analyse the most frequent morphofunctional features of the lower urinary tract observed during videourodynamic examination in patients with neurogenic bladder due to multiple sclerosis; (b) investigate the role of the videourodynamic examination in the clinical management of these patients; and (c) demonstrate the relationship between morphological and functional variables. MATERIALS AND METHODS: We performed videourodynamic examinations in 75 patients affected by neurogenic bladder secondary to multiple sclerosis. RESULTS: The introduction of pharmacological therapy, based on clinical and functional evaluation of the lower urinary tract, is correlated with satisfactory morphofunctional outcomes, reducing moderate-to-severe postvoid residual (PVR; $p < 0.1$) and compliance ($p < 0.05$) at the price of reduced bladder sensation. Clinical management of these patients based on morphological evaluation of the lower urinary tract decreased the occurrence of detrusor-sphincter dyssynergy (DSD) and detrusor overactivity incontinence at the following examination. CONCLUSIONS: Our study confirmed a relationship between detrusor overactivity and hypertonic bladder, bladder diverticula, vesicoureteral reflux, between detrusor underactivity and PVR and between DSD and bladder diverticula. Our data show how the videourodynamic examination may improve evaluation and urological management of these patients.
PMID: 21225364 [PubMed - as supplied by publisher]

209. Rev Neurol. 2011 Jan 16;52(2):127.
[The social dimension of the quality of life in multiple sclerosis.]
[Article in Spanish]
Rivera-Navarro J, Benito-Leon J.
Universidad de Salamanca. Facultad de Ciencias Sociales, Salamanca, Espana.
PMID: 21271554 [PubMed - as supplied by publisher]

210. Rev Neurol. 2011 Jan 16;52(2):127-128.
[The social dimension of the quality of life in multiple sclerosis. Reply.]
[Article in Spanish]
Olascoaga J.
Hospital Donostia, 20014 San Sebastian, Espana.
PMID: 21271553 [PubMed - as supplied by publisher]

211. Telemed J E Health. 2011 Jan 9. [Epub ahead of print]
Web-Based Self-Management for Patients with Multiple Sclerosis: A Practical, Randomized Trial.
Miller DM, Moore SM, Fox RJ, Atreja A, Fu AZ, Lee JC, Saupe W, Stadtler M, Chakraborty S, Harris CM, Rudick RA.
1 Cleveland Clinic , Cleveland, Ohio.
Abstract Objective: No studies have addressed the use of electronic personal health records (e-PHRs) for self-management in complex neurological disorders. We assessed and tested an Internet-based self-management system that utilized the e-PHR and determined its impact on self-assessed well-being, clinician-assessed well-being, and healthcare utilization in patients with multiple sclerosis (MS). Materials and Methods: Subjects were randomized to usual care (a secure Web-based messaging system) or active intervention, which included secure messaging, self-monitoring, self-management of MS symptoms, and communication about upcoming clinic visits. Computers and Internet access were provided. Subjects were included if they had MS, lived within the county or region surrounding our MS center, had at least two appointments at our center in the previous 12 months, and demonstrated basic typing and computer skills. Study duration was 12 months. Results: Of 220 subjects completing informed consent, 206 met the inclusion criteria. At the study's end, 83 subjects remained in the usual care group and 84 in the enhanced care group. Both groups used the available system components. The groups did not significantly differ on the primary endpoints or healthcare utilization. Conclusions: Self-management support is an emerging aspect of chronic care management. We established the feasibility of conducting a randomized, controlled trial using e-PHRs for patient self-management. We did not find that e-PHR-enabled self-management augmented multidisciplinary MS center-based care, possibly because the differences between interventions were not great enough.
PMID: 21214498 [PubMed - as supplied by publisher]

212. Thorax. 2011 Jan 13. [Epub ahead of print]
Sarcoidosis complicating treatment with natalizumab for Crohn's disease.
Parisinos CA, Lees CW, Wallace WA, Satsangi J.
Gastrointestinal Unit, Western General Hospital, Edinburgh, UK.
Natalizumab is a humanised monoclonal antibody targeting the lymphocyte adhesion molecule a4 integrin, with proven efficacy in multiple sclerosis (MS) and Crohn's disease (CD). The development of sarcoidosis with extrapulmonary involvement is reported in two patients with refractory CD who had received maintenance therapy with natalizumab. This complication has not been previously reported. It is hypothesised that the effect of natalizumab in altering lymphocyte mucosal trafficking may underlie the development of sarcoidosis in these patients.
PMID: 21233484 [PubMed - as supplied by publisher]

213. Trends Mol Med. 2011 Jan 18. [Epub ahead of print]
EAE: imperfect but useful models of multiple sclerosis.
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Department of Immunobiology, Biomedical Primate Research Center, Lange Kleiweg 161, 2288 GJ Rijswijk, The Netherlands; Department of Medical Physiology, University Medical Center Groningen, Groningen, The Netherlands; Department of Immunology, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands; MS Center ErasMS, Rotterdam, The Netherlands.
The high failure rate of immunotherapies in multiple sclerosis (MS) clinical trials demonstrates problems in translating new treatment concepts from animal models to the patient. One main reason for this 'immunotherapy gap' is the usage of immunologically immature, microbiologically clean and genetically homogeneous rodent strains. Another reason is the artificial nature of the experimental autoimmune encephalomyelitis model, which favors CD4+ T cell driven autoimmune mechanisms, whereas CD8+ T cells are prevalent in MS lesions. In this paper, we discuss preclinical models in humanized rodents and non-human primates that are genetically closer to MS. We also discuss models that best reproduce specific aspects of MS pathology and how these can potentially improve preclinical selection of promising therapies from the discovery pipeline.
PMID: 21251877 [PubMed - as supplied by publisher]

214. Ugeskr Laeger. 2011 Jan 10;173(2):123-6.
[Risk of affective disorder in multiple sclerosis].
[Article in Danish]
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An increased risk for depression has been found in multiple sclerosis (MS). The purpose of the present study has been to give suggestions to guidelines for diagnosis and treatment of depression in MS in Denmark based on the international literature and recommendations. The method was a review of the relevant literature. The study recommends assessment of all MS patients for depression. Treatment of depression with serotonin reuptake inhibitors and/or cognitive behavioural therapy is recommended, depending on the severity of the illness. Caution is recommended in patients receiving beta interferon treatment.
PMID: 21219844 [PubMed - indexed for MEDLINE]

215. Value Health. 2011 Jan;14(1):61-9.
The economic burden of Medicare-eligible patients by multiple sclerosis type.
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JEN Associates, Inc., Cambridge, MA, USA.
OBJECTIVE: Although the global rate of multiple sclerosis (MS) is low, a few studies have documented high costs. Costs are highly variable depending on MS stage. This study was designed to assess the economic burden of Medicare-eligible patients by MS type in the United States using a claims-based classification algorithm to examine cost variation by disease stage. METHODS: A sample of 2003 to 2006 Medicare patients was selected. Cases were classified as pre-existing progressive MS or pre-existing relapsing-remitting MS (RRMS); the latter were further subdivided into relapsing, remitting, or stable. RESULTS: The sample had 5044 MS subjects, of whom 34.4% had prevalent progressive MS and 65.6% had prevalent RRMS. There were many chronic, comorbid conditions. The mean all-cause Medicare expenditures (not including self-administered medications) per person-year for MS in 2006 were $23,630 for prevalent progressive patients and $5887 for prevalent RRMS patients. Within the RRMS type, Medicare expenditures per person per month in 2006 were $1418 for relapsing patients, $608 for remitting patients, and $331 for stable patients. CONCLUSIONS: There are substantial cost advantages to Medicare for keeping RRMS patients in a stable health state and in keeping them from advancing in disability severity. The overall cost advantage would be diminished by the large cost burden of comorbidity, which would likely remain fixed with improved MS therapies.
PMID: 21211487 [PubMed - in process]

217. Zhonghua Nei Ke Za Zhi. 2010 Nov;49(11):935-938.

[Serum uric acid level and related clinical features in neuromyelitis optica.]

[Article in Chinese]

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OBJECTIVE: To investigate serum uric acid (UA) levels and related clinical characteristics of neuromyelitis optica (NMO). METHODS: The serum uric acid levels were measured in 65 patients with NMO, compared to control groups which were 76 cases with multiple sclerosis (MS), 126 cases with cerebral vascular diseases (CVD) and 130 healthy controls (HC). The disability severity in NMO was assessed by the Expanded Disability Status Scale (EDSS). Magnetic resonance imaging (MRI) was performed to strengthen assessment the involved lesions. Serum AQP4 antibody was tested in a cell based immunofluorescence assay. RESULTS: In male groups, serum UA levels in NMO patients [(298.90 ± 74.14) μmol/L] were significantly lower than that in CVD [(355.37 ± 50.30) μmol/L] and HC subjects [(340.33 ± 58.23) μmol/L, $P < 0.05$]. No difference was found between NMO and MS [(292.36 ± 92.95) μmol/L] groups. In female groups, serum UA levels in NMO patients [(198.21 ± 62.62) μmol/L] were significantly lower than that in CVD [(274.51 ± 70.66) μmol/L] and HC subjects [(243.26 ± 60.65) μmol/L, $P < 0.05$]. No difference was found between NMO and MS [(232.29 ± 71.95) μmol/L] groups. UA levels were significantly lower in females [(198.21 ± 62.62) μmol/L] than in males [(298.90 ± 74.14) μmol/L]. UA levels were significantly lower in patients with EDSS ≥ 5 [(195.48 ± 83.70) μmol/L] than EDSS < 5 [(241.00 ± 63.20) μmol/L] NMO patients. In our study UA levels were not correlated with longitude of spinal lesions, activity revealed by MRI and AQP4 antibody tires. CONCLUSION: Lower serum UA levels were found in patients with NMO and related to more severe symptoms.

PMID: 21211206 [PubMed - as supplied by publisher]