Literatur-Dauerrecherche

Multiple Sklerose

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Schüttelfrost, Schwitzen, Unwohlsein.

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Harnprotein, häufi ge Blasenentleerung, Harninkontinenz, starker Harndrang, nephrotisches Syndrom, Glomerulosklerose, ... Nekrose an der Injektionsstelle, grippeähnliche Symptome, Fieber, Schmerzen, Thoraxschmerzen, periphere Ödeme, Asthenie,

Hypertonie, Infektionen der oberen Atemwege, Sinusitis, vermehrtes Husten, Dyspnoe, Urtikaria, Pruritus, Alopezie, ... Hautausschlag, Konjunktivitis, Sehstörungen, Ohrenschmerzen, Vasodilatation, Hypertonie, Harnverhaltung, pos.

Krampfanfälle, Kopfschmerzen, Schwindel, Schlafl osigkeit, Migräne, Parästhesie, Verwirrtheit, Suizidversuch, emotionale ... Angst, Menorrhagie, Dysmenorrhoe, Menstruationsstörungen, Metrorrhagie, Impotenz, Bronchospasmus, pulmonale arterielle urämisches Syndrom, Neutropenie, Leukopenie, Lymphadenopathie, Palpitationen, Kardiomyopathie, Tachykardie, Hypothyreose, ... Schilddrüsenerkrankungen, Diarrhoe, Verstopfung, Übelkeit, Erbrechen, abdominelle Schmerzen, Pankreatitis, Anstieg der

Auftitrierung der Dosis empfohlen, um die Verträglichkeit von Betaferon zu verbessern. Grippeähnliche Symptome lassen ... eines nicht-steroidalen Entzündungshemmers verringern. Die Häufigkeit von Reaktionen an der Injektionsstelle

Wirkungen häufi ge, diese klingen aber im Allgemeinen bei weiterer Behandlung ab. Die am häufi gsten beobachteten ... waren ein grippeähnlicher Symptomenkomplex und Reaktionen an der Injektionsstelle. Zu Beginn der Behandlung wird eine


Nebenwirkungen:

manifestierte. Die Ereignisse wurden zu unterschiedlichen Zeitpunkten während der Behandlung gemeldet und können mehrere ... Jahre nach Beginn der Behandlung mit Interferon beta auftreten. Bei Diagnose einer TMA ist eine umgehende Behandlung

kardiotoxische Wirkung, Grippe-ähnliche Symptome, die unter Beta-Interferonen auftreten können, sich für Patienten mit vorbestehender relevanter Herzerkrankung jedoch als belastend erweisen. Seltene Fälle von Kardiomyopathie wurden berichtet.

Symptome, besonders bei Patienten mit einem erhöhten Risiko von Nierenerkrankungen, wird empfohlen. Eine sofortige ... Syndroms ist erforderlich und ein Abbruch der Behandlung mit Betaferon sollte in Erwägung gezogen werden. Vorsicht

1. Nabilone for Chronic Pain Management: A Review of Clinical Effectiveness and Guidelines [Internet].
Kim J, Grobelna A. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Aug. CADTH Rapid Response Reports.

People with diseases that were once considered generally fatal, such as cancer and HIV/AIDS, are now surviving their acute illness with an increased quantity of life. However, in many cases, a poor quality of life (QoL) ensues due to chronic pain caused by persisting illness, ongoing treatment, or lasting damage after resolution or cure of the disease. Chronic pain, also caused by many other conditions, such as fibromyalgia, multiple sclerosis (MS), and neuropathy, is difficult to treat, a major contributor to time away from work, and associated with increased risk of suicide.

PMID: 29949325

2. The role of magnesium in edema and blood brain barrier disruption.

Author information: (1)Discipline of Anatomy and Pathology & Adelaide Centre for Neuroscience Research, School of Medical Sciences, The University of Adelaide, Adelaide, South Australia, Australia (2)Department of Pharmacology, “Gr. T. Popa” University of Medicine and Pharmacy, Iasi, Romania (3)Departments of Physiology and of Histology and Embryology, Istanbul Faculty of Medicine, Istanbul University, Capa 34093 Istanbul, Turkey.

The blood-brain barrier (BBB) is constituted primarily of brain capillary endothelial cells and is a prerequisite for the maintenance of brain homeostasis that is essential for optimal brain function. However, a variety of pathological conditions, such as sepsis, multiple sclerosis and epilepsy disrupt the BBB integrity and lead to the development of brain edema. Ionized magnesium (Mg2+) is a crucial cofactor that plays an essential role within the cell and regulates a variety of biochemical reactions. Changes in intra- and extracellular Mg2+ concentrations influence the functions of cells and tissues. A growing body of evidence suggests that Mg2+ plays a pivotal role in ameliorating BBB disruption via a number of mechanisms during certain neurological diseases. Systemic delivery of Mg2+ may constitute an alternative approach in the future, both to improve BBB integrity and to decrease brain edema in the course of a variety of diseases involving brain tissue.

PMID: 29920006

Sturgill EL(1), Wittwer RL.

Author information: (1)From the Wright-Patterson Medical Center, Wright-Patterson Air Force Base, Ohio.

Patients with upper motor neuron disease, such as multiple sclerosis, can present with severe spasticity in the perioperative period. In most cases, this can be managed with a combination of preoperative oral medications, regional or neuraxial anesthetic techniques, and intravenous muscle relaxants. We describe the clinical presentation of a patient with multiple sclerosis and the successful use of intravenous dantrolene sodium postoperatively for the treatment of exacerbated spasticity refractory to traditional management.

DOI: 10.1213/XAA.0000000000000801 PMID: 29851691

Prox1 is essential for oligodendrocyte survival and regulates oligodendrocyte apoptosis via the regulation of NOXA.

Chang W(1), Teng J(2).

Author information: (1)Department of Neurology, the Center Hospital of Xinxiang, Xinxiang, China. (2)Department of Neurology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou University, Zhengzhou, China.

Demyelinating diseases, such as multiple sclerosis, are known to result from acute or chronic injury to the myelin shear and inadequate remyelination. Its underlying molecular mechanisms, however, remain unclear. The transcription factor prospero homeobox 1 (Prox1) plays an essential role during embryonic development of the central nervous system and cell differentiation. Thus, we aimed to investigate the role of Prox1 in the survival and differentiation of oligodendrocytes. Cell viability was measured by MTT assay. Flow cytometry was conducted to analyze cell apoptosis. Ectopic-Prox1 and shProx1 were used for the overexpression and knockdown respectively of Prox1 in FBD-102b cells. Real-time reverse transcriptase polymerase chain reaction and western blot analysis were used to assess the alterations of signaling pathway-related mRNAs and proteins, respectively. Results showed that Prox1 was upregulated in differentiating oligodendrocytes, and Prox1 knockdown inhibited the differentiation of oligodendrocytes. In addition, overexpression of Prox1 promoted oligodendrocyte differentiation, as shown by the change in myelin basic protein expression. The overexpression of Prox1 had no effect on oligodendrocyte survival, while Prox1 knockdown impaired cell survival. Further study demonstrated that Prox1 knockdown promoted oligodendrocyte apoptosis and activated NOXA, a pro-apoptotic member of the Bcl-2 protein family. Knockdown of NOXA by siRNA abrogated Prox1 knockdown-induced apoptosis. Our findings indicated that Prox1 regulated the differentiation of oligodendrocyte precursor cells via the regulation of NOXA. Therefore, Prox1 could be a potential modulator of demyelinating diseases in clinical settings.

DOI: 10.1093/abbs/gmy061  PMID: 29931031


Gpr97/Adgrg3 ameliorates experimental autoimmune encephalomyelitis by regulating cytokine expression.


Author information: (1)Shanghai Research Center for Model Organisms, Shanghai 201203, China. (2)Department of Medical Genetics, Shanghai Jiao Tong University School of Medicine (SJTUSM), Shanghai 200025, China. (3)State Key Laboratory of Medical Genomics, Research Center for Experimental Medicine of Rui-Jin Hospital, Shanghai 200025, China.

Multiple sclerosis and its primary animal model, experimental autoimmune encephalomyelitis (EAE), are inflammatory diseases of the central nervous system (CNS) characterized by immune-mediated demyelination and neurodegeneration that may be mediated by inhibition of the nuclear factor-κB (NF-κB) signaling pathway. Gpr97, encoded by Adgrg3, has been reported to regulate the activity of NF-κB. In this study, using a previously established Adgrg3-knockout mouse model, we investigated the roles of Gpr97 in the development of autoimmune CNS disease in mice. We found a marked increase in the expression of Adgrg3 in spinal cords of mice with EAE. Adgrg3-deficient (Adgrg3/-/-) mice with EAE exhibited increases in peak severity and the cumulative disease score compared with littermate controls, followed by a notable increase of leukocyte infiltration and more extensive demyelination. The percentages of Th1/Th17 cells in the CNS were significantly increased in Adgrg3/-/- mice and accompanied by high levels of interleukin (IL)-6, interferon-γ, tumor necrosis factor-α, and IL-17. An in vitro culture assay verified that Gpr97 regulated proinflammatory cytokine production. Taken together, our results show that Gpr97 plays an important role in the development of EAE and may have a therapeutic potential for the treatment of CNS autoimmunity.

DOI: 10.1093/abbs/gmy060  PMID: 29860267
Consensus Recommendations of the Multiple Sclerosis Study Group and Portuguese Neuroradiological Society for the Use of the Magnetic Resonance Imaging in Multiple Sclerosis in Clinical Practice: Part 1.

Abreu P(1), Pedrosa R(2), Sá MJ(3), Cerqueira J(4), Sousa L(5), Da Silva AM(6), Pinheiro J(7), De Sá J(8), Batista S(5), Simões RM(9), Pereira DJ(10), Vilela P(11), Vale J(9).


INTRODUCTION: Magnetic resonance imaging is established as a recognizable tool in the diagnosis and monitoring of multiple sclerosis patients. In the present, among multiple sclerosis centers, there are different magnetic resonance imaging sequences and protocols used to study multiple sclerosis that may hamper the optimal use of magnetic resonance imaging in multiple sclerosis. In this context, the Group of Studies of Multiple Sclerosis and the Portuguese Society of Neuroradiology, after a joint discussion, appointed a committee of experts to create recommendations adapted to the national reality on the use of magnetic resonance imaging in multiple sclerosis. The purpose of this document is to publish the first Portuguese consensus recommendations on the use of magnetic resonance imaging in multiple sclerosis in clinical practice. MATERIAL AND METHODS: The Group of Studies of Multiple Sclerosis and the Portuguese Society of Neuroradiology, after discussion of the topic in national meetings and after a working group meeting held in Figueira da Foz on May 2017, have appointed a committee of experts that have developed a joint discussion and reviewed the consensus paper; comments and suggestions were considered. Technical magnetic resonance imaging protocols regarding diagnostic, monitoring and the recommended information to be included in the magnetic resonance imaging report will be published in a separate paper. RESULTS: We provide some practical guidelines to promote standardized strategies to be applied in the clinical practice setting of Portuguese healthcare professionals regarding the use of magnetic resonance imaging in multiple sclerosis. CONCLUSION: We hope that these first Portuguese magnetic resonance imaging guidelines, based on the best available scientific evidence and practices, will serve to optimize multiple sclerosis management and improve multiple sclerosis patient care across Portugal.

Publisher: Introdução: A esclerose múltipla caracteriza-se pela presença de lesões inflamatórias a nível do encéfalo e medula espinhal. A ressonância magnética é atualmente um exame indispensável no diagnóstico, na avaliação da atividade da doença e na resposta ao tratamento. Embora na nossa prática as vantagens da ressonância magnética estejam bem estabelecidas, continuam a existir dificuldades técnicas (uso de sequências e protocolos não padronizados) e clínicas (frequência de exames não adequada) que podem dificultar o diagnóstico e o seguimento dos doentes. Neste contexto, o Grupo de Estudos de Esclerose Múltipla e a Sociedade Portuguesa de Neuroradiologia, após discussão conjunta, designaram um comité de peritos para a criação de recomendações adaptadas à realidade nacional sobre a utilização da ressonância magnética na esclerose múltipla. O objetivo deste documento é publicar as primeiras recomendação de consenso portuguesas sobre a utilização da ressonância magnética na esclerose múltipla clínica. Material e Métodos: O Grupo de Estudos de Esclerose Múltipla e a Sociedade Portuguesa de Neuroradiologia, após discussão do tema em reuniões de âmbito nacional e de uma reunião do grupo de trabalho que teve lugar na Figueira da Foz em maio de 2017, designaram um comité de peritos que elaboraram por método de consenso vários protocolos padronizados sobre o uso da ressonância magnética no diagnóstico e seguimento da esclerose múltipla. O documento teve como
base a melhor evidência científica e a opinião dos peritos. Posteriormente, o documento foi enviado para escrutínio a maioria dos responsáveis de consulta de esclerose múltipla e dos departamentos de neurorradiologia; os comentários e sugestões foram considerados. Os protocolos técnicos referentes à aquisição de imagem e a informação que deverá constar no relatório destes exames serão publicados numa publicação separada. Resultados: Neste artigo são propostas várias orientações práticas para promover estratégias padronizadas para serem aplicadas na prática clínica dos profissionais de saúde portugueses no que se refere ao uso da ressonância magnética na esclerose múltipla. Conclusão: Os autores esperam que estas primeiras orientações portuguesas, sobre a utilização da ressonância magnética na esclerose múltipla na prática clínica, baseadas nas melhores evidências e práticas clínicas disponíveis, sirvam para otimizar a gestão da esclerose múltipla e melhorar o tratamento destes doentes em Portugal. PMID: 29916361

7. Acta Neurol Belg. 2018 Jun 6. doi: 10.1007/s13760-018-0948-2. [Epub ahead of print] Tumefactive demyelinating lesions in a patient with multiple sclerosis receiving natalizumab. Moghadasi AN(1)(2), Baghbanian SM(3). Author information: (1)MS Research Centre, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran. (2)Sina Hospital, Tehran University of Medical Sciences, Hasan Abad Square, 11367-46911, Tehran, Iran. (3)Neurology Department, Booolisina Hospital, Mazandaran University of Medical Sciences, Pasdaran Boulevard, Sari, Iran. sm.baghbanian@mazums.ac.ir. DOI: 10.1007/s13760-018-0948-2 PMID: 29876751

8. Acta Neurol Belg. 2018 Jun 5. doi: 10.1007/s13760-018-0954-4. [Epub ahead of print] Identification of candidate biomarkers in converting and non-converting clinically isolated syndrome by proteomics analysis of cerebrospinal fluid. Timirci-Kahraman O(1), Karaaslan Z(2), Tuzun E(3), Kurtuncu M(2), Baykal AT(4), Gunduz T(2), Tuzuner MB(5), Akgun E(4), Gurel B(4), Eraksoy M(2), Kucukali CI(6). Author information: (1)Department of Molecular Medicine, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey. (2)Department of Neurology, Faculty of Medicine, Istanbul University, Istanbul, Turkey. (3)Department of Neuroscience, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey. (4)Department of Medical Biochemistry, Faculty of Medicine, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey. (5)Acibadem Labmed R&D Laboratory, Istanbul, Turkey. (6)Department of Neuroscience, Aziz Sancar Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey. cemsmile@gmail.com. Multiple sclerosis (MS) often starts in the form of clinically isolated syndrome (CIS) and only some of the CIS patients progress to relapsing-remitting MS (RRMS). Biomarkers to predict conversion from CIS to MS are thus greatly needed for making correct treatment decisions. To identify a predictive cerebrospinal fluid (CSF) protein, we analyzed the first-attack CSF samples of CIS patients who converted (CIS-MS) (n = 23) and did not convert (CIS-CIS) (n = 19) to RRMS in a follow-up period of 5 years using proteomics analysis by liquid chromatography tandem-mass spectrometry (LC-MS/MS) and verified by ELISA. Label-free differential proteomics analysis of CSF ensured that 637 proteins were identified and 132 of these proteins were found to be statistically significant. Further investigation with the ingenuity pathway analysis (IPA) software led to identification of three pathway networks mostly comprised proteins involved in inflammatory response, cellular growth and tissue proliferation. CSF levels of four of the most differentially expressed proteins belonging to the cellular proliferation network function, chitinase-3-like protein 1 (CHI3L1), tumor necrosis factor receptor superfamily member 21 (TNFRSF21), homeobox protein Hox-B3 (HOXB3) and iduronate 2-sulfatase (IDS), were measured by ELISA. CSF levels of HOXB3 were significantly increased in CIS-MS patients. Our results indicate that cell and tissue proliferation functions are dysregulated in MS as early as the first clinical episode. HOXB3 has emerged as a potential novel biomarker which might be used for prediction of CIS-MS conversion. DOI: 10.1007/s13760-018-0954-4 PMID: 29873030

**Free Kappa light chains in neuroinflammatory disorders: Complement rather than substitute?**

Bayart JL(1), Muls N(2), van Pesch V(1)(2)(3).

Author information: (1)Cliniques Universitaires Saint-Luc, Department of Laboratory Medicine, Université Catholique de Louvain, Brussels, Belgium. (2)Neurochemistry Unit, Institute of Neuroscience, Université Catholique de Louvain, Brussels, Belgium. (3)Cliniques Universitaires Saint-Luc, Neurology Department, Université Catholique de Louvain, Brussels, Belgium.

OBJECTIVES: The detection of cerebrospinal fluid (CSF)-specific IgG oligoclonal bands (OCB) by isoelectric focusing (IEF) is widely used to help diagnose inflammatory neurological disorders (IND), including multiple sclerosis. However, the quantification of free light chains (FLC) is increasingly evaluated as a surrogate method to determine the presence of an intrathecal inflammatory process. The objective of this study was to evaluate the diagnostic performance of kappa (κ) FLC measurement in comparison with OCB detection by IEF.

MATERIAL AND METHODS: We measured serum and CSF κFLCs by turbidimetry using the SPAplus automated analyser and calculated the κ index in 142 samples from OCB-positive and negative MS, as well as from patients with inflammatory and non-inflammatory neurological disorders (IND and NIND).

RESULTS: The κFLC index was significantly increased in OCB-positive MS and IND patients versus OCB-negative patients. Its performance was relatively comparable to that of IEF for MS diagnosis. When using a κFLC index cutoff value of 6.29, sensitivity increased from 61.2% to 75.7% in comparison with IEF for diagnosing IND (P = .0051), with a slightly lower non-statistically significant specificity (82.1% vs 100%). When considering both OCB status positivity or a κFLC index superior to 6.29 to diagnose IND status, sensitivity raised to 80.6% (P < .05) with an equal specificity.

CONCLUSION: Our results demonstrate that the κFLC index does not discriminate MS from other IND patients, but is a reliable technique to detect intrathecal inflammation. However, κFLC quantification should probably be considered as a complementary method, rather than a substitute, to OCB detection.

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Management of Moderate to Severe Psoriasis in Routine Clinical Practice in Spanish Hospitals.

[Article in English, Spanish]

Author information: (1)Servicio de Dermatología, Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, España. Electronic address: jjlopez@fhalcorcon.es. (2)Servicio de Dermatología, Hospital Universitario Infantia Leonor, Madrid, España. (3)Servicio de Dermatología, Complejo Hospitalario Universitario de Vigo, Vigo, Pontevedra, España. (4)Servicio de Dermatología, Hospital Universitario Reina Sofía, Córdoba, España. (5)Servicio de Dermatología, Hospital Clínico San Carlos, Madrid, España. (6)Servicio de Dermatología, Hospital Universitari del Vall d'Hebron, Barcelona, España. (7)Servicio de Dermatología, Hospital General Universitario de Alicante, Alicante, España.

BACKGROUND: There is currently little information available on the management of patients with psoriasis in the daily clinical practice of dermatologists in Spain. OBJECTIVE: The aim of this study was to survey a group of Spanish dermatologists with particular expertise in the management of psoriasis to determine their opinions on the protocols used in routine clinical practice. MATERIAL AND METHODS: A cross-sectional study based on an online survey about the management of psoriasis sent to 75 dermatologists. The survey, which was specifically designed for the study, included 12 questions on different aspects of clinical practice in the treatment of moderate to severe psoriasis. RESULTS: The response rate was 96% (n=72). Biologics were the most widely used monotherapy option. In total, 64.3% of respondents reported that their patients used conventional systemic therapies for 1 to 2 years before switching to a biologic drug and that the main reason for the switch was unstable control of disease activity. Overall, 85.7% assigned a “high” or “very high” importance to the use of a Psoriasis Area Severity Index score of <3 as a treatment goal. The drugs of choice among the respondents were etanercept for pediatric patients (78.6%), adalimumab and etanercept for patients with psoriatic arthritis (64.3%), and ustekinumab in patients frequently away from home (78.6%) and patients with a history of multiple sclerosis, demyelinating diseases (64.3%), or poor adherence to treatment (71.4%). CONCLUSION: This study provides a unique overview of the opinions of a representative sample of expert dermatologists on the current use of biologics for the treatment of psoriasis in Spain.

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Neoplasms of the Neuroendocrine Pancreas: An Update in the Classification, Definition, and Molecular Genetic Advances.

Guilmette JM(1), Nosé V.

Author information: (1)Departments of Pathology, Massachusetts General Hospital, Boston, MA.

This review focuses on discussing the main modifications of the recently published 2017 WHO Classification of Neoplasms of the Neuroendocrine Pancreas (panNEN). Recent updates separate pancreatic neuroendocrine tumors into 2 broad categories: well-differentiated pancreatic neuroendocrine tumors (panNET) and poorly differentiated pancreatic neuroendocrine carcinoma (panNEC), and incorporates a new subcategory of "well-differentiated high-grade NET (G3)" to the well-differentiated NET category. This new classification algorithm aims to improve the prediction of clinical outcomes and survival and help clinicians select better therapeutic strategies for patient care and management. In addition, these neuroendocrine neoplasms are capable of producing large quantities of hormones leading to clinical hormone hypersecretion syndromes. These functioning tumors include, insulinomas, glucagonomas, somatostatinomas, gastrinomas, VIPomas, serotonin-producing tumors, and ACTH-producing tumors. Although most panNENs arise as sporadic diseases, a subset of these heterogeneous tumors present as parts on inherited genetic syndromes, such as multiple endocrine neoplasia type 1, von Hippel-Lindau, neurofibromatosis type 1, tuberous sclerosis, and glucagon cell hyperplasia and neoplasia syndromes. Characteristic clinical and morphologic findings for certain functioning and syndromic panNENs should alert both pathologists and clinicians as appropriate patient management and possible genetic counseling may be necessary.

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CXCL9, CXCL10, CXCL11, and their receptor (CXCR3) in neuroinflammation and neurodegeneration.

Koper OM(1), Kamińska J(1), Sawicki K(2), Kemona H(1).

Author information: (1)Department of Clinical Laboratory Diagnostics, Medical University of Białystok, Poland. (2)Department of Neurosurgery, Medical Clinical Hospital in Białystok, Poland.

The aim of this review is to present data from the available literature concerning CXCL9, CXCL10 and CXCL11, as well as their receptor 3 (CXCR3) in selected diseases of the central nervous system (CNS), such as tickborne encephalitis (TBE), neuroborreliosis (NB), Alzheimer's disease (AD), and multiple sclerosis (MS). CXCL9, CXCL10, and CXCL11 lack glutamic acid-leucine-arginine (ELR), and are unique, because they are more closely related to each other than to any other chemokine. The aforementioned chemokines are especially involved in Th1-type response and in various diseases, as their expression correlates with the tissue infiltration of T cells. Their production is strongly induced by interferon gamma (IFN-γ), the most typical Th1 cytokine. They act by binding to the CXC3 receptor. Knowledge about the action mechanism of CXCR3 and its ligands may be useful in the treatment of CNS diseases. However, data in the literature concerning the evaluation of CXCL9, CXCL10, CXCL11, and their receptor with the use of the enzyme-linked immunosorbent assay (ELISA) method is limited.

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Waliszewska-Prosoł M(1), Nowakowska-Kotas M(1), Kotas R(2), Bańkowski T(3), Pokryszko-Dragan A(1), Podemski R(1).

Author information: (1)Department of Neurology, Wroclaw Medical University, Poland. (2)Department of Psychiatry, Regional Specialist Hospital, Legnica, Poland. (3)Department of Cardiology, Wroclaw Medical University, Poland.

BACKGROUND: The clinical course of multiple sclerosis (MS) can vary significantly among patients and is affected by exogenous and endogenous factors. Among these, stress and personality type have been gaining more attention. OBJECTIVES: The aim of this study was to investigate the parameters of event-related potentials (ERPs) with regards to stress perception and personality type, as well as cognitive performance in MS patients. MATERIAL AND METHODS: The study group consisted of 30 MS patients and 26 healthy controls. Auditory ERPs were performed in both groups, including an analysis of P300 and N200 response parameters. The Perceived Stress Scale (PSS) was used in the MS group to measure the perception of stress. The D-type Scale (DS14) scale was used to determine the features of Type D personality, characterized by social inhibition and negative affectivity. RESULTS: The score on the PSS corresponded with a moderate or high level of stress perception in 63% of MS patients, while 23% of patients presented with a Type D personality. P300 latencies were significantly longer (p = 0.001), N200 amplitudes were significantly higher (p = 0.004), and N200 latencies were longer in MS patients than in the controls. Strong positive correlations were found between N200 and P300 amplitudes, as well as between the DS14 and PSS results. CONCLUSIONS: Most MS patients experience moderate to severe stress. ERP abnormalities were found in MS patients who did not have overt cognitive impairment and showed correlations with stress levels and negative affectivity. Event-related potentials may be useful in assessing the influence of stress and emotions on the course of MS.

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Pathophysiological implications of actin-free Gc-globulin concentration changes in blood plasma and cerebrospinal fluid collected from patients with Alzheimer’s disease and other neurological disorders.

Kulakowska A(1), Tarasiuk J(1), Kapica-Topczewska K(1), Chorąży M(1), Pogorzelski R(1), Kulczyńska-Przybik A(2), Mroczo B(2), Bucki R(3).

Author information: (1)Department of Neurology, Medical University of Białystok, Poland. (2)Department of Neurodegeneration Diagnostics, Medical University of Białystok, Poland. (3)Department of Microbiological and Nanobiomedical Engineering, Medical University of Białystok, Poland.

BACKGROUND: The extracellular actin scavenging system (EASS) is composed of plasma Gc-globulin and gelsolin, and is responsible for the elimination of toxic actin from the bloodstream. OBJECTIVES: In this study, we assessed the actin-free Gc-globulin concentrations in blood plasma and cerebrospinal fluid (CSF) obtained from subjects with neurodegenerative and inflammatory diseases of the central nervous system (CNS) as well as in a control group. MATERIAL AND METHODS: Using an enzyme-linked immunosorbent assay (ELISA), we measured the actinfree Gc-globulin concentrations in blood plasma and CSF obtained from subjects diagnosed with Alzheimer's disease (AD) (n = 20), amyotrophic lateral sclerosis (ALS) (n = 12), multiple sclerosis (MS) (n = 42), tick-borne encephalitis (TBE) (n = 12), and from a control group (n = 20). RESULTS: The concentrations of free Gc-globulin in plasma collected from patients diagnosed with AD (509.6 ±87.6 mg/L) and ALS (455.5 ±99.8 mg/L) did not differ significantly between each other, but were significantly higher compared to the reference group (311.7 ±87.5 mg/L) (p < 0.001 and p < 0.006, respectively) as well as to MS (310.8 ±66.6 mg/L) (p < 0.001 and p < 0.001, respectively) and TBE (256.7 ±76 mg/L) (p < 0.001 and p < 0.003, respectively). In CSF collected from patients diagnosed with AD and ALS, the concentrations of free Gc-globulin were 2.6 ±1.1 mg/L and 2.7 ±1.9 mg/L, respectively. They did not differ significantly between each other and were significantly higher compared to the reference group (1.5 ±0.9 mg/L) (p < 0.005 and p < 0.041, respectively). Interestingly, in patients with AD, significantly higher values of Gcglobulin were detected compared to multiple sclerosis patients (1.7 ±0.9 mg/L) (p < 0.013). CONCLUSIONS: Higher concentrations of free Gc-globulin in blood plasma and CSF collected from patients suffering from neurodegenerative diseases may indicate a potential role of this protein in their pathogenesis, and represent a potential tool for the diagnosis of CNS diseases.

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Vaccine Development for Epstein-Barr Virus.

Cohen JI(1).

Author information: (1)Laboratory of Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. jcohen@niaid.nih.gov.

Epstein-Barr virus (EBV) is the primary cause of infectious mononucleosis and is associated with several malignancies, including nasopharyngeal carcinoma, gastric carcinoma, Hodgkin lymphoma, Burkitt lymphoma, and lymphomas in immunocompromised persons, as well as multiple sclerosis. A vaccine is currently unavailable. While monomeric EBV gp350 was shown in a phase 2 trial to reduce the incidence of infectious mononucleosis, but not the rate of EBV infection, newer formulations of gp350 including multimeric forms, viruslike particles, and nanoparticles may be more effective. A vaccine that also includes additional viral glycoproteins, lytic proteins, or latency proteins might improve the effectiveness of an EBV gp350 vaccine. Clinical trials to determine if an EBV vaccine can reduce the rate of infectious mononucleosis or posttransplant lymphoproliferative disease should be performed. The former is important since infectious mononucleosis can be associated with debilitating fatigue as well as other complications, and EBV infectious mononucleosis is associated with increased rates of Hodgkin lymphoma and multiple sclerosis. A vaccine to reduce EBV posttransplant lymphoproliferative disease would be an important proof of principle to prevent an EBV-associated malignancy. Trials of an EBV vaccine to reduce the incidence of Hodgkin lymphoma, multiple sclerosis, or Burkitt lymphoma would be difficult but feasible.

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The Relationship of Wound Healing with Psoriasis and Multiple Sclerosis.
Morhenn VB(1).
Author information: (1)Department of Dermatology, San Francisco VA Medical Center, San Francisco, California.
Significance: Better understanding of wound healing could lead to improved treatment(s) of multiple sclerosis (MS) and psoriasis (Pso). Recent Advances: New concepts in the events of wound healing, such as the roles of the innate and adaptive immune systems, have generated targets for treating these debilitating diseases. Innovation: That in MS and Pso defective wound healing is responsible for the diseases' progression has not been hypothesized to date. Conclusion: Impaired initiation of wound repair by oligodendrocyte precursor cells or oligodendrocytes may play a role in MS, and a lack of inhibition of the proliferative phase in wound healing may explain the pathophysiology involved in Pso.
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BDNF Polymorphism: A Review of Its Diagnostic and Clinical Relevance in Neurodegenerative Disorders.
Shen T(1), You Y(2), Joseph C(1), Mirzaei M(3), Klistorner A(1)(2), Graham SL(1)(2), Gupta V(1).
Author information: (1)1Faculty of Medicine and Health Sciences, Macquarie University, Australia. (2)2Save Sight Institute, Sydney University, Sydney, Australia. (3)3Faculty of Science and Engineering, Macquarie University, Australia.
Brain-derived neurotrophic factor (BDNF) has a unique role in the neuronal development, differentiation, and survival in the developing and adult nervous system. A common single-nucleotide polymorphism in the pro-region of the human BDNF gene, resulting in a valine to methionine substitution (Val66Met), has been associated with the susceptibility, incidence, and clinical features of several neurodegenerative disorders. Much research has been dedicated to evaluating the effects of polymorphism in the past decade, and functional effects of this genetic variation. A better understanding of how this naturally occurring polymorphism associates with or influences physiology, anatomy, and cognition in both healthy and diseased adults in neurodegenerative conditions will help understand neurochemical mechanisms and definable clinical outcomes in humans. Here we review the role and relevance of the BDNF Val66Met polymorphism in neurodegenerative diseases, with particular emphasis on glaucoma, multiple sclerosis (MS), Alzheimer's disease (AD) and Parkinson's disease (PD). Several controversies and unresolved issues, including small effect sizes, possible ethnicity, gender, and age effects of the BDNF Val66Met are also discussed with respect to future research.
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Improved Detection of New MS Lesions during Follow-Up Using an Automated MR Coregistration-Fusion Method.

Galletto Pregliasco A(1), Collin A(2), Guéguen A(2), Metten MA(3), Aboab J(1), Deschamps R(1), Gout O(1), Duron L(2), Sadik JC(2), Savatovsky J(2), Lecler A(4).


BACKGROUND AND PURPOSE: MR imaging is the key examination in the follow-up of patients with MS, by identification of new high-signal T2 brain lesions. However, identifying new lesions when scrolling through 2 follow-up MR images can be difficult and time-consuming. Our aim was to compare an automated coregistration-fusion reading approach with the standard approach by identifying new high-signal T2 brain lesions in patients with multiple sclerosis during follow-up MR imaging. MATERIALS AND METHODS: This prospective monocenter study included 94 patients (mean age, 38.9 years) treated for MS with dimethyl fumarate from January 2014 to August 2016. One senior neuroradiologist and 1 junior radiologist checked for new high-signal T2 brain lesions, independently analyzing blinded image datasets with automated coregistration-fusion or the standard scroll-through approach with a 3-week delay between the 2 readings. A consensus reading with a second senior neuroradiologist served as a criterion standard for analyses. A Poisson regression and logistic regression were used to compare the 2 methods. Intra- and interobserver agreement was assessed by the κ coefficient. RESULTS: There were significantly more new high-signal T2 lesions per patient detected with the coregistration-fusion method (7 versus 4, P < .001). The coregistration-fusion method detected significantly more patients with at least 1 new high-signal T2 lesion (59% versus 46%, P = .02) and was associated with significantly faster overall reading time (86 seconds faster, P < .001) and higher reader confidence (91% versus 40%, P < 1 × 10^-4). Inter- and intraobserver agreement was excellent for counting new high-signal T2 lesions. CONCLUSIONS: Our study showed that an automated coregistration-fusion method was more sensitive for detecting new high-signal T2 lesions in patients with MS and reducing reading time. This method could help to improve follow-up care.

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Morphology-Specific Discrimination between MS White Matter Lesions and Benign White Matter Hyperintensities Using Ultra-High-Field MRI.

Hosseini Z(1)(2), Matusinec J(3), Rudko DA(4)(5), Liu J(2), Kwan BYM(6), Salehi F(6), Sharma M(6)(7), Kremenchutzky M(7), Menon RS(1)(2)(8), Drangova M(9)(2)(8).

Author information: (1)From the Biomedical Engineering Graduate Program (Z.H., R.S.M., M.D.). (2)Imaging Research Laboratories (Z.H., J.L., R.S.M., M.D.), Robarts Research Institute. (3)Departments of Medicine (J.M.). (4)Department of Neurology and Neurosurgery (D.A.R.), McConnell Brain Imaging Centre, Montreal Neurological Institute. (5)Department of Biomedical Engineering (D.A.R.), McGill University, Montreal, Quebec, Canada. (6)Medical Imaging (B.Y.M.K., F.S., M.S.). (7)Department of Clinical Neurological Sciences (M.S., M.K.), Western University and London Health Sciences Centre, London, Ontario, Canada. (8)Medical Biophysics (R.S.M., M.D.), Schulich School of Medicine and Dentistry; Western University, London, Ontario, Canada. (9)From the Biomedical Engineering Graduate Program (Z.H., R.S.M., M.D.) mdrangova@robarts.ca.

BACKGROUND AND PURPOSE: Recently published North American Imaging in Multiple Sclerosis guidelines call for derivation of a specific radiologic definition of MS WM lesions and mimics. The purpose of this study was to use SWI and magnetization-prepared FLAIR images for sensitive differentiation of MS from benign WM lesions using the morphologic characteristics of WM lesions.

MATERIALS AND METHODS: Seventeen patients with relapsing-remitting MS and 18 healthy control subjects were enrolled retrospectively. For each subject, FLAIR and multiecho gradient-echo images were acquired using 7T MR imaging. Optimized postprocessing was used to generate single-slice SWI of cerebral veins. SWI/FLAIR images were registered, and 3 trained readers performed lesion assessment. Morphology, location of lesions, and the time required for assessment were recorded. Analyses were performed on 3 different pools: 1) lesions of >3 mm, 2) nonconfluent lesions of >3 mm, and 3) nonconfluent lesions of >3 mm with no or a single central vein. RESULTS: The SWI/FLAIR acquisition and processing protocol enabled effective assessment of central veins and hypointense rims in WM lesions. Assessment of nonconfluent lesions with ≥1 central vein enabled the most specific and sensitive differentiation of patients with MS from controls. A threshold of 67% perivenous WM lesions separated patients with MS from controls with a sensitivity of 94% and specificity of 100%. Lesion assessment took an average of 12 minutes 10 seconds and 4 minutes 33 seconds for patients with MS and control subjects, respectively. CONCLUSIONS: Nonconfluent lesions of >3 mm with ≥1 central vein were the most sensitive and specific differentiators between patients with MS and control subjects.

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Placement of selected new FDA-approved drugs in Medicare Part D formularies, 2009-2013.
Stuart BC(1), Tom SE, Choi M, Johnson A, Sun K, Qato D, Obi EN, Zacker C, Park Y, Arcona S.
Author information: (1)Department of Pharmaceutical Health Services Research, University of Maryland Baltimore, 220 Arch St, 12th Fl, Baltimore, MD 21201. Email: bstuart@rx.umaryland.edu.
OBJECTIVES: To assess formulary decisions by Part D plans for selected newly approved drugs. STUDY DESIGN: Retrospective cohort study. METHODS: Formulary placement and restrictions were identified for 33 drugs in 8 therapeutic classes (antihyperglycemics, anticoagulants, antiplatelets, disease-modifying agents for multiple sclerosis [MS] and rheumatoid arthritis [RA], chronic obstructive pulmonary disease [COPD] drugs, antiepileptics, and antipsychotics) in 863 Part D plans with continuous CMS contracts between 2009 and 2013. Multivariable models estimated the impact of drug characteristics and Part D plan characteristics on probability of drug adoption and, for adopters, evaluated factors associated with months to adoption and requirements for prior authorization (PA) or step therapy (ST). RESULTS: First Part D formulary placements varied from 2 to 14 months post FDA approval. On average, 56.7% of plans placed each drug within 6 months and 64.1% placed within 1 year of the National Drug Code assignment date. The most rapid adoption was for antipsychotics and antiepileptics. The slowest was for COPD drugs. More than 90% of disease-modifying agents for MS and RA were subject to PA. ST was uncommon except for antihyperglycemic agents. In adjusted analyses, enhanced benefit plans had a 4% higher probability of formulary placement (P <.01), and each additional star in the CMS star rating system increased the probability of adoption by 4% (P <.01). Overall, Medicare Advantage prescription drug plans had higher placement rates due to greater reliance on enhanced plan offerings and higher star ratings.
CONCLUSIONS: We found significant heterogeneity in formulary placement and restrictions for 33 new drugs in the Part D marketplace between 2009 and 2013. Further research is necessary to determine whether this pattern applies to other drug classes.
PMID: 29939507

A Review of Podocyte Biology.
Garg P.
BACKGROUND: Podocyte biology is a developing science that promises to help improve understanding of the mechanistic nature of multiple diseases associated with proteinuria. Proteinuria in nephrotic syndrome has been linked to mechanistic dysfunctions in the renal glomerulus involving the function of podocyte epithelial cells, including podocyte foot process effacement. SUMMARY: Developments in imaging technology are improving knowledge of the detailed structure of the human renal glomerulus and cortex. Podocyte foot processes attach themselves to the glomerular capillaries at the glomerular basement membrane (GBM) forming intercellular junctions that form slit diaphragm filtration barriers that help maintain normal renal function. Damage in this area has been implicated in glomerular disease. Injured podocytes undergo effacement whereby they lose their structure and spread out, leading to a reduction in filtration barrier function. Effacement is typically associated with the presence of proteinuria in focal segmental glomerulosclerosis, minimal change disease, and diabetes. It is thought to be due to a breakdown in the actin cytoskeleton of the foot processes, complex contractile apparatuses that allow podocytes to dynamically reorganize according to changes in filtration requirements. The process of podocyte depletion correlates with the development of glomerular sclerosis and chronic kidney disease. Focal adhesion complexes that interact with the underlying GBM bind the podocytes within the glomerular structure and prevent their detachment. Key Messages: Knowledge of glomerular podocyte biology is helping to advance our understanding of the science and mechanics of the glomerular filtering process, opening the way to a variety of new potential applications for clinical targeting.
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**Improvement During Inpatient Rehabilitation Among Older Adults with Guillain-Barré Syndrome, Multiple Sclerosis, Parkinson Disease, and Stroke.**

Andrews AW(1), Middleton A.

Author information: (1)Professor - Department of Physical Therapy Education, School of Health Sciences - Elon University, Elon, NC. Research Assistant Professor, Division of Rehabilitation Sciences, University of Texas Medical Branch, Galveston, TX; and Assistant Professor, Division of Physical Therapy - College of Health Professions, Medical University of South Carolina, Charleston, SC.

OBJECTIVE: To quantify the improvement in independence experienced by patients with the following diagnoses: Guillain-Barré Syndrome (GBS), Multiple Sclerosis (MS), Parkinson Disease (PD), and stroke following inpatient rehabilitation. DESIGN: Subjects who were admitted to inpatient rehabilitation hospitals in 2012-2013 with an incident diagnosis of: GBS (n = 1079), MS (n = 1438), PD (n = 11,834), or stroke (n = 131,313) were included. The main outcome measure was improvement in Functional Independence Measure® (FIM) scores on self-care, mobility, and cognition during inpatient rehabilitation. We estimated percent improvement from a linear mixed-effects model adjusted for patients' age, sex, race/ethnicity, comorbidity count, diagnostic group (GBS, MS, PD, and stroke), and admission score. RESULTS: All patient diagnostic groups receiving inpatient rehabilitation improved across all three domains. The largest adjusted percent improvements were observed in the mobility domain and the smallest in the cognition domain for all groups. Percent improvement in mobility ranged from 84.9% (MS) to 144.0% (GBS), self-care from 49.5% (MS) to 84.1% (GBS), and cognition from 34.0% (PD) to 51.7% (GBS). Patients with GBS demonstrated the greatest percent improvement across all three domains. CONCLUSIONS: Patients with GBS, MS, PD, and stroke should improve during inpatient rehabilitation but anticipated outcomes for patients with GBS should be even higher.

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**A controlled clinical trial on the effects of exercise on cognition and mobility in adults with multiple sclerosis.**

Felippe LA(1), Salgado PR, Silvestre DS, Santos SMS, Christofoletti G.

Author information: (1)Faculty of Medicine, Universidade Federal University de Mato Grosso do Sul, Campo Grande, MS, Brazil (LAF, GC); Multiple Sclerosis Outpatient clinic, hospital complex, Campo Grande, Brazil (PRS); Institute of Health, Universidade Federal University de Mato Grosso do Sul, Campo Grande, MS, Brazil (DSS, GC); and Department of Physiotherapy at the Universidade Estadual de Londrina, Londrina, Brazil (SMSS).

OBJECTIVE: To investigate the effects of a 6-month exercise program on cognition and mobility in participants with multiple sclerosis. DESIGN: Prospective, single blind, controlled clinical trial. SETTING: A community rehabilitation program within a large metropolitan health service. PARTICIPANTS: Twenty-eight patients with multiple sclerosis, referred for outpatient rehabilitation. INTERVENTIONS: Participants were allocated to one of two groups and undertook a cognitive-motor exercise program or monitoring (control group). MAIN OUTCOME MEASURES: Cognition and mobility. Cognition was evaluated using the Mini-Mental State Examination and the Frontal Assessment Battery. Mobility was assessed with the Timed Get-Up-and-Go-Test, applied with and without dual task distractors. RESULTS: The findings showed benefits provided by exercise on cognition and mobility. Differently, participants of the control group did not have significant changes in cognition scores after 6 months of follow-up, and had a worse performance in mobility tests. CONCLUSION: Six months of exercise provided benefits to cognition and mobility in adults with multiple sclerosis. This trial was registered prospectively with the Brazilian Clinical Trials Register, ID: RBR-9gh4km, (http://www.ensaiosclinicos.gov.br/rg/?q=RBR-9gh4km).

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Tuberous sclerosis complex: review based on new diagnostic criteria.

Portocarrero LKL(1), Quental KN(1), Samorano LP(1), Oliveira ZNP(1), Rivitti-Machado MCDM(1).

Author information: (1)Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo, SP, Brazil.

Tuberous sclerosis complex is a multisystemic, autosomal dominant genetic disorder with complete penetrance, that can evolve with hamartomas in multiple organs, such as skin, central nervous system, kidney and lung. Due to the wide phenotypic variability, the disease is often not recognized. Tuberous sclerosis complex affects one in 10,000 newborns and most patients are diagnosed during the first 15 months of life. The diagnostic criteria for tuberous sclerosis were reviewed in 2012, at the second International Tuberous Sclerosis Complex Consensus Conference. The diagnosis is based on genetic criteria, by the identification of inactivating pathogenic mutation of tumor suppressor genes TSC1 and TSC2, and clinical criteria, including cutaneous, renal, pulmonary, cardiac and neurological manifestations. The treatment of tuberous sclerosis complex consists, mainly, in management of the symptoms caused by hamartomas and in prevention of organ failure. Multidisciplinary approach is recommended, in order to obtain better clinical outcomes.

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Comparative pathogenesis of enteric clostridial infections in humans and animals.

Uzal FA(1), Navarro MA(2), Li J(3), Freedman JC(3), Shrestha A(3), McClane BA(3).

Author information: (1)California Animal Health and Food Safety Laboratory System, San Bernardino Branch, University of California, Davis, CA, USA. Electronic address: fuzal@caahfs.ucdavis.edu. (2)California Animal Health and Food Safety Laboratory System, San Bernardino Branch, University of California, Davis, CA, USA. (3)Department of Microbiology and Molecular Genetics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA.

Several enteric clostridial diseases can affect humans and animals. Of these, the enteric infections caused by Clostridium perfringens and Clostridium difficile are amongst the most prevalent and they are reviewed here. C. perfringens type A strains encoding alpha toxin (CPA) are frequently associated with enteric disease of many animal mammalian species, but their role in these diseased mammals remains to be clarified. C. perfringens type B encoding CPA, beta (CPB) and epsilon (ETX) toxins causes necro-hemorrhagic enteritis, mostly in sheep, and these strains have been recently suggested to be involved in multiple sclerosis in humans, although evidence of this involvement is lacking. C. perfringens type C strains encode CPA and CPB and cause necrotizing enteritis in humans and animals, while CPA and ETX producing type D strains of C. perfringens produce enterotoxemia in sheep, goats and cattle, but are not known to cause spontaneous disease in humans. The role of C. perfringens type E in animal or human disease remains poorly defined. The newly revised toxinotype F encodes CPA and enterotoxin (CPE), the latter being responsible for food poisoning in humans, and the less prevalent antibiotic associated and sporadic diarrhea. The role of these strains in animal disease has not been fully described and remains controversial. Another newly created toxinotype, G, encodes CPA and necrotic enteritis toxin B-like (NetB), and is responsible for avian necrotic enteritis, but has not been associated with human disease. C. difficile produces colitis and/or enterocolitis in humans and multiple animal species. The main virulence factors of this microorganism are toxins A, B and an ADP-ribosyltransferase (CDT). Other clostridia causing enteric diseases in humans and/or animals are Clostridium spiroforme, Clostridium piliforme, Clostridium colinum, Clostridium sordellii, Clostridium chauvoei, Clostridium septicum, Clostridium botulinum, Clostridium butyricum and Clostridium neonateale. The zoonotic transmission of some, but not all these clostridial species, has been demonstrated.

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The NRF2 pathway as potential biomarker for dimethyl fumarate treatment in multiple sclerosis.

Hammer A(1), Waschbisch A(1)(2), Kuhbandner K(1), Bayas A(3), Lee DH(1), Duscha A(4), Haghiika A(4), Gold R(4), Linker RA(1).

Author information:  (1)Department of Neurology University Hospital Erlangen Friedrich-Alexander-University Erlangen-Nürnberg Erlangen 91054 Germany. (2)Present address: Department of Neurology University Hospital Rheinisch-Westfälische Technische Hochschule (RWTH) Aachen Aachen 52074 Germany. (3)Department of Neurology Hospital Augsburg Augsburg 86156 Germany. (4)Department of Neurology Ruhr-University Bochum Bochum 44791 Germany.

Objective: Immunological studies have demonstrated a plethora of beneficial effects of dimethyl fumarate (DMF) on various cell types. However, the cellular and molecular targets are incompletely understood and response markers are scarce. Here, we focus on the relation between nuclear factor (erythroid-derived 2)-like 2 (NRF2) pathway induction under DMF therapy and the composition of the blood immune cell compartment and clinical efficacy in relapsing-remitting multiple sclerosis (MS) patients. Methods: We explored effects of DMF on peripheral immune cell subsets by flow cytometric and transcriptional analysis of serial blood samples obtained from 43 MS patients during the first year of therapy. Results: Gene expression analysis proved activation of NRF2 signaling under DMF therapy that was paralleled by a temporal expansion of FoxP3+ regulatory T cells, CD56bright natural killer cells, plasmacytoid dendritic cells, and a decrease in CD8+ T cells, B cells, and type 1 myeloid dendritic cells. In a subgroup of 28 patients with completely available clinical data, individuals with higher levels of the NRF2 target gene NAD(P)H quinone dehydrogenase 1 (NQO1) 4-6 weeks after DMF therapy initiation were more likely to achieve no evidence of disease activity status 1 year later. The degree of NQO1 induction further correlated with patient age. Interpretation: We demonstrate that positive effects of DMF on the clinical outcome are paralleled by induction of the antioxidant NRF2 transcriptional pathway and a shift toward regulatory immune cell subsets in the periphery. Our data identify a role of the NRF2 pathway as potential biomarker for DMF treatment in MS.

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Precision medicine for multiple sclerosis promotes preventative medicine.

Hansen MR(1), Okuda DT(1).

Author information:  (1)UT Southwestern Medical Center, Department of Neurology and Neurotherapeutics, Neuroinnovation Program, Multiple Sclerosis and Neuroimmunology Imaging Program, Clinical Center for Multiple Sclerosis, Dallas, Texas.

Multiple sclerosis (MS) is a chronic, lifelong disease, currently without a cure that is responsible for significant neurological injury in young adults. Precision medicine for MS aims to provide a more exacting and refined approach toward management by providing recommendations based on disease subtype, clinical status, existing radiological data, para-clinical data, and other biological markers. To achieve better outcomes, the three stages of care-diagnosis, treatment, and management-should be optimized. However, as the temporal profile of disease behavior is highly variable in MS, and unlike outcomes from other chronic conditions (i.e., hypertension, diabetes mellitus, etc.), should precision medicine for MS be one that focuses more on disease prevention and lifestyle modifications beyond recommendations for the use of disease-modifying therapies? As scientific advancements continue within the field of neuroimmunology, and until reliable biomarkers that predict disease outcomes are available, success may be better achieved by focusing on modifiable factors to reduce future disability.


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Combined neuropathological pathways account for age-related risk of dementia.

Power MC(1), Mormino E(2), Soldan A(3), James BD(4)(5), Yu L(6), Armstrong NM(7), Bangen KJ(8)(9), Delano-Wood L(8)(9), Lamar M(4)(10), Lim YY(11), Nudelman K(12), Zahodne L(13), Gross AL(7)(14)(15), Mungas D(16), Widaman KF(17), Schneider J(4)(6)(18).

Author information: (1)Department of Epidemiology and Biostatistics, George Washington University Milken Institute School of Public Health, Washington, DC. (2)Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA. (3)Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD. (4)Rush Alzheimer's Disease Center, Rush University, Chicago, IL. (5)Department of Internal Medicine, Rush University, Chicago, IL. (6)Department of Neurological Sciences, Rush University, Chicago, IL. (7)Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD. (8)VA San Diego Healthcare System, San Diego, CA. (9)Department of Psychiatry, University of California San Diego, San Diego, CA. (10)Department of Behavioral Sciences, Rush University Medical Center, Chicago, IL. (11)Florey Institute of Neuroscience and Mental Health, Parkville, VIC, Australia. (12)Department of Radiology and Imaging Sciences, Indiana University-Purdue University at Indianapolis, Indianapolis, IN. (13)Department of Psychology, University of Michigan, Ann Arbor, MI. (14)Johns Hopkins Center on Aging and Health, Baltimore, MD. (15)Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD. (16)Department of Neurology, University of California-Davis, Davis, CA. (17)Graduate School of Education, University of California Riverside, Riverside, CA. (18)Department of Pathology, Rush University Medical Center, Chicago, IL.

OBJECTIVE: Our objectives were to characterize the inter-relation of known dementia-related neuropathologies in one comprehensive model and quantify the extent to which accumulation of neuropathologies accounts for the association between age and dementia. METHODS: We used data from 1,362 autopsied participants of three community-based clinicopathological cohorts: the Religious Orders Study, the Rush Memory and Aging Project, and the Minority Aging Research Study. We estimated a series of structural equation models summarizing a priori hypothesized neuropathological pathways between age and dementia risk individually and collectively. RESULTS: At time of death (mean age, 89 years), 44% of our sample had a clinical dementia diagnosis. The vascular, amyloid/tau, neocortical Lewy body, and TAR DNA-binding protein 43 (TDP-43)/hippocampal sclerosis pathology pathways each accounted for a substantial proportion of the association between age and dementia. When considered collectively, the four pathways fully accounted for all variance in dementia risk previously attributable to age. Pathways involving amyloid/tau, neocortical Lewy bodies, and TDP-43/hippocampal sclerosis were interdependent, attributable to the importance of amyloid beta plaques in all three. The importance of the pathways varied, with the vascular pathway accounting for 32% of the association between age and dementia, whereas the remaining three inter-related degenerative pathways together accounted for 68% (amyloid/tau, 24%; the Lewy body, 1%; and TDP-43/hippocampal sclerosis, 43%). INTERPRETATION: Age-related increases in dementia risk can be attributed to accumulation of multiple pathologies, each of which contributes to dementia risk. Multipronged approaches may be necessary if we are to develop effective therapies. Ann Neurol 2018.

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**Genome sequencing uncovers phenocopies in primary progressive multiple sclerosis.**


Author information: (1)UCSF Weill Institute for Neurosciences, University of California San Francisco, San Francisco, CA. (2)Department of Neurology, University of California San Francisco, San Francisco, CA. (3)Laboratory of Human Genetics of Neurological Disorders, Institute of Experimental Neurology (INSpe), Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy. (4)Department of Neurology and Neuro-rehabilitation, San Raffaele Scientific Institute, Milan, Italy. (5)Department of Neurology and Neurotherapeutics, University of Texas Southwestern Medical, Dallas, TX. (6)Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia. (7)Department of Anatomy and Neuroscience, The University of Melbourne, Parkville, VIC, Australia. (8)Laboratory of Genomics of Neurological Diseases and Department of Neurology, Policlinico San Donato Hospital and Scientific Institute, San Donato Milanese, Italy. (9)Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy. (10)Institute for Human Genetics, University of California San Francisco, San Francisco, CA. (11)Graduate Program in Bioinformatics, University of California San Francisco, San Francisco, CA.

**OBJECTIVE:** Primary progressive multiple sclerosis (PPMS) causes accumulation of neurological disability from disease onset without clinical attacks typical of relapsing multiple sclerosis (RMS). However, whether genetic variation influences the disease course remains unclear. We aimed to determine whether mutations causative of neurological disorders that share features with multiple sclerosis (MS) contribute to risk for developing PPMS.

**METHODS:** We examined whole-genome sequencing (WGS) data from 38 PPMS and 81 healthy subjects of European ancestry. We selected pathogenic variants exclusively found in PPMS patients that cause monogenic neurological disorders and performed two rounds of replication genotyping in 746 PPMS, 3,049 RMS, and 1,000 healthy subjects.

**RESULTS:** WGS and replication studies identified three pathogenic variants in PPMS patients that cause neurological disorders sharing features with MS: KIF5A p.Ala361Val in spastic paraplegia 10; MLC1 p.Pro92Ser in megalencephalic leukodystrophy with subcortical cysts, and REEP1 c.606+43G>T in Spastic Paraplegia 31. Moreover, we detected a significant enrichment of HSP-related mutations in PPMS patients compared to controls (risk ratio [RR] = 1.95; 95% confidence interval [CI], 1.27-2.98; p = 0.002), as well as in SPMS patients compared to controls (RR = 1.57; 95% CI, 1.18-2.10; p = 0.002). Importantly, this enrichment was not detected in RMS.

**INTERPRETATION:** This study provides evidence to support the hypothesis that rare Mendelian genetic variants contribute to the risk for developing progressive forms of MS. Ann Neurol 2017.

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**HLA-G gene polymorphism and soluble HLA-G serum level in patients with multiple sclerosis.**


Author information: (1)Isfahan Medical Students Research Center (IMSRC), Isfahan University of Medical Sciences, Isfahan, Iran. (2)Department of Immunology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. (3)School of Medicine, Tarbiat Modarres University, Tehran, Iran. (4)Department of Neurology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. (5)Department of Genetic and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. (6)Isfahan Eye Research Center (IERC), Feiz Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.

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In vitro and computational studies on the effects of ARE deletion and targeted mutations on the expression of interferon beta-1a in HEK293T cells.

Norouzi R(1), Hojati Z(2), Dehbashi M(1).

Author information: (1) Division of Genetics, Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan, 81746-73441, Iran. (2) Division of Genetics, Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan, 81746-73441, Iran. z.hojati@sci.ui.ac.ir.

Interferon beta (IFNβ) is transiently expressed in response to viral infections and widely used to treat relapsing-remitting multiple sclerosis (MS). We introduced mutations in the IFNβ gene (in the 27th and 101st codons and in the Kozak sequence, and also deletion of 3' and 5' unstable, untranslated region, UTR) with the aim of increasing the expression of IFNβ. Computational analyses of mutant and wild-type RNAs and proteins of IFNβ by RNAfold, ASAView, HOPE and Ramachandran plot, and iStable web servers showed that the mutations could decrease RNA stability, protein solvent accessibility, and protein stability but could not change correct folding. Two recombinant IFNβ101 and IFNβ101+27 constructs were designed by site-directed mutagenesis. The wild-type IFNβ gene also was used as a control. In vitro experiments by quantitative real-time PCR, dot blot, SDS-PAGE, and Western blot assays showed an increased expression level of recombinant IFNβs. 79.9-fold, 99.7-fold, and 190-fold elevations in the mRNA expression of IFNβ, IFNβ101, and IFNβ101+27 were seen, respectively, in comparison with the endogenous IFNβ mRNA in untransfected HEK293T cells. The IFNβ mRNA expression was increased 2.38-fold and 1.25-fold for 101+27 and 101 mutated forms, respectively, in comparison with the IFNβ wild-type construct. An elevation in IFNβ protein production was also clearly detected in the transfected HEK293T cell containing recombinant IFNβ101 and IFNβ101+27 constructs. Finally, these directed mutations in the IFNβ gene successfully elevated protein and mRNA production but in silico analyses of mutant mRNAs showed decreased mRNA stability, unlike previous studies, in comparison with the wild-type mRNA.

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Moral Cognition and Multiple Sclerosis: A Neuropsychological Study.

Realmuto S(1), Dodich A(2), Meli R(1), Canessa N(3), Ragonese P(1), Salemi G(1), Cerami C(2).

Author information: (1) Experimental Biomedicine and Clinical Neuroscience Department (BioNeC), University of Palermo, Palermo, Italy. (2) Clinical Neuroscience Department, San Raffaele Hospital and Scientific Institute, Milan, Italy. (3) NEIS Center, Istituto Universitario di Studi Superiori, Pavia, Italy.

Objectives: Recent literature proved that social cognition impairments may characterize the neuropsychological profile of Multiple Sclerosis (MS) patients. However, little is still known about moral cognition in MS. In this study, we evaluated non-social, social, and moral cognitive performances in 45 relapsing-remitting MS patients. Methods: Patients underwent the Brief International Cognitive Assessment for Multiple Sclerosis battery, the Cognitive Estimation and Stroop tasks, the Ekman-60 Faces test, the Reading the Mind in the Eye and Story-based Empathy task. Additionally, a task of moral dilemmas involving both “instrumental” and “incidental” conditions was administered to patients. Forty-five age-, gender- and education-matched healthy control subjects (HC) were enrolled for comparisons. Results: The majority of patients (i.e., 77.6%) showed deficits at non-social tasks, particularly in the executive domains. A subset of MS sample (i.e., 24%) presented with emotion recognition and socio-affective processing impairments. Overall, MS patients showed comparable levels of moral judgment with respect to HC. The rate of yes/no response in resolution of moral dilemmas and scores of attribution of emotional valence were comparable between groups. Nevertheless, lower moral permissibility and emotional arousal, particularly for the instrumental dilemmas, characterized the MS profile. Significant correlations between the attribution of emotional valence to moral actions and mentalizing scores emerged. Conclusions: Our findings expand current literature on MS supporting not only deficits in executive and socio-emotional domains but also low levels of permissibility of immoral actions and emotional detachment in the moral judgment process.

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Longitudinal analysis of verbal episodic memory in patients with relapsing-remitting multiple sclerosis.

Boa INF(1), Rimkus CM(1), Campanhola KR(1), Pereira SLA(1), Junqueira TF(1), Machado MAR(1), Callegaro D(1), Otaduy MCG(1), Leite CDC(1), Miotto EC(1).

Author information:  (1)Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, Departamento de Neurologia, São Paulo SP, Brasil.

OBJECTIVE: A 4.5-year follow-up study was conducted to characterize baseline verbal episodic memory (VEM) and its behavior and to assess the effects of relapsing-remitting multiple sclerosis (RRMS) on this domain. METHODS: Twenty-nine patients with RRMS underwent two neuropsychological assessments performed an average of 4.5 years apart. Twenty-six control participants underwent a single neuropsychological assessment. A significance level of p < 0.005 was adopted to denote a significant difference between the groups on the Mann Whitney and Wilcoxon paired statistical analyses. RESULTS: No statistical difference was found in the results of the VEM tests between the first and second neuropsychological assessments of the patients. However, a statistical difference was evident between the patient and control groups in the results of the VEM tests. CONCLUSION: The patient group showed changes in the VEM relative to the control group. After approximately 4.5 years of disease, the patient performance on the VEM stabilized or improved.

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Suicidal ideation, anxiety, and depression in patients with multiple sclerosis.

Tauli CB(1)(2)(3), Grippe TC(1)(3), Dias RM(1), Dias-Carneiro RPC(4), Carneiro NM(1), Aguilar ACR(1), Silva FMD(1), Bezerra F(2), Almeida LK(2), Massarente VL(4), Giovannelli EC(4), Tilbery CP(4), Brandão CO(5), Santos LMB(5), Santos-Neto LD(3).

Author information:  (1)Hospital de Base de Brasília, Departamento de Neurologia, Brasília DF, Brasil. (2)Universidade Católica de Brasília, Brasília DF, Brasil. (3)Universidade de Brasília, Departamento de Medicina Interna, Brasília DF, Brasil. (4)Santa Casa de São Paulo, Disciplina de Neurologia, Centro de Atendimento e Tratamento da Esclerose Múltipla, São Paulo SP, Brazil. (5)Universidade de Campinas, Departamento de Neuroimunologia, Campinas SP, Brasil.

INTRODUCTION: Psychiatric disorders frequently occur in patients with multiple sclerosis (MS); however, limited reports are available on these comorbidities. We aimed to investigate the relationships among MS, anxiety, depression, and suicidal ideation. METHODS: One hundred and thirty two patients with relapsing-remitting MS were evaluated using the Expanded Disability Status Scale, Beck Depression Inventory-II (BDI-II), Beck Scale for Suicide Ideation (BSI), and Hospital Anxiety and Depression Scale. RESULTS: A hierarchical regression analysis was performed to evaluate the variables. The regression equation significantly predicted the BSI score (R² = 0.306; adjusted R² = 0.273; F (9, 125) = 9.18; p < 0.0005), and the BDI-II score was the only variable that contributed significantly to this model (p < 0.0005). CONCLUSIONS: A high prevalence of depression and anxiety, and a higher rate of suicidal ideation were identified in MS patients compared to the general population. The presence of depressive symptoms appeared to have a direct influence on the risk of suicide.

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Baseline plasma cell gene signature predicts improvement in systemic sclerosis skin scores following treatment with inebilizumab (MEDI-551) and correlates with disease activity in systemic lupus and chronic obstructive pulmonary disease.

Streicher K(1), Sridhar S(1), Kuziora M(1), Morehouse CA(1), Higgs BW(1), Sebastian Y(1), Groves CJ(1), Pilataxi F(1), Brohawn PZ(1), Herbst R(1), Ranade K(1).

Author information: (1)MedImmune, Gaithersburg, MD, 20878, USA.

OBJECTIVES: B cells impact systemic sclerosis (SSc) progression through multiple pathogenic mechanisms. CD19 inhibition in mice reduced skin thickness, collagen production, and autoantibody levels, consistent with CD19 expression on plasma cells (PCs), the source of antibody production. Plasma cell depletion could effectively reduce collagen deposition and inflammation in SSc; therefore, we investigated effects on SSc disease activity. METHODS: A PC gene signature was evaluated in SSc skin biopsies in two phase I clinical trials. Microarray data from tissue from public studies of chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), dermatomyositis (DM), systemic lupus erythematosus (SLE), atopic dermatitis (AD), and blood from a phase IIb clinical trial in SLE were assessed. RESULTS: The PC signature was elevated (FC=5, p<0.0001) in SSc skin specimens compared to healthy donor skin and correlated with baseline modified Rodnan skin score (mRSS) (r=0.64, p=0.0004). High baseline PC signature patients showed greater mRSS improvement (35±16%; p=6.30x10^-4) following anti-CD19 treatment (MEDI-551) versus low PC signature patients (8±12%, p=0.104). The PC signature was over-expressed in tissue from SLE, DM, COPD, and IPF relative to controls (all FC>2, p<0.001). The PC signature also showed statistically significant difference between moderate and severe SLE patients (SLEDAI cut off at 10, FC=1.44, p=3.9 x 10^-3) and significantly correlated to degree of emphysema in COPD (r=0.53, p=7.55 x 10^-8). CONCLUSIONS: Results support a role for PCs in the pathogenesis of SSc and other autoimmune or pulmonary indications. Elevated pre-treatment PC signature was associated with increased benefit from MEDI-551 in SSc. This article is protected by copyright. All rights reserved.
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Consumer engagement critical to success in an Australian research project: reflections from those involved.

This paper describes the people, activities and methods of consumer engagement in a complex research project, and reflects on the influence this had on the research and people involved, and enablers and challenges of engagement. The 2.5-year Integrating and Deriving Evidence Experiences and Preferences (IN-DEEP) study was conducted to develop online consumer summaries of multiple sclerosis (MS) treatment evidence in partnership with a three-member consumer advisory group. Engagement methods included 6-monthly face-to-face meetings and email contact. Advisory group members were active in planning, conduct and dissemination and translational phases of the research. Engaging consumers in this way improved the quality of the research process and outputs by: being more responsive to, and reflective of, the experiences of Australians with MS; expanding the research reach and depth; and improving the researchers' capacity to manage study challenges. Advisory group members found contributing their expertise to MS research satisfying and empowering, whereas researchers gained confidence in the research direction. Managing the unpredictability of MS was a substantive challenge; the key enabler was the 'brokering role' of the researcher based at an MS organisation. Meaningfully engaging consumers with a range of skills, experiences and networks can make important and unforeseen contributions to research success.
DOI: 10.1071/PY17107  PMID: 29875031

Association of AIRE Polymorphism and the Susceptibility to Multiple Sclerosis in Iranian Population.  
Author information: (1)Department of Pharmaceutical Biotechnology, Faculty of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran. (2)Department of Immunology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. (3)Department of Genetics and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.  
Background: Multiple Sclerosis (MS) is the most common cause of neurologic disability in young adults. Recently, the AIRE gene was identified as a genetic risk factor for several autoimmune diseases in genome wide association studies. The aim of this study was to further investigate the possible role of the AIRE gene in susceptibility to MS in Iranian population. Methods: A total of 112 MS patients and 94 ethnically matched controls were included in the study. The Single-Nucleotide Polymorphism (SNP) (rs1800520, C>G) with a global MAF=0.2282/1143 was selected and genotyped using HRM real-time PCR method. Results: Results showed that AIRE SNP rs1800520 was significantly less common in the MS patients than in healthy controls (17.8 vs. 28.7%, pc=0.032, OR=0.54, 95% CI 0.279, 1.042). Also, the frequency of allele G was significantly higher among the control group than in the case group (37.77 vs. 25%, pc=0.014). Interestingly, mRNA transcribed on the rs1800520 SNP showed decreased free energy than the wild type suggesting that its increased stability may be responsible for the different activities of the polymorphic AIRE molecule. Conclusions: This is the first study investigating the relationship between AIRE gene and the susceptibility to MS. These results indicated that the rs1800520 SNP is not a susceptibility gene variant for the development of MS in Iranian population.  
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Conflict of interest statement: Conflict of Interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.


The Evaluation of Astaxanthin Effects on Differentiation of Human Adipose Derived Stem Cells into Oligodendrocyte Precursor Cells.  
Ghasemi N(1).  
Author information: (1)Department of Anatomical Science and Molecular Biology, Faculty of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.  
Background: Multiple Sclerosis (MS) has been explained as an autoimmune mediated disorder in central nerve system. Since conventional therapies for MS are not able to stop or reverse the destruction of nerve tissue, stem cell-based therapy has been proposed for the treatment of MS. Astaxanthin (AST) is a red fat-soluble xanthophyll with neuroprotection activity. The aim of this study was evaluation of pre-inducer function of AST on differentiation of human Adipose-Derived Stem Cells (hADSCs) into oligodendrocyte precursor cells. Methods: After stem cell isolation, culture and characterization by flow cytometry, hanging drop technique was done for embryoid body formation. In the following, hADSCs were differentiated into oligodendrocyte cells in the presence of AST at various concentrations (1, 5, and 10 ng/ml). Finally, immunocytochemistry and real-time PCR techniques were used for assessment of oligodendrocyte differentiation. Results: Flow cytometry results indicated that hADSCs were CD44, CD49-positive, but were negative for CD14, CD45 markers. In addition, immunocytochemistry results revealed that, in AST treated groups, the mean percentage of Olig 2 and A2B5 positive cells increased especially in 5 ng/ml AST treated group compared to control group (p<0.001). Moreover, real-time PCR analysis confirmed the results of immunocytochemistry. Conclusion: Since hADSCs have the potential to differentiate into multi lineage cells and due to important functions of AST in regulating various cellular processes, it seems that AST can be used as a promoter for oligodendrocyte differentiation of hADSCs for being used in cell transplantation in multiple sclerosis.  
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Sulfasalazine alters microglia phenotype by competing endogenous RNA effect of miR-136-5p and long non-coding RNA HOTAIR in cuprizone-induced demyelination.

Duan C(1), Liu Y(1), Li Y(1), Chen H(2), Liu X(3), Chen X(4), Yue J(1), Zhou X(5), Yang J(6).

Author information: (1)Department of Pharmacology, School of Basic Medical Sciences, Wuhan University, Wuhan 430071, China. (2)Department of Pathology and Pathophysiology, School of Basic Medical Sciences, Wuhan University, Wuhan 430071, China. (3)Department of Pharmacology, School of Basic Medical Sciences, Wuhan University, Wuhan 430071, China; Hubei Key Laboratory of Medical Information Analysis and Tumor Diagnosis & Treatment, South-central University For Nationalities, Wuhan 430074, China. (4)Department of Laboratory Medicine, Zhongnan Hospital of Wuhan University, Wuhan University, Wuhan 430071, Hubei, China. (5)Department of Cardiology, Renmin Hospital, Wuhan University, Wuhan 430071, China. (6)Department of Pharmacology, School of Basic Medical Sciences, Wuhan University, Wuhan 430071, China. Electronic address: jing_yang@whu.edu.cn.

Sulfasalazine (SF) promotes remyelination and improves the outcome of multiple sclerosis (MS) patients. However, the underlining mechanism remains elusive. Here, we examined whether SF blocks microglia switching to a pro-inflammatory M1-like phenotype through a competing endogenous RNA (ceRNA) effects in cuprizone-induced demyelination. The microglia reprogramming effects of SF in the mice model of cuprizone-induced demyelination was measured by histological, immunohistochemical and molecular biological methods. We also measured the effects of the condition media from SF-treated microglia on the differentiation of OLN-93 cells. Insights of the mechanism of ceRNAs of miR-136-5p and long non-coding RNA (lncRNA) HOTAIR were gained from bioinformatic analysis, luciferase assays and RNA binding protein immunoprecipitation. Microglia switched to a pro-inflammatory M1-like phenotype in cuprizone-induced demyelination. Conversely, SF inhibited the M1-like polarization with the increased remyelination which was attenuated by microglia depletion. SF inhibited production of M1-like factors TNF-α and INF-γ in microglia, and thereby promoted the differentiation of OLN-93 oligodendrocytes. SF down-regulated lncRNA HOTAIR but up-regulated miR-136-5p, and thus inactivated AKT2-NF-κB in cuprizone-treated microglia. Importantly, lncRNA HOTAIR overexpression reversed the increased miR-136-5p expression by SF and thereby attenuated the inhibition of AKT2-mediated NF-κB activation. Mimic of miR-136-5p inhibited cuprizone-induced activation of AKT2-NF-κB in the microglia. In summary, SF blocks microglia switching to a pro-inflammatory M1-like phenotype by ceRNA effect of miR-136-5p and lncRNA HOTAIR in cuprizone-induced demyelination. Our findings show the therapeutic potential of SF for human MS probably by targeting epigenetic regulation in microglia.

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Dexmedetomidine, an Alpha 2a Adrenergic Receptor Agonist, Mitigates Experimental Autoimmune Encephalomyelitis by Desensitization of CXCR7 in Microglia.

Huang Y(1), Hu S(1), Li Y(1), Xue D(2), Wu X(1).

Author information: (1)Department of Anesthesiology, The Third Affiliated Hospital of Wenzhou Medical University (Ruian People's Hospital), Ruian, Zhejiang 325200, China. (2)Department of Plastic Surgery, The Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310000, China.

The autoimmune disease multiple sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE), is characterized by an ascending paralysis that is characterized by extensive infiltration of the central nervous system by inflammatory cells. Although several studies to some extent uncover the cellular mechanisms of microglia that govern EAE pathogenesis, the molecular mechanisms that orchestrate the movement of microglia remain unknown, and potential novel therapeutic strategies are still required. In this study, we report that dexmedetomidine, an alpha 2a adrenergic receptor agonist, attenuates the clinical severity of EAE with less infiltration of microglia. During EAE, dexmedetomidine inhibits SDF-1 and I-TAC-induced chemotaxis of microglia mediated by CXCR7 but not CXCR4 or CXCR3. Most importantly, the alpha 2a adrenergic receptor is essential in dexmedetomidine-induced CXCR7 desensitization in microglia. Further experiments confirmed that CXCR7 desensitization required atypical protein kinase C ζ activation, while conventional and novel protein kinase C isoforms were not involved. Altogether, our data elucidate the mechanism of dexmedetomidine-induced CXCR7 desensitization in microglia and amelioration in EAE, which might lead to a better understanding of the therapeutic effects of dexmedetomidine as well as its implications for CXCR7 desensitization in autoimmune disease.

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Homodimer Architecture of QTRT2, the Noncatalytic Subunit of the Eukaryotic tRNA-Guanine Transglycosylase.

Behrens C(1), Biela I(1), Petitot-Bécard S(2), Botzanowski T(2), Cianférani S(2), Sager CP(1), Klebe G(1), Heine A(1), Reuter K(1). Author information: (1)Institut für Pharmazeutische Chemie, Philipps-Universität Marburg, Marbacher Weg 6, D-35032 Marburg, Germany. (2)Laboratoire de Spectrométrie de Masse BioOrganique, Université de Strasbourg, CNRS, IPHC UMR 7178, 67000 Strasbourg, France.

The bacterial enzyme tRNA-guanine transglycosylase (TGT) is involved in the biosynthesis of queuosine, a modified nucleoside present in the anticodon wobble position of tRNAHis, tRNATyr, tRNAAsp, and tRNAAsn. Although it forms a stable homodimer endowed with two active sites, it is, for steric reasons, able to bind and convert only one tRNA molecule at a time. In contrast, its mammalian counterpart constitutes a heterodimer consisting of a catalytic and a noncatalytic subunit, termed QTRT1 and QTRT2, respectively. Both subunits are homologous to the bacterial enzyme, yet only QTRT1 possesses all the residues required for substrate binding and catalysis. In mice, genetic inactivation of the TGT results in the uncontrolled oxidation of tetrahydrobiopterin and, accordingly, phenylketonuria-like symptoms. For this reason and because of the recent finding that mammalian TGT may be utilized for the treatment of multiple sclerosis, this enzyme is of potential medical relevance, rendering detailed knowledge of its biochemistry and structural architecture highly desirable. In this study, we performed the kinetic characterization of the murine enzyme, investigated potential quaternary structures of QTRT1 and QTRT2 via noncovalent mass spectrometry, and, finally, determined the crystal structure of the murine noncatalytic TGT subunit, QTRT2. In the crystal, QTRT2 is clearly present as a homodimer that is strikingly similar to that formed by bacterial TGT. In particular, a cluster of four aromatic residues within the interface of the bacterial TGT, which constitutes a “hot spot” for dimer stability, is present in a similar constellation in QTRT2.

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Microenvironment proteinases, proteinase-activated receptor regulation, cancer and inflammation.

Eftekhari R(1)(2), Lima SG(1), Liu Y(1), Mihara K(1), Saifeddine M(1), Noorbakhsh F(2), Scarisbrick IA(3), Hollenberg MD(1).

Author information: (1)Inflammation Research Network-Snyder Institute for Chronic Disease, Departments of Physiology and Pharmacology and Medicine, University of Calgary Cumming School of Medicine, 3330 Hospital Drive NW, Calgary, AB, T2N 4N1, Canada. (2)Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran 1416753955, Iran. (3)Department of Physical Medicine and Rehabilitation, Rehabilitation Medicine Research Center, Mayo Clinic, Rochester, MN 55905, USA.

We propose that in the microenvironment of inflammatory tissues, including tumours, extracellular proteinases can modulate cell signalling in part by regulating proteinase-activated receptors (PARs). We have been exploring this mechanism in a variety of inflammation and tumour-related settings that include tumour-derived cultured cells from prostate and bladder cancer, as well as immune inflammatory cells that are involved in the pathology of inflammatory diseases including multiple sclerosis. Our work shows that proteinase signalling via the PARs affects prostate and bladder cancer-derived tumour cell behaviour and can regulate calcium signalling in human T-cell and macrophage-related inflammatory cells as well as in murine splenocytes. Further, we find that the tumour-derived prostate cancer cells and immune-related cells (Jurkat, THP1, mouse splenocytes) can produce PAR-regulating proteinases (including kallikreins: KLKs), that can control tissue function by both a paracrine and autocrine mechanism. We suggest that this PAR-driven signalling process involving secreted microenvironment proteinases can play a key role in cancer and inflammatory diseases including multiple sclerosis.

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BDNF and Tau as biomarkers of severity in multiple sclerosis.


Author information: (1)Unidad de Investigacion en Enfermedades Neurologicas, Hospital de Especialidades, Centro Medico Nacional SXXI, IMSS, Mexico. (2)Hospital Psiquiatrico Hector Tovar Acosta, IMSS, Mexico. (3)Servicio de Neurologia, Hospital de Especialidades, Centro Medico Nacional SXXI, IMSS, Mexico. (4)Hospital de Especialidades, Centro Medico Nacional SXXI, IMSS, Mexico.

AIM: Determine if serum levels of tau and BDNF can be used as severity biomarkers in multiple sclerosis (MS).

PATIENTS & METHODS: Subjects with MS, older than 18 and younger than 55 years old were included; 74 patients with a diagnosis of relapsing-remitting MS, 11 with secondary-progressive MS, and 88 controls were included. Total tau and BDNF were measured by Western blot. RESULTS: Increased tau and decreased BDNF in MS patients compared with controls was found. Total-tau has a peak in relapsing-remitting MS, the second decile of the multiple sclerosis severity score, and in the lowest expanded disability status scale and is no different than controls for secondary-progressive MS patients and the most severe cases of MS. CONCLUSION: BDNF is a good biomarker for diagnosis of MS but not for severity or progression. Tau appears to have a more active role in the progression of MS.

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The possible anti-apoptotic and antioxidant effects of acetyl l-carnitine as an add-on therapy on a relapsing-remitting model of experimental autoimmune encephalomyelitis in rats.

Zidan A(1), Hedya SE(2), Elfeky DM(2), Abdin AA(2).

Author information: (1)Department of pharmacology, Faculty of medicine, Tanta University, Egypt. Electronic address: amr.zeidan@med.tanta.edu.eg. (2)Department of pharmacology, Faculty of medicine, Tanta University, Egypt.

Multiple sclerosis (MS) is a progressive inflammatory autoimmune demyelinating disease of the brain and spinal cord. Glucocorticoids (GCs) are the standard treatment of MS, however they have several drawbacks like oxidative stress and apoptosis. This study was designed to evaluate some possible antioxidant, anti-apoptotic and immune modulatory effects of Acetyl-l-carnitine (ALCAR) when used either alone or as an add-on therapy with dexamethasone for treatment of a relapsing-remitting (RR) experimental autoimmune encephalomyelitis (EAE) as a model of MS. This experiment was performed on 50 female Sprague Dawley rats divided into; normal control group, untreated EAE group, EAE group treated by dexamethasone, EAE group treated by ALCAR, and EAE group treated by both dexamethasone and ALCAR. The clinical score of the motor deficit of EAE was recorded daily. At the end of experiment, rats were sacrificed and the brain and spinal cord were processed for assessment of reduced glutathione (GSH), malondialdehyde (MDA) and caspase-3 activity. Histopathological changes and immunohistochemical expression of Bcl-2 and CD4+ T cell were carried out. Combination of both dexamethasone and ALCAR provided marked antioxidant and anti-apoptotic effects represented by significant decrease in MDA, caspase-3 and significant increase in GSH, Bcl-2 expression, and it also exhibited marked immunosuppressive effect represented by significant decrease in CD4+ T cells expression with significant improvement in clinical outcome when compared to untreated EAE group or to dexamethasone treated group. These findings pave the way for using ALCAR as an adjuvant therapy during long-term use of dexamethasone in MS.

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A population study of Norwegian psychiatric patients referred for clinical brain scanning.

Beyer MK(1), Dalaker TO(2), Greve OJ(2), Pignatiello SE(3), Agartz I(4).

Author information: (1)Department of Radiology and Nuclear Medicine, Oslo University Hospital, Norway and Department of Life Sciences and Health, Oslo and Akershus University College of Applied Sciences, Norway. (2)Department of Radiology, Stavanger University Hospital, Norway. (3)Department of Psychiatry, Lovisenberg Hospital, Oslo, Norway. (4)Norwegian Centre for Mental Disorders Research and K.G. Jebsen Centre for Psychosis Research, Institute of Clinical Medicine, University of Oslo, Norway and Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway.

Background: Patients with psychiatric conditions are often referred for a brain scan during the course of their diagnostic workup. Aims: The aim of our study is to determine frequency and type of organic brain pathology, the relationship to age, gender and psychiatric diagnosis. Method: We investigated magnetic resonance imaging and computed tomography brain scans from consecutively referred patients over a 10-year period (January 2002-December 2011). The reasons for referral, estimated psychiatric diagnosis, and the pathology discovered for each patient were registered. Results: A total of 34% of patients demonstrated organic brain pathology, of which 32.8% were considered clinically relevant. This represents a higher frequency of relevant pathology than reported in healthy subjects. Age (P < 0.001) and diagnosis (P = 0.016) were the most important determinants for frequency of pathological findings. Conclusions: Brain imaging in clinical psychiatry resulted in approximately 30% positive findings mainly associated with increasing pathologies with age, but also with diagnosis. Declaration of interest: Both T.O.D. and M.K.B. have received honoraria from Novartis for scientific lectures about multiple sclerosis. M.K.B. also received honoraria from Biogen for scientific lectures. The other authors have no conflicts of interest.

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Computer-assisted rehabilitation of attention in pediatric multiple sclerosis and ADHD patients: a pilot trial.

Simone M(1), Viterbo RG(2), Margari L(1), Iaffaldano P(3).

Author information: (1)Child Neuropsychiatry Unit, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari “Aldo Moro”, Bari, Italy. (2)MS Centre, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari “Aldo Moro”, Bari, Piazza G. Cesare, 11, 70121, Bari, Italy. (3)MS Centre, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari “Aldo Moro”, Bari, Piazza G. Cesare, 11, 70121, Bari, Italy. pietro.iaffaldano@uniba.it.

BACKGROUND: The treatment of cognitive deficits is challenging in pediatric onset multiple sclerosis (POMS) and in patients with attention deficit hyperactivity disorder (ADHD). We performed a pilot double-blind RCT to evaluate the efficacy of a home-based computerized-program for retraining attention in two cohorts of POMS and ADHD patients. METHODS: POMS and ADHD patients failing in at least 2/4 attention tests on a neuropsychological battery were randomized to specific or nonspecific computerized training (ST, nST), performed in one-hour sessions, twice/week for 3 months. The primary outcome was the effect of the training on global neuropsychological performances measured by the cognitive impairment index (CII). The efficacy of the intervention was evaluated in each disease group by using repeated measures ANOVA.

RESULTS: Sixteen POMS (9 females, age 15.75 ± 1.74 years) and 20 ADHD (2 females, age 11.19 ± 2.49 years) patients were enrolled. In POMS patients the ST exposure was associated to a significantly more pronounced improvement of the CII (p < 0.0001) and on cognitive test exploring attention, concentration, planning strategies and visuo-spatial memory performances in comparison to nST exposure. In ADHD patients the difference between the ST and nST on the CII was not statistical significant (p = 0.06), but a greater effect of the ST was found only on cognitive test exploring attention and delayed recall of visuo-spatial memory performances. CONCLUSIONS: Our data suggest that a cognitive rehabilitation program that targets attention is a suitable tool for improving global cognitive functioning in POMS patients, whereas it has a less pronounced transfer effect in ADHD patients. TRIAL REGISTRATION: ClinicalTrials.gov; NCT03190902 ; registration date: June 15, 2017; retrospectively registered. DOI: 10.1186/s12883-018-1087-3 PMID: 29884144
Environmental exposures and the risk of multiple sclerosis in Saudi Arabia.

Al Wutayd O(1)(2), Mohamed AG(3), Saeedi J(4), Al Otaibi H(5), Al Jumah M(6).

Author information: (1)Unaizah College of Medicine, Qassim University, Qassim, Saudi Arabia. (2)Unaizah College of Medicine and Medical Sciences - Qassim University, Unaizah, Qassim, Saudi Arabia. (3)King Khalid University Hospital, Riyadh, Saudi Arabia. (4)Princess Norah Bint Abdulrahman University, Riyadh, Saudi Arabia. (5)King Fahad General Hospital, Ministry of Health, Jedda, Saudi Arabia. (6)King Fahad Medical City, MOH, KAIMRC/KSAU-HS, Riyadh, Saudi Arabia. jumahm@gmail.com.

BACKGROUND: Multiple sclerosis (MS) is the most common non-traumatic condition that leads to disability among young individuals. It is associated with demyelination, inflammation, and neurodegeneration within the central nervous system. Information on risk factors of multiple sclerosis is crucial for the prevention and control of the disease. The aim of this study was to determine risk factors of MS among adults in Saudi Arabia. METHODS: A matched multicenter case-control study, including 307 MS patients and 307 healthy controls, was conducted in MS clinics and wards in 3 main cities of Saudi Arabia. Age, gender, and hospital were matched. Information on demographics, family history of MS, past medical and family history, sun exposure at different age periods, tobacco use, diet, consanguinity, and coffee consumption was obtained from self-administered questionnaires. ORs and 95% confidence intervals (CIs) were calculated. A conditional logistic regression model was used to control for potential confounding factors. RESULTS: The conditional logistic regression adjusted for age and gender showed that being the first child in the family (Adjusted Odds Ratio (AOR) 1.68, 95% CI: 1.03-2.74), having a family history of MS (AOR 5.83, 95% CI: 2.83-12), eating fast food ≥5 times weekly (AOR 2.05, 95% CI: 1.03-4.08), and having had measles (AOR 3.77, 95% CI: 2.05-6.96), were independently associated with an increased risk of MS. In contrast, eating ≥5 servings of fruit per week (AOR 0.25, 95% CI: 0.16-0.38), drinking coffee daily (AOR 0.46, 95% CI: 0.31-0.68), and having a high level of sun exposure at the primary school level and university level (AOR 0.57, 95% CI: 0.38-0.85 and AOR 0.48, 95% CI: 0.30-0.76, respectively) were independently associated with a decreased risk of MS. CONCLUSIONS: Our study suggested that high levels of sun exposure during primary school and university, consumption of fruits and drinking coffee protect against MS. In contrast, eating fast food was associated with an increased risk of the disease. Encouraging outdoor activity and healthy diets in school, especially for females, is highly recommended.

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A case of oligodendroglioma and multiple sclerosis: Occam’s razor or Hickam’s dictum?

Shirani A(1), Wu GF(1), Giannini C(2), Cross AH(1).

Author information: (1)Department of Neurology, Washington University in Saint Louis School of Medicine, St Louis, Missouri, USA. (2)Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, USA.

Tumefactive appearing lesions on brain imaging can cause a diagnostic dilemma. We report a middle-aged man who presented with right-sided optic neuritis. A brain MRI showed enhancement of the right optic nerve, and non-enhancing white matter lesions including a 3 cm right frontal lesion with adjacent gyral expansion. Cerebrospinal fluid analysis showed five oligoclonal bands not present in serum. Glatiramer acetate was started for suspected tumefactive multiple sclerosis (MS). A follow-up brain MRI 6 months later showed persistence of the frontal gyral expansion. A brain biopsy led to the diagnosis of an oligodendroglioma, isocitrate dehydrogenase-mutant and 1p/19q co-deleted (WHO grade II), managed with surgical resection and radiotherapy. Postoperative brain MRI showed a new enhancing periventricular lesion, making the choice of optimal disease-modifying therapy for MS challenging. This case highlights the possibility of coexistence of MS and oligodendroglioma, and emphasises the importance of a tissue diagnosis when atypical MS imaging features are present.

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Are adverse outcome rates higher in multiple sclerosis patients after total hip arthroplasty?

Newman JM(1), Khlopas A(2), Sodhi N(2), Curtis GL(2), Sultan AA(2), George J(2), Higuera CA(2), Mont MA(2).

Author information: (1)Department of Orthopaedic Surgery, SUNY Downstate Medical Center, New York, New York, USA. (2)Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, Ohio, USA.

Aims: This study compared multiple sclerosis (MS) patients who underwent primary total hip arthroplasty (THA) with a matched cohort. Specifically, we evaluated: 1) implant survivorship; 2) functional outcomes (modified Harris Hip Scores (mHHS), Hip Disability and Osteoarthritis Outcome Score, Joint Replacement (HOOS JR), and modified Multiple Sclerosis Impact Scale (mMSIS) scores (with the MS cohort also evaluated based on the disease phenotype)); 3) physical therapy duration and return to function; 4) radiographic outcomes; and 5) complications. Patients and Methods: We reviewed our institution’s database to identify MS patients who underwent THA between January 2008 and June 2016. A total of 34 MS patients (41 hips) were matched in a 1:2 ratio to a cohort of THA patients who did not have MS, based on age, body mass index (BMI), and Charlson/Deyo score. Patient records were reviewed for complications, and their functional outcomes and radiographs were reviewed at their most recent follow-up. Results: Compared with the matched cohort, MS patients had lower all-cause implant survivorship at eight years (91.5% (95% confidence interval (CI) 82.7 to 100) vs 98.7% (95% CI 96.2 to 100)) (p = 0.033), lower mHHS scores (66 vs 80, p < 0.001), and HOOS JR scores (79 vs 88, p = 0.009). Multiple sclerosis patients also required more physiotherapy (five weeks vs three weeks, p = 0.002) and took longer to return to baseline (seven weeks vs five weeks, p = 0.010) than the matched cohort. Furthermore, MS patients had more complications than the non-MS patients (six vs zero, p < 0.001). The worse outcomes of the MS group can potentially be explained by predisposition of these patients to mechanical complications and progression of their disease during the period of this study, as demonstrated by worsening of the mMSIS scores (2.9 vs 3.4; p = 0.008). Conclusion: MS patients had lower implant survivorship, lower functional outcome scores, and increased complication rates; in addition, MS patients took longer to return to their baseline functional level after THA. Cite this article: Bone Joint J 2018;100-B:875-81.

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Impaired plasticity of macrophages in X-linked adrenoleukodystrophy.

Weinhofer I(1), Zierfuss B(1), Hametner S(2)(3), Wagner M(1)(4), Popitsch N(5)(6), Machacek C(7), Bartolini B(8), Zlabinger G(9), Ohradanova-Repic A(7), Stockinger H(7), Köhler W(10), Höftberger R(11), Regelsberger G(11), Forss-Petter S(1), Lassmann H(2), Berger J(1).

Author information: (1)Department of Pathobiology of the Nervous System, Center for Brain Research, Medical University of Vienna, Vienna, Austria. (2)Department of Neuroimmunology, Center for Brain Research, Medical University of Vienna, Vienna, Austria. (3)Institute of Neuropathology, University Medical Center Goettingen, Germany. (4)Department of Clinical Science, Intervention and Technology; Karolinska Institutet, Stockholm, Sweden. (5)Wellcome Trust Centre for Human Genetics, University of Oxford, UK. (6)Children's Cancer Research Institute, Vienna, Austria. (7)Institute for Hygiene and Applied Immunology, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria. (8)Department of Laboratory Medicine, Medical University of Vienna, Vienna, Austria. (9)Institute of Immunology, Medical University of Vienna, Vienna, Austria. (10)Department of Neurology, University Hospital Leipzig, Leipzig, Germany. (11)Institute of Neurology, Medical University of Vienna, Vienna, Austria.

X-linked adrenoleukodystrophy is caused by ATP-binding cassette transporter D1 (ABCD1) mutations and manifests by default as slowly progressive spinal cord axonopathy with associated demyelination (adrenomyeloneuropathy). In 60% of male cases, however, X-linked adrenoleukodystrophy converts to devastating cerebral inflammation and demyelination (cerebral adrenoleukodystrophy) with infiltrating blood-derived monocytes and macrophages and cytotoxic T cells that can only be stopped by allogeneic haematopoietic stem cell transplantation or gene therapy at an early stage of the disease. Recently, we identified monocytes/macrophages but not T cells to be severely affected metabolically by ABCD1 deficiency. Here we found by whole transcriptome analysis that, although monocytes of patients with X-linked adrenoleukodystrophy have normal capacity for macrophage differentiation and phagocytosis, they are pro-inflammatory skewed also in patients with adrenomyeloneuropathy in the absence of cerebral inflammation. Following lipopolysaccharide activation, the ingestion of myelin debris, normally triggering anti-inflammatory polarization, did not fully reverse the pro-inflammatory status of X-linked adrenoleukodystrophy macrophages. Immunohistochemistry on post-mortem cerebral adrenoleukodystrophy lesions reflected the activation pattern by prominent presence of enlarged lipid-laden macrophages strongly positive for the pro-inflammatory marker co-stimulatory molecule CD86. Comparative analyses of lesions with matching macrophage density in cases of cerebral adrenoleukodystrophy and acute multiple sclerosis showed a similar extent of pro-inflammatory activation but a striking reduction of anti-inflammatory mannose receptor (CD206) and haemoglobin-haptoglobin receptor (CD163) expression on cerebral adrenoleukodystrophy macrophages. Accordingly, ABCD1-deficiency leads to an impaired plasticity of macrophages that is reflected in incomplete establishment of anti-inflammatory responses, thus possibly contributing to the devastating rapidly progressive demyelination in cerebral adrenoleukodystrophy that only in rare cases arrests spontaneously. These findings emphasize monocytes/macrophages as crucial therapeutic targets for preventing or stopping myelin destruction in patients with X-linked adrenoleukodystrophy.

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**Serum neurofilament as a predictor of disease worsening and brain and spinal cord atrophy in multiple sclerosis.**


Author information:  (1)Neurologic Clinic and Polyclinic, Departments of Medicine, Biomedicine and Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland. (2)Clinical Trial Unit, Department of Clinical Research, University Hospital Basel, University of Basel, Basel, Switzerland. (3)Neurocentre of Southern Switzerland, Ospedale Civico, Lugano, Switzerland. (4)Medical Image Analysis Center (MIAC AG), Basel, Switzerland. (5)Division of Diagnostic and Interventional Neuroradiology, Department of Radiology and Nuclear Medicine, University Hospital Basel, University of Basel, Basel, Switzerland. (6)Department of Biomedical Engineering, University Basel, Switzerland.

Neuro-axonal injury is a key factor in the development of permanent disability in multiple sclerosis. Neurofilament light chain in peripheral blood has recently emerged as a biofluid marker reflecting neuro-axonal damage in this disease. We aimed at comparing serum neurofilament light chain levels in multiple sclerosis and healthy controls, to determine their association with measures of disease activity and their ability to predict future clinical worsening as well as brain and spinal cord volume loss. Neurofilament light chain was measured by single molecule array assay in 2183 serum samples collected as part of an ongoing cohort study from 259 patients with multiple sclerosis (189 relapsing and 70 progressive) and 259 healthy control subjects. Clinical assessment, serum sampling and MRI were done annually; median follow-up time was 6.5 years. Brain volumes were quantified by structural image evaluation using normalization of atrophy, and structural image evaluation using normalization of atrophy, cross-sectional, cervical spinal cord volumes using spinal cord image analyser (cordial). Results were analysed using ordinary linear regression models and generalized estimating equation modelling. Serum neurofilament light chain was higher in patients with a clinically isolated syndrome or relapsing remitting multiple sclerosis as well as in patients with secondary or primary progressive multiple sclerosis than in healthy controls (age adjusted P < 0.001 for both). Serum neurofilament light chain above the 90th percentile of healthy controls values was an independent predictor of Expanded Disability Status Scale worsening in the subsequent year (P < 0.001). The probability of Expanded Disability Status Scale worsening gradually increased by higher serum neurofilament light chain percentile category. Contrast enhancing and new/enlarging lesions were independently associated with increased serum neurofilament light chain (17.8% and 4.9% increase per lesion respectively; P < 0.001). The higher the serum neurofilament light chain percentile level, the more pronounced was future brain and cervical spinal volume loss: serum neurofilament light chain above the 97.5th percentile was associated with an additional average loss in brain volume of 1.5% (P < 0.001) and spinal cord volume of 2.5% over 5 years (P = 0.009). Serum neurofilament light chain correlated with concurrent and future clinical and MRI measures of disease activity and severity. High serum neurofilament light chain levels were associated with both brain and spinal cord volume loss. Neurofilament light chain levels are a real-time, easy to measure marker of neuro-axonal injury that is conceptually more comprehensive than brain MRI.

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Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated.


Author information:  (1)Penn Alzheimer's Disease Core Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (2)Penn Udall Center of Excellence in Parkinson's Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (3)Penn Center for Neurodegenerative Disease Research, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (4)Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (5)Department of Biostatistics and Epidemiology, and Informatics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (6)University-town Hospital of Chongqing Medical University, China. (7)Department of Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (8)Penn Frontotemporal Degeneration Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (9)Memory and Aging Center, Department of Neurology, University of California at San Francisco, San Francisco, CA, USA. (10)Parkinson's Disease Research, Education and Clinical Center, Michael J. Crescenz Veterans Affairs Medical Center, Philadelphia, PA, USA. (11)Penn Memory Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. (12)Department of Psychiatry, University of Pennsylvania, Philadelphia, PA, USA. (13)Translational Neurology Head of the Interdisciplinary Brain Center at Massachusetts General Hospital, Harvard Medical School. (14)Neurological Clinic of the Caritas Clinic of Saarbrücken St. Theresia, Germany.

Lewy bodies commonly occur in Alzheimer's disease, and Alzheimer's disease pathology is frequent in Lewy body diseases, but the burden of co-pathologies across neurodegenerative diseases is unknown. We assessed the extent of tau, amyloid-β, α-synuclein and TDP-43 proteinopathies in 766 autopsied individuals representing a broad spectrum of clinical neurodegenerative disease. We interrogated pathological Alzheimer's disease (n = 247); other tauopathies (n = 95) including Pick's disease, corticobasal disease and progressive supranuclear palsy; the synucleinopathies (n = 164) including multiple system atrophy and Lewy body disease; the TDP-43 proteinopathies (n = 188) including frontotemporal lobar degeneration with TDP-43 inclusions and amyotrophic lateral sclerosis; and a minimal pathology group (n = 72). Each group was divided into subgroups without or with co-pathologies. Age and sex matched logistic regression models compared co-pathology prevalence between groups. Co-pathology prevalence was similar between the minimal pathology group and most neurodegenerative diseases for each proteinopathy: tau was nearly universal (92-100%), amyloid-β common (20-57%); α-synuclein less common (4-16%); and TDP-43 the rarest (0-16%). In several neurodegenerative diseases, co-pathology increased: in Alzheimer's disease, α-synuclein (41-55%) and TDP-43 (33-40%) increased; in progressive supranuclear palsy, α-synuclein increased (22%); in corticobasal disease, TDP-43 increased (24%); and in neocortical Lewy body disease, amyloid-β (80%) and TDP-43 (22%) increased. Total co-pathology prevalence varied across groups (27-68%), and was increased in high Alzheimer's disease, progressive supranuclear palsy, and neocortical Lewy body disease (70-81%). Increased age at death was observed in the minimal pathology group, amyotrophic lateral sclerosis, and multiple system atrophy cases with co-pathologies. In amyotrophic lateral sclerosis and neocortical Lewy body disease, co-pathologies associated with APOE ε4. Lewy body disease cases with Alzheimer's disease co-pathology had substantially lower Mini-Mental State Examination scores than pure Lewy body disease. Our data imply that increased age and APOE ε4 status are risk factors for co-pathologies independent of neurodegenerative disease; that neurodegenerative disease severity influences co-pathology as evidenced by the prevalence of co-pathology in high Alzheimer's disease and neocortical Lewy body disease, but not intermediate Alzheimer's disease or limbic Lewy body disease; and that tau and α-synuclein strains may also modify co-pathologies since tauopathies and synucleinopathies had differing co-pathologies and burdens. These findings have implications for clinical trials that focus on monotherapies targeting tau, amyloid-β, α-synuclein and TDP-43.

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The compartmentalized inflammatory response in the multiple sclerosis brain is composed of tissue-resident CD8+ T lymphocytes and B cells.


Author information: (1)Department of Neuroimmunology, Center for Brain Research, Medical University of Vienna, Vienna, Austria. (2)Department of Neurology, Brain Research Institute, Niigata University, Niigata, Japan. (3)INSERM U1043 - CNRS UMR 5282, Centre de Physiopathologie Toulouse-Purpan, Université Toulouse III, Toulouse, F-31000, France. (4)Department of Neurology, Anne Romney Center for Neurologic Disease, Harvard Medical School, Boston, USA. (5)Epilepsy Center Bethel, Krankenhaus Mara, Bielefeld, Germany.

Multiple sclerosis is an inflammatory demyelinating disease in which active demyelination and neurodegeneration are associated with lymphocyte infiltrates in the brain. However, so far little is known regarding the phenotype and function of these infiltrating lymphocyte populations. In this study, we performed an in-depth phenotypic characterization of T and B cell infiltrates in a large set of multiple sclerosis cases with different disease and lesion stages and compared the findings with those seen in inflammatory, non-inflammatory and normal human controls. In multiple sclerosis lesions, we found a dominance of CD8+ T cells and a prominent contribution of CD20+ B cells in all disease courses and lesion stages, including acute multiple sclerosis cases with very short disease duration, while CD4+ T cells were sparse. A dominance of CD8+ T cells was also seen in other inflammatory controls, such as Rasmussen's encephalitis and viral encephalitis, but the contribution of B cells in these diseases was modest. Phenotypic analysis of the CD8+ T cells suggested that part of the infiltrating cells in active lesions proliferate, show an activated cytotoxic phenotype and are in part destroyed by apoptosis. Further characterization of the remaining cells suggest that CD8+ T cells acquire features of tissue-resident memory cells, which may be focally reactivated in active lesions of acute, relapsing and progressive multiple sclerosis, while B cells, at least in part, gradually transform into plasma cells. The loss of surface molecules involved in the egress of leucocytes from inflamed tissue, such as S1P1 or CCR7, and the upregulation of CD103 expression may be responsible for the compartmentalization of the inflammatory response in established lesions. Similar phenotypic changes of tissue-infiltrating CD8+ T cells were also seen in Rasmussen's encephalitis. Our data underline the potential importance of CD8+ T lymphocytes and B cells in the inflammatory response in established multiple sclerosis lesions. Tissue-resident T and B cells may represent guardians of previous inflammatory brain disease, which can be reactivated and sustain the inflammatory response, when they are re-exposed to their specific antigen.

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The intestinal barrier in multiple sclerosis: implications for pathophysiology and therapeutics.

Camara-Lemarroy CR(1)(2), Metz L(1)(2), Meddings JB(3), Sharkey KA(2)(4), Wee Yong V(1)(2).

Author information: (1)Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. (2)Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. (3)Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada. (4)Department of Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada.

Biological barriers are essential for the maintenance of homeostasis in health and disease. Breakdown of the intestinal barrier is an essential aspect of the pathophysiology of gastrointestinal inflammatory diseases, such as inflammatory bowel disease. A wealth of recent studies has shown that the intestinal microbiome, part of the brain-gut axis, could play a role in the pathophysiology of multiple sclerosis. However, an essential component of this axis, the intestinal barrier, has received much less attention. In this review, we describe the intestinal barrier as the physical and functional zone of interaction between the luminal microbiome and the host. Besides its essential role in the regulation of homeostatic processes, the intestinal barrier contains the gut mucosal immune system, a guardian of the integrity of the intestinal tract and the whole organism. Gastrointestinal disorders with intestinal barrier breakdown show evidence of CNS demyelination, and content of the intestinal microbiome entering into the circulation can impact the functions of CNS microglia. We highlight currently available studies suggesting that there is intestinal barrier dysfunction in multiple sclerosis. Finally, we address the mechanisms by which commonly used disease-modifying drugs in multiple sclerosis could alter the intestinal barrier and the microbiome, and we discuss the potential of barrier-stabilizing strategies, including probiotics and stabilization of tight junctions, as novel therapeutic avenues in multiple sclerosis.

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Lack of junctional adhesion molecule (JAM)-B ameliorates experimental autoimmune encephalomyelitis.


Author information: (1)Theodor Kocher Institute, University of Bern, Bern, Switzerland. (2)Department of Tissue Morphogenesis, Max Planck Institute for Molecular Biomedicine, Münster, Germany. (3)Department of Pathology and Immunology, University of Geneva, CMU Geneva, Switzerland. (4)Centre de Recherche en Cancérologie de Marseille, INSERM, CNRS, Aix-Marseille University, Marseille, France. (5)Theodor Kocher Institute, University of Bern, Bern, Switzerland. Electronic address: bengel@tki.unibe.ch.

In multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) autoaggressive CD4+ T cells cross the blood-brain barrier (BBB) and cause neuroinflammation. Therapeutic targeting of CD4+ T-cell trafficking into the CNS by blocking α4-integrins has proven beneficial for the treatment of MS but comes with associated risks, probably due to blocking CD8+ T-cell mediated CNS immune surveillance. Our recent observations show that CD8+ T cells also rely on α4β1-integrins to cross the BBB. Besides vascular cell adhesion molecule-1 (VCAM-1), we identified junctional adhesion molecule-B (JAM-B) as a novel vascular α4β1-integrin ligand involved in CD8+ T-cell migration across the BBB. This prompted us to investigate, if JAM-B also mediates CD4+ T-cell migration across the BBB. We first ensured that encephalitogenic T cells can bind to JAM-B in vitro and next compared EAE pathogenesis in JAM-B-/- C57BL/6J mice and their wild-type littermates. Following immunization with MOGaa35-55 peptide, JAM-B-/- mice developed ameliorated EAE compared to their wild-type littermates. At the same time, we isolated higher numbers of CD45+ infiltrating immune cells from the CNS of JAM-B-/- C57BL/6J mice suffering from EAE. Immunofluorescence staining revealed that the majority of CD45+ inflammatory cells accumulated in the leptomeningeal and perivascular spaces of the CNS behind the BBB but do not gain access to the CNS parenchyma. Trapping of CNS inflammatory cells was not due to increased inflammatory cell proliferation. Neither a loss of BBB integrity or BBB polarity potentially affecting local chemokine gradients nor a lack of focal gelatinase activation required for CNS parenchymal immune cell entry across the glia limitans could be detected in JAM-B-/- mice. Lack of a role for JAM-B in the effector phase of EAE was supported by the observation that we did not detect any role for JAM-B in EAE pathogenesis, when EAE was elicited by in vitro activated MOG aa35-55-specific CD4+ effector T cells. On the other hand, we also failed to demonstrate any role of JAM-B in in vivo priming, proliferation or polarization of MOGaa35-55-specific CD4+ T cells in peripheral immune organs. Finally, our study excludes expression of and thus a role for JAM-B on peripheral and CNS infiltrating myeloid cells. Taken together, although endothelial JAM-B is not required for immune cell trafficking across the BBB in EAE, in its absence accumulation of inflammatory cells mainly in CNS leptomeningeal spaces leads to amelioration of EAE.
Thalamic and hippocampal volume associated with memory functions in multiple sclerosis.  
Author information: (1)Department of Psychology, Université du Québec à Montréal, CP 8888, succ. Centre-ville, Montreal H3C 3P8, Canada. (2)Centre de Recherche du Centre Hospitalier de l'Université de Montréal, 900 Rue Saint-Denis, Montréal, QC H2X 3H8, Canada. (3)McConnell Brain Imaging Centre, Montreal Neurological Institute, 3801 University Street, QC H3A 2B4 Montreal, Canada. (4)Department of Psychiatry, Centre Hospitalier de l'Université de Montréal, 1051 Rue Sanguinet, Montréal, QC H2X 3E4, Canada. (5)Department of Psychology, Université du Québec à Montréal, CP 8888, succ. Centre-ville, Montreal H3C 3P8, Canada; Centre de Recherche du Centre Hospitalier de l'Université de Montréal, 900 Rue Saint-Denis, Montréal, QC H2X 3H8, Canada. Electronic address: rouleau.isabelle@uqam.ca.  
OBJECTIVES: Although multiple sclerosis (MS) has long been considered to primarily affect white matter, it is now recognized that cognitive deficits in MS are also related to neocortical, thalamic and hippocampal damage. However, the association between damage to these structures and memory deficits in MS is unclear. This study examines whether MS patients with cognitive impairment have a reduction of hippocampal and/or thalamic volumes compared to cognitively intact patients, and whether these volume reductions correlate with various aspects of memory function. METHODOLOGY: Volumetric MRI measures of thalamus and hippocampus of forty-one patients with MS were performed. The patients were divided in two groups depending on the presence or absence of cognitive impairment, based on their neuropsychological tests scores. RESULTS: Right hippocampal volume was found to be associated with learning, and the left thalamic volume was found to predict performance in verbal memory. Cognitively impaired patients had a tendency to have a reduced left thalamic volume compared to cognitively intact patients. CONCLUSIONS: This study does not support a direct relationship between hippocampal atrophy and verbal memory. These results add to the growing evidence of the involvement of thalamus in cognitive impairment in MS and its association with verbal memory deficits.  
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Driven to decay: Excitability and synaptic abnormalities in amyotrophic lateral sclerosis.  
Fogarty MJ(1).  
Author information: (1)Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN, USA; School of Biomedical Sciences, The University of Queensland, St Lucia, Australia. Electronic address: fogarty.matthew@mayo.edu.  
Amyotrophic lateral sclerosis (ALS) is the most common motor neuron (MN) disease and is clinically characterised by the death of corticospinal motor neurons (CSMNs), spinal and brainstem MNs and the degeneration of the corticospinal tract. Degeneration of CSMNs and MNs leads inexorably to muscle wastage and weakness, progressing to eventual death within 3-5 years of diagnosis. The CSMNs, located within layer V of the primary motor cortex, project axons constituting the corticospinal tract, forming synaptic connections with brainstem and spinal cord interneurons and MNs. Clinical ALS may be divided into familial (~10% of cases) or sporadic (~90% of cases), based on apparent random incidence. The emergence of transgenic murine models, expressing different ALS-associated mutations has accelerated our understanding of ALS pathogenesis, although precise mechanisms remain elusive. Multiple avenues of investigation suggest that cortical electrical abnormalities have pre-eminence in the pathophysiology of ALS. In addition, glutamate-mediated functional and structural alterations in both CSMNs and MNs are present in both sporadic and familial forms of ALS. This review aims to promulgate debate in the field with regard to the common aetiology of sporadic and familial ALS. A specific focus on a nexus point in ALS pathogenesis, namely, the synaptic and intrinsic hyperexcitability of CSMNs and MNs and alterations to their structure are comprehensively detailed. The association of extramotor dysfunction with neuronal structural/functional alterations will be discussed. Finally, the implications of the latest research on the dying-forward and dying-back controversy are considered.  
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[Emerging Cellular and Molecular Strategies for Enhancing Central Nervous System (CNS) Remyelination.]

Abu-Rub M(1), Miller RH(2).
Author information:  
(1)Department of Neurology, George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA. aburub@gwu.edu. 
(2)Department of Anatomy and Regenerative Biology, George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA. rhm3@gwu.edu.

Myelination is critical for the normal functioning of the central nervous system (CNS) in vertebrates. Conditions in which the development of myelin is perturbed result in severely compromised individuals often with shorter lifespans, while loss of myelin in the adult results in a variety of functional deficits. Although some form of spontaneous remyelination often takes place, the repair process as a whole often fails. Several lines of evidence suggest it is feasible to develop strategies that enhance the capacity of the CNS to undergo remyelination and potentially reverse functional deficits. Such strategies include cellular therapies using either neural or mesenchymal stem cells as well as molecular regulators of oligodendrocyte development and differentiation. Given the prevalence of demyelinating diseases and their effects on the quality of life for affected individuals it is imperative that effective therapies are developed. Here we discuss some of the new approaches to CNS myelin repair that hold promise for reducing the burden of diseases characterized by myelin loss.

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[Managing Multiple Sclerosis: Treatment Initiation, Modification, and Sequencing.]

Freedman MS(1), Selchen D(2), Prat A(3), Giacomini PS(4).
Author information:  
(1)1Division of Neurology, Department of Medicine, University of Ottawa and the Ottawa Hospital Research Institute, Ottawa, ON, Canada. 
(2)4St. Michael’s Hospital, University of Toronto, Toronto, ON, Canada. 
(3)3CRCHUM and Department of Neuroscience, Faculty of Medicine, Université de Montréal, Montréal, QC, Canada. 
(4)2Montreal Neurological Institute, McGill University, Montréal, QC, Canada.

Recent therapeutic advances in the management of multiple sclerosis (MS) have raised questions about the selection of appropriate patient candidates for various treatments and, if the plan is to move from one treatment to another, the appropriate sequencing of these therapies. The selected approach should provide optimal disease management without limiting future therapeutic options based on safety concerns, and recognize potential future treatments and the possibility of combination therapies. Additional challenges include incorporation of patient needs and preferences into the overall therapeutic approach, in order to ensure optimal outcomes in the short and long term. The objective of this manuscript is to provide an overview of what is currently known regarding the impact of various therapies for MS on future therapeutic choices (sequencing). In this context, we reviewed the available evidence in support of various treatments and, based on the presence of disease activity, suggested a scheme for switching or escalating therapy with the main focus on sequencing of therapeutic approaches.

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Intermittent Fasting Confers Protection in CNS Autoimmunity by Altering the Gut Microbiota.

Cignarella F(1), Cantoni C(1), Ghezzi L(2), Salter A(3), Dorsett Y(4), Chen L(4), Phillips D(4), Weinstock GM(4), Fontana L(5), Cross AH(6), Zhou Y(7), Piccio L(8).

Author information: (1)Department of Neurology, Washington University School of Medicine, Campus Box 8111, 660 S. Euclid Avenue, St. Louis, MO 63110, USA. (2)Department of Neurology, Washington University School of Medicine, Campus Box 8111, 660 S. Euclid Avenue, St. Louis, MO 63110, USA; Neurology Unit, Department of Pathophysiology and Transplantation, University of Milan, Fondazione Ca Granda, IRCCS Ospedale Policlinico, Milan, Italy. (3)Division of Biostatistics, Washington University School of Medicine, St. Louis, MO 63110, USA. (4)Jackson Laboratory for Genomic Medicine, Farmington, CT, USA. (5)Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA; Department of Clinical and Experimental Sciences, Brescia University Medical School, Brescia, Italy; CEINGE Biotecnologie Avanzate, Napoli, Italy. (6)Department of Neurology, Washington University School of Medicine, Campus Box 8111, 660 S. Euclid Avenue, St. Louis, MO 63110, USA; Hope Center for Neurological Disorders, Washington University School of Medicine, St Louis, MO, USA. (7)Jackson Laboratory for Genomic Medicine, Farmington, CT, USA. Electronic address: yazhou@uchc.edu. (8)Department of Neurology, Washington University School of Medicine, Campus Box 8111, 660 S. Euclid Avenue, St. Louis, MO 63110, USA; Hope Center for Neurological Disorders, Washington University School of Medicine, St Louis, MO, USA. Electronic address: piccio1@wustl.edu.

Multiple sclerosis (MS) is more common in western countries with diet being a potential contributing factor. Here we show that intermittent fasting (IF) ameliorated clinical course and pathology of the MS model, experimental autoimmune encephalomyelitis (EAE). IF led to increased gut bacteria richness, enrichment of the Lactobacillaceae, Bacteroidaceae, and Prevotellaceae families and enhanced antioxidative microbial metabolic pathways. IF altered T cells in the gut with a reduction of IL-17 producing T cells and an increase in regulatory T cells. Fecal microbiome transplantation from mice on IF ameliorated EAE in immunized recipient mice on a normal diet, suggesting that IF effects are at least partially mediated by the gut flora. In a pilot clinical trial in MS patients, intermittent energy restriction altered blood adipokines and the gut flora resembling protective changes observed in mice. In conclusion, IF has potent immunomodulatory effects that are at least partially mediated by the gut microbiome.

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Design, Synthesis, and Biological Evaluation of Tetrahydro-β-carboline Derivatives as Selective Sub-Nanomolar Gelatinase Inhibitors.


Author information: (1)Dipartimento di Farmacia-Scienze del Farmaco, Università di Bari "Aldo Moro", Via Orabona, 4, 70126, Bari, Italy. (2)Istituto Tumori IRCCS Giovanni Paolo II, Bari, Italy. (3)D4T S.r.l Colosseum Combinatorial Chemistry Centre for Technology, Via della Ricerca Scientifica snc, Ed. PP2-Macroarea Scienze, 00133, Rome, Italy. (4)Dipartimento di Scienze cliniche e Medicina Traslazionale, Università di Roma "Tor Vergata", Via Montpellier, 1, 00133, Rome, Italy. Targeting matrix metalloproteinases (MMPs) is a pursued strategy for treating several pathological conditions, such as multiple sclerosis and cancer. Herein, a series of novel tetrahydro-β-carboline derivatives with outstanding inhibitory activity toward MMPs are present. In particular, compounds 9 f, 9 g, 9 h and 9 i show sub-nanomolar IC50 values. Interestingly, compounds 9 g and 9 i also provide remarkable selectivity toward gelatinases; IC50 <0.15 nm for both toward MMP-2 and IC50 =0.63 and 0.58 nm, respectively, toward MMP-9. Molecular docking simulations, performed by employing quantum mechanics based partial charges, shed light on the rationale behind binding involving specific interactions with key residues of S1’ and S3’ domains. Taken together, these studies indicate that tetrahydro-β-carboline derivatives represent a promising scaffold for the design of novel inhibitors able to target MMPs and selectively bias gelatinases, over the desirable range of the pharmacokinetics spectrum.

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Fake news? Biotin interference in thyroid immunoassays.

Koehler VF(1), Mann U(2), Nassour A(3), Mann WA(4).

Author information: (1)Medical Department IV, University Munich, Campus Grosshadern, Marchioninistraße 15, 81377 Munich, Germany. Electronic address: Viktoria.Koehler@med.uni-muenchen.de. (2)Department of Neurology, Endokrinologikum Frankfurt, Stresemannallee 1/3, 60596 Frankfurt/Main, Germany. (3)Department of laboratory medicine and microbiology, Am Prime Parc 13, 65479 Raunheim, Germany. (4)Department of Endocrinology, Endokrinologikum Frankfurt, Stresemannallee 1/3, 60596 Frankfurt/Main, Germany.

We report on a 47 year old male patient with multiple sclerosis (MS) presenting in our outpatient neurology clinic in Frankfurt/Main for therapy evaluation. Before change of treatment laboratory investigations were performed. Thyroid function tests (TFTs) with a streptavidin/biotin based immunoassay revealed severe hyperthyroidism with positive thyroid autoantibodies suggestive for Graves' disease. Clinical presentation and thyroid sonography were unremarkable. Due to the discordance between clinical presentation and TFTs, we repeated medical history, in which the patient reported taking high-doses of biotin (300 mg/day) for MS. Recent studies with patients suffering from primary and secondary progressive MS, indicated promising effects of high-dose biotin on MS-related disability. In immunoassays relying on streptavidin-biotin interaction, biotin intake can cause falsely high or low results. Two weeks after withdrawing biotin, biotin/streptavidin dependant assays showed no longer the biochemical picture of severe hyperthyroidism. Biotin intake should be paused for at least two to five days prior to the use of biotin/streptavidin dependant assays. Alternatively, non-biotin/streptavidin dependant assays (radioimmunoassay, gas chromatography-mass spectrometry/liquid chromatography-mass spectrometry) may be used.

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SHANK3 variant as a cause of nonsyndromal autism in an 11-year-old boy and a review of published literature.

Kanani F(1), Study D(2), Balasubramanian M(1).

Author information: (1)Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, Sheffield. (2)Wellcome Genome Campus, Cambridge, UK.

Autism spectrum disorder (ASD) encompasses a spectrum of pervasive neuropsychiatric disorders characterized by deficits in social interaction, communication, unusual and repetitive behaviours. The aetiology of ASD is believed to involve complex interactions between genetic and environmental factors; it can be further classified as syndromic or nonsyndromic, according to whether it is the primary diagnosis or secondary to an existing condition where both common and rare genetic variants contribute to the development of ASD or are clearly causal. The prevalence of ASD in children is increasing with higher rates of diagnosis and an estimated one in 100 affected in the UK. Given that heritability is a major contributing factor, we aim to discuss research findings to-date in the context of a high-risk autism candidate gene, SHANK3 (SH3 and multiple ankyrin repeat domain 3), with its loss resulting in synaptic function disruption. We present a 10-year-old patient with a pathogenic de novo heterozygous c.1231delC, p.Arg411Val frameshift variant in SHANK3. He presented with severe autism, attention deficit hyperactivity disorder and pathological demand avoidance, on a background of developmental impairment and language regression. The number of genes associated with autism is ever increasing. It is a heterogeneous group of disorders with no single gene conferring pathogenesis in the majority of cases. Genetic abnormalities can be detected in ~15% of ASD and these range from copy number variants in 16p11.2 and 15q13.2q13.3 to several well-known genetic disorders including tuberous sclerosis and fragile X syndrome. Further, high confidence autism genes include but are not limited to NRXN, NLGN3, NLGN4, SHANK2 and SHANK3.

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Early sign of microangiopathy in systemic sclerosis: The significance of cold stress test in dynamic laser Doppler flowmetry.


Author information: (1)Department of Dermatology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan. (2)Department of Dermatology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan. (3)Department of Dermatology, University of California Davis School of Medicine, Sacramento, USA. (4)National Institute of Environmental Health Sciences, National Health Research Institutes, Miaoli County, Taiwan. (5)Department of Dermatology, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.

BACKGROUND: Skin physiology measurement is receiving more attention for detecting vasculopathy in systemic sclerosis (SSc). Laser Doppler flowmetry (LDF) is a widely used physiological measurement to assess cutaneous microcirculation. However, findings of LDF may be normal during early stage of microangiopathy in SSc. OBJECTIVE: We hypothesized that cold stress test combined with LDF could detect early-stage microangiopathy in patients with SSc. METHODS: A 67-year-old male came with multiple ulcersations on his fingers for one year. After excluding diseases such as diabetes mellitus-related peripheral arterial occlusive disease and smoking-related Buerger's disease, the diagnosis of SSc was made according to the 2013 ACR/EULAR criteria. We performed LDF and angiography for a patient with SSc and compared the results. RESULTS: Although occlusions of right ulnar and digital arteries were obvious in angiography, the baseline skin temperature and perfusion unit on right fingers remained within normal limits. While the microcirculatory abnormalities measured by LDF alone are subtle, LDF combined with cold stress test detected a significant slow recovery of skin blood flow 40 minutes after cold immersion. CONCLUSIONS: In conclusion, there may be discordance between macrovasculopathy and baseline microcirculatory blood flow in SSc. In such a case, cold immersion test is essential to measure the dynamic change and slow recovery of blood flow.

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Comparing lesion detection of infratentorial multiple sclerosis lesions between T2-weighted spin-echo, 2D-FLAIR, and 3D-FLAIR sequences.

Wang KY(1), Uribe TA(2), Lincoln CM(2).

Author information: (1)Department of Radiology, Baylor College of Medicine, Houston, TX, United States. Electronic address: yujiw@bcm.edu. (2)Department of Radiology, Baylor College of Medicine, Houston, TX, United States.

PURPOSE: Infratentorial lesions in patients with multiple sclerosis are associated with long-term disability. Two-dimensional fluid-attenuated inversion recovery demonstrates poor infratentorial lesion detection when compared to T2-weighted spin echo. Evidence of improved detection with 3D fluid-attenuated inversion recovery has been conflicting. This study compares the infratentorial lesion detection performance, observer performance, and signal and contrast properties between T2-weighted spin echo, 2D, and 3D fluid-attenuated inversion recovery. METHODS: Two board-certified radiologists independently reviewed and counted infratentorial lesions from 85 brain MRIs in patients with clinically definite multiple sclerosis and concurrent 3D, 2D fluid-attenuated inversion recovery, and T2-weighted spin echo sequences. Contrast-to-noise and signal-to-noise ratios were measured for 25 MRIs. Wilcoxon signed-rank test was used for pairwise comparisons of the combined average infratentorial lesion count, contrast-to-noise, and signal-to-noise ratios, and was adjusted for three pairwise comparisons using Bonferroni correction. A corrected p value < 0.05 was considered statistically significant. RESULTS: The number of lesions on 3D fluid-attenuated inversion recovery was significantly higher than those on 2D (p < 0.001) and T2-weighted spin echo (p < 0.001). Results of contrast-to-noise and signal-to-noise ratios were overall mixed and predominantly not concordant with lesion count findings, with T2-weighted spin echo demonstrating the highest signal-to-noise ratios and contrast-to-noise ratio of lesion compared with white matter but the lowest contrast-to-noise ratio of lesion compared with gray matter. CONCLUSION: The 3D fluid-attenuated inversion recovery sequence addresses the disadvantage of poor infratentorial lesion detection on 2D, while still maintaining the advantage over T2-weighted spin echo in the detection of lesions adjacent to the cerebrospinal fluid.

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Safety and Effectiveness of Fingolimod in Real-World Multiple Sclerosis Portuguese Patients.

Ribeiro de Barros AH(1), Fiadeiro Sequeira JP, Lopes de Sousa AS, Cheganças Capela CM, Gomes Pedroza RM, Dos Santos Manita MA.

Author information: (1)Department of Neurology, Centro Hospitalar de Lisboa Central, Hospital de Santo António dos Capuchos, Alameda Santo António dos Capuchos, Lisboa, Portugal.

OBJECTIVES: The aim of this study was to evaluate postmarketing fingolimod safety and effectiveness in a real-world clinical population. METHODS: This was a retrospective, single-center study with active multiple sclerosis patients treated with fingolimod with at least 12 months of follow-up. Demographic and clinical and imaging characteristics, including annualized relapse rate (ARR), Expanded Disability Status Score, previous treatment, adverse events, treatment duration, and reason for discontinuation, were analyzed.

RESULTS: Sixty-three patients were included; 61.9% were females. Mean age and mean disease duration were 30.9 ± 9.3 years and 11.4 ± 6.9 years, respectively. Fifty-one patients received prior first-line disease-modifying therapies, 11 patients were previously treated with natalizumab, and 1 was treatment naive. The ARR decreased by 75.3% for the total population at the end of the first year of treatment (P < 0.0001). The proportion of relapse-free patients improved significantly. All patients previously treated with natalizumab switched because of safety concerns, although the ARR kept low after treatment initiation. Only 3 patients (4.8%) discontinued treatment because of adverse drug reactions, and 2 (3.2%) because of lack of effectiveness. CONCLUSIONS: In this real-world audit, fingolimod appeared to be effective after first-line treatment failure in reducing disease activity and progression of disability throughout the observational period and may be an effective option after natalizumab. Fingolimod was well tolerated with low rates of discontinuation and adverse events.

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Progressive multiple sclerosis patients have a higher burden of autonomic dysfunction compared to relapsing remitting phenotype.

Adamec I(1), Crnošija L(1), Junaković A(1), Krbot Skorić M(1), Habek M(2).

Author information: (1)University Hospital Center Zagreb, Department of Neurology, Referral Center for Autonomic Nervous System Disorders, Zagreb, Croatia. (2)University Hospital Center Zagreb, Department of Neurology, Referral Center for Autonomic Nervous System Disorders, Zagreb, Croatia; School of Medicine, University of Zagreb, Zagreb, Croatia. Electronic address: mhabek@mef.hr.

OBJECTIVE: To determine autonomic dysfunction (AD) differences in patients with relapsing remitting multiple sclerosis (pwRRMS) and progressive MS (pwPMS). METHODS: Composite autonomic scoring scale (CASS) and heart rate variability (HRV) were performed in 40 pwRRMS and 30 pwPMS. RESULTS: pwPMS had a significantly higher sudomotor index and total CASS score compared to pwRRMS (p < 0.001 and p < 0.001, respectively). Disease duration positively correlated with sudomotor index and total CASS (rs = 0.409, p < 0.001 and rs = 0.472, p < 0.001, respectively), while the Expanded Disability Status Scale (EDSS) positively correlated with sudomotor index and total CASS (rs = 0.411, p < 0.001 and rs = 0.402, p = 0.001, respectively) in all patients. Type of multiple sclerosis (pwRRMS or pwPMS) corrected for age, sex and disease duration, was a statistically significant predictor of CASS value (B = 1.215, p = 0.019). Compared to pwRRMS, pwPMS had a significantly lower standard deviation of NN intervals (SDNN), low frequency (LF), and high frequency (HF), during both the supine and tilt-up phases (all p-values <0.006). pwPMS had a significantly lower LF/HF (p = 0.008) during tilt-up. CONCLUSION: There is a significant difference in autonomic function in pwRRMS and pwPMS; with pwPMS having a higher burden of AD, which is particularly evident for sweating dysfunction. SIGNIFICANCE: Further research is needed to establish whether parasympathetic and sudomotor dysfunction may serve as markers of progressive MS.

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**Rey Figure Test with recognition trial: normative data for Lebanese adults.**

Darwish H(1)(2), Zeinoun P(3), Farran N(1), Fares S(1).

Author information:  
(1)a Rafic Hariri School of Nursing, American University of Beirut, Beirut, Lebanon.  
(2)b American University of Beirut Medical Center, Nehme and Therese Tohme Multiple Sclerosis Center, Beirut, Lebanon.  
(3)c Department of Psychology, American University of Beirut, Beirut, Lebanon.

**OBJECTIVE:** This study aimed to provide normative data for four trials of the Rey figure Test - a complex design used to assess visuoconstructional abilities, aspects of visual memory, and aspects of executive functioning. Despite its frequent clinical and research use in the Arab region, published studies regarding the measures' adaptation or normative data remain absent. **METHOD:** We administered the Rey figure on a convenience sample of Lebanese (n = 254) aged 30 years to 99. **RESULTS:** We examined the impact of relevant demographics, and found that age, gender, and years of education impacted scores, and norms were derived based on these variables. Such normative data for the Rey figure enhance its practicality and psychometric adequacy for use in research and clinical settings in Lebanon.  

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**Prospective memory in clinical populations.**

Raskin SA(1)(2).

Author information:  
(1)a Neuroscience Program, Trinity College, Hartford, CT, USA.  
(2)b Department of Psychology, Trinity College, Hartford, CT, USA.

**OBJECTIVE:** Prospective memory (PM) has emerged as a form of episodic memory that is frequently impaired in a variety of clinical populations. Neuropsychologists who routinely evaluate these populations are often unaware of the possibility of PM deficits or the impact these deficits may have on everyday functioning. The objective of this special issue is to provide an overview of the nature of prospective deficits in a range of clinical populations, to discuss neuropsychological assessment techniques, and to critically evaluate management strategies. **METHOD:** We solicited papers from established researchers and issued a general call for papers for the special issue on PM in clinical populations. **RESULTS:** We received submissions from the nine authors that we solicited. These submissions range from developmental disorders, including autism, attention deficit hyperactivity disorder, and dyslexia; to disorders of adulthood, such as schizophrenia, HIV, brain injury, and multiple sclerosis; and finally disorders that tend to occur at older ages, such as Parkinson's disease and mild cognitive impairment. In addition, we have included four original research articles that provide novel data on other populations. These are children and adolescents with 22q11.2 deletion syndrome, first-degree relatives of people with schizophrenia, individuals with mild brain injury, and individuals with idiopathic REM sleep behavioral disorder. **CONCLUSIONS:** The issue highlights the need for clinical neuropsychologists to be aware of the possible existence of deficits in PM in a variety of clinical populations and the importance of both assessment and management strategies to reduce the impact on daily life.  

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Interactions between dietary inflammatory index, nutritional state and Multiple Sclerosis clinical condition.

Da Costa Silva BY(1), De Carvalho Sampaio HA(2), Shivappa N(3), Hébert J(3), Silva Albuquerque LD(4), Ferreira Carioca AA(5), Costa D’Almeida JA(6), Costa Maia CS(7), Pereira De Melo ML(8).

Author information: (1)Post-graduate Program in Collective Health, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil; Research Group on Nutrition and Chronic Diseases, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil. Electronic address: brunayhang@gmail.com. (2)Post-graduate Program in Collective Health, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil; Research Group on Nutrition and Chronic Diseases, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil. (3)South Carolina Statewide Cancer Prevention and Control Program, University of South Carolina, Columbia, SC, 29208, USA; Department of Epidemiology and Biostatistics, Arnold School of Public Health, University of South Carolina, Columbia, SC, 29208, USA; Connecting Health Innovations LLC, Columbia, SC, 29201, USA. (4)Graduate Course in Nutrition, University of Fortaleza, Av. Washington Soares, 1321 Edson Queiroz, Fortaleza, CE, 60811-905, Brazil. (5)Research Group on Nutrition and Chronic Diseases, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil; University of São Paulo, Department of Nutrition, Av. Dr. Arnaldo, 925 Sumaré, São Paulo, SP, 01255-00, Brazil. (6)Fortaleza General Hospital Neurology Outpatient Department, Rua Ávila Goulart, 900 Papicu, Fortaleza, CE, 60175-295, Brazil. (7)Masters in Health and Nutrition, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil. (8)Research Group on Nutrition and Chronic Diseases, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil; Fortaleza General Hospital Neurology Outpatient Department, Rua Ávila Goulart, 900 Papicu, Fortaleza, CE, 60175-295, Brazil; Masters in Health and Nutrition, Ceará State University, Av. Dr. Silas Munguba, 1700 Campus do Itaperi, Fortaleza, CE, 60741-000, Brazil.

BACKGROUND & AIMS: The Dietary Inflammatory Index (DII) consists of a tool that assesses dietary inflammatory potential based on the assignment of an inflammatory score to a variety of nutrients, seasonings and bioactive compounds. Pro-inflammatory diets are associated to weight and abdominal fat excess. High Body Mass Index (BMI) and Waist Circumference (WC) seem to contribute to a worse prognosis in Multiple Sclerosis (MS) patients. Therefore, this study seeks to investigate the relation between anthropometric indexes and body adiposity with the clinical condition and the Dietary Inflammatory Index of MS individuals. METHODS: This is a cross-sectional, analytical study that included 137 MS patients residing in the Brazilian northeast. Through a structured questionnaire and medical records consultation, we collected data on demographics, nutritional state, arterial pressure, clinical and dietary variables. Clinical variables included the MS type, number of pulse therapies and attack rate in the last two years, number of days of most recent pulse therapy and muscular strength assessment scores (MRC) and most recent disability level (EDSS). The nutritional state was evaluated based on BMI, WC, waist-hip ratio (WHR), Body Roundness Index (BRI), Body Shape z score Index (ABSIz) and body fat percentage (%BF). The DII was calculated according to a validated methodology. RESULTS: The ABSIz presented a positive correlation with regards to the EDSS score (r = 0.294. p = 0.001). WC and WHR presented a negative correlation in relation to the number of pulse therapy days (r = -0.255. p = 0.022 and r = -0.251. p = 0.024). BMI and %BF were not correlated to clinical variables (p > 0.05). The DII was positively correlated to the BMI in people with progressive MS (r = 0.556. p = 0.025). CONCLUSIONS: The DII may interfere in the nutritional state of MS patients and the nutritional state may affect disability levels but it is necessary to establish which nutritional indicator can better predict the relation between DII and the clinical condition of MS patients. Copyright © 2018 European Society for Clinical Nutrition and Metabolism. Published by Elsevier Ltd. All rights reserved.

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Investigation of grey matter abnormalities in multiple sclerosis patients by combined use of double inversion recovery sequences and diffusion tensor MRI at 3.0 Tesla.


Author information: (1)Department of Neurology, China-Japan Union Hospital of Jilin, University of Changchun, Jilin, 130031, PR China. (2)Department of Radiology, China-Japan Union Hospital of Jilin, University of Changchun, Jilin, 130031, PR China. (3)Department of Radiology, China-Japan Union Hospital of Jilin, University of Changchun, Jilin, 130031, PR China. (4)Department of Neurology, China-Japan Union Hospital of Jilin, University of Changchun, Jilin, 130031, PR China. Electronic address: 360243570@qq.com.

AIM: To investigate the grey matter abnormalities in multiple sclerosis (MS) patients by combined use of double inversion recovery (DIR) sequences and diffusion tensor (DTI) magnetic resonance imaging (MRI) at 3 T.

MATERIALS AND METHODS: Twenty relapsing-remitting MS (RRMS) patients and 20 healthy control were enrolled in this study. All participants underwent DIR and DTI MRI and completed the Mini-Mental State Examination (MMSE) and Expanded Disability Status Scale (EDSS). The cortical lesions and normal-appearing grey matter (NAGM) of the patient group, as well as the NAGM of the control group were quantitatively analysed using the DIR and DTI images. The average NAGM mean diffusion (MD) and fractional anisotropy (FA) values of the patient group and control group were measured and compared. The correlation between NAGM MD and FA values and the number of cortical lesions, cognitive impairment, as well as the degree of nerve damage were analysed.

RESULTS: The NAGM of the patient group had average MD and FA values that were significantly different compared with the control group. In addition, the NAGM FA values of the MS patients were negatively correlated with the MMSE score, but positively correlated with the EDSS score. The NAGM MD values of the MS patients were also negatively correlated with the MMSE score, but positively correlated with the EDSS score.

CONCLUSIONS: The NAGM of MS patients has microstructural damages. The extent of such damage was correlated with the number of cortical lesions. The severity of the damage also correlated with increased severity of cognitive impairment and neural defects.

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HRCT findings of collagen vascular disease-related interstitial pneumonia (CVD-IP): a comparative study among individual underlying diseases.

Tanaka N(1), Kunihiro Y(2), Kubo M(3), Kawano R(4), Oishi K(3), Ueda K(5), Gondo T(6).

Author information: (1)Department of Radiology, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan; Department of Radiology, Saiseikai Yamaguchi General Hospital, 2-11 Midoricho, Yamaguchi, Yamaguchi 753-8517, Japan. Electronic address: ntanaka@yamaguchi.saiseikai.or.jp. (2)Department of Radiology, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan; Department of Radiology, National Hospital Organization, Yamaguchi - Ube Medical Center, 685 Higashikiwiwa, Ube, Yamaguchi 755-0241, Japan. (3)Department of Medicine and Clinical Science, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan. (4)Center for Clinical Research, 1-1-1 Minamikogushi, Ube, Yamaguchi 755-8505, Japan. (5)Department of Surgery and Clinical Science, Yamaguchi University Graduate School of Medicine, 1-1-1 Minamikogushi, Ube, Yamaguchi, 755-8505, Japan. (6)Division of Pathology, Fujisawa City Hospital, 2-6-1 Fujisawa, Fujisawa, Kanagawa 251-8550, Japan.

AIM: To identify characteristic high-resolution computed tomography (CT) findings for individual collagen vascular disease (CVD)-related interstitial pneumonias (IPs). MATERIALS AND METHODS: The HRCT findings of 187 patients with CVD, including 55 patients with rheumatoid arthritis (RA), 50 with systemic sclerosis (SSc), 46 with polymyositis/dermatomyositis (PM/DM), 15 with mixed connective tissue disease, 11 with primary Sjögren's syndrome, and 10 with systemic lupus erythematosus, were evaluated. Lung parenchymal abnormalities were compared among CVDs using χ² test, Kruskal-Wallis test, and multiple logistic regression analysis. A CT-pathology correlation was performed in 23 patients. RESULTS: In RA-IP, honeycombing was identified as the significant indicator based on multiple logistic regression analyses. Traction bronchiectasis (81.8%) was further identified as the most frequent finding based on χ² test. In SSc IP, lymph node enlargement and oesophageal dilatation were identified as the indicators based on multiple logistic regression analyses, and ground-glass opacity (GGO) was the most extensive based on Kruskal-Wallis test, and multiple logistic regression analysis. A CT-pathology correlation was performed in 23 patients. RESULTS: In PM/DM IP, airspace consolidation and the absence of honeycombing were identified as the indicators based on multiple logistic regression analyses, and predominance of consolidation over GGO (32.6%) and predominant subpleural distribution of GGO/consolidation (41.3%) were further identified as the most frequent findings based on χ² test, which reflects the higher frequency of the pathological NSIP and/or the organising pneumonia patterns present in the CT-pathology correlation. CONCLUSION: Several characteristic high-resolution CT findings with utility for estimating underlying CVD were identified.

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**Does MR spectroscopy of normal-appearing cervical spinal cord in patients with multiple sclerosis have diagnostic value in assessing disease progression? A prospective comparative analysis.**

Basha MAA(1), Bessar MA(2), Ahmed AF(2), Elfiki IM(2), Elkhatif THM(3), Mohamed AME(4).

Author information: (1)Department of Diagnostic Radiology, Zagazig University, Egypt. Electronic address: drmohammad_basha@yahoo.com. (2)Department of Diagnostic Radiology, Zagazig University, Egypt. (3)Department of Neurology, Zagazig University, Egypt. (4)Department of Ophthalmology, Zagazig University, Egypt.

AIM: To clarify the role of magnetic resonance spectroscopy (MRS) in examining the normal-appearing cervical spinal cord of patients with multiple sclerosis (MS) to detect metabolite abnormalities in this disease and to assess its progression. MATERIAL AND METHODS: Thirty-six patients with MS and 30 healthy controls were enrolled. Each patient was submitted to MRS performed using a 1.5 T magnetic resonance imaging (MRI) scanner. The spectra of total N-acetyl-aspartate (tNAA), choline (Cho), creatine (Cr), and myoinositol (M-Ins), as well as the metabolite ratios of tNAA/Cr, tNAA/Cho, Cho/Cr, and M-Ins/Cr of the two groups were measured and compared. The correlations between the metabolite concentrations, disease duration, and clinical disability (expanded disability status scale, EDSS) were further explored. RESULTS: Significantly lower tNAA and higher M-Ins were observed in MS patients than in healthy controls. The tNAA/Cr and tNAA/Cho ratios were significantly lower in MS patients than in healthy controls. In MS patients, the EDSS was correlated with the tNAA/Cr ratio. The spinal cord cross-sectional area was significantly smaller in MS patients than in healthy controls. CONCLUSION: Reduced tNAA and increased M-Ins are important, sensitive indices for differentiating between MS patients and healthy controls. In MS patients, before lesions appear, MRS of the spinal cord may provide crucial information for assessing disease progression.

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**Improvement in overactive bladder symptoms in patients using functional electrical stimulation of the common peroneal nerve for walking.**

Hare N(1), Georgopoulos P(1), Philips KE(1), Johnson JE(1), Seary C(1), Panicker JN(1)(2), Stevenson VL(1)(2).

Author information: (1)1 The National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK. (2)2 Institute of Neurology, University College London, London, UK.

OBJECTIVE: Functional electrical stimulation is used to improve walking speed and reduces falls in people with upper motor neurone foot-drop. Following anecdotal observations of changes in bladder symptoms, an observational study was performed to explore this association further. DESIGN: A total of 47 consecutive patients attending for setup with functional electrical stimulation during a six-month period were asked to complete a questionnaire assessing bladder symptoms (ICIQ-OAB (International Consultation on Incontinence Questionnaire Overactive Bladder)) at baseline and three months during routine appointments. SUBJECTS: In all, 35 (75%) had multiple sclerosis and the other 12 subjects had a total of 9 diagnoses including 3 with stroke. Other conditions included cerebral palsy, motor neurone disease, hereditary spastic paraparesis, meningioma and spinocerebellar ataxias. RESULTS: Improvement in overactive bladder symptoms was not significant in the whole cohort, however, was significant in patients with multiple sclerosis (n = 35; mean change in ICIQ-OAB score 1.0, P = 0.043). Specifically, significant improvements were seen in urgency and urge incontinence in multiple sclerosis patients. There was a significant negative correlation of moderate strength within the multiple sclerosis cohort between baseline walking speed and subsequent change in ICIQ-OAB score (correlation coefficient of r = -0.40, P = 0.046). Thus, greater changes in bladder symptoms were seen with lower baseline walking speeds. CONCLUSION: The results of this exploratory study suggest that functional electrical stimulation use does improve overactive bladder symptoms in people with multiple sclerosis. Further exploration is needed to study this association and explore whether the mechanism is similar to that of percutaneous tibial nerve stimulation, a recognized treatment for the overactive bladder.

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Genome-wide association studies of multiple sclerosis.  
Cotsapas C(1)(2), Mitrovic M(1)(2).  
Author information:  (1)Departments of Neurology and Genetics Yale School of Medicine New Haven CT USA. (2)Broad Institute of MIT and Harvard Cambridge MA USA.  
Large-scale genetic studies of multiple sclerosis have identified over 230 risk effects across the human genome, making it a prototypical common disease with complex genetic architecture. Here, after a brief historical background on the discovery and definition of the disease, we summarise the last fifteen years of genetic discoveries and map out the challenges that remain to translate these findings into an aetiological framework and actionable clinical understanding.  
DOI: 10.1002/cti2.1018  PMCID: PMC5983059 PMID: 29881546

Disability Outcome Measures in Phase III Clinical Trials in Multiple Sclerosis.  
Uitdehaag BMJ(1).  
Author information:  (1)Department of Neurology, Amsterdam Neuroscience, VUmc MS Center Amsterdam, VU University Medical Center, De Boelelaan 1117, 1081, HV Amsterdam, The Netherlands. bmj.uitdehaag@vumc.nl.  
Accumulating neurological disability has a substantial impact on the lives of patients with multiple sclerosis (MS). As well as the established Expanded Disability Status Scale (EDSS), several other outcome measures are now available for assessing disability progression in MS. This review extends the findings of a previous analysis of relapsing-remitting MS (RRMS) trials published up to 2012, to determine whether there has been a shift in outcome measures used to assess disability in phase III clinical trials in RRMS and progressive MS. Forty relevant trials were identified (RRMS, n = 16; progressive MS, n = 18; other/mixed phenotypes, n = 6). Sustained EDSS worsening, particularly over 3 months, was included as an endpoint in almost all identified trials. Other disability-related endpoints included the Multiple Sclerosis Functional Composite z-score and scores for the physical component summary of the Multiple Sclerosis Impact Scale and Medical Outcomes Study Short-Form (36-item) Health Survey. Tests assessing manual dexterity, ambulation, vision and cognition were also employed, and in some trials, composite endpoints were used. However, there was no obvious trend in choice of disability outcome measures over time. Sustained EDSS worsening over short time periods continues to be the most widely used measure of disability progression in pivotal MS trials, despite its well-recognised limitations. A new tool set is needed for use in MS clinical trials that detects the benefit of potential treatments that slow (or reverse) progressive disability.  
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Atypical Post-Injection Reactions with Delayed Onset Following Glatiramer Acetate 40 mg: Need for Titration?


Author information: (1)Neurocenter of Southern Switzerland, Ospedale Regionale di Lugano, Lugano, Switzerland. chiara.zecca@eoc.ch. (2)Neuroimmunology and Neuromuscular Diseases Unit, IRCCS Fondazione Istituto Neurologico Carlo Besta, Milan, Italy. chiara.zecca@eoc.ch. (3)Neuroimmunology and Neuromuscular Diseases Unit, IRCCS Fondazione Istituto Neurologico Carlo Besta, Milan, Italy. (4)IRCCS-Instituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy. (5)Neurocenter of Southern Switzerland, Ospedale Regionale di Lugano, Lugano, Switzerland.

BACKGROUND: Glatiramer acetate (GA) 20 mg/day (GA20) is associated with immediate post-injection reactions (PIRs). For convenience of use, approved GA 40 mg three times weekly (GA40) delivers a similar weekly dose. The dose and concentration of a single GA40 injection are, however, twice as high as for GA20, and post-injection adverse events may differ. Cases of atypical PIRs to GA40 prompted us to systematically monitor such events. OBJECTIVE: The aim was to characterize atypical PIRs in multiple sclerosis (MS) patients treated with GA40. METHODS: Clinical practice data were prospectively collected in consecutive relapsing-remitting MS patients. Descriptive statistics for categorical and continuous variables, Mann-Whitney and Chi-squared tests for baseline comparisons, and Cox regression models for association of variables to first atypical PIRs were applied. RESULTS: Forty-six out of 173 patients (26.6%) given GA40 experienced any PIRs. Of those, 38 (22.0%) had atypical, 14 (8.1%) had combined typical and atypical, and 26 (15.0%) had recurrent atypical PIRs, most frequently shivering (13.3%) and nausea/vomiting (8.1%). Compared to typical PIRs, onset of atypical PIRs was significantly delayed (median 30 vs 1 min, p < 0.0001), and their median duration longer (median 120 vs 6 min, p = 0.00013). Previous exposure to GA20 was associated with a lower risk of atypical PIRs [hazard ratio (HR) = 0.35, 95% confidence interval (CI) 0.17-0.72, p = 0.0039]. Patients experiencing PIRs with GA20 were at elevated risk for atypical PIRs with GA40 (HR = 5.75, 95% CI 1.66-19.94, p = 0.0059). CONCLUSIONS: Atypical PIRs with GA40, especially gastrointestinal symptoms and/or fever/shivering, had a delayed onset and occurred in a significant proportion of our patients. Their real prevalence should be assessed in appropriately designed studies accounting for nocebo responses. Initial dose titration might reduce PIR frequency.

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Frequency and clinical characteristics of Multiple Sclerosis rebounds after withdrawal of Fingolimod.

Evangelopoulos ME(1)(2), Miclea A(2), Schrewe L(2), Briner M(2), Salmen A(2), Engelhardt B(3), Huwiler A(4), Chan A(2), Hoepner R(2).

Author information: (1)Department of Neurology, Eginition University Hospital, National and Kapodistrian University of Athens, Athens, Greece. (2)Department of Neurology, Bern University Hospital and University of Bern, Switzerland. (3)Theodor Kocher Institute, University of Bern, Bern, Switzerland. (4)Institute of Pharmacology, University of Bern, Bern, Switzerland.

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Author information: (1)Department of Neurology, University Rostock, Rostock, Germany. (2)Department of Neurology, Medical University of Vienna, Vienna, Austria. (3)Department of Neurology, Neuroimmunology Section, University of Rostock, Rostock, Germany. (4)Steinbeis Transfer Centre for Proteome Analysis, Rostock, Germany.

BACKGROUND: Multiple sclerosis (MS) affects predominantly young women. Currently available disease-modifying drugs have neither been approved during pregnancy nor nursing. AIMS: Evaluating the effect of treatment with intravenous immunoglobulin (IVIg) in MS patients with desire to have a baby. METHODS: In all, 70 MS patients were either treated with IVIg before conception, during first trimester of pregnancy and 12 months postnatal (group I, n = 38) or started IVIg after delivery for 12 months (group II, n = 23) or were untreated (group III, n = 9). Relapse rates and disease progression were analyzed. RESULTS: Pre-gestational relapse rates differed between groups. Lowest relapse rates were observed during late pregnancy, followed by an elevated relapse rate after delivery compared to the pre-pregnancy year and the first trimester. Only in group I, the postnatal relapse rate did not exceed the relapse rate before conception. IVIg treatment did not influence disease progression after delivery. CONCLUSIONS: In MS patients, IVIg treatment during and/or after delivery is an option to reduce the incidence of relapses during pregnancy and the postnatal period. Surprisingly, untreated patients becoming pregnant showed an increase in the relapse rate in the first trimester compared with the pre-gestational period. How alterations of hormone status during pregnancy affect disease activity in MS has to be further investigated.

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Rationale and design of the tele-exercise and multiple sclerosis (TEAMS) study: A comparative effectiveness trial between a clinic- and home-based telerehabilitation intervention for adults with multiple sclerosis (MS) living in the deep south.


Author information: (1)Department of Occupational Therapy, School of Health Professions, University of Alabama at Birmingham, Birmingham, AL, United States; UAB-Lakeshore Research Collaborative, School of Health Professions, United States. (2)Department of Health Services Administration, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States; UAB-Lakeshore Research Collaborative, School of Health Professions, United States. (3)Department of Physical Therapy, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States; UAB-Lakeshore Research Collaborative, School of Health Professions, United States. (4)Department of Health Behavior, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States; UAB-Lakeshore Research Collaborative, School of Health Professions, United States. (5)Tanner Foundation for Neurological Diseases, Birmingham, AL, United States. (6)Department of Health Services Administration, School of Public Health, University of Alabama at Birmingham, Birmingham, AL, United States; UAB-Lakeshore Research Collaborative, School of Health Professions, United States. Electronic address: tapan@uab.edu.

Long-term exercise/rehabilitation is an integral component of the continual care for people with multiple sclerosis (MS). However, access to this care, which includes comprehensive exercise/rehabilitation services to people with MS, remains a significant challenge, especially in rural, low-income areas. Telerehabilitation, or what we refer to as teleexercise, can help fill service gaps for underserved MS populations in this region. This pragmatic, cluster randomized controlled effectiveness trial will compare a 12-week, 20 session complementary and alternative medicine (CAM) intervention composed of neurorehabilitative (functional) exercise, yoga and Pilates delivered at home, using pre-loaded tablets and Interactive Voice Response (IVR) system technology (TeleCAM), to the same intervention delivered in clinic by a therapist (DirectCAM). Eight hundred and twenty people with MS are being recruited across Alabama, Mississippi and Tennessee. Primary self-reported patient-centered health outcomes are: pain, fatigue, quality of life and physical activity. Secondary outcomes include four physical functioning measures: balance, endurance, gait, and strength. Each of these outcomes will be examined by age, race, sex, severity of MS and other demographics to determine if outcomes are beneficial across all groups (i.e., heterogeneity of treatment effect). The project is important to people with MS and/or caregivers because it aims to reduce their barriers to receiving exercise treatment and increases the convenience and appeal of such programs through technology. Clinical Trials.gov Identifier: NCT03117881.

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The Place of PET to Assess New Therapeutic Effectiveness in Neurodegenerative Diseases.


Author information: (1)UMR 1253, iBrain, Université de Tours, Inserm, Tours, France. (2)CHRU de Tours, Unité de Radiopharmacie, Tours, France. (3)CHRU de Tours, Service de Médecine Nucléaire in vitro, Tours, France. (4)INSERM CIC 1415, University Hospital, Tours, France. (5)CHRU de Tours, Service de Médecine Nucléaire in vivo, Tours, France.

In vivo exploration of neurodegenerative diseases by positron emission tomography (PET) imaging has matured over the last 20 years, using dedicated radiopharmaceuticals targeting cellular metabolism, neurotransmission, neuroinflammation, or abnormal protein aggregates (beta-amyloid and intracellular microtubule inclusions containing hyperphosphorylated tau). The ability of PET to characterize biological processes at the cellular and molecular levels enables early detection and identification of molecular mechanisms associated with disease progression, by providing accurate, reliable, and longitudinally reproducible quantitative biomarkers. Thus, PET imaging has become a relevant imaging method for monitoring response to therapy, approved as an outcome measure in bioclinical trials. The aim of this paper is to review and discuss the current inputs of PET in the assessment of therapeutic effectiveness in neurodegenerative diseases connected by common pathophysiological mechanisms, including Parkinson's disease, Huntington's disease, dementia, amyotrophic lateral sclerosis, multiple sclerosis, and also in psychiatric disorders. We also discuss opportunities for PET imaging to drive more personalized neuroprotective and therapeutic strategies, taking into account individual variability, within the growing framework of precision medicine.

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The Management of Lower Urinary Tract Dysfunction in Multiple Sclerosis.

Tornic J(1), Panicker JN(2).

Author information: (1)Department of Uro-Neurology, The National Hospital For Neurology and Neurosurgery and UCL Institute for Neurology, Queen Square, London, WC1N 3BG, UK. jure.tornic@nhs.net. (2)Department of Uro-Neurology, The National Hospital For Neurology and Neurosurgery and UCL Institute for Neurology, Queen Square, London, WC1N 3BG, UK.

PURPOSE OF REVIEW: Multiple sclerosis (MS) is the most frequent neuroinflammatory disease of the central nervous system and is commonly associated with lower urinary tract (LUT) dysfunction. As a consequence, health-related quality of life is often impaired and the upper urinary tract might be at risk for damage. The aim of this review is to give an overview of current treatment options for LUT dysfunction in patients with MS. RECENT FINDINGS: The treatment is tailored to the type of dysfunction-storage or voiding dysfunction-beginning with conservative treatment options and ending with invasive therapies and surgery. Additionally, alternative options, e.g., different intravesical therapies or cannabinoids, have been evaluated in recent years with promising results. Current available therapies offer different possible treatments for LUT dysfunction in patients with MS. They address either voiding or storage dysfunction and therefore ameliorate LUT symptoms improve quality of life and protect the upper urinary tract.

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Using the Anterior Visual System to Assess Neuroprotection and Remyelination in Multiple Sclerosis Trials.

Silbermann E(1), Wooliscroft L(2)(3), Bourdette D(2).

Author information: (1)Department of Neurology, Oregon Health & Science University, Mail code: L226, 3181 S.W. Sam Jackson Park Road, Portland, OR, 97239, USA. silberme@ohsu.edu. (2)Department of Neurology, Oregon Health & Science University, Mail code: L226, 3181 S.W. Sam Jackson Park Road, Portland, OR, 97239, USA. (3)Department of Veterans Affairs Portland Health Care System, Portland, OR, 97239, USA.

PURPOSE OF REVIEW: Clinical trials using agents directed at neuroprotection and remyelination in multiple sclerosis (MS) are needed. As optic neuritis (ON) is common in people with MS and the pathology of ON is similar to other MS lesions in the brain, measurements of the anterior visual system are frequently utilized in neuroprotection and remyelination trials. Understanding the strengths and weaknesses of the measurements is vital when interpreting the results of this research.

RECENT FINDINGS: Techniques such as visual evoked potentials (VEP) and optical coherence tomography (OCT) are well established in MS and are thought to measure axonal integrity and myelination. Novel imaging techniques can also be used in conjunction with these measurements to provide better insight into optic nerve structure and function. Magnetization transfer imaging (MTR) together with optic nerve area and volume measures neurodegeneration; diffusion tensor imaging (DTI) measures myelination status and neurodegeneration. However, these techniques require various levels of experience to interpret, and all can be confounded by ocular motion and surrounding fat and bone. This article provides a review of established and novel techniques to measure the anterior visual system in multiple sclerosis with a focus on the evidence to support their use as outcome measures in clinical trials focused on neuroprotection and remyelination therapies.

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Rice J(1), Cameron M(2).

Author information: (1)Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, L226, Portland, OR, 97239, USA. (2)Oregon Health & Science University, 3181 SW Sam Jackson Park Rd, L226, Portland, OR, 97239, USA. cameromi@ohsu.edu.

PURPOSE OF REVIEW: Cannabis and cannabinoids have been used medically and recreationally for thousands of years and recently there has been a growing body of research in this area. With increased access now that medical marijuana is available in many jurisdictions, patients and providers want to know more about the evidence for benefits and risks of cannabinoid use. This paper provides an overview of the available cannabinoid-based formulations, a summary of the highest quality evidence for the use of cannabinoids for treating spasticity and pain associated with multiple sclerosis (MS), and a discussion of possible dosing regimens based on information from these studies. RECENT FINDINGS: Two recent high-quality systematic reviews concluded that the only strong evidence for medical marijuana in neurological disorders was for reducing the symptoms of patient-reported spasticity and central pain in MS and that the only complementary and alternative medicine (CAM) intervention in MS with strong supportive evidence was cannabinoids. Based on this review, they concluded that nabiximols (Sativex oral spray), oral cannabis extract (OCE), and synthetic tetrahydrocannabinol (THC) are probably effective at reducing patient-reported symptoms of spasticity in people with MS, but OCE and synthetic THC were not found to be effective for reducing physician-administered measures of spasticity. In addition, nabiximols, OCE, and synthetic THC are probably effective at reducing MS-related pain. Cannabinoids were generally well-tolerated. However, cannabis use has been associated with an increased risk of psychosis and schizophrenia in at-risk individuals, there is growing evidence that cannabis can increase the risk for cardiovascular diseases, including myocardial infarction (MI), hypertension, heart failure, and stroke, and a recently recognized adverse effect of cannabis is cannabinoid hyperemesis syndrome. The medical use of cannabinoids remains controversial. While cannabinoids have been studied for a variety of neurologic disorders, there is strongest evidence to indicate benefits in treatment of spasticity and neuropathic pain in multiple sclerosis. Although the best dose for an individual remains uncertain, most participants in the studies discussed in this paper used between 20 and 40 mg of THC a day in divided doses. Adverse events in studies were generally more common in the groups using cannabinoid products but serious adverse events were rare and cannabis products were generally well-tolerated. Cannabis use does appear to be associated with increased risk of certain adverse events, including psychosis, cardiovascular diseases, and cannabinoid hyperemesis syndrome.

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MRI in multiple sclerosis: what is changing?

Filippi M(1), Preziosa P, Rocca MA.

Author information: (1)Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Vita-Salute San Raffaele University, Milan, Italy.

PURPOSE OF REVIEW: To summarize recent findings from the application of MRI in the diagnostic work-up of patients with suspected multiple sclerosis (MS), and to review the insights into disease pathophysiology and the utility of MRI for monitoring treatment response. RECENT FINDINGS: New evidence from the application of MRI in patients with clinically isolated syndromes has guided the 2017 revision of the McDonald criteria for MS diagnosis, which has simplified their clinical use while preserving accuracy. Other MRI measures (e.g., cortical lesions and central vein signs) may improve diagnostic specificity, but their assessment still needs to be standardized, and their reliability confirmed. Novel MRI techniques are providing fundamental insights into the pathological substrates of the disease and are helping to give a better understanding of its clinical manifestations. Combined clinical-MRI measures of disease activity and progression, together with the use of clinically relevant MRI measures (e.g., brain atrophy) might improve treatment monitoring, but these are still not ready for the clinical setting. SUMMARY: Advances in MRI technology are improving the diagnostic work-up and monitoring of MS, even in the earliest phases of the disease, and are providing MRI measures that are more specific and sensitive to disease pathological substrates.

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**Novel cytoprotective mediator, stable gastric pentadecapeptide BPC 157. Vascular recruitment and gastrointestinal tract healing.**

Sikiric P(1), Rucman R(1), Turkovic B(1), Sever M(1), Klicek R(1), Radic B(1), Drmic D(1), Stupnisek M(1), Misic M(1), Vuletic LB(1), Pavlov KH(1), Barisic I(1), Kokot A(1), Peklic M(1), Strbe S(1), Blagaic AB(1), Tvrdeic A(1), Rokotov DS(1), Vrcic H(1), Staresinic M(1), Seiwerth S(1).

Author information: (1)Department of Pharmacology, Medical Faculty, University of Zagreb, Zagreb, Croatia; Department of Pathology, Medical Faculty, University of Zagreb, Zagreb. Croatia.

Years ago, we revealed a novel cytoprotective mediator, stable gastric pentadecapeptide BPC 157, particular anti-ulcer peptide that heals different organs lesions when given as a therapy, native in human gastric juice while maintaining GI-tract mucosal integrity, already tested in trials (ulcerative colitis and now multiple sclerosis). The stomach cytoprotection is the most fundamental concept, stomach cell protection and endothelium protection are largely elaborated, but so far cell, protection and endothelium protection outside of the stomach were not implemented in the therapy. However, having managed these two points, stomach cell protection and endothelium protection, either one or together, even much more than standard cytoprotective agents do, BPC 157 employed large scale of its beneficial effects seen in various organs. Providing endothelium protection, BPC 157 was shown to prevent formation and reverse established thrombosis in anastomosed abdominal aorta as well as venous thrombosis after inferior caval vein occlusion, and attenuate bleeding prolongation and thrombocytopenia after amputation, without or with anticoagulants, or venous occlusion, and finally counteract effect of L-NAME and/or L-arginine. Now, with BPC 157 application, we reveal the third most important part of the cytoprotection concept: with the stomach cell and endothelium protection to recover mucosal integrity, BPC 157 as prototype cytoprotective agent should also control blood vessel function, depending upon injury, perforated defect or vessel obstruction. After a perforated injury (i.e., stomach), BPC 157 therapy activates blood vessels "running" towards defect. After obstruction (i.e., inferior caval vein), BPC 157 activates vessels "running" towards bypassing defect, collaterals functioning. Reestablished blood flow, and largely reversed injurious course may practically implement the cytoprotection concept.

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**Using Acutely Dissociated and Purified Oligodendrocyte Precursor Cells for High-Throughput Drug Screening to Identify Compounds that Promote Oligodendrocyte Differentiation.**

Lariosa-Willingham K(1), Leonoudakis D(1).

Author information: (1)Teva Pharmaceuticals Biologics Discovery, Redwood City, California.

Multiple sclerosis (MS) is an autoimmune disease that involves an immune-mediated inflammatory response in the central nervous system and optic nerve resulting in demyelination and neural degeneration, the cause of which is unknown. The adult central nervous system has the capacity to remyelinate axons by generating new oligodendrocytes (OLs). To identify clinical candidate compounds that may promote remyelination, we have developed a high-throughput screening (HTS) assay to identify compounds that promote the differentiation of oligodendrocyte precursor cells (OPCs) into OLs. Using acutely dissociated and purified rat OPCs coupled with immunofluorescent image quantification, we have developed an OL differentiation assay. Building on OPC culturing techniques developed over the past 30 years, we have scaled up the isolation and purification process to generate sufficient quantities for HTS. We then describe the use of these acutely derived OPCs in an assay designed to identify compounds that promote differentiation into OLs. We have validated this assay with a known promoter of differentiation, thyroid hormone, and subsequently used the assay to screen the NIH clinical collection library (Lariosa-Willingham, et al., 2016). © 2018 by John Wiley & Sons, Inc.

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Tolerability and Safety Profile of a New Brand-Generic Product of Glatiramer Acetate in Iranian Patients with Relapsing-Remitting Multiple Sclerosis: An Observational Cohort Study.

Abolfazli R(1), Pournourmohammadi S(2), Shamshiri A(3), Samadzadeh S(1).

Author information:  
(1)Neurology Department, Tehran University of Medical Sciences, Amiralam Hospital, Tehran, Iran.  
(2)Medical Affairs Department, Zahravi Pharmaceutical Company, Tehran, Iran.  
(3)School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

Background: The aim of this study was to evaluate the safety, tolerability, and efficacy of a brand-generic glatiramer acetate product in patients with relapsing-remitting multiple sclerosis over a 12-month period. A noninterventional cohort study was conducted on 185 patients. The patients had a confirmed and documented diagnosis of relapsing-remitting multiple sclerosis as defined by the Revised McDonald Criteria (2010), were ambulatory with a Kurtzke Expanded Disability Status Scale score of 0 to 5.5, and their treatment by glatiramer acetate 40 mg/mL was just started. Methods: Adverse drug reactions, relapse rate, magnetic resonance imaging parameters, and Expanded Disability Status Scale score were evaluated over 1 year. Results: Of 185 enrolled patients from 21 different cities, 170 completed the study. The mean (SD) Expanded Disability Status Scale score was 1.97 (0.75) at the time of screening. The mean age was 33 years with an average of 4-year multiple sclerosis history, and 83% were women. Hepatic disorder and depression were the most frequent medical history. The most common adverse drug reactions were local pain (45.4%) and erythema (38.9%). The immediate postinjection reactions included dyspnea (10.3%), anxiety (9.7%), palpitation (8.1%), urticaria (5.4%), flushing (3.24%), chest pain (2.16%), and throat constriction (0.54%). The percentage of relapse-free patients at Month 12 was 87%, and the annual relapse rate was 0.134. An increase in the Expanded Disability Status Scale score was observed in 20% of patients, and new T2 and gadolinium-enhancing lesions were found in 34.7% and 9.4%, respectively. The rate of treatment failure was 1.6% and 4.3% according to the Modified Rio and Rio scores, respectively.

Conclusions: The 40 mg brand-generic glatiramer acetate product was well tolerated in this selected group of Iranian patients with relapsing-remitting multiple sclerosis, and patient adherence was favorable over 1 year. (Curr Ther Res Clin Exp. 2018; 79:XXX-XXX).

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Current Status and Future Prospects of Small-Molecule Protein-Protein Interaction (PPI) Inhibitors of Tumor Necrosis Factor (TNF) and Receptor Activator of NF-κB Ligand (RANKL).


Author information:  
(1)Hellenic Army Academy, Vari, Greece.  
(2)NovaMechanics Ltd, Nicosia, Cyprus.  
(3)Division of Immunology, Biomedical Sciences Research Center ‘Alexander Fleming’, Vari, Greece.  
(4)Veterinary School, University of Thessaly, Karditsa, Greece.  
(5)Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Athens, Greece.

The overexpression of Tumor Necrosis Factor (TNF) is directly related to the development of several autoimmune diseases, such as rheumatoid and psoriatic arthritis, inflammatory bowel disease, Crohn’s disease, refractory asthma, and multiple sclerosis. Receptor activator of nuclear factor kappa-B ligand (RANKL) belongs to the TNF family and is the primary mediator of osteoclast-induced bone resorption through interaction with its receptor RANK. The function of RANKL is physiologically inhibited by the action of osteoprotegerin (OPG), which is a decoy receptor that binds to RANKL and prevents the process of osteoclastogenesis. Malfunction among RANK/RANKL/OPG can also result in bone loss diseases, including postmenopausal osteoporosis, rheumatoid arthritis, bone metastasis and multiple myeloma. To disrupt the unwanted functions of TNF and RANKL, current attempts focus on blocking TNF and RANKL binding to their receptors. In this review, we present the research efforts toward the development of low-molecular-weight pharmaceuticals that directly block the detrimental actions of TNF and RANKL.

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Involvement of the Amygdala in Memory and Psychosocial Functioning in Pediatric-Onset Multiple Sclerosis.


Author information: (1)a Department of Psychology, York University, Toronto, Canada. (2)b Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. (3)c Neurosciences and Mental Health Program, The Hospital for Sick Children, Toronto, Canada. (4)d Division of Neurology, Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada. (5)e McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Canada. (6)f Translational Medicine Program, The Hospital for Sick Children, Toronto, Canada.

Youth with multiple sclerosis (MS) often experience cognitive impairment and psychosocial disturbances. We describe the relationship between memory function, psychosocial skills, and brain volume in 32 patients with pediatric-onset MS and 30 controls. Amygdala volume was significantly lower in patients compared with controls. In general, poorer memory was associated with reduced functional communication skills and reduced amygdala volume. Greater amygdala volume in patients correlated with parent-reported functional communication and social skills. Adjusting for whole-brain volume, right amygdala volume was positively associated with visual memory; left amygdala volume was a stronger predictor of parent-reported social skills.

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Quality of life and psychological well-being in the early stages of multiple sclerosis (MS): Importance of adopting a biopsychosocial model.

Strober LB(1).

Author information: (1)Kessler Foundation, East Hanover, NJ, USA; Rutgers, The State University of New Jersey, New Jersey Medical School, Department of Physical Medicine and Rehabilitation, Newark, NJ, USA. Electronic address: lstrober@kesslerfoundation.org.

BACKGROUND: Reductions in quality of life (QOL) exist among individuals with multiple sclerosis (MS).
OBJECTIVE: The present investigation aimed to adopt a biopsychosocial model in examining QOL in the early stages of MS.
METHODS: Individuals with MS (34 with average to low QOL and 35 with high QOL) were compared on measures of disease symptoms, psychological functioning, personality, self-efficacy, locus of control (LOC), social support, and coping to determine the most salient predictors of QOL.
RESULTS: Individuals were matched on disease course and duration. Individuals with lower QOL reported more fatigue, sleep problems, pain, depression, and anxiety (d = 0.83-1.49, p's < 0.001). They also reported lower levels of self-efficacy, LOC, and social support (d = 0.75-1.50 p's < 0.01). They indicated higher levels of neuroticism (d = 1.31, p < .001) and lower levels of extraversion (d = 1.21, p < .001) and reported greater levels of disengagement as a means of coping (d = 0.75, p = .002). Those with high QOL endorsed more use of adaptive coping (d = 0.52 - 0.86, p's < 0.05). When taken together, LOC and anxiety were the most significant predictors, accounting for 40% of the variance.
CONCLUSION: Even early on in the illness, there exists differing levels of QOL. Identifying the psychological and social variables as well as the disease related factors is important, and in this case, may make a much greater contribution. Efforts to assure routine assessment and effective intervention aimed at these factors are warranted, particularly as an early intervention to assure maintenance/improvement in QOL among individuals with MS.

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Barriers and solutions to participation in exercise for moderately disabled people with multiple sclerosis not currently exercising: a consensus development study using nominal group technique.

Moffat F(1), Paul L(2).

Author information: (1)a School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK. (2)b Nursing and Healthcare School, University of Glasgow, Glasgow, UK.

BACKGROUND: Multiple sclerosis (MS) is a chronic, progressive neurological condition. The aim of this study was to explore consensus on the barriers and solutions to exercise for people with MS living in Scotland.

METHOD: Thirty-five people with MS, not regularly exercising, were recruited and took part in five Nominal Group Technique groups throughout Scotland. Background information was collected on participants prior to each group. Participants individually and silently listed their barriers and solutions to participating in exercise. Group discussion then clarified, amended and merged ideas. Participants then ranked ideas by choosing five barriers and solutions to exercise participation. Data were analyzed using descriptive statistics and by carrying out a thematic grouping.

RESULTS: Consensus was that fatigue was a barrier to exercise participation. Other identified barriers were a lack of support and advice, the impairments arising from the condition and time. No single item achieved consensus for solutions but exercising with others, receiving support, having a positive attitude, finding time and minimizing environmental barriers were all suggested as solutions to assist in exercise participation.

CONCLUSIONS: People with MS should be provided with information on how to manage their fatigue alongside any exercise prescription. Information and support should be given on how to personalize exercise to suit individual needs and abilities to overcome some of the barriers suggested within this study. Implications for rehabilitation: More exercise opportunities are required. Exercise should be personalized to address the individual needs of the person with MS. Any identified barriers to exercise should be addressed.

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A concerns report survey of physical activity support needs of people with moderate-to-severe MS disability and family caregivers.

Fakolade A(1), Latimer-Cheung A(2), Parsons T(1), Finlayson M(1).

Author information: (1)a School of Rehabilitation Therapy, Queen’s University, Kingston, Canada. (2)b School of Kinesiology and Health Studies, Queen’s University, Kingston, Canada.

PURPOSE: To identify the most pressing needs for community resources to support physical activity participation, determinants of perceived need, and barriers to co-participation in physical activity among people with multiple sclerosis (MS) who have moderate-to-severe disability and the family caregivers providing assistance to such individuals. METHODS: Seventy-eight people with MS and 46 family caregivers participated in this cross-sectional survey study, guided by the Concerns Report Methodology. RESULTS: The results show differences between groups in rankings for some need items. However, three need items were prioritized by both people with MS and the family caregivers: (1) information about available resources to support physical activity participation, with Need Indexes of 76.6% and 52.3%, respectively; (2) programs that support joint participation of people with MS together with their caregivers in physical activity, with Need Indexes of 62.0% and 68.9%, respectively; and (3) programs that have affordable total cost of participation, with Need Indexes of 50.7% and 52.3%, respectively. A broad range of factors (i.e., education, living situation, type of community, marital status, employment, and income, as well as comorbidity status) was significantly associated with one or more of these need items. Several modifiable impairment-related, personal and logistical factors were identified by both groups as barriers to co-participation in physical activity. CONCLUSIONS: The findings highlight the complexity of developing community resources that target physical activity promotion in MS dyads. Importantly, our findings suggest that resources designed to influence dyadic physical activity participation need to include content that are responsive and tailored to both the needs of the person with MS and the unique needs of the family caregiver. The results also underscore the importance of reinforcing physical activity as a shared behavior and providing information about affordable options for exercising together to the benefit of each individual and the dyad (i.e., partnership). Overall, our findings provide a possible starting point to guide the identification of potential participants that might benefit the most from future intervention development work. Implications for rehabilitation MS has life-altering consequences for people with the disease and the family caregivers who support such individuals. Rehabilitation professionals need to reinforce physical activity as a shared behavior and provide information about affordable options for exercising together to the benefit of each individual and the dyad. A "one-size-fits-all" approach is not appropriate, therefore, clinicians need to identify flexible and pragmatic strategies to increase dyadic participation in the presence of unique caregiver and care-recipients barriers that might impede such an increase.

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Views of healthcare professionals on training for and delivery of a fatigue self-management program for persons with multiple sclerosis.

Peters S(1), Wilkinson A(2), Mulligan H(2).

Author information: (1)a Department of Medical Psychology and Psychotherapy Medical Sociology and Rehabilitation Sciences, Julius-Maximillian University of Wurzburg, Würzburg, Germany. (2)b Centre for Health, Activity, and Rehabilitation Research, School of Physiotherapy, University of Otago, Dunedin, New Zealand.

PURPOSE: To explore the experiences and perspectives of the healthcare professionals who were trained to and delivered "Minimise Fatigue, Maximise Life" (MFML), a patient-centered group-based fatigue self-management program for persons with multiple sclerosis. METHODS: A qualitative descriptive study with semi-structured individual interviews at two time points. Data were analyzed for themes. Six healthcare professional facilitators who were trained to and delivered "Minimise Fatigue, Maximise Life" participated in a first interview, and five in a second. Participants were all female, aged between 23 and 66 years old and either occupational therapists or physiotherapists. RESULTS: Two themes were evident in the data. The first, "Reciprocity," showed how the healthcare professionals were trained to deliver MFML, then reciprocated in the program delivery as active participants, which then provided feelings of personal reward and expansion of their usual practice. The second, "Enhancements," encompassed suggested directions for future training and deliveries of the program. CONCLUSION: This study suggests that multidimensional patient centered interventions also benefit the healthcare professionals who provide them because it expands their practice. Healthcare professionals who recognize the benefits of innovative and patient-centered interventions, supports both the patients with whom they work, and adds value to the health services they provide. Implications for rehabilitation Healthcare professionals who undergo training to facilitate delivery of self-management programs, which are based in an empowerment model, report an enhancement or expansion of their traditional practice. An empowerment-based program delivered in a group situation encourages and facilitates people to draw on their own and peers' knowledge and expertise to problem solve for self-management. Healthcare professional education should facilitate the healthcare professional's learning, and ability and willingness to acknowledge the richness in knowledge and expertise held by their patients.

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Therapeutic potential of medicinal marijuana: an educational primer for health care professionals.

Mouhamed Y(#)(1), Vishnyakov A(#)1, Qorri B(#)2, Sambi M(#)2, Frank SS1, Nowierski C1, Lamba A1, Bhatti U1, Szewczuk MR2.

Author information: (1)Graduate Diploma & Professional Master in Medical Sciences, School of Medicine, Queen’s University, Kingston, ON, Canada. (2)Department of Biomedical and Molecular Sciences, Queen’s University, Kingston, ON, Canada. (#)Contributed equally

With the proposed Canadian July 2018 legalization of marijuana through the Cannabis Act, a thorough critical analysis of the current trials on the efficacy of medicinal marijuana (MM) as a treatment option is necessary. This review is particularly important for primary care physicians whose patients may be interested in using MM as an alternative therapy. In response to increased interest in MM, Health Canada released a document in 2013 for general practitioners (GPs) as an educational tool on the efficacy of MM in treating some chronic and acute conditions. Although additional studies have filled in some of the gaps since the release of the Health Canada document, conflicting and inconclusive results continue to pose a challenge for physicians. This review aims to supplement the Health Canada document by providing physicians with a critical yet concise update on the recent advancements made regarding the efficacy of MM as a potential therapeutic option. An update to the literature of 2013 is important given the upcoming changes in legislation on the use of marijuana. Also, we briefly highlight the current recommendations provided by Canadian medical colleges on the parameters that need to be considered prior to authorizing MM use, routes of administration as well as a general overview of the endocannabinoid system as it pertains to cannabis. Lastly, we outline the appropriate medical conditions for which the authorization of MM may present as a practical alternative option in improving patient outcomes as well as individual considerations of which GPs should be mindful. The purpose of this paper is to offer physicians an educational tool that provides a necessary, evidence-based analysis of the therapeutic potential of MM and to ensure physicians are making decisions on the therapeutic use of MM in good faith.

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Conflict of interest statement: Disclosure B Qorri is a recipient of the Queen’s Graduate Award (QGA) and the 2017 Terry Fox Research Institute Transdisciplinary Training Program in Cancer Research. M Sambi is a recipient of the QGA. The authors report no other conflicts of interest in this work.
STAT4 gene polymorphism in two major autoimmune diseases (multiple sclerosis and juvenile onset systemic lupus erythematosus) and its relation to disease severity.

Nageeb RS(1), Omran AA(2), Nageeb GS(3), Yousef MA(3), Mohammad YAA(3), Fawzy A(4).

Author information:  (1)1Department of Neurology, Faculty of Medicine, Zagazig University, Sharkia, Egypt. (2)2Department of Clinical Pathology, Faculty of Medicine, Zagazig University, Sharkia, Egypt. (3)3Department of Rheumatology and Rehabilitation, Faculty of Medicine, Zagazig University, Sharkia, Egypt. (4)4Department of Chemistry, Faculty of Medicine, Zagazig University, Sharkia, Egypt.

Background: Multiple sclerosis (MS) and systemic lupus erythematosus (SLE) are chronic autoimmune mediated diseases with strong genetic and environmental components. The aim of this study is to evaluate the association of STAT4 gene polymorphism with multiple sclerosis (MS) and juvenile onset systemic lupus erythematosus (JO-SLE) and its relation to disease severity.

Methods: Group 1 consisted of 40 MS patients while group 2 included 40 JO-SLE patients. Forty healthy volunteers (controls) were included in this study. STAT4 genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP).

Results: The STAT4 CC genotype and GC genotype frequencies were significantly more detected in MS and JO-SLE patients than in controls. The frequency of the STAT4 C allele was significantly higher in patients with MS and those with JSLE compared to controls. Malar rash, photosensitivity, and hair falling were significantly more detected in CC subtype. Increased 24-h protein in urine (mg/24 h) and ANA positivity, anti-ds-DNA, anti Sm antibodies' detection and decreased C3 and C4 levels showed a significantly difference in CC patients. Meanwhile, only increased 24-h protein in urine (mg/24 h) and ANA positivity were significantly more detected in GC patients. STAT4 CC genotype showed a significant increase in the SLE activity index (SLEAI) score and damage index as compared to the STAT4 GG genotype patients. No significant difference was detected in MS Kurtzke's Expanded Disability Status Scale (EDSS) comparing different STATE 4 genotypes.

Conclusions: STAT4 polymorphism was significantly associated with MS and JO-SLE. Though homozygous JO-SLE patients are more risky for severe disease manifestations, homozygous MS patients are not risky for severe disease disability.

DOI: 10.1186/s41983-018-0011-5  PMCID: PMC5970152 PMID: 29881250

Conflict of interest statement: A written consent was taken from all of the participants after explaining the details and benefits as well as risks to them. The study was approved from the Institutional Ethics Committee of Faculty of Medicine, Zagazig University. Consent for publication is not applicable in this section. The authors declare that they have no competing interests. Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
Registry Cohort Study to Determine Risk for Multiple Sclerosis after Vaccination for Pandemic Influenza A(H1N1) with Arepanrix, Manitoba, Canada.
Mahmud SM, Bozat-Emre S, Mostaço-Guidolin LC, Marrie RA.
To investigate a potential risk for multiple sclerosis (MS) after vaccination with Arepanrix, the GlaxoSmithKline AS03-adjuvanted influenza A(H1N1)pdm09 vaccine, we used the province-wide immunization registry for Manitoba, Canada, to match 341,347 persons vaccinated during the 2009 pandemic to 485,941 unvaccinated persons on age, sex, address, and a propensity score measuring the probability of vaccination. We used a previously validated algorithm to identify MS cases from provincial hospital, physician, and prescription drug claims databases. After 12 months of follow-up, the age-adjusted incidence rate of MS was 17.7 cases per 100,000 person-years in the Arepanrix cohort and 24.2 per 100,000 in the unvaccinated cohort. The corresponding adjusted hazard ratio was 0.9. We observed similar patterns when we measured incidence over the entire follow-up period. The AS03 adjuvant, a candidate for inclusion in future pandemic vaccines, does not appear to increase the short-term risk for MS when included in influenza vaccines.
DOI: 10.3201/eid2407.161783  PMID: 29912696
Long-term exposure to air pollution and the incidence of multiple sclerosis: A population-based cohort study.

Bai L(1), Burnett RT(2), Kwong JC(3), Hystad P(4), van Donkelaar A(5), Brook JR(6), Tu K(7), Copes R(8), Goldberg MS(9), Martin RV(10), Murray BJ(11), Kopp A(1), Chen H(12).

Author information: (1)Institute for Clinical Evaluative Sciences, Toronto, ON, Canada. (2)Population Studies Division, Health Canada, Ottawa, ON, Canada. (3)Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; Public Health Ontario, Toronto, ON, Canada; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada. (4)College of Public Health and Human Sciences, Oregon State University, Corvallis, USA. (5)Department of Physics and Atmospheric Science, Dalhousie University, Halifax, NS, Canada. (6)Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada; Air Quality Research Division, Environment and Climate Change Canada, Ottawa, ON, Canada. (7)Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada; Toronto Western Hospital Family Health Team, University Health Network, Canada. (8)Public Health Ontario, Toronto, ON, Canada; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada. (9)Department of Medicine, McGill University, Montreal, QC, Canada. (10)Department of Physics and Atmospheric Science, Dalhousie University, Halifax, NS, Canada; Harvard-Smithsonian Center for Astrophysics, Cambridge, MA, USA. (11)Division of Neurology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Canada. (12)Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; Public Health Ontario, Toronto, ON, Canada; Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada. Electronic address: hong.chen@oahpp.ca.

BACKGROUND: Evidence of the adverse neurological effects of exposure to ambient air pollution is emerging, but little is known about its effect on the development of multiple sclerosis (MS), the most common autoimmune disease of the central nervous system. OBJECTIVES: To investigate the associations between MS incidence and long-term exposures to fine particles (PM2.5), nitrogen dioxide (NO2), and ozone (O3) METHODS: We conducted a population-based cohort study to investigate the associations between long-term exposures to PM2.5, NO2, and O3 and the incidence of MS. Our study population included all Canadian-born residents aged 20-40 years who lived in the province of Ontario, Canada from 2001 to 2013. Incident MS was ascertained from a validated registry. We assigned estimates of annual concentrations of these pollutants to the residential postal codes of subjects for each year during the 13 years of follow-up. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for each pollutant separately using random-effects Cox proportional hazards models. We conducted various sensitivity analyses, such as lagging exposure up to 5 years and adjusting for access to neurological care, annual average temperature, and population density. RESULTS: Between 2001 and 2013, we identified 6203 incident cases of MS. The adjusted HR of incident MS was 0.96 (95% CI: 0.86-1.07) for PM2.5, 0.91 (95% CI: 0.81-1.02) for NO2, and 1.09 (95% CI: 0.98-1.23) for O3. These results were robust to various sensitivity analyses conducted. CONCLUSIONS: In this large population-based cohort, we did not observe significant associations between MS incidence and long-term exposures to PM2.5, NO2, and O3 in adults in Ontario, 2001-2013.

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Anxiety is common and independently associated with clinical features of epilepsy.

Munger Clary HM(1), Snively BM(2), Hamberger MJ(3).

Author information: (1)Department of Neurology, Wake Forest School of Medicine, Winston-Salem, NC, USA. Electronic address: hmungerc@wakehealth.edu. (2)Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA. Electronic address: bmellen@wakehealth.edu. (3)Department of Neurology, Columbia University Medical Center, New York, NY, USA. Electronic address: mh61@columbia.edu.

OBJECTIVE: The objective of this study was to assess for independent association of anxiety symptoms with epilepsy localization and other epilepsy-related and demographic factors in a large tertiary care adult epilepsy population. METHODS: Among 540 adults, anxiety was measured by the Symptom Checklist 90-R (SCL-90R) anxiety subscale, and detailed demographics, epilepsy localization, and depression scores (SCL-90R) were collected. High anxiety was defined by SCL-90R anxiety T-score ≥ 60. Stepwise multiple logistic regression was carried out to assess for independent association of high anxiety scores with demographic and clinical factors. RESULTS: High anxiety symptoms were present in 46.1% of participants (N = 250). Focal or unknown epilepsy type and depression scores were independently associated with high anxiety (adjusted odds ratios (OR): 2.89 (95% confidence interval [CI] = 1.33-6.29, p = 0.007) and 2.12 (95% CI = 1.83-2.45, p < 0.001), respectively; depression odds per 5-point increase in scale). Among the focal epilepsy subpopulation, mesial temporal sclerosis was also independently associated with high anxiety, with adjusted OR: 2.12 (95% CI = 1.11-4.04, p = 0.023). Lower education, non-white race/ethnicity, Spanish native language, prior head trauma, antiseizure drug polytherapy, and left focus or bilateral foci (in focal epilepsy) were associated with high anxiety in simple logistic regression, but these associations were not independent. A total of 46 individuals (18.4% of those with high anxiety) scored high for anxiety but not depression. Only 26% of those with high anxiety symptoms were taking a potentially anxiolytic medication. CONCLUSION: Anxiety symptoms, often without concomitant depression, were highly prevalent in this epilepsy sample and independently associated with focal/unknown epilepsy and mesial temporal sclerosis. These results strongly support the value of screening specifically for anxiety in the epilepsy clinic, to direct patients to appropriate treatment.

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Dietary responses to a multiple sclerosis diagnosis: a qualitative study.

Russell RD(1), Black Lj(1), Sherriff JL(1), Begley A(2).

BACKGROUND/OBJECTIVES: Multiple sclerosis (MS) is an immune-mediated disease with no known cure and insufficient evidence to support a special therapeutic diet to alter symptom management or disease progression. Several studies have reported dietary changes made by people with MS, but there has been limited investigation into experiences surrounding diet in those recently diagnosed. This study explored responses to diet after a recent diagnosis of MS in people living in Western Australia.

SUBJECTS/METHODS: Eleven adults with MS (mean time since diagnosis 8 months) participated in semi-structured interviews focusing on responses to diet since MS diagnosis. Interviews were transcribed, coded and analysed using grounded theory principles. RESULTS: Three theme responses emerged; (1) the perceived incompatibility of lack of/or generalised dietary advice with disease seriousness at the time of diagnosis; (2) extensive personal research and information seeking with difficulty judging credibility, and (3) self-experimentation with diet to either control MS symptoms or to cure MS. CONCLUSIONS: Given the seriousness of the disease, there is a perceived gap in dietary information provided at the time of diagnosis. Healthcare professionals should address concerns with alternative therapeutic diets advertised to treat or cure MS, and clearly convey the reasoning for the general healthy dietary recommendations. This would better align advice with the perceptions about the role of diet in MS, assist people with MS in need of information and minimise dietary self-experimentation. Future research should explore the importance of diet for those who have had MS for a longer period of time.

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Late onset and young onset relapsing remitting multiple sclerosis. Evidence from a retrospective long-term follow-up study.

D’Amico E(1), Patti F(1), Zhanghi A(1), Chisari CG(1), Lo Fermo S(1), Zappia M(1).

Author information: (1)Department “G.F. Ingrassia”, MS center University of Catania.

BACKGROUND: Late onset multiple sclerosis (LOMS) shows prevalence of about 10-20% in natural history MS studies. Scarce data is published about the long-term disease trajectory in the cohort of late onset relapsing remitting MS (LORRMS). The aim of this study is to identify the risk factors to reach Expanded Disability Status Scale (EDSS) 6.0 in LORRMS (> 40 years) and young-onset RRMS (YORRMS; 18-40 years). METHODS: Clinical and radiological (magnetic resonance imaging of the brain, MRI) follow-up data were collected. Disability was assessed by EDSS. Cox proportional hazards model was run to evaluate the demographic and clinical predictors to reach EDSS 6.0 in the two cohorts. RESULTS: 671 RRMS patients were enrolled, 143 (21.3%) were LORRMS and 528 (78.7%) were YORRMS. In LORRMS age at onset was 47.8±5.3 (mean ± SD) years and duration of follow up was 120.7±52.7 months. In YORRMS age at onset was 27.2±2.7 years and duration of follow up was 149.9±92.7 months. The survival curves analyses showed higher probability of reaching EDSS 6.0 for LORRMS in a shorter time (months) than YORRMS (94.2 vs 103.2 months; Log Rank 8.8; p <.05). YORRMS showed more brain MRI inflammatory features than LORRMS. In multivariate Cox model, age at onset [Exp(B) value of 6.5; CI 1.9-22.6; p <.001] and male gender [Exp(B) value of 1.7; CI 1.0-2.8; p <.05] were the strongest predictors of reaching EDSS 6.0.

CONCLUSIONS: Male population suffering from LORRMS reached severe disability faster than YORRMS, even if YORRMS showed more brain inflammatory features at MRI. This article is protected by copyright. All rights reserved.

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Auras as a prognostic factor in anterior temporal lobe resections for mesial temporal sclerosis.

da Cruz Adry RAR(1), Muguins LC(1), Pereira CU(2), da Silva Júnior SC(1), de Araújo Filho GM(3), Marques LHN(4).

Author information: (1)Serviço de Neurocirurgia. Departamento de Ciências Neurológicas, Hospital de Base de São José do Rio Preto - Faculidade de Medicina de São José do Rio Preto, São José do Rio Preto-SP, Brazil. (2)Universidade Federal de Sergipe. Aracaju-SE, Brasil. (3)Serviço de Psiquiatria. Departamento de Psiquiatria e Psicologia Médica, Hospital de Base de São José do Rio Preto - Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto-SP, Brazil. (4)Serviço de Neurologia. Departamento de Ciências Neurológicas, Hospital de Base de São José do Rio Preto - Faculdade de Medicina de São José do Rio Preto, São José do Rio Preto-SP, Brazil.

INTRODUCTION: Anterior temporal lobectomy for mesial temporal sclerosis is a very effective measure to control seizures, and the probability of being seizure-free is approximately 70-90%. However, 30% of patients still experience seizures after surgery. An Aura is a subjective ictal phenomenon that may precede an observable seizure. Nevertheless, few are the studies associating the prognostic factor with aura, although, being the initial symptoms of epileptic seizures, many types of auras have significant localizing or lateralizing value. This study hypothesized that the type of preoperative aura may predict the postsurgical outcome in patients with medically refractory temporal lobe epilepsy due to mesial temporal sclerosis.

METHODS: Of 1214 patients evaluated for surgery in the epilepsy Center of Faculdade de Medicina de São José do Rio Preto (FAMERP), a tertiary Brazilian epilepsy center, 400 underwent ATL for MTS. Number and type of auras was analyzed and compared with Engel classification for outcome. RESULTS: Analyzing the patients by the type of aura, those who had extratemporal auras had worst result in post-surgical in Engel classification. While mesial auras apparently is a good prognostic factor. Patients without aura also had worse prognosis. Simple and multiple aura had no difference. In order to identify the most appropriate candidates for ATL, is very important to consider the prognostic factors associated with favorable for counseling patients in daily practice. This article is protected by copyright. All rights reserved.

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Multiple Sclerosis and Epilepsy: much more than a coincidence.

Calabrese M(1).
Author information: (1)Dept. of Neurosciences, Biomedicine and Movement, University of Verona.

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system. Although inflammatory lesions of the white matter are the hallmark of the disease, several neuropathological and imaging studies have clearly confirmed that the grey matter is not spared by the disease. The most recent data suggest that a chronic meningeal inflammation leads to a subpial demyelination resulting in a surface-in gradient of neuronal loss. This article is protected by copyright. All rights reserved.

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Risk of opportunistic infections in patients treated with alemtuzumab for multiple sclerosis.

Buonomo AR(1), Zappulo E(1), Viceconte G(1), Scotto R(1), Borgia G(1), Gentile I(1).
Author information: (1)a Department of Clinical Medicine and Surgery - Section of Infectious Diseases, University of Naples “Federico II”, Naples, Italy.

INTRODUCTION: Alemtuzumab is a monoclonal anti CD-52 antibody recently approved for use in relapsing-remitting multiple sclerosis (MS). Given that the targeted antigen is primarily expressed on B and T lymphocytes, the administration of this biological drug is associated with rapid but protracted peripheral lymphopenia. Areas covered: The impact on infective risk of this immune impairment is still to be fully understood. In this review, we attempt to summarize all the available literature concerning opportunistic infections occurring in patients with MS receiving alemtuzumab. Infective adverse events were observed in more than 70% of patients in phase 2/3 RCTs, mainly of mild-to-moderate severity. Nevertheless, several post-marketing reports documented cases of serious, rare, and unexpected infections. Expert Opinion: Predictive risk factors and prognostic features of opportunistic infections in this setting still need to be exactly assessed. At present, the only recommended preventive measures consist in anti-herpetic prophylaxis, Listeria-free diet, Tuberculosis prophylaxis and annual Papillomavirus screening. Given the non-negligible risk of unpredicted infective events, we advise physicians to take into account patients’ history of infectious diseases and vaccine status and to consider supplementary prophylactic strategies, including screening for Toxoplasma gondii and viral hepatitis serostatus as well as pre-emptive approaches to avert CMV reactivation and Pneumocystosis.

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Altered birefringence of peripapillary retinal nerve fiber layer in multiple sclerosis measured by polarization sensitive optical coherence tomography.


Author information: (1)1Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, 1638 NW 10th Avenue, McKnight Vision Research Building-Room 202A, Miami, FL 33136 USA. (2)2Department of Neurology, University of Miami Miller School of Medicine, Miami, FL USA. (3)3State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China. (4)4Department of Ophthalmology, Third Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China.

Background: The retina has been used to study the pathophysiology of multiple sclerosis (MS). Peripapillary retinal nerve fiber layer (pRNFL) thinning has been suggested as an ocular biomarker of neurodegeneration in MS. The goal of this project was to determine the birefringence of the pRNFL by measuring the fiber birefringence using polarization sensitive optical coherence tomography (PS-OCT).

Methods: Sixty-six MS patients without history of optic neuritis (age: 39.9 ± 11.0 yrs. old, 53 females and 13 males) and 66 age- and gender-matched normal controls (age: 40.7 ± 11.4 yrs. old) were recruited. Custom built PS-OCT was used to measure phase retardation per unit depth (PR/UD, proportional to the birefringence) and pRNFL thickness in each quadrant of the pRNFL. In addition, clinical manifestation was used to correlate with the pRNFL birefringence.

Results: The pRNFL was thinner in the temporal and inferior quadrants in MS patients compared with normal controls (P < 0.05). The PR/UD of the pRNFL was significantly decreased in MS patients (P < 0.05) in all quadrants except for the nasal quadrant. In both groups, the PR/UD from all four quadrants was not related to the averaged pRNFL thickness (P > 0.05). In MS patients, the PR/UD was not related to the expanded disability status scale (EDSS) nor disease duration (r ranged from -0.17 to 0.02, P > 0.05). Conclusion: This is the first study using PS-OCT to study the pRNFL birefringence in MS patients. Decreased birefringence of the pRNFL may indicate microtubule abnormality, and could be a potential biomarker for detecting early neurodegeneration in MS.

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Conflict of interest statement: All research methods are in accordance with the tenets of the Declaration of Helsinki and approved by the ethics committee board of the University of Miami. All subjects were recruited voluntarily and were informed about the purposes, methods, and the potential risks of the study. A signed consent form was obtained from each volunteer. All study subjects gave informant consent. The authors declare that they have no competing interests.
Collaboration between a human group and artificial intelligence can improve prediction of multiple sclerosis course: a proof-of-principle study.

Tacchella A(#)(1), Romano S(#)(2), Ferraldeschi M(2), Salvetti M(2)(3), Zaccaria A(1), Crisanti A(4), Grassi F(5).

Author information:  (1)Institute for Complex Systems, National Research Council - UOS Sapienza, Rome, 00185, Italy. (2)Center for Experimental Neurological Therapies (CENTERS), Dept. of Neurosciences, Mental Health and Sensory Organs, Sapienza University of Rome, Rome, 00189, Italy. (3)IRCCS Neuromed, Istituto Neurologico Mediterraneo, Pozzilli, 86077, Italy. (4)Department of Physics, Sapienza University of Rome, Rome, 00185, Italy. (5)Institute Pasteur-Cenci Bolognetti Foundation, Dept. Physiology and Pharmacology, Sapienza University of Rome, Rome, 00185, Italy. (#)Contributed equally

Background: Multiple sclerosis has an extremely variable natural course. In most patients, disease starts with a relapsing-remitting (RR) phase, which proceeds to a secondary progressive (SP) form. The duration of the RR phase is hard to predict, and to date predictions on the rate of disease progression remain suboptimal. This limits the opportunity to tailor therapy on an individual patient's prognosis, in spite of the choice of several therapeutic options. Approaches to improve clinical decisions, such as collective intelligence of human groups and machine learning algorithms are widely investigated.

Methods: Medical students and a machine learning algorithm predicted the course of disease on the basis of randomly chosen clinical records of patients that attended at the Multiple Sclerosis service of Sant'Andrea hospital in Rome. Results: A significant improvement of predictive ability was obtained when predictions were combined with a weight that depends on the consistence of human (or algorithm) forecasts on a given clinical record.

Conclusions: In this work we present proof-of-principle that human-machine hybrid predictions yield better prognoses than machine learning algorithms or groups of humans alone. To strengthen this preliminary result, we propose a crowdsourcing initiative to collect prognoses by physicians on an expanded set of patients.

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Conflict of interest statement: No competing interests were disclosed.
A Specific Reduction in Aβ1-42 vs. a Universal Loss of Aβ Peptides in CSF Differentiates Alzheimer's Disease From Meningitis and Multiple Sclerosis.


Author information: (1)Department of Psychiatry and Psychotherapy, Friedrich-Alexander-University Erlangen-Nuremberg, University Hospital Erlangen, Erlangen, Germany. (2)Institute of Clinical Microbiology, Immunology and Hygiene, Friedrich-Alexander-University Erlangen-Nuremberg, University Hospital Erlangen, Erlangen, Germany. (3)Department of Neurodegeneration Diagnostics, Medical University of Bialystok, Bialystok, Poland. (4)Department of Neurology, Friedrich-Alexander-University Erlangen-Nuremberg, University Hospital Erlangen, Erlangen, Germany. (5)Department of Neurology, Ludwig-Maximilian-University, Munich, Germany.

A reduced concentration of Aβ1-42 in CSF is one of the established biomarkers of Alzheimer's disease. Reduced CSF concentrations of Aβ1-42 have also been shown in multiple sclerosis, viral encephalitis and bacterial meningitis. As neuroinflammation is one of the neuropathological hallmarks of Alzheimer's disease, an infectious origin of the disease has been proposed. According to this hypothesis, amyloid pathology is a consequence of a microbial infection and the resulting immune defense. Accordingly, changes in CSF levels of amyloid-β peptides should be similar in AD and inflammatory brain diseases. Aβ1-42 and Aβ1-40 levels were measured in cerebrospinal fluid by ELISA and Western blotting in 34 patients with bacterial meningitis (n = 9), multiple sclerosis (n = 5) or Alzheimer's disease (n = 9) and in suitable controls (n = 11). Reduced concentrations of Aβ1-42 were detected in patients with bacterial meningitis, multiple sclerosis and Alzheimer's disease. However, due to a concurrent reduction in Aβ1-40 in multiple sclerosis and meningitis patients, the ratio of Aβ1-42/Aβ1-40 was reduced only in the CSF of Alzheimer's disease patients. Urea-SDS-PAGE followed by Western blotting revealed that all Aβ peptide variants are reduced in bacterial meningitis, whereas in Alzheimer's disease, only Aβ1-42 is reduced. These results have two implications. First, they confirm the discriminatory diagnostic power of the Aβ1-42/Aβ1-40 ratio. Second, the differential pattern of Aβ peptide reductions suggests that the amyloid pathology in meningitis and multiple sclerosis differs from that in AD and does not support the notion of AD as an infection-triggered immunopathology.

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Microglia in Alzheimer's Disease: Activated, Dysfunctional or Degenerative.


Author information: (1)Departamento Bioquímica y Biología Molecular, Facultad de Farmacia, Universidad de Sevilla, Seville, Spain. (2)Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío, CSIC, Universidad de Sevilla, Seville, Spain. (3)Centro de Investigacion Biomedica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain. (4)Departamento Biología Celular, Genética y Fisiología, Facultad de Ciencias, Instituto de Biomedicina de Malaga (IBIMA), Universidad de Málaga, Málaga, Spain.

Microglial activation has been considered a crucial player in the pathological process of multiple human neurodegenerative diseases. In some of these pathologies, such as Amyotrophic Lateral Sclerosis or Multiple Sclerosis, the immune system and microglial cells (as part of the cerebral immunity) play a central role. In other degenerative processes, such as Alzheimer's disease (AD), the role of microglia is far to be elucidated. In this "mini-review" article, we briefly highlight our recent data comparing the microglial response between amyloidogenic transgenic models, such as APP/PS1 and AD patients. Since the AD pathology could display regional heterogeneity, we focus our work at the hippocampal formation. In APP based models a prominent microglial response is triggered around amyloid-beta (Aβ) plaques. These strongly activated microglial cells could drive the AD pathology and, in consequence, could be implicated in the neurodegenerative process observed in models. On the contrary, the microglial response in human samples is, at least, partial or attenuated. This patent difference could simply reflect the lower and probably slower Aβ production observed in human hippocampal samples, in comparison with models, or could reflect the observation of a chronic long-standing microglial activation. Beside this differential response, we also observed microglial degeneration in Braak V-VI individuals that, indeed, could compromise their normal role of surveying the brain environment and respond to the damage. This microglial degeneration, particularly relevant at the dentate gyrus, might be mediated by the accumulation of toxic soluble phospho-tau species. The consequences of this probably deficient immunological protection, observed in AD patients, are unknown.

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Into the Moment: Does Mindfulness Affect Biological Pathways in Multiple Sclerosis?


Author information: (1)Department of Neurology, Antwerp University Hospital, Antwerp, Belgium. (2)Laboratory of Experimental Hematology, Faculty of Medicine and Health Sciences, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium. (3)Department of Neurology, ULB-Hôpital Erasme, Brussels, Belgium. (4)Department of Neurology, Translational Neurosciences, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium. (5)Department of Neurology, Laboratory for Neurobiology, Born-Bunge Institute, University of Antwerp, Antwerp, Belgium.

Mindfulness was introduced in the Western world by Jon Kabat-Zinn in 1979. He defined it as "awareness that arises through paying attention, on purpose, in the present moment, non-judgmentally." Since then, research on mindfulness-based interventions (MBIs) has increased exponentially both in health and disease, including in patients with neurodegenerative diseases such as dementia and Parkinson's disease. Research on the effect of mindfulness and multiple sclerosis (MS) only recently gained interest. Several studies completed since 2010 provided evidence that mindfulness improves quality of life (QoL), depression and fatigue in MS patients. In addition to patient-reported outcome measures, potential effects on cognitive function have been investigated only to a very limited extent. However, research on laboratory biomarkers and neuroimaging, capable to deliver proof-of-concept of this behavioral treatment in MS, is mainly lacking. In this perspective, we illustrate possible neurobiological mechanisms, including the tripartite interaction between the brain, the immune system and neuroendocrine regulation, through which this treatment might affect multiple sclerosis symptoms. We propose to (1) include immunological and/or neuroimaging biomarkers as standard outcome measures in future research dedicated to mindfulness and MS to help explain the clinical improvements seen in fatigue and depression; (2) to investigate effects on enhancing cognitive reserve and cognitive function; and (3) to investigate the effects of mindfulness on the disease course in MS.

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Metabolic Profiles for Primary Progressive Multiple Sclerosis Stratification and Disease Course Monitoring.


Author information: (1)Metabolomic Discoveries GmbH, Potsdam, Germany. (2)Institut für Biochemie und Biologie, Universität Potsdam, Potsdam, Germany. (3)Bioinformatik, Max-Planck-Institut für Molekulare Pflanzenphysiologie, Potsdam, Germany. (4)Zentrum für Molekulare Neurobiologie Hamburg, Institut für Neuroimmunologie und Multiple Sklerose, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany. (5)Klinik und Poliklinik für Neurologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany. (6)Neurodegenerative Erkrankungen, Hertie-Institut für klinische Hirnforschung, Eberhardt-Karls-Universität Tübingen, Tübingen, Germany. (7)Department of Neurology, Christian-Albrechts-Universität zu Kiel, Kiel, Germany. (8)Fraunhofer IME ScreeningPort, Hamburg, Germany.

Primary progressive multiple sclerosis (PPMS) shows a highly variable disease progression with poor prognosis and a characteristic accumulation of disabilities in patients. These hallmarks of PPMS make it difficult to diagnose and currently impossible to efficiently treat. This study aimed to identify plasma metabolite profiles that allow diagnosis of PPMS and its differentiation from the relapsing-remitting subtype (RRMS), primary neurodegenerative disease (Parkinson's disease, PD), and healthy controls (HCs) and that significantly change during the disease course and could serve as surrogate markers of multiple sclerosis (MS)-associated neurodegeneration over time. We applied untargeted high-resolution metabolomics to plasma samples to identify PPMS-specific signatures, validated our findings in independent sex- and age-matched PPMS and HC cohorts and built discriminatory models by partial least square discriminant analysis (PLS-DA). This signature was compared to sex- and age-matched RRMS patients, to patients with PD and HC. Finally, we investigated these metabolites in a longitudinal cohort of PPMS patients over a 24-month period. PLS-DA yielded predictive models for classification along with a set of 20 PPMS-specific informative metabolite markers. These metabolites suggest disease-specific alterations in glycerophospholipid and linoleic acid pathways. Notably, the glycerophospholipid LysoPC(20:0) significantly decreased during the observation period. These findings show potential for diagnosis and disease course monitoring, and might serve as biomarkers to assess treatment efficacy in future clinical trials for neuroprotective MS therapies.

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Mucosal-Associated Invariant T Cells in Autoimmune Diseases.

Chiba A(1), Murayama G(1), Miyake S(1).

Author information: (1)Department of Immunology, Juntendo University School of Medicine, Tokyo, Japan.

Mucosal-associated invariant T (MAIT) cells are innate T cells restricted by MHC-related molecule 1 (MR1). MAIT cells express semi-invariant T-cell receptors TRAV1-2-TRAJ33/12/20 in humans and TRAV1-TRAJ33 in mice. MAIT cells recognize vitamin B2 biosynthesis derivatives presented by MR1. Similar to other innate lymphocytes, MAIT cells are also activated by cytokines in the absence of exogenous antigens. MAIT cells have the capacity to produce cytokines, such as IFNγ, TNFα, and IL-17, and cytotoxic proteins, including perforin and granzyme B. MAIT cells were originally named after their preferential location in the mucosal tissue of the gut, but they are also abundant in other peripheral organs, including the liver and lungs. In humans, the frequency of MAIT cells is high in peripheral blood, and these cells constitute approximately 5% of circulating CD3+ cells. Their abundance in tissues and rapid activation following stimulation have led to great interest in their function in various types of immune diseases. In this review, first, we will briefly introduce key information of MAIT cell biology required for better understanding their roles in immune responses, and then describe how MAIT cells are associated with autoimmune and other immune diseases in humans. Moreover, we will discuss their functions based on information from animal models of autoimmune and immunological diseases.

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Distinct Gene Profiles of Bone Marrow-Derived Macrophages and Microglia During Neurotropic Coronavirus-Induced Demyelination.

Savarin C(1), Dutta R(1), Bergmann CC(1).

Author information: (1)Department of Neurosciences, NC-30, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, OH, United States.

Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) characterized by demyelination and axonal loss. Demyelinating lesions are associated with infiltrating T lymphocytes, bone marrow-derived macrophages (BMDM), and activated resident microglia. Tissue damage is thought to be mediated by T cell produced cytokines and chemokines, which activate microglia and/or BMDM to both strip myelin and produce toxic factors, ultimately damaging axons and promoting disability. However, the relative contributions of BMDM and microglia to demyelinating pathology are unclear, as their identification in MS tissue is difficult due to similar morphology and indistinguishable surface markers when activated. The CD4 T cell-induced autoimmune murine model of MS, experimental autoimmune encephalitis (EAE), in which BMDM are essential for demyelination, has revealed pathogenic and repair-promoting phenotypes associated with BMDM and microglia, respectively. Using a murine model of demyelination induced by a gliatropic coronavirus, in which BMDM are redundant for demyelination, we herein characterize gene expression profiles of BMDM versus microglia associated with demyelination. While gene expression in CNS infiltrating BMDM was upregulated early following infection and subsequently sustained, microglia expressed a more dynamic gene profile with extensive mRNA upregulation coinciding with peak demyelination after viral control. This delayed microglia response comprised a highly pro-inflammatory and phagocytic profile. Furthermore, while BMDM exhibited a mixed phenotype of M1 and M2 markers, microglia repressed the vast majority of M2-markers. Overall, these data support a pro-inflammatory and pathogenic role of microglia temporally remote from viral control, whereas BMDM retained their gene expression profile independent of the changing environment. As demyelination is caused by multifactorial insults, our results highlight the plasticity of microglia in responding to distinct inflammatory settings, which may be relevant for MS pathogenesis.

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Multiple Sklerose: Veröffentlichungen Juni 2018

Gestational Hypothyroxinemia Affects Its Offspring With a Reduced Suppressive Capacity Impairing the Outcome of the Experimental Autoimmune Encephalomyelitis.
Author information: (1)Departamento de Ciencias Biológicas, Facultad de Ciencias de la Vida, Universidad Andrés Bello, Santiago, Chile. (2)Millennium Institute on Immunology and Immunotherapy, Santiago, Chile. (3)Departamento de Genética Molecular y Microbiología, Facultad de Ciencias Biológicas, Pontificia Universidad Católica de Chile, Santiago, Chile. (4)Medizinischen Fakultät, Eberhard Karls Universität, Tübingen, Germany. (5)Departamento Biomédico, Facultad de Ciencias de la Salud, Universidad de Antofagasta, Antofagasta, Chile. (6)Centro de Investigaciones Biomédicas, Facultad de Ciencias de la Vida y Facultad de Medicina, Universidad Andrés Bello, Santiago, Chile. (7)Departamento de Endocrinología, Escuela de Medicina, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile.
Hypothyroxinemia (Hpx) is a thyroid hormone deficiency (THD) condition highly frequent during pregnancy, which although asymptomatic for the mother, it can impair the cognitive function of the offspring. Previous studies have shown that maternal hypothyroidism increases the severity of experimental autoimmune encephalomyelitis (EAE), an autoimmune disease model for multiple sclerosis (MS). Here, we analyzed the immune response after EAE induction in the adult offspring gestated in Hpx. Mice gestated in Hpx showed an early appearance of EAE symptoms and the increase of all parameters of the disease such as: the pathological score, spinal cord demyelination, and immune cell infiltration in comparison to the adult offspring gestated in euthyroidism. Isolated CD4+CD25+ T cells from spleen of the offspring gestated in Hpx that suffer EAE showed reduced capacity to suppress proliferation of effector T cells (TEff) after being stimulated with anti-CD3 and anti-CD28 antibodies. Moreover, adoptive transfer experiments of CD4+CD25+ T cells from the offspring gestated in Hpx suffering EAE to mice that were induced with EAE showed that the receptor mice suffer more intense EAE pathological score. Even though, no significant differences were detected in the frequency of Treg cells and IL-10 content in the blood, spleen, and brain between mice gestated in Hpx or euthyroidism. T cells CD4+CD25+ from spleen have reduced capacity to differentiate in vitro to Treg and to produce IL-10. Thus, our data support the notion that maternal Hpx can imprint the immune response of the offspring suffering EAE probably due to a reduced capacity to trigger suppression. Such "imprints" on the immune system could contribute to explaining as to why adult offspring gestated in Hpx suffer earlier and more intense EAE.
DOI: 10.3389/fimmu.2018.01257  PMCID: PMC5997919 PMID: 29928277

Dysregulated MicroRNA Involvement in Multiple Sclerosis by Induction of T Helper 17 Cell Differentiation.
Chen C(1), Zhou Y(1), Wang J(1), Yan Y(1)(2), Peng L(1), Qiu W(1).
Author information: (1)Department of Neurology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China. (2)Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, National Engineering Laboratory for Resource Development of Endangered Crude Drugs in Northwest of China, College of Life Sciences, Shaanxi Normal University, Xi'an, China.
Multiple sclerosis (MS) is an immune-mediated demyelinating disease of the central nervous system. Growing evidence has proven that T helper 17 (Th17) cells are one of the regulators of neuroinflammation mechanisms in MS disease. Researchers have demonstrated that some microRNAs (miRNAs) are associated with disease activity and duration, even with different MS patterns. miRNAs regulate CD4+ T cells to differentiate toward various T cell subtypes including Th17 cells. In this review, we discuss the possible mechanisms of miRNAs in MS pathophysiology by regulating CD4+ T cell differentiation into Th17 cells, and potential miRNA targets for current disease-modifying treatments.
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**IL-3 Is a Marker of Encephalitogenic T Cells, but Not Essential for CNS Autoimmunity.**

Lee PW(1), Xin MK(1), Pei W(2), Yang Y(2), Lovett-Racke AE(1).

Author information: (1)Department of Microbial Infection and Immunity, The Ohio State University, Columbus, OH, United States. (2)Department of Neurology, The Ohio State University, Columbus, OH, United States.

Identifying molecules that are differentially expressed in encephalitogenic T cells is critical to the development of novel and specific therapies for multiple sclerosis (MS). In this study, IL-3 was identified as a molecule highly expressed in encephalitogenic Th1 and Th17 cells, but not in myelin-specific non-encephalitogenic Th1 and Th17 cells. However, B10.PL IL-3-deficient mice remained susceptible to experimental autoimmune encephalomyelitis (EAE), a mouse model of MS. Furthermore, B10.PL myelin-specific T cell receptor transgenic IL-3(-/-) Th1 and Th17 cells were capable of transferring EAE to wild-type mice. Antibody neutralization of IL-3 produced by encephalitogenic Th1 and Th17 cells failed to alter their ability to transfer EAE. Thus, IL-3 is highly expressed in myelin-specific T cells capable of inducing EAE compared to activated, non-encephalitogenic myelin-specific T cells. However, loss of IL-3 in encephalitogenic T cells does not reduce their pathogenicity, indicating that IL-3 is a marker of encephalitogenic T cells, but not a critical element in their pathogenic capacity.

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**Detection of Glycan Shedding in the Blood: New Class of Multiple Sclerosis Biomarkers?**


Author information: (1)Department of Biomedicine/Pharmacology, Aarhus University, Aarhus, Denmark. (2)Department of Clinical Microbiology, Copenhagen University Hospital, Copenhagen, Denmark. (3)Department of Immunology and Microbiology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. (4)Department of Biomedical Sciences, Faculty of Health, University of Copenhagen, Copenhagen, Denmark. (5)Department of Health Science and Technology, Aalborg University, Aalborg, Denmark. (6)Department of Endocrinology, Bispebjerg Hospital Copenhagen, Copenhagen, Denmark. (7)Department of Micro- and Nanotechnology, Technical University of Denmark, Kongens Lyngby, Denmark.

Introduction: Multiple sclerosis (MS) is a devastating autoimmune disease, afflicting people in the prime of their lives. Presently, after initial clinical presentation, there are no reliable markers for whether a patient will develop MS, or whether their prognosis will be aggressive or relapsing-remitting. Furthermore, many MS patients do not respond to treatment. Thus, markers for diagnosis, prognosis, and treatment-responsiveness are lacking for a disease, where a precision medicine approach would be valuable. The glycocalyx (GLX) is the carbohydrate-rich outer surface of the blood vessel wall and is the first interaction between the blood and the vessel. We hypothesized that cleavage of the GLX may be an early stage predictor of immune attack, blood-brain barrier (BBB) breakdown, and disease severity in MS. Methods: Two experimental models of MS, experimental autoimmune encephalitis (EAE), were included in this study. EAE was induced in C57BL/6J mice and Lewis rats, which were monitored for weight loss and clinical presentation in comparison to healthy controls. Plasma samples were obtained longitudinally from mice until peak disease severity and at peak disease severity in rats. Soluble GLX-associated glycosaminoglycans (GAG) and proteoglycans (PG) were detected in plasma samples. Results: All animals receiving EAE emulsion developed fulminant EAE (100% penetrance). Increased plasma levels of chondroitin sulfate were detected before the onset of clinical symptoms and remained elevated at peak disease severity. Hyaluronic acid was increased at the height of the disease, whereas heparan sulfate was transiently increased during early stages only. By contrast, syndecans 1, 3, and 4 were detected in EAE samples as well as healthy controls, with no significant differences between the two groups. Discussion: In this study, we present data supporting the shedding of the GLX as a new class of biomarker for MS. In particular, soluble, sugar-based GLX components are associated with disease severity in two models of MS, molecules that would not be detected in proteomics-based screens of MS patient samples. Patient studies are presently underway.

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Profiling of Canonical and Non-Traditional Cytokine Levels in Interferon-β-Treated Relapsing-Remitting-Multiple Sclerosis Patients.


Author information:  (1)Department of Medical, Oral and Biotechnological Sciences, School of Medicine and Health Sciences, University "G.d'Annunzio" Chieti-Pescara, Chieti, Italy. (2)Department of Medicine and Ageing Sciences, School of Hygiene and Preventive Medicine, University "G.d'Annunzio" Chieti-Pescara, Chieti, Italy. (3)Department of Neurology, Hospital General Universitario Gregorio Marañón, Madrid, Spain. (4)Department of Clinical Immunology and IdISSC, Hospital Clínico San Carlos, Madrid, Spain. (5)Department of Immunology, Complutense University School of Medicine, Madrid, Spain. (6)Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy.

Background: Multiple sclerosis (MS) is a chronic, progressive autoimmune disease of the central nervous system in which inflammation plays a key role in the induction, development, and progression. Most of the MS patients present with relapsing-remitting (RR) form, characterized by flare-ups followed by periods of recovery. Many inflammatory and anti-inflammatory cytokines have been proposed as backers in MS pathogenesis, and the balance between these differing cytokines can regulate MS severity. Interferon (IFN)-β, a current disease-modifying therapy for MS, has demonstrated beneficial effects in reducing disease severity in MS patients. However, its immunoregulatory and anti-inflammatory actions in MS are not wholly understood. The aim of the study was to define, in clinically stable patients with RR-MS, the serum concentration of several cytokines, canonical or not, and their modulation by IFN-β therapy.

Methods: Relapsing-remitting-MS patients were enrolled and diagnosed according to revised Mc Donald Diagnostic Criteria. A set of cytokines [including non-canonical neurotransmitter acetylcholine (ACh) and adipokines] and B-cell differentiation molecules, as potential biomarkers, were evaluated in 30 non-treated RR-MS patients compared to 30 IFN-β-treated MS patients and 30 age, gender, and body mass index-matched healthy controls (HC). Results: Naïve MS patients showed significantly higher levels of interleukin (IL)-1β, IL-12/IL-23p40, IL-18, high-mobility group box protein-1, and IL-18 binding protein (IL-18BP) than MS-treated patients (p < 0.001 for all) and HC (p < 0.01). IFN-β therapy has significantly downmodulated IL-1β, IL-12/IL-23p40, IL-18 to normal levels (p < 0.001), whereas it has decreased IL-18BP (p < 0.001). ACh was significantly higher in the IFN-β-treated than HC and non-treated MS patients (p < 0.001). No significant differences were observed either in adipokines concentration or in B-cell-associated molecules among the three study groups. Conclusion: Although more experimental evidence are required, we speculate that the efficacy of treatment of MS with IFN-β is mediated, at least in part, by its ability to work on several levels to slow down the disease progression. Proposed actions include the modulation of IL-1-inflammasome axis and modulation of ACh, B-cell activating factor/a proliferation-inducing ligand system, and several adipokines.

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The Role of Natural Killer Group 2, Member D in Chronic Inflammation and Autoimmunity.

Babic M(1)(2), Romagnani C(1)(2).

Author information:  (1)Innate Immunity, German Rheumatism Research Center (DRFZ), Leibniz Association, Berlin, Germany. (2)Medical Department I, Charité - Universitätsmedizin Berlin, Berlin, Germany.

Current medicine and medical science puts great effort into elucidating the basis of chronicity and finding appropriate treatments for inflammatory diseases; however, the mechanisms driving aberrant immune responses are mostly unknown and deserve further study. Of particular interest is the identification of checkpoints that regulate the function and differentiation of pro-inflammatory cells during pathogenesis, along with means of their modulation for therapeutic purposes. Natural killer group 2, member D (NKG2D) is a potent activator of the immune system, known as a sensor for “induced-self” ligands, i.e., cellular danger signals that, in the context of chronic inflammation and autoimmunity, can be presented by cells being exposed to an inflammatory cytokine milieu, endoplasmic reticulum stress, or cell death. Engagement by such ligands can be translated by NKG2D into activation or costimulation of NK cells and different subsets of T cells, respectively, contributing to the regulation of the inflammatory response. In this review, we discuss the current knowledge on the contribution of the NKG2D-NKG2DL signaling axis during intestinal inflammation, type 1 diabetes, multiple sclerosis, and rheumatoid arthritis, where the role of NKG2D has been associated either by aberrant expression of the receptor and its ligands and/or by functional data in corresponding mouse models.

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Manresa-Arraut A(1), Johansen FF(1), Brakebusch C(2), Issazadeh-Navikas S(1), Hasseldam H(1).

Author information:  (1)Neuroinflammation Unit, Biotech Research and Innovation Centre (BRIC), Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. (2)Cytoskeletal Organization Group, Biotech Research and Innovation Centre (BRIC), Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

T-cells are known to be intimately involved in the pathogenesis of multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE). T-cell activation is controlled by a range of intracellular signaling pathways regulating cellular responses such as proliferation, cytokine production, integrin expression, and migration. These processes are crucial for the T-cells' ability to mediate inflammatory processes in autoimmune diseases such as MS. RhoA is a ubiquitously expressed small GTPase well described as a regulator of the actin cytoskeleton. It is essential for embryonic development and together with other Rho GTPases controls various cellular processes such as cell development, shaping, proliferation, and locomotion. However, the specific contribution of RhoA to these processes in T-cells in general, and in autoreactive T-cells in particular, has not been fully characterized. Using mice with a T-cell specific deletion of the RhoA gene (RhoAfl/flLckCre+), we investigated the role of RhoA in T-cell development, functionality, and encephalitogenic potential in EAE. We show that lack of RhoA specifically in T-cells results in reduced numbers of mature T-cells in thymus and spleen but normal counts in peripheral blood. EAE induction in RhoAfl/flLckCre+ mice results in significantly reduced disease incidence and severity, which coincides with a reduced CNS T-cell infiltration. Besides presenting reduced migratory capacity, both naïve and autoreactive effector T-cells from RhoAfl/flLckCre+ mice show decreased viability, proliferative capacity, and an activation profile associated with reduced production of Th1 pro-inflammatory cytokines. Our study demonstrates that RhoA is a central regulator of several archetypical T-cell responses, and furthermore points toward RhoA as a new potential therapeutic target in diseases such as MS, where T-cell activity plays a central role.

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Author information: (1)Department of Immunology, Hospital Clinic i Provincial, Barcelona, Spain.
(2)Neuroimmunology Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

The identification of activated T-lymphocytes restricted to myelin-derived immunogenic peptides in multiple sclerosis (MS) and aquaporin-4-water channel in neuromyelitis optica (NMO) in the blood of patients opened the possibility for developing highly selective and disease-specific therapeutic approaches. Antigen presenting cells and in particular dendritic cells (DCs) represent a strategy to inhibit pro-inflammatory T helper cells. DCs are located in peripheral and lymphoid tissues and are essential for homeostasis of T cell-dependent immune responses. The expression of a particular set of receptors involved in pathogen recognition confers to DCs the property to initiate immune responses. However, in the absence of danger signals different DC subsets have been revealed to induce active tolerance by inducing regulatory T cells, inhibiting pro-inflammatory T helper cells responses or both. Interestingly, several protocols to generate clinical-grade tolerogenic DC (Tol-DC) in vitro have been described, offering the possibility to restore the homeostasis to central nervous system-related antigens. In this review, we discuss about different DC subsets and their role in tolerance induction, the different protocols to generate Tol-DCs and preclinical studies in animal models as well as describe recent characterization of Tol-DCs for clinical application in autoimmune diseases and in particular in MS and NMO patients. In addition, we discuss the clinical trials ongoing based on Tol-DCs to treat different autoimmune diseases.

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Relapsing-Remitting Multiple Sclerosis Is Characterized by a T Follicular Cell Pro-Inflammatory Shift, Reverted by Dimethyl Fumarate Treatment.


Author information: (1)Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany. (2)Institute for Multiple Sclerosis Research and Neuroimmunology, University Medical Centre Göttingen, Göttingen, Germany. (3)Centre de Recherche en Transplantation et Immunologie UMR 1064, INSERM, Université de Nantes, Nantes, France. (4)Institut de Transplantation Urologie Néphrologie (IdISBa), Palma, Spain. (5)Research Unit, Institut d'Investigació Sanitària de les Illes Balears and Hospital Universitari Son Espases, Palma, Spain.

Multiple sclerosis (MS) is considered a T cell-mediated autoimmune disease, although several evidences also demonstrate a B cell involvement in its etiology. Follicular T helper (Tfh) cells, a CXCR5-expressing CD4+ T cell subpopulation, are essential in the regulation of B cell differentiation and maintenance of humoral immunity. Alterations in circulating (c)Tfh distribution and/or function have been associated with autoimmune diseases including MS. Dimethyl fumarate (DMF) is a recently approved first-line treatment for relapsing-remitting MS (RRMS) patients whose mechanism of action is not completely understood. The aim of our study was to compare cTfh subpopulations between RRMS patients and healthy subjects and evaluate the impact of DMF treatment on these subpopulations, relating them to changes in B cells and humoral response. We analyzed, by flow cytometry, the distribution of cTfh1 (CXCR3+CCR6-), cTfh2 (CXCR3-CR6-), cTfh17 (CXCR3-CR6+), and the recently described cTfh17.1 (CXCR3+CCR6+) subpopulations of CD4+ Tfh (CD45RA-CXCR5+) cells in a cohort of 29 untreated RRMS compared to healthy subjects. CD4+ non-follicular T helper (Th) cells (CD45RA-CXCR5-) were also studied. We also evaluated the effect of DMF treatment on these subpopulations after 6 and 12 months treatment. Untreated RRMS patients presented higher percentages of cTfh17.1 cells and lower percentages of cTfh2 cells consistent with a pro-inflammatory bias compared to healthy subjects. DMF treatment induced a progressive increase in cTfh2 cells, accompanied by a decrease in cTfh1 and the pathogenic cTfh17.1 cells. A similar decrease of non-follicular Th1 and Th17.1 cells in addition to an increase in the anti-inflammatory Th2 subpopulation were also detected upon DMF treatment, accompanied by an increase in naïve B cells and a decrease in switched memory B cells and serum levels of IgA, IgG2, and IgG3. Interestingly, this effect was not observed in three patients in whom DMF had to be discontinued due to an absence of clinical response. Our results demonstrate a possibly pathogenic cTfh pro-inflammatory profile in RRMS patients, defined by high cTfh17.1 and low cTfh2 subpopulations that is reverted by DMF treatment. Monitoring cTfh subsets during treatment may become a biological marker of DMF effectiveness.

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CD28 Costimulation of T Helper 1 Cells Enhances Cytokine Release In Vivo.

Langenhorst D(1), Haack S(1), Göb S(1), Uri A(1), Lühder F(2), Vanhove B(3)(4)(5), Hüning T(1), Beyersdorf N(1).

Author information: (1)Institute for Virology and Immunobiology, University of Würzburg, Würzburg, Germany. (2)Institute for Multiple Sclerosis Research and Neuroimmunology, University Medical Centre Göttingen, Göttingen, Germany. (3)Centre de Recherche en Transplantation et Immunologie UMR 1064, INSERM, Université de Nantes, Nantes, France. (4)Institut de Transplantation Urologie Néphrologie (ITUN), CHU Nantes, Nantes, France. (5)OSE Immunotherapeutics S.A., Nantes, France.

Compared to naïve T cells, differentiated T cells are thought to be less dependent on CD28 costimulation for full activation. To revisit the role of CD28 costimulation in mouse T cell recall responses, we adoptively transferred in vitro generated OT-II T helper (Th) 1 cells into C57BL/6 mice (Thy1.2+) and then either blocked CD28-ligand interactions with Fab fragments of the anti-CD28 monoclonal antibody (mAb) E18 or deleted CD28 expression using inducible CD28 knock-out OT-II mice as T cell donors. After injection of ovalbumin protein in adjuvant into the recipient mice we observed that systemic interferon (IFN)γ release strongly depended on CD28 costimulation of the Th1 cells, while secondary clonal expansion was not reduced in the absence of CD28 costimulation. For human memory CD4+ T cell responses we also noted that cytokine release was reduced upon inhibition of CD28 costimulation. Together, our data highlight the so far underestimated role of CD28 costimulation for the reactivation of fully differentiated CD4+ T cells.

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T Follicular Helper-Like Cells Are Involved in the Pathogenesis of Experimental Autoimmune Encephalomyelitis.


Author information: (1)Department of Neurology, Tangdu Hospital, Fourth Military Medical University, Xi'an, China. (2)Department of Immunology, Fourth Military Medical University, Xi'an, China. (3)Department of Neurology, Air Force General Hospital PLA, Beijing, China. (4)Department of Neurology, Xi'an Children's Hospital, Xi'an, China.

Multiple sclerosis (MS) and experimental autoimmune encephalomyelitis (EAE) have been proved to be T cell-mediated autoimmune diseases. Recent researches indicate that humoral immunity is also involved in the pathogenesis of these disorders. T follicular helper (Tfh) cells are critical for B cell differentiation and antibody production. However, the role of Tfh cells in MS and EAE remains unclear. Here, we found elevated frequencies of CD4+CXCR5+PD-1+ Tfh-like cells in both MS patients and EAE. In EAE mice, Tfh-like cells, together with B cells, were found in the ectopic lymphoid structures in spinal cords. Moreover, Tfh-like cells promoted the antibody production via IL-21/IL-21R and CD40 ligand/CD40 interaction and the synergy effect of STAT3 and non-canonical NF-kB signaling pathway inside B cells. Moreover, adoptive transfer of Tfh-like cells could increase the severity and delay the remission of EAE. In conclusion, our data indicate that Tfh-like cells contribute to the pathogenesis of EAE.

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Natural Killer Cells Regulate Th17 Cells After Autologous Hematopoietic Stem Cell Transplantation for Relapsing Remitting Multiple Sclerosis.

Darlington PJ(1), Stopnicki B(1), Touil T(2), Doucet JS(2), Fawaz L(2), Roberts ME(2), Boivin MN(2)(3), Arbour N(4), Freedman MS(5), Atkins HL(6), Bar-Or A(2)(7).

Author information: (1)Departments of Exercise Science and Biology, PERFO University, Montreal, QC, Canada. (2)Neuroimmunology Unit, McGill University and Montreal Neurological Institute, Montreal, QC, Canada. (3)Clinical Biological Imaging and Genetic Repository, McGill University, Montreal, QC, Canada. (4)Department of Neurosciences, Université de Montréal, Centre de Recherche du Centre Hospitalier de l'Université de Montréal (CRCHUM), Montréal, QC, Canada. (5)Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada. (6)Blood and Marrow Transplant Program, Ottawa General Hospital, Ottawa, ON, Canada. (7)Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States.

In autoimmunity, the balance of different helper T (Th) cell subsets can influence the tissue damage caused by autoreactive T cells. Pro-inflammatory Th1 and Th17 T cells are implicated as mediators of several human autoimmune conditions such as multiple sclerosis (MS). Autologous hematopoietic stem cell transplantation (aHSCT) has been tested in phase 2 clinical trials for MS patients with aggressive disease. Abrogation of new clinical relapses and brain lesions can be seen after ablative aHSCT, accompanied by significant reductions in Th17, but not Th1, cell populations and activity. The cause of this selective decrease in Th17 cell responses following ablative aHSCT is not completely understood. We identified an increase in the kinetics of natural killer (NK) cell reconstitution, relative to CD4+ T cells, in MS patients post-aHSCT, resulting in an increased NK cell:CD4+ T cell ratio that correlated with the degree of decrease in Th17 responses. Ex vivo removal of NK cells from post-aHSCT peripheral blood mononuclear cells resulted in higher Th17 cell responses, indicating that NK cells can regulate Th17 activity. NK cells were also found to be cytotoxic to memory Th17 cells, and this toxicity is mediated through NKG2D-dependent necrosis. Surprisingly, NK cells induced memory T cells to secrete more IL-17A. This was preceded by an early rise in T cell expression of RORC and IL17A mRNA, and could be blocked with neutralizing antibodies against CD58, a costimulatory receptor expressed on NK cells. Thus, NK cells provide initial co-stimulation that supports the induction of a Th17 response, followed by NKG2D-dependent cytotoxicity that limits these cells. Together these data suggest that rapid reconstitution of NK cells following aHSCT contribute to the suppression of the re-emergence of Th17 cells. This highlights the importance of NK cells in shaping the reconstituting immune system following aHSCT in MS patients.

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Comprehensive Antiretroviral Restriction Factor Profiling Reveals the Evolutionary Imprint of the ex Vivo and in Vivo IFN-β Response in HTLV-1-Associated Neuroinflammation.


Author information: (1)Oncovirology Program, Instituto Nacional de Câncer (INCA), Rio de Janeiro, Brazil. (2)Microbiology Immunology and Tropical Medicine, George Washington University, Washington, DC, United States. (3)Department of Microbiology and Immunology, Rega Institute for Medical Research, KU Leuven, Leuven, Belgium. (4)Departamento de Moléstias Infecciosas e Parasitárias, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil. (5)Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine, Baltimore, MD, United States. (6)Fundação Oswaldo Cruz, Instituto Gonçalo Moniz (IGM), Salvador-Bahia, Brazil. (7)Escola Bahiana de Medicina e Saúde Pública, Salvador-Bahia, Brazil.

HTLV-1-Associated Myelopathy (HAM/TSP) is a progressive neuroinflammatory disorder for which no disease-modifying treatment exists. Modest clinical benefit from type I interferons (IFN-α/β) in HAM/TSP contrasts with its recently identified IFN-inducible gene signature. In addition, IFN-α treatment in vivo decreases proviral load and immune activation in HAM/TSP, whereas IFN-β therapy decreases tax mRNA and lymphoproliferation. We hypothesize this “IFN paradox” in HAM/TSP might be explained by both cell type- and gene-specific effects of type I IFN in HTLV-1-associated pathogenesis. Therefore, we analyzed ex vivo transcriptomes of CD4+ T cells, PBMCs and whole blood in healthy controls, HTLV-1-infected individuals, and HAM/TSP patients. First, we used a targeted approach, simultaneously quantifying HTLV-1 mRNA (HBZ, Tax), proviral load and 42 host genes with known antiretroviral (anti-HIV) activity in purified CD4+ T cells. This revealed two major clusters (“antiviral/protective” vs. “proviral/deleterious”), as evidenced by significant negative (TRIM5/TRIM22/BST2) vs. positive correlation (ISG15/PAF1/CDKN1A) with HTLV-1 viral markers and clinical status. Surprisingly, we found a significant inversion of antiretroviral activity of host restriction factors, as evidenced by opposite correlation to in vivo HIV-1 vs. HTLV-1 RNA levels. The anti-HTLV-1 effect of antiviral cluster genes was significantly correlated to their adaptive chimp/human evolution score, for both Tax mRNA and PVL. Six genes of the proposed antiviral cluster underwent lentivirus-driven purifying selection during primate evolution (TRIM5/TRIM22/BST2/APOBEC3F-G-H), underscoring the cross-retroviral evolutionary imprint. Secondly, we examined the genome-wide type I IFN response in HAM/TSP patients, following short-term ex vivo culture of PBMCs with either IFN-α or IFN-β. Microarray analysis evidenced 12 antiretroviral genes (including TRIM5α/TRIM22/BST2) were significantly up-regulated by IFN-β, but not IFN-α, in HAM/TSP. This was paralleled by a significant decrease in lymphoproliferation by IFN-β, but not IFN-α treatment. Finally, using published ex vivo whole blood transcriptomic data of independent cohorts, we validated the significant positive correlation between TRIM5, TRIM22, and BST2 in HTLV-1-infected individuals and HAM/TSP patients, which was independent of the HAM/TSP disease signature. In conclusion, our results provide ex vivo mechanistic evidence for the observed immunovirological effect of in vivo IFN-β treatment in HAM/TSP, reconcile an apparent IFN paradox in HTLV-1 research and identify biomarkers/targets for a precision medicine approach.

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Emerging Biosensing Technologies for Neuroinflammatory and Neurodegenerative Disease Diagnostics.

Abreu CM(1)(2), Soares-Dos-Reis R(3)(4)(5), Melo PN(6)(7), Relvas JB(7), Guimarães J(3)(4)(8), Sá MJ(3)(9)(10), Cruz AP(1), Mendes Pinto I(1).

Author information: (1)International Iberian Nanotechnology Laboratory, Braga, Portugal. (2)Medical School, Swansea University, Swansea, United Kingdom. (3)Neurology Department, Centro Hospitalar de São João, Porto, Portugal. (4)Department of Clinical Neurosciences and Mental Health, Faculdade de Medicina, Universidade do Porto, Porto, Portugal. (5)Department of Biomedicine, Faculdade de Medicina, Universidade do Porto, Porto, Portugal. (6)Graduate Programme in Areas of Basic and Applied Biology, Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto, Porto, Portugal. (7)Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal. (8)Center for Drug Discovery and Innovative Medicines (MedInUP), Universidade do Porto, Porto, Portugal. (9)Energy, Environment and Health Research Unit (FP-ENAS), University Fernando Pessoa, Porto, Portugal. (10)Faculty of Health Sciences, University Fernando Pessoa, Porto, Portugal.

Neuroinflammation plays a critical role in the onset and progression of many neurological disorders, including Multiple Sclerosis, Alzheimer’s and Parkinson’s diseases. In these clinical conditions the underlying neuroinflammatory processes are significantly heterogeneous. Nevertheless, a common link is the chronic activation of innate immune responses and imbalanced secretion of pro and anti-inflammatory mediators. In light of this, the discovery of robust biomarkers is crucial for screening, early diagnosis, and monitoring of neurological diseases. However, the difficulty to investigate biochemical processes directly in the central nervous system (CNS) is challenging. In recent years, biomarkers of CNS inflammatory responses have been identified in different body fluids, such as blood, cerebrospinal fluid, and tears. In addition, progress in micro and nanotechnology has enabled the development of biosensing platforms capable of detecting in real-time, multiple biomarkers in clinically relevant samples. Biosensing technologies are approaching maturity where they will become deployed in community settings, at which point screening programs and personalized medicine will become a reality. In this multidisciplinary review, our goal is to highlight both clinical and recent technological advances toward the development of multiplex-based solutions for effective neuroinflammatory and neurodegenerative disease diagnostics and monitoring.

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The forgotten effects of thyrotropin-releasing hormone: Metabolic functions and medical applications.

Fröhlich E(1), Wahl R(2).

Author information: (1)Internal Medicine (Dept. of Endocrinology and Diabetology, Angiology, Nephrology and Clinical Chemistry), University of Tuebingen, Otfrid-Muellerstrasse 10, 72076 Tuebingen, Germany; Center for Medical Research, Medical University Graz, Stiftungstr. 24, 8010 Graz, Austria. (2)Internal Medicine (Dept. of Endocrinology and Diabetology, Angiology, Nephrology and Clinical Chemistry), University of Tuebingen, Otfrid-Muellerstrasse 10, 72076 Tuebingen, Germany. Electronic address: richard.wahl@med.uni-tuebingen.de.

Thyrotropin-releasing hormone (TRH) causes a variety of thyroidal and non-thyroidal effects, the best known being the feedback regulation of thyroid hormone levels. This was employed in the TRH stimulation test, which is currently little used. The role of TRH as a cancer biomarker is minor, but exaggerated responses to TSH and prolactin levels in breast cancer led to the hypothesis of a potential role for TRH in the pathogenesis of this disease. TRH is a rapidly degraded peptide with multiple targets, limiting its suitability as a biomarker and drug candidate. Although some studies reported efficacy in neural diseases (depression, spinal cord injury, amyotrophic lateral sclerosis, etc.), therapeutic use of TRH is presently restricted to spinocerebellar degenerative disease. Regulation of TRH production in the hypothalamus, patterns of expression of TRH and its receptor in the body, its role in energy metabolism and in prolactin secretion are addressed in this review.

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Ghai S(1), Ghai I(2).
Author information: (1)Institute of Sports Science, Leibniz University Hanover, Hanover, Germany. (2)Victor Chang Cardiac Research Institute, Sydney, NSW, Australia.
Rhythmic auditory cueing has been shown to enhance gait performance in several movement disorders. The "entrainment effect" generated by the stimulations can enhance auditory motor coupling and instigate plasticity. However, a consensus as to its influence over gait training among patients with multiple sclerosis is still warranted. A systematic review and meta-analysis was carried out to analyze the effects of rhythmic auditory cueing in studies gait performance in patients with multiple sclerosis. This systematic identification of published literature was performed according to PRISMA guidelines, from inception until Dec 2017, on online databases: Web of science, PEDro, EBSCO, MEDLINE, Cochrane, EMBASE, and PROQUEST. Studies were critically appraised using PEDro scale. Of 602 records, five studies (PEDro score: 5.7 ± 1.3) involving 188 participants (144 females/40 males) met our inclusion criteria. The meta-analysis revealed enhancements in spatiotemporal parameters of gait i.e., velocity (Hedge's g: 0.67), stride length (0.70), and cadence (1.0), and reduction in timed 25 feet walking test (-0.17). Underlying neurophysiological mechanisms, and clinical implications are discussed. This present review bridges the gaps in literature by suggesting application of rhythmic auditory cueing in conventional rehabilitation approaches to enhance gait performance in the multiple sclerosis community.
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Cheong WL(1), Mohan D(2), Warren N(3), Reidpath DD(2).
Author information: (1)School of Pharmacy, Monash University Malaysia, Bandar Sunway, Malaysia. (2)Jeffrey Cheah School of Medicine and Health Sciences (JCSMHS), Monash University Malaysia, Bandar Sunway, Malaysia. (3)School of Social Sciences, Monash University, Clayton, Australia.
Background: Multiple sclerosis is thought to be relatively uncommon in the Asia Pacific region with prevalence estimated between 0 and 20 per 100,000. There is reason to doubt these estimates due to the lack of data from many countries and the growing evidence of variability in prevalence across small geographic areas. This study was conducted to systematically review the population prevalence, incidence, mortality and disability progression estimates of MS within the Asia Pacific region. Methods: The systematic review was conducted on articles from 1985 till 31st July 2017 within the PubMed/MEDLINE, EMBASE, SCOPUS, and The Cochrane Library databases. The review included articles that were population-based studies conducted on patients with MS in the Asia Pacific region that reported either incidence, prevalence, mortality, or disease progression. Hospital-based studies and non-research articles were excluded to ensure that only information representative of the population was included for analysis. Data appraisal and extraction was done by independent reviewers. This review was registered with PROSPERO (ID: CRD42017082760). Findings: Of the 2,757 articles found, 16 studies were included. Information on 6 (18.75%) of 32 Asia Pacific countries was found, with data representing 8% of the total population. Prevalence estimates were available for 6 countries while estimates for incidence (3 countries), mortality (4 countries), and disease progression (2 countries) were limited. Interpretation: The lack of epidemiological data available in the Asia Pacific region creates a blind spot in the surveillance of MS which obscures the true burden of MS, causing patients to struggle to receive the resources and funding that they need.
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Onset Symptoms, Tobacco Smoking, and Progressive-Onset Phenotype Are Associated With a Delayed Onset of Multiple Sclerosis, and Marijuana Use With an Earlier Onset.

Tao C(1), Simpson S Jr(1)(2), Taylor BV(1), Blizzard L(1), Lucas RM(3), Ponsonby AL(4), Broadley S(5); AusLong/Ausimmune Investigators Group, van der Mei l(1).


Author information: (1)Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia. (2)Institute for Health & Ageing, Australian Catholic University, Melbourne, VIC, Australia. (3)National Centre for Epidemiology and Population Health, Canberra, ACT, Australia. (4)Murdoch Children's Research Institute, University of Melbourne, Melbourne, VIC, Australia. (5)School of Medicine, Griffith University, Gold Coast, QLD, Australia.

Background: Age at symptom onset (ASO) is a prognostic factor that could affect the accrual of disability in multiple sclerosis (MS) patients. Some factors are known to influence the risk of multiple sclerosis (MS), but their influence on the ASO is less well-investigated. Objective: Examine the associations between known or emerging MS risk factors and ASO. Methods: This was a multicenter study, incident cases (n = 279) with first clinical diagnosis of demyelinating event aged 18-59 years recruited at four Australian centres (latitudes 27°-43°S), from 1 November 2003 to 31 December 2006. Environmental/behavioral variables and initial symptoms were recorded at baseline interview. Linear regression was used to assess the association between risk factors and ASO. Results: Five factors were significantly associated with ASO: a history of tobacco smoking was associated with 3.05-years later ASO (p = 0.002); a history of marijuana use was associated with 6.03-years earlier ASO (p < 0.001); progressive-onset cases had 5.61-years later ASO (p = 0.001); an initial presentation of bowel & bladder and cerebral dysfunctional were associated with 3.39 (p = 0.017) and 4.37-years (p = 0.006) later ASO, respectively. Other factors, including sex, offspring number, latitude of study site, history of infectious mononucleosis, HLA-DR15 & HLA-A2 genotype, 25(OH)D levels, and ultraviolet radiation exposure were not associated with ASO. Including all five significant variables into one model explained 12% of the total variance in ASO. Conclusion: We found a novel association between a history of tobacco smoking and later onset, whereas marijuana use was associated with earlier onset. Behavioral factors seem important drivers of MS onset timing although much of the variance remains unexplained.

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Resective Surgery for Double Epileptic Foci Overlapping Anterior and Posterior Language Areas: A Case of Epilepsy With Tuberous Sclerosis Complex.

Okanishi T(1), Fujimoto A(2), Nishimura M(3), Niimi K(4), Kanai S(1), Enoki H(1).

Author information: (1)Department of Child Neurology, Seirei Hamamatsu General Hospital, Hamamatsu, Japan. (2)Comprehensive Epilepsy Center, Seirei Hamamatsu General Hospital, Hamamatsu, Japan. (3)Department of Clinical Laboratory, Seirei Hamamatsu General Hospital, Hamamatsu, Japan. (4)Department of Rehabilitation, Seirei Hamamatsu General Hospital, Hamamatsu, Japan.

Tuberous sclerosis complex is a genetic systematic disorder characterized by hamartomas in multiple organs. Cortical tubers, the hamartomas in the cerebrum, cause multifocal refractory seizures. In certain cases, epileptic foci potentially involve language areas, and hence, extra- and intraoperative cortical mapping can help identify anterior and posterior areas, thus avoiding postsurgical language impairment. We report on a 21-year-old female with tuberous sclerosis complex experiencing refractory partial seizures due to two epileptic foci in the left hemisphere overlapping anterior and posterior language areas. To completely evaluate both language areas, we performed stepwise resections beginning from the anterior to the posterior epileptic focus. Although the patient presented with expressive aphasia following anterior resection, it was possible to conduct language tests during every resection. Postoperatively, she presented with expressive aphasia, comprehension deficits, left-right disorientations, and arithmetic deficits. The language dysfunctions almost disappeared at 5 weeks after the surgery and were completely resolved at 6 months after surgery. At postoperative 9 months, she was free from seizures.

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Author information: (1)Multiple Sclerosis and Neural Regeneration Research Group, Hospital Universitari i Politècnic La Fe, València, Spain. (2)Neuroimmunology Unit, Hospital Universitari i Politècnic La Fe, València, Spain. (3)Radiology Department, Hospital Universitari i Politècnic La Fe, València, Spain. (4)Neuroimmunology Unit, Hospital Clínic de València, Valencia, Spain. (5)Hospital Universitari de Elda, Alicante, Spain.

The clinical diagnosis of patients with autoantibodies directed to conformational myelin oligodendrocyte glycoprotein MOG-IgG, can be challenging because of atypical clinical presentation. MOG-IgG seropositivity has been reported in several demyelinating diseases, including relapsing opticospinal syndromes [in the neuromyelitis optica spectrum disorders (NMOSD) and less frequently, in multiple sclerosis (MS)], but it has rarely been associated with the progressive course of disease. To contribute to the characterization of MOG-related demyelination, we describe the case of a patient with progressive demyelinating opticospinal disease, IgG-oligoclonal bands (OCB), and serum MOG-IgG.

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Investigating Domain-Specific Cognitive Impairment Among Patients With Multiple Sclerosis Using Touchscreen Cognitive Testing in Routine Clinical Care.


Author information: (1)Cambridge Cognition, Cambridge, United Kingdom. (2)College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, United Kingdom. (3)Anne Rowling Regenerative Neurology Clinic, University of Edinburgh, Edinburgh, United Kingdom. (4)Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom. (5)Forth Valley Royal Hospital, Larbert, United Kingdom. (6)Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, United Kingdom.

Cognitive dysfunction is present in up to 70% of patients with multiple sclerosis (MS) and has been reported at all stages and in all subtypes of the disease. These deficits have been reported across a variety of cognitive domains, but are generally under-recognized and incompletely evaluated in routine clinical practice. The aim of this study was to investigate the spectrum of cognitive impairment in patients with MS presenting to a specialist MS clinic using the Cambridge Neuropsychological Test Automated Battery (CANTAB), administered on a touchscreen platform. Ninety MS patients completed computerized CANTAB tasks assessing working memory, executive function, processing speed, attention, and episodic memory. Scores were adjusted for age, sex, and level of education and classified as normal or impaired based on comparison with a large normative data pool. We also investigated the impact of clinical and demographic variables which could potentially influence cognitive performance including patient educational level (a proxy for cognitive reserve), disease status (duration, course, and severity of MS), and depression. CANTAB testing detected cognitive impairment in 40 patients (44% of the sample). The most frequently impaired domain was executive function, present in 55% of cognitively impaired individuals. Disease duration and severity were significantly associated with performance across various cognitive domains. Patients with depressive symptoms were also more likely to exhibit impaired processing speed. Results from this study confirm that cognitive impairment is common and occurs across a range of domains among MS patients attending routine clinical visits. CANTAB tasks provide a sensitive and practical approach to cognitive testing in MS patients as part of a holistic patient assessment.

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Association of Pre-Disease Body Mass Index With Multiple Sclerosis Prognosis.


Both high body mass index (BMI) and smoking tobacco are known risk factors for developing multiple sclerosis (MS). However, it is unclear whether BMI, like smoking, is a risk factor for the secondary progressive (SP) course. We, therefore, sought to determine if high/low BMI at age 20 is associated to risk of SP development, in the context of smoking status. Using data from MS patients with BMI and smoking information available, we examined relapsing onset patients with MS onset after 20 years of age. Cox regressions were conducted on smokers and non-smokers, with BMI as the main exposure. In total, 5,598 relapsing onset MS patients were included. The models demonstrated that BMI > 30 was associated to increased risk of SPMS in smokers (hazard ratio 1.50, p = 0.036). This association of obesity at age 20 with increased risk of SP was not observed in non-smokers (hazard rate 0.97, p = 0.900). Since the risk is confined to smokers, the interaction observed may give insight to disease driving mechanisms.

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Cortical Excitability and Interhemispheric Connectivity in Early Relapsing-Remitting Multiple Sclerosis Studied With TMS-EEG.

Zipser CM(1), Premoli I(1), Belardinelli P(1), Castellanos N(2), Rivolta D(3), Heidegger T(4), Müller-Dahlhaus F(1)(5), Ziemann U(1). Author information: (1)Department of Neurology and Stroke, Hertie Institute for Clinical Brain Research, Eberhard Karls University of Tübingen, Tübingen, Germany. (2)Instituto de Investigación y Formación en Ciencias Cognitivas, Madrid, Spain. (3)Department of Education Science, Psychology and Communication Science, University of Bari Aldo Moro, Bari, Italy. (4)Department of Neurology, Goethe University Frankfurt, Frankfurt am Main, Germany. (5)Department of Psychiatry and Psychotherapy, University Medical Center Mainz, Mainz, Germany.

Evoked potentials (EPs) are well established in clinical practice for diagnosis and prognosis in multiple sclerosis (MS). However, their value is limited to the assessment of their respective functional systems. Here, we used transcranial magnetic stimulation (TMS) coupled with electroencephalography (TMS-EEG) to investigate cortical excitability and spatiotemporal dynamics of TMS-evoked neural activity in MS patients. Thirteen patients with early relapsing-remitting MS (RRMS) with a median Expanded Disability Status Scale (EDSS) of 1.0 (range 0-2.5) and 16 age- and gender-matched healthy controls received single-pulse TMS of left and right primary motor cortex (L-M1 and R-M1), respectively. Resting motor threshold for L-M1 and R-M1 was increased in MS patients. Latencies and amplitudes of N45, P70, N100, P180, and N280 TMS-evoked EEG potentials (TEPs) were not different between groups, except a significantly increased amplitude of the N280 TEP in the MS group, both for L-M1 and R-M1 stimulation. Interhemispheric signal propagation (ISP), estimated from the area under the curve of TEPs in the non-stimulated vs. stimulated M1, also did not differ between groups. In summary, findings show that ISP and TEPs were preserved in early-stage RRMS, except for an exaggerated N280 amplitude. Our findings indicate that TMS-EEG is feasible in testing excitability and connectivity in cortical neural networks in MS patients, complementary to conventional EPs. However, relevance and pathophysiological correlates of the enhanced N280 will need further study.

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**Autophagy Disruptions Associated With Altered Optineurin Expression in Extraregion Regions in a Rotenone Model of Parkinson's Disease.**


Author information: (1)School of Health Sciences, Purdue University, West Lafayette, IN, United States. (2)Purdue Institute for Integrative Neuroscience, Purdue University, West Lafayette, IN, United States.

The motor features of Parkinson's disease (PD) primarily result from a lesion to the nigrostriatal dopamine system. Numerous non-motor symptoms occur in PD, many of which are postulated to stem from pathology outside of the nigrostriatal dopamine system. Perturbations to protein trafficking, disruption of mitochondrial integrity, and impaired autophagy have repeatedly been implicated in dopaminergic neuron cell death. Previously, we demonstrated that multiple markers of autophagy are disrupted in a rotenone model of PD, with alterations occurring prior to an overt lesion to the nigrostriatal dopamine system. Whether these events occur in extra-nigral nuclei in PD and when relative to a lesion in the nigrostriatal dopamine system are generally unknown. The primary goal of these studies was to determine whether autophagy disruptions, in non-dopaminergic neuronal populations occur in an environmental model of PD utilizing a mitochondrial toxin. Here, we utilized the rat rotenone PD model, with sampling time-points before and after an overt lesion to the nigrostriatal dopamine system. In analyzing autophagy changes, we focused on optineurin (OPTN) and the autophagy marker, LC3. OPTN is an autophagy cargo adapter protein genetically linked to amyotrophic lateral sclerosis and glaucoma. In the present study, we observed OPTN enrichment in all PD-relevant brain regions examined. Further, alterations in OPTN and LC3 expression and colocalized puncta suggest specific impairments to autophagy that will inform future mechanistic studies. Thus, our data suggest that autophagy disruptions may be critical to PD pathogenesis in non-dopaminergic neurons and the onset of non-motor symptoms.

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**The Anti-neuroinflammatory Activity of Tectorigenin Pretreatment via Downregulated NF-κB and ERK/JNK Pathways in BV-2 Microglial and Microglia Inactivation in Mice With Lipopolysaccharide.**

Lim HS(1), Kim YJ(1)(2), Kim BY(1), Park G(3), Jeong SJ(1)(4).

Author information: (1)Herbal Medicine Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea. (2)College of Pharmacy, Chungnam National University, Daejeon, South Korea. (3)Ektos Industries Co. Ltd., Daejeon, South Korea. (4)Korean Medicine Life Science, University of Science & Technology, Daejeon, South Korea.

The activation of microglia is decisively involved with the neurodegeneration observed in many neuroinflammatory pathologies, such as multiple sclerosis, Parkinson's disease, and Alzheimer's disease. Tectorigenin (TEC) is an isoflavone isolated from various medicinal plants, such as Pueraria thunbergiana Benth, Belamcanda chinensis, and Iris unguicularis. In the present study, the neuroinflammatory effects of TEC were evaluated in both lipopolysaccharide (LPS)-treated BV-2 microglial and mouse models. TEC remarkably inhibited reactive oxygen species (ROS) generation. TEC also inhibits the production and expression of nitric oxide (NO), prostaglandin E2 (PGE2), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) in LPS-stimulated BV-2 cells. In addition, TEC suppressed the LPS-induced activation of nuclear factor-κB (NF-κB), phosphorylation of extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK) to regulate the inflammatory mediators, such as inducible NO synthase (iNOS), cyclooxygenase-2 (COX-2), TNF-α, and IL-6. These results indicate that TEC may inhibit neuronal inflammation through the downregulation of inflammatory mediators, including iNOS, COX-2, TNF-α, and IL-6 by suppressing NF-κB/ERK/JNK-related signaling pathways. Furthermore, cotreatment with TEC and ERK inhibitor SCH772984 or JNK inhibitor SP600125 suppressed the overproduction of LPS-induced NO production in BV-2 cells. Consistent with the results of in vitro experiments, an LPS-induced brain inflammation mouse model, administration of TEC effectively decrease the levels of malondialdehyde, iNOS in hippocampus, and prevented increases in the levels of TNF-α and IL-6 in the serum. TEC showed marked attenuation of microglial activation. Finally, TEC inhibited protein expression of toll-like receptor 4 and myeloid differentiation factor 88 in LPS-activated BV-2 microglia and mouse models. Taken altogether, the cumulative findings suggested that TEC holds the potential to develop as a neuroprotective drug for the intervention of neuroinflammatory disorders.

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**Effects of Muscle Function and Limb Loading Asymmetries on Gait and Balance in People With Multiple Sclerosis.**

Rudroff T(1)(2), Proessl F(1).

Author information:  
(1)Department of Health and Exercise Science, Colorado State University, Fort Collins, CO, United States.  
(2)Department of Radiology, University of Colorado School of Medicine, Aurora, CO, United States.

People with MS (PwMS) often have a more- and less-affected side of the body which results in a variety of asymmetries, including measures of power, strength, muscle activity, and limb loading. Though many studies have identified asymmetries, their impact on gait and balance in PwMS is currently unclear. In this mini-review we first summarize previous findings of asymmetries in muscle function and limb loading and their impact on gait and balance in PwMS. We then provide potential explanations for this lack of consistency in the current literature, and propose study guidelines to improve future lower limb asymmetry studies. Making use of a unified approach to study lower limb asymmetry may then provide more clarity regarding their impact on mobility, specifically gait and balance, in PwMS.

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**Stability of Mental Toughness, Sleep Disturbances, and Physical Activity in Patients With Multiple Sclerosis (MS)-A Longitudinal and Pilot Study.**


Author information:  
(1)Center for Affective-, Stress- and Sleep Disorders, Psychiatric Clinics (UPK), University of Basel, Basel, Switzerland.  
(2)Sleep Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran.  
(3)Department of Psychology, Education & Psychology Faculty, University of Isfahan, Isfahan, Iran.  
(4)Isfahan Neurosciences Research Center, Alzahra Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.  
(5)Sport Science Section, Department of Sport, Exercise and Health, University of Basel, Basel, Switzerland.  
(6)Kliniken Valens, Valens, Switzerland.  
(7)Kermanshah University of Medical Sciences (KUMS), Sleep Disorders Research Center and Substance Abuse Prevention Research Center, Kermanshah, Iran.

Background: Previous research of patients with multiple sclerosis (MS) focused prevalently on fatigue, depression, and cognitive dysfunction during the clinical course. By contrast, research on the longer-term characteristics of physical activity (PA), psychological functioning, and sleep problems is scarce. The aims of the present study were therefore to examine changes in PA, mental toughness (MT) as a proxy of psychological functioning, and sleep disturbances over a 2-year period of time after disease onset. Methods: A total of 18 patients with diagnosed MS (mean age: M = 34.29 years) took part in this longitudinal study. First, 1-4 weeks after the first symptoms, a neurologist diagnosed the MS. Second, they completed a series of questionnaires covering socio-demographic data, PA, MT, and sleep disturbances. Third, the same questionnaires were completed again 2 years later (follow-up). Last, a neurologist assessed the degree of disability with the Expanded Disability Status Scale (EDSS). Results: Two years after MS onset, patients had lower levels of vigorous PA, but no statistically significant changes in moderate PA were observed. Further, walking time increased and sedentary time decreased. Patients with sleep disturbances at disease onset also reported poor sleep 2 years later. MT scores remained stable over time. EDSS scores worsened, though, change in EDSS was not associated with PA, MT, or sleep. Conclusions: Two years after disease onset, patients with MS reported similar MT levels and sleep disturbances. PA shifted from vigorous PA toward walking and a less sedentary lifestyle, while moderate PA remained unchanged. The pattern of results of the present pilot study suggests that at the early stage of the MS course, there is no obstacle for being physically active, nor did sleep and MT as a proxy of psychological functioning decrease in a substantial way.

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**Pulmonary Arterial Hypertension in Patient Treated for multiple sclerosis with 4aminopyridine.**


Author information: (1)Département de pneumologie, CHRU de Nancy, rue du Morvan, 54500, Vandœuvre-lès-Nancy, France. (2)Centre Régional de Pharmacovigilance, CHRU de Nancy, Hôpital Central, 29, avenue du Maréchal de Lattre de Tassigny, Nancy, France. (3)Inserm, U1116; Université de Lorraine, Nancy, France.

4-aminopyridine (4-AP) is a recent treatment indicated to improve walking in patient with multiple sclerosis. We report the first case of pulmonary arterial hypertension (PAH) that we attribute to the use of 4-AP. A 64-year-old woman with multiple sclerosis presented with dyspnea. After excluding other secondary causes of pulmonary hypertension, a diagnosis of severe PAH due to 4-AP was made based on right heart catheterization. History revealed that the dyspnea began with the initiation of 4-AP. After discontinuation of 4-AP therapy and initiation of ambrisentan and tadalafil, dyspnea and pulmonary arterial pressure have improved significantly and one specific PAH-treatment was stopped. 4-AP is an outward rectifying potassium channel blocker with a vasoconstrictor effect in animal’s pulmonary artery. According to the chronological sequence of events, the lack of other etiology and its pharmacological plausibility, 4-AP is highly suspected to have induced our patient's PAH. This article is protected by copyright. All rights reserved.

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**Cervical dysplasia in a patient with multiple sclerosis treated with natalizumab.**

Durrieu G(1), Dardonville Q(1), Clanet M(2), Montastruc JL(1).

Author information: (1)Service de Pharmacologie Médicale et Clinique, Centre Midi-Pyrénées de Pharmacovigilance, de Pharmacocépidémiologie et d'Informations sur le Médicament, Pharmacopôle Midi-Pyrénéennes, INSERM, UMR 1027, CIC INSERM 1436, Toulouse, France. (2)Service de Neurologie, Centre Hospitalier Universitaire, Toulouse, France.

We describe one report of a cervical dysplasia in a patient receiving natalizumab for Multiple Sclerosis. Other cases were identified in the WHO's global individual case safety report (ICSR) database, Vigibase®. These data underline the importance of monitoring HPV infection in patients with MS treated by natalizumab. This article is protected by copyright. All rights reserved.

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[Chronic diseases in neuromotor rehabilitation medicine.]

[Article in Italian; Abstract available in Italian from the publisher]


Author information: (1)Dipartimento di Scienze Clinico-Chirurgiche, Diagnostiche e Pediatriche, Università degli Studi di Pavia, Pavia. (2)Unità Neuroriabilitazione e Spinale, ICS Maugeri SPA SB, Istituto di Pavia, IRCCS, Pavia. (3)Centro Studi Attività Motorie, ICS Maugeri SPA SB, Istituto di Pavia, IRCCS, Pavia. (4)Scuola di Specializzazione in Medicina Fisica e Riabilitativa, Dipartimento di Scienze Clinico-Chirurgiche, Diagnostiche e Pediatriche, Università degli Studi di Pavia, Pavia.

OBJECTIVES: Chronic diseases are a major problem, whose importance is nowadays raising up. Up to 86% of deaths are directly related to chronic diseases in Europe as they represent large amount of total diseases, with a major impact on global health spending. METHODS: Patients suffering from heterogeneous disabilities (such as Parkinson's disease, stroke, multiple sclerosis, osteoporosis, osteoarthritis) often show an interaction between the main disease and comorbidity and multimorbidity. RESULTS: Therefore, the complicate interaction between all these ailments must be faced following specific care pathways. Within the latter ones, pharmacological, physical/cognitive and other (surgical and non-surgical) treatments should be reconciled in order to produce a synergic effect to counteract patient's clinical problems. CONCLUSIONS: Finally, neuromotor rehabilitation medicine should not only be considered as a step following the acute phase but also as an effective tool of secondary and tertiary prevention aimed to avoid relapses and re-hospitalization as well as to improve patient's quality of life.

Publisher: Le malattie croniche rappresentano un problema di notevoli dimensioni, attualmente in crescita. Si stima che in Europa siano responsabili dell'86% delle morti e che abbiano grande incidenza sulla spesa sanitaria globale. Nell'individuo affetto da malattie di frequente riscontro in riabilitazione neuromotoria (malattia di Parkinson, ictus, sclerosi multipla, osteoporosi, osteoartrosi) è spesso presente un'interazione tra la malattia di base e le comorbidità e le multimorbidità. La conseguente sovrapposizione di condizioni cliniche differenti richiede la creazione di specifici percorsi diagnostici terapeutici assistenziali al cui interno i trattamenti farmacologici, con esercizi fisici e cognitivi e di tipo diverso (chirurgici e non) non devono tra loro confliggere ma essere "correlati" cioè compatibili tra loro e sinergici pure nella loro diversità. Infine la medicina riabilitativa neuromotoria va considerata non solo come atto successivo alla fase acuta ma anche come valido strumento di prevenzione secondaria e terziaria al fine di ridurre il numero e la durata dei ricoveri in strutture per acuti e di migliorare la qualità di vita del paziente. Copyright© by Aracne Editrice, Roma, Italy.

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Conflict of interest statement: The authors of this article have no conflict of interests to disclose.
Psychiatric comorbidity increases mortality in immune-mediated inflammatory diseases.

Marrie RA(1), Walld R(2), Bolton JM(3), Sareen J(3), Patten SB(4), Singer A(5), Lix LM(6), Hitchon CA(7), El-Gabalawy R(8), Katz A(9), Fisk JD(10), Bernstein CN(7); CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease.

Author information: (1)Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. Electronic address: rmarrie@hsc.mb.ca. (2)Manitoba Centre for Health Policy, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. (3)Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. (4)Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Canada. (5)Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. (6)Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. (7)Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. (8)Department of Clinical Health Psychology, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; Department of Anesthesia and Perioperative Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. (9)Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; Manitoba Centre for Health Policy, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada; Department of Family Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada. (10)Departments of Psychiatry, Psychology & Neuroscience, and Medicine, Dalhousie University, Halifax, Canada.

OBJECTIVE: We determined the association between any common mental disorder (CMD: depression, anxiety disorder, bipolar disorder) and mortality and suicide in three immune-mediated inflammatory diseases (IMID), inflammatory bowel disease (IBD), multiple sclerosis (MS) and rheumatoid arthritis (RA), versus age-, sex- and geographically-matched controls. METHODS: Using administrative data, we identified 28,384 IMID cases (IBD: 8695; MS: 5496; RA: 14,503) and 141,672 matched controls. We determined annual rates of mortality, suicide and suicide attempts. We evaluated the association of any CMD with all-cause mortality and suicide using multivariable Cox regression models. RESULTS: In the IMID cohort, any CMD was associated with increased mortality. We observed a greater than additive interaction between depression and IMID status (attributable proportion 5.2%), but a less than additive interaction with anxiety (attributable proportion -13%). Findings were similar for MS and RA. In IBD, a less than additive interaction existed with depression and anxiety on mortality risk. The IMID cohort with any CMD had an increased suicide risk versus the matched cohort without CMD. CONCLUSION: CMD are associated with increased mortality and suicide risk in IMID. In MS and RA, the effects of depression on mortality risk are greater than associations of these IMID and depression alone.

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Modulation in miR-200a/SIRT1 axis is associated with apoptosis in MPP+-induced SH-SY5Y cells.

Salimian N(1), Peymani M(2), Ghaedi K(3), Esfahani MHN(4).

Author information: (1)Department of Biology, Faculty of Basic Sciences, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran. (2)Department of Biology, Faculty of Basic Sciences, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran. (3)Department of Biology, Faculty of Sciences, University of Isfahan, Isfahan, Iran; Department of Cellular Biotechnology at Cell Science Research Center, Royan Institute for Biotechnology, ACECR, Isfahan, Iran. (4)Department of Cellular Biotechnology at Cell Science Research Center, Royan Institute for Biotechnology, ACECR, Isfahan, Iran.

Previous studies have shown that miR-200a is markedly deregulated in various neurodegenerative disorders including Alzheimer's disease (AD), Multiple Sclerosis (MS) and PD. Furthermore, studies have shown the key role of miR-200a on expression of SIRT1 and apoptosis. Therefore, we hypothesized that miR-200a/SIRT1 axis should have a crucial role in apoptosis of DA neurons. In this study, human SH-SY5Y cells were treated with MPP+ and expression of miR-200a, SIRT1 and its target genes were assessed. Our results confirmed that expression of miR-200a significantly up-regulated during treating of human SH-SY5Y cells with MPP+ in order to induce oxidative stress and apoptosis. Additionally, transcript level of SIRT1 in these cells showed significant down-regulation confirming that SIRT1 is indeed decreased due to miR-200a up-regulation during apoptosis. Moreover, expression of P53, FOXO1 and BCL2 were modulated. In this study, we indicated that miR-200a/SIRT1 axis directly correlates with apoptosis and P53 signaling pathway. In conclusion, miR-200a and its target gene, SIRT1, may exert a possible role in induction of apoptosis in DA neurons through regulating P53, apoptosis and FOXO signaling pathways.

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Correction: High resolution HLA analysis reveals independent class I haplotypes and amino-acid motifs protective for multiple sclerosis.


Author information: (1)Center for Genetics, Children's Hospital Oakland Research Institute, Oakland, CA, USA. sjmack@chori.org. (2)University of Minnesota Twin Cities, Minneapolis, MN, USA. (3)Center for Genetics, Children's Hospital Oakland Research Institute, Oakland, CA, USA. (4)Histocompatibility, Immunogenetics & Disease Profiling Laboratory, Stanford Blood Center, Palo Alto, CA, USA. (5)Illumina, San Diego, CA, USA. (6)Department of Neurology, University of California, San Francisco, CA, USA.

Erratum for Genes Immun. 2018 Jan 8: Since the publication of this article, the authors have found that the numbers of patients and controls were reversed. This study included 412 MS patients and 419 controls. This correction applies to the Abstract, the final paragraph of the Introduction, and the first paragraph of the Materials and Methods. This was entirely a reporting error and does not impact the Results or Conclusions.

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Secondary findings from next-generation sequencing: what does actionable in childhood really mean?

Richer J(1), Laberge AM(2)(3).

Author information: (1)Department of Medical Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada. (2)Department of Pediatrics, Université de Montréal, Montréal, Quebec, Canada. anne-marie.laberge.hsj@ssss.gouv.qc.ca. (3)Medical Genetics Division and Research Center, Centre Hospitalier Universitaire Sainte-Justine, Montréal, Quebec, Canada. anne-marie.laberge.hsj@ssss.gouv.qc.ca.

PURPOSE: We aimed to assess the definition of actionability of secondary findings in childhood, using a screening framework. METHODS: For 31 disorders on the American College of Medical Genetics and Genomics SF v.2.0 list, World Health Organization screening criteria were applied to assess actionability in childhood. RESULTS: The age of onset was variable. We categorized disorders based on the proportion of cases that presented in childhood: rare (n = 6), fewer than half the cases (n = 9), the majority of cases (n = 12), or unclear (n = 4). The age at initiation of intervention was based on the youngest age of onset reported, not evidence of the benefit of early intervention. For 15 disorders, guidelines were supported by a moderate quality of evidence for at least one recommendation. Only tuberous sclerosis complex had recommendations based on high-quality evidence. All others were based on evidence of low or very low quality. CONCLUSION: We propose that actionability in childhood should be based on the proportion of cases that manifest in childhood and the quality of the evidence supporting intervention recommendations. Ideally, disclosure in childhood would be limited to disorders for which a majority of cases present in childhood and for which interventions are supported by evidence of at least moderate quality (i.e., multiple endocrine neoplasia type 2, retinoblastoma, tuberous sclerosis complex, Marfan syndrome, and Wilson's disease).

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[MODERN APPROACHES TO THE TREATMENT OF MULTIPLE SCLEROSIS (REVIEW AND CLINICAL CASE)].

[Article in Russian]

Khamidulla A(1), Kabdrrakhmanova G(1), Utepaliyeva A(1), Darin D(1), Urasheva Z(1).

Author information: (1)West Kazakhstan Marat Ospanov State Medical University, Actobe, Kazakhstan.

Multiple sclerosis is a chronic dysimmune neurodegenerative disease of the central nervous system, that affects people of working age and inevitably leads to disability. Treatment of the disease is one of the urgent problems of modern clinical neurology, which is explained by the variety of clinical variants of the flow, the lack of an effective method of treatment. This article is devoted to a review of modern approaches to the issues of etiology, pathogenesis and treatment of multiple sclerosis. Also, the classification of multiple sclerosis depending on the course of the disease, data on modern approaches to the treatment of multiple sclerosis, the criteria for the appointment of differentiated therapy depending on the course of the disease with the use of Disease-Modifying Drugs (DMDs) are given. The main strategies for the use of DMDs are described: escalation and de-escalation. The authors of the article presented a clinical case of observation and treatment of a patient with a remitting-relapsing type of multiple sclerosis with a rapid transformation to the secondary-progressive course. The analysis of the dynamics of clinical manifestations with the reflection of the degree of progression on the EDSS scale, analysis of the the radiological study data, as well as the analysis of the prescription of the drugs of the first-line and the second-line treatment to this patient during the observation period from 2010 to 2017 are given.

PMID: 29905552
The neuropathology of the adult cerebellum.

Koeppen AH(1).

Author information: (1)Research, Neurology, and Pathology Services, Veterans Affairs Medical Center and Departments of Neurology and Pathology, Albany Medical College, Albany, NY, United States. Electronic address: arnulf.koeppen@med.va.gov.

This chapter summarizes the neuropathologic features of nonneoplastic disorders of the adult cerebellum. Gait ataxia and extremity dysmetria are clinical manifestations of diseases that interrupt the complex cerebellar circuitry between the neurons of the cerebellar cortex, the cerebellar nuclei (especially the dentate nuclei), and the inferior olivary nuclei. The cerebellum is a prominent target of several sporadic and hereditary neurodegenerative diseases, including multiple system atrophy, spinocerebellar ataxia, and Friedreich ataxia. Purkinje cells display selective vulnerability to hypoxia but a surprising resistance to hypoglycemia. A classic toxin that damages the cerebellar cortex is methylmercury, but the most common injurious agent to Purkinje cells is ethanol. Many drugs cause ataxia, but doubts continue about phenytoin. Ischemic lesions of the cerebellum due to arterial thrombosis or embolism cause a spectrum of symptoms and signs, depending on the territory involved. Large hemorrhages have an unfavorable prognosis because they displace critical brainstem structures or penetrate into the fourth ventricle. Fungal infections and toxoplasmosis of the cerebellum, and cerebellar progressive multifocal leukoencephalopathy, have become rarer because of improved control of the acquired immunodeficiency syndrome. Ataxia is a prominent feature of prion disease. Adult-onset Niemann-Pick type C1 disease and Kufs disease may have a predominantly ataxic clinical phenotype. The adult cerebellum is also vulnerable to several leukodystrophies. A rare but widely recognized complication of cancer is paraneoplastic cerebellar degeneration.

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Prion-like mechanisms in amyotrophic lateral sclerosis.

Ayers JI(1), Cashman NR(2).

Author information: (1)Department of Neuroscience, Center for Translational Research in Neurodegenerative Disease (CTRND), University of Florida, Gainesville, FL, United States. (2)Department of Medicine, Centre for Brain Health, University of British Columbia, Vancouver, BC, Canada. Electronic address: neil.cashman@vch.ca.

The prion hypothesis - a protein conformation capable of replicating without a nucleic acid genome - was heretical at the time of its discovery. However, the characteristics of the disease-misfolded prion protein and its ability to transmit disease, replicate, and spread are now widely accepted throughout the scientific community. In fact, in the last decade a wealth of evidence has emerged supporting similar properties observed for many of the misfolded proteins implicated in other neurodegenerative diseases, such as Alzheimer disease, Parkinson disease, tauopathies, and as described in this chapter, amyotrophic lateral sclerosis (ALS). Multiple studies have now demonstrated the ability for superoxide dismutase-1, 43-kDa transactive response (TAR) DNA-binding protein, fused-in sarcoma, and most recently, C9orf72-encoded polypeptides to display properties similar to those of prions. The majority of these are cell-free and in vitro assays, while superoxide dismutase-1 remains the only ALS-linked protein to demonstrate several prion-like properties in vivo. In this chapter, we provide an introduction to ALS and review the recent literature linking several proteins implicated in the familial forms of the disease to properties of the prion protein.

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Patients With Migraine Have Substantial Reductions in Measures of Visual Quality of Life.


Author information: (1)Department of Ophthalmology and Visual Sciences, John A. Moran Eye Center, Salt Lake City, UT, USA. (2)Department of Neurology, University of Utah, Salt Lake City, UT, USA. (3)Division of Epidemiology, Department of Internal Medicine, University of Utah, Salt Lake City, UT, USA. (4)Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, USA. (5)Veterans Affairs Salt Lake City Health Care System, Salt Lake City, UT, USA.

OBJECTIVE: Migraine is associated with several important visual symptoms, during both acute attacks and headache-free intervals. The purpose of this investigation was to use validated vision-related quality of life instruments to assess the effect of migraine on visual quality of life. BACKGROUND: Many migraineurs experience visual aura, increased photophobia during and between headache attacks, and increased symptoms of dry eye with structural changes in corneal nerve endings. Other visual symptoms associated with migraine include positive persistent visual phenomenon (visual snow) and transient vision changes. Previous research looking at the disability associated with migraine has shown that patient-reported quality of life data can be useful in determining the severity of disease burden. Recent published literature has suggested that visual symptoms related to migraine represent a proportionally minor burden to patients, compared to other manifestations of migraine, but no previous studies have assessed how migraine affects visual quality of life.

METHODS: In this cross-sectional quantitative survey, visual quality of life in individuals with chronic and episodic migraine was assessed using the National Eye Institute Visual Function Questionnaire-25, and the 10-item National Eye Institute Visual Function Questionnaire-25 Neuro-Ophthalmic Supplement. Overall headache severity and impact was assessed using the Migraine-specific Quality of Life Questionnaire (Version 2.1) and the Headache Impact Test-6. Participants were recruited from Headache and Neuro-ophthalmology subspecialty clinics. The target sample size was 30 participants per subgroup. The results were compared to those from disease-free controls and to results from other neuro-ophthalmic disease quality of life studies.

RESULTS: Among 29 participants with chronic migraine, vision-specific quality of life scores were all statistically significantly decreased compared to disease-free controls. The National Eye Institute Visual Function Questionnaire-25 median composite score was 85 for chronic migraineurs and 96 for controls (P < .001). The 10-item National Eye Institute Visual Function Questionnaire-25 Neuro-Ophthalmic Supplement median score was 72 for chronic migraineurs and 95 for controls (P < .001). Among 37 participants with episodic migraine, vision-specific quality of life scores were also decreased compared to disease-free controls. In the episodic migraine group, decreases in the National Eye Institute Visual Function Questionnaire-25 scores were not statistically significant (median score 91, P = .01 compared to the control group), but decreases in the 10-item National Eye Institute Visual Function Questionnaire-25 Neuro-Ophthalmic Supplement remained statistically significant (median score 85, P = .003 compared to the control group). Chronic migraineurs had decreased visual quality of life scores compared to those with episodic migraines. Participants with chronic migraine had visual quality of life scores that were as poor as those previously published for patients with other neuro-ophthalmic disorders such as multiple sclerosis, myasthenia gravis, and ischemic optic neuropathy.

CONCLUSIONS: Visual quality of life is significantly adversely affected in migraine sufferers. In fact, patients with chronic migraine may have visual quality of life impacts that are as significant as those associated with other common neuro-ophthalmic disorders. Future studies of the overall disease burden in patients with migraine should include an evaluation of the effects on visual functioning.

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How patients with multiple sclerosis weigh treatment risks and benefits.

Bruce JM(1), Jarmolowicz DP(2), Lynch S(3), Thelen J(1), Lim SL(1), Smith J(1), Catley D(4), Bruce AS(4).

Author information: (1)Department of Psychology and Department of Biomedical and Health Informatics, University of Missouri-Kansas City. (2)Department of Applied Behavior Science, University of Kansas-Lawrence. (3)Department of Neurology, University of Kansas Medical Center. (4)Center for Healthy Lifestyles and Nutrition, Children’s Mercy Hospital.

OBJECTIVE: Although the effectiveness and risks of multiple sclerosis (MS) therapies are established, relatively little is known about how these benefits and risks are perceived and weighed by patients. This risk-benefit trade-off is important for clinicians, industry, and regulators to consider when determining which therapies to develop, approve for clinical use, and recommend to individual patients. The primary objective of the present study was to describe individual differences in how MS patients weigh risks and benefits when making treatment decisions.

METHOD: Two hundred ninety patients with MS completed tasks assessing their willingness to take a hypothetical disease-modifying therapy (DMT) at varying levels of efficacy, side effect probability, and side effect severity. Patients also completed questionnaires assessing MS knowledge, medication beliefs, health care climate, and disease severity.

RESULTS: Patients with a primary progressive course reported increased DMT willingness compared to patients with relapsing-remitting and secondary progressive courses. Patients were less willing to initiate a DMT across a range of efficacies and side effects if they had never taken a DMT, reported more complementary and alternative health beliefs, or reported a history of discontinuing DMTs due to side effects. More MS knowledge was associated with more willingness to initiate a DMT.

CONCLUSIONS: The results represent an initial step in understanding how patients with chronic disease balance the risks and benefits of medication initiation. Extension of this research may have implications for pharmaceutical development, physician-patient interaction, adherence intervention, and disease education.
The capability set for work - correlates of sustainable employability in workers with multiple sclerosis.

van Gorp DAM(1)(2)(3)(4), van der Klink J JL(5), Abma Fl(6), Jongen PJ(6)(7), van Lieshout I(8), Arnoldus EPJ(9), Beenakker EAC(10), Bos HM(11), van Eijk JJL(12), Feron JC(13), Frecuin STFM(14), de Gans K(15), Hengstman GJD(16), Hupperts RMM(17), Mostert JP(18), Pop PHM(19), Verhagen WIM(20), Zemel D(21), Heerings MAP(22), Reneman MF(23), Middelkoop HAM(24)(25), Visser LH(9)(26), van der Heide K(22)(24)(9).

Author information: (1)National Multiple Sclerosis Foundation, Mathenesserlaan 378, Rotterdam, 3023 HB, The Netherlands. dennis.vangorp@phd.uvh.nl. (2)Department of Psychology, Section Health, Medical and Neuropsychology, Leiden University, PO Box 9555, Leiden, 2300 RB, The Netherlands. dennis.vangorp@phd.uvh.nl. (3)Department of Neurology, Elisabeth-TweeSteden Hospital, PO Box 90151, Tilburg, 5000 LC, The Netherlands. dennis.vangorp@phd.uvh.nl. (4)Department of Care Ethics, University of Humanistic Studies, PO Box 797, Utrecht, 3500 AT, The Netherlands. dennis.vangorp@phd.uvh.nl. (5)Tilburg School of Social and Behavioural Sciences, Tranzo Scientific Centre for Care and Welfare, Tilburg University, PO Box 90153, Tilburg, 5000 LE, The Netherlands. (6)Department of Community & Occupational Medicine, University of Groningen, University Medical Centre Groningen, PO Box 30001, Groningen, 9700 RB, The Netherlands. (7)MS4 Research Institute, Ubbersweg 34, Nijmegen, 5522 KJ, The Netherlands. (8)van Lieshout Arbo Advies, PO Box 325, Uden, 5400 AH, The Netherlands. (9)Department of Neurology, Elisabeth-TweeSteden Hospital, PO Box 90151, Tilburg, 5000 LC, The Netherlands. (10)Department of Neurology, Medical Centre Leeuwarden, PO Box 888, Leeuwarden, 8901 BR, The Netherlands. (11)Department of Neurology, St. Anna Hospital, PO Box 90, Geldrop, 5660 AB, The Netherlands. (12)Department of Neurology, Jeroen Bosch Hospital, PO Box 90153, s-Hertogenbosch, 2000 ME, The Netherlands. (13)Department of Neurology, Amphia Hospital, PO Box 90158, Breda, 4800 RK, The Netherlands. (14)Department of Neurology, St. Antonius Hospital, PO Box 2500, Nieuwegein, 3430 EM, The Netherlands. (15)Department of Neurology, Groene Hart Hospital, PO Box 1098, Gouda, 2800 BB, The Netherlands. (16)Department of Neurology, Catharina Hospital, PO Box 1350, Eindhoven, 5602 ZA, The Netherlands. (17)Department of Neurology, Zuyderland Medical Centre, PO Box 5500, Sittard, 6130 MB, The Netherlands. (18)Department of Neurology, Rijnstate Hospital, PO Box 9555, Arnhem, 6800 TA, The Netherlands. (19)Department of Neurology, VieCuri Medical Centre, PO Box 1926, Venlo, 5900 BX, The Netherlands. (20)Department of Neurology, Canisius-Wilhelmina Hospital, PO Box 9015, Nijmegen, 6500 GS, The Netherlands. (21)Department of Neurology, Albert Schweitzer Hospital, PO Box 444, Dordrecht, 3300 AK, the Netherlands. (22)National Multiple Sclerosis Foundation, Mathenesserlaan 378, Rotterdam, 3023 HB, The Netherlands. (23)Department of Rehabilitation Medicine, University Medical Centre Groningen, University of Groningen, PO Box 30.002, Haren, 9750 RA, the Netherlands. (24)Department of Psychology, Section Health, Medical and Neuropsychology, Leiden University, PO Box 9555, Leiden, 2300 RB, The Netherlands. (25)Department of Neurology, Leiden University Medical Centre, PO Box 9600, Leiden, 2300 RC, The Netherlands. (26)Department of Care Ethics, University of Humanistic Studies, PO Box 797, Utrecht, 3500 AT, The Netherlands.

BACKGROUND: The aim of this study was to examine whether work capabilities differ between workers with Multiple Sclerosis (MS) and workers from the general population. The second aim was to investigate whether the capability set was related to work and health outcomes. METHODS: A total of 163 workers with MS from the MS@Work study and 163 workers from the general population were matched for gender, age, educational level and working hours. All participants completed online questionnaires on demographics, health and work functioning. The Capability Set for Work Questionnaire was used to explore whether a set of seven work values is considered valuable (A), is enabled in the work context (B), and can be achieved by the individual (C). When all three criteria are met a work value can be considered part of the individual's 'capability set'. RESULTS: Group differences and relationships with work and health outcomes were examined. Despite lower physical work functioning (U = 4250, p = 0.001), lower work ability (U = 10591, p = 0.006) and worse self-reported health (U = 9091, p ≤ 0.001) workers with MS had a larger capability set (U = 9649, p ≤ 0.001) than the general population. In workers with MS, a larger capability set was associated with better physical work functioning (r = 0.30), work ability (r = 0.25), self-rated health (r = 0.25); and with less absenteeism (r = -0.26), presenteeism (r = -0.31), cognitive/neuropsychiatric impairment (r = -0.35), depression (r = -0.43), anxiety (r = -0.31) and fatigue (r = -0.34). CONCLUSIONS: Workers with MS have a larger capability set than workers from the general population. In workers with MS a larger capability set was associated with better work and health outcomes. TRIAL REGISTRATION: This observational study is registered under NL43098.008.12: ‘Voorspellers van arbeidsparticipatie bij mensen met relapsing-remitting Multiple Sclerose’. The study is registered at the Dutch CCBO register (https://www.toetsingonline.nl). This study is approved by the METC Brabant, 12 February 2014. First participants are enrolled 1st of March 2014.

Dance for the rehabilitation of balance and gait in adults with neurological conditions other than Parkinson's disease: A systematic review.


Author information:  (1)Department of Physical Therapy, University of Toronto, 160-500 University Ave, Toronto, ON, M5G 1V7, Canada. (2)Toronto Rehabilitation Institute, University Health Network, 550 University Ave, Toronto, ON, M5G 2A2, Canada. (3)Rehabilitation Sciences Institute, University of Toronto, 160-500 University Ave, Toronto, ON, M5G 1V7, Canada. (4)Health System Quality and Funding Division, Ontario Ministry of Health and Long-Term Care, 1075 Bay St., Toronto, ON, M5S 2B1, Canada. (5)Department of Respiratory Medicine, West Park Healthcare Centre, 82 Buttonwood Ave, Toronto, ON, M6M 2E6, Canada.

Purpose: To conduct a systematic review that examined the effect of dance interventions on balance, gait and functional mobility outcomes in adults with neurological conditions other than Parkinson's disease.

Methods: A systematic search of relevant databases was conducted. Data extraction and methodological appraisal were performed by two independent authors. Results: Nine studies were included (4 pre-post studies with no control group, 3 case reports, and 2 controlled studies) and results of the methodological quality assessment ranged from poor to good. Study groups included stroke, multiple sclerosis, spinal cord injury, and Huntington's disease. Dance interventions varied in frequency, type and duration, and only 1 study reported intensity. Study dropout rates ranged from 20-44%, and 88-100% of dance classes were attended. Only 3 studies mentioned adverse events, of which there were none. A summary of results revealed significant changes in spatiotemporal gait parameters, Berg Balance Scale scores, Timed Up and Go test and six-minute walk test that were similar to or greater than those previously reported in a review of dance for individuals with Parkinson's disease. Conclusions: There is emerging evidence to support the use of dance as a feasible intervention for adults with neurological conditions. Further investigation of the effects of dance with randomized controlled trials using larger sample sizes and better reporting of the intervention, participant tolerance, and adverse events is warranted.

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Down-regulation of RORA gene expression in the blood of multiple sclerosis patients.

Sayad A(1), Salmani T(1), Hemmesi MK(2), Ganji M(1), Ghafouri-Fard S(1), Hatami M(1), Soudyab M(3), Taheri M(1)(4).

Author information:  (1)Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran. (2)School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. (3)Department of Medical Genetics, Mashhad University of Medical Sciences, Mashhad, Iran. (4)Urogenital Stem Cell Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Multiple sclerosis (MS) is an autoimmune disease characterized by recurrent episodes of demyelination and loss of oligodendrocytes. The demyelination process is caused by various subsets of CD4+ T cells with a Th1 and Th17 phenotype. The retinoid acid-related orphan receptor A (RORA) is expressed in Th17 cells and promote Th17 differentiation. In this study, we compared the expression level of RORA gene in the blood of 50 relapsing-remitting MS (RRMS) patients who were treated with IFN-β and 50 healthy controls by TaqMan Quantitative Real-Time PCR. We found that RORA expression was significantly down-regulated in MS patients compared with controls (P= 0.006). However, there was no significant correlation between RORA gene expression and Kurtzke Expanded Disability Status Scale (EDSS). Our findings suggest a possible contribution of IFN-β in the downregulation of RORA. In addition, RORA downregulation may be a potential indicator of positive response to interferon beta treatment of multiple sclerosis patients.

DOI: 10.3233/HAB-180341  PMID: 29889063
Thalamic white matter in multiple sclerosis: A combined diffusion-tensor imaging and quantitative susceptibility mapping study.

Bergsland N(1), Schweser F(1)(2), Dwyer MG(1)(2), Weinstock-Guttman B(3), Benedict RHB(3), Zivadinov R(1)(2).

Author information: (1)Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, New York. (2)Center for Biomedical Imaging, Clinical and Translational Science Institute, University at Buffalo, The State University of New York, Buffalo, New York. (3)Jacobs Comprehensive MS Treatment and Research Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, New York.

Thalamic white matter (WM) injury in multiple sclerosis (MS) remains relatively poorly understood. Combining multiple imaging modalities, sensitive to different tissue properties, may aid in further characterizing thalamic damage. Forty-five MS patients and 17 demographically-matched healthy controls (HC) were scanned with 3T MRI to obtain quantitative measures of diffusivity and magnetic susceptibility. Participants underwent cognitive evaluation with the Brief International Cognitive Assessment for Multiple Sclerosis battery. Tract-based spatial statistics identified thalamic WM. Non-parametric combination (NPC) analysis was used to perform joint inference on fractional anisotropy (FA), mean diffusivity (MD) and magnetic susceptibility measures. The association of surrounding WM lesions and thalamic WM pathology was investigated with lesion probability mapping. Compared to HCs, the greatest extent of thalamic WM damage was reflected by the combination of increased MD and decreased magnetic susceptibility (63.0% of thalamic WM, peak p = .001). Controlling for thalamic volume resulted in decreased FA and magnetic susceptibility (34.1%, peak p = .004) as showing the greatest extent. In MS patients, the most widespread association with information processing speed was found with the combination of MD and magnetic susceptibility (67.6%, peak p = .0005), although this was not evident after controlling for thalamic volume. For memory measures, MD alone yielded the most widespread associations (45.9%, peak p = .012 or 76.7%, peak p = .001), even after considering thalamic volume, albeit with smaller percentages. White matter lesions were related to decreased FA (peak p = .0063) and increased MD (peak p = .007), but not magnetic susceptibility, of thalamic WM. Our study highlights the complex nature of thalamic pathology in MS.

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The tale of histone modifications and its role in multiple sclerosis.

He H(1), Hu Z(1), Xiao H(1), Zhou F(1), Yang B(2).

Author information: (1)Department of Neurology, 2nd Xiangya Hospital, Central South University, No 139, Renmin Road, Changsha, Hunan Province, China. (2)Department of Neurology, 2nd Xiangya Hospital, Central South University, No 139, Renmin Road, Changsha, Hunan Province, China. yangbinbin@csu.edu.cn.

Epigenetics defines the persistent modifications of gene expression in a manner that does not involve the corresponding alterations in DNA sequences. It includes modifications of DNA nucleotides, nucleosomal remodeling, and post-translational modifications (PTMs). It is becoming evident that PTMs which act singly or in combination to form "histone codes" orchestrate the chromatin structure and dynamic functions. PTMs of histone tails have been demonstrated to influence numerous biological developments, as well as disease onset and progression. Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating and neurodegenerative disease of the central nervous system, of which the precise pathophysiological mechanisms remain to be fully elucidated. There is a wealth of emerging evidence that epigenetic modifications may confer risk for MS, which provides new insights into MS. Histone PTMs, one of the key events that regulate gene activation, seem to play a prominent role in the epigenetic mechanism of MS. In this review, we summarize recent studies in our understanding of the epigenetic language encompassing histone, with special emphasis on histone acetylation and histone lysine methylation, two of the best characterized histone modifications. We also discuss how the current studies address histone acetylation and histone lysine methylation influencing pathophysiology of MS and how future studies could be designed to establish optimized therapeutic strategies for MS.

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[The role of MRI in measuring the effectivity of disease modifying treatments II].
[Article in Hungarian; Abstract available in Hungarian from the publisher]
Author information: (1)Szegedi Tudományegyetem, Neurológiai Klinika, Szeged. (2)Szegedi Tudományegyetem, Radiológiai Klinika, Szeged. (3)MTA-SZTE, Idegtudományi Kutatócsoport, Szeged. The paraclinical examinations, principally the MRI have an increasing significance in the diagnosis of multiple sclerosis. However, MRI markers also have a prominent role in monitoring of the disease-course and activity, and also in the planning of possible therapeutic changes. In accordance with previously published international guidelines, in this article we propose a protocol for the monitoring the treatment efficacy in multiple sclerosis. This could be the basis of a consensus based guideline to be implemented in Hungary.
Publisher: A sclerosis multiplex diagnosztikájában egyre kiemeltebb szerepet kapnak a paraklinikai, elsősorban az MR-vizsgálatok. Azonban az MR-markereknek ezen túl kiemelt szerepük van még a betegség lefolyása, a betegségaktivitás monito-rizálásában, valamint az esetleges terápiaváltás megtervezésében is. Ebben az ajánlásban a sclerosis multiplex kezelése hatékonyságának monitorizálására teszünk javaslatot a korábban publikált nemzetközi irányelveknek megfelelően. DOI: 10.18071/isz.71.0081  PMID: 29889466

[The role of MRI in measuring the effectiveness of disease modifying treatments I].
[Article in Hungarian; Abstract available in Hungarian from the publisher]
Author information: (1) Szegedi Tudományegyetem, Neurológiai Klinika, Szeged. (2) Szegedi Tudományegyetem, Radiológiai Klinika, Szeged. (3) MTA-SZTE, Idegtudományi Kutatócsoport, Szeged. MRI has a significant role in the diagnosis of multiple sclerosis. The newer and newer treatment options of the disease make it necessary to monitor the effectiveness of the therapy. Besides the clinical signs (clinical relapses and progression), the different MRI parameters can also reflect the disease activity. In our current article we summarize those MRI markers, which best predict the long-term disability, based on the international standards.
Publisher: Az MRI szerepe a sclerosis multiplex diagnosztikájában kiemelt jelentőségű. Az újabb és újabb kezelési lehetőségek a terápia hatékonyságának monitorizálását is szükségessé teszik. A klinikai tünetek (relapszusok és az állapot prog-rezzsódja) mellett a különböző MR-paraméterek is szerepet kapnak a betegségaktivitás mérésében. Ebben a közleményben a nemzetközi ajánlások alapján összefoglaljuk azokat az MR-markereket, melyek előre tudják jelezni a hosszú távú rokkantságot. DOI: 10.18071/isz.71.0077  PMID: 29889465
Multiple sclerosis (MS) is a rare disease of the central nervous system considering the total population, the prevalence in Hungary is 83.9/100,000. The first MS registry was established in Denmark in the middle of the 1950’s. This was followed by the establishment of several national, then international databases with the number of enrolled patients in the hundred-thousands. At the beginning, the primary goal of the registries were the epidemiological surveys, focusing on the number of patients, the prevalence, the incidence, the mortality and the co-morbidity. As of today, however, with the rapid advancement and development of new disease modifying therapies (DMT) with different effectiveness and adverse reactions, the therapeutic use of the registries became even more essential: the modern, up-to-date, well established registries become integral part of the DMT’s’ monitoring. The Multiple Sclerosis Registry of Szeged was first established as a “paper-based” database, then, in 2012, it was upgraded to an electronic, easily contactable and usable internet-based registry. As of today, it contains the socio-demographic and clinical data of more than 600 patients; we constantly add new patients as well as keep the registry up-to-date with the refreshment of old patients’ data. Aside from the “classical” clinical data, it can be used for the recording and assessment of the MRI scans and the data on psychopathological and quality of life assessments, which are becoming more and more important in everyday MS management. The establishment of the internet-based registry incredibly helped both the monitorization of the effectiveness of DMTs, and the success of the new epidemiological and psychopathological surveys.

Publisher: A sclerosis multiplex (SM) a teljes populáció tekintetében ritka megbetegedés, magyarországi prevalenciája 83,9/100 000. Az első SM-regisztert az 1950-es évek közepén Dániában hozták létre, melyet világszerte először nemzeti, majd nemzetközi, akár 100 000-es nagyságrészú beteg adatait tartalmazó regiszterek megszületése követett. A regiszterek elsődleges célja korábban az epidemiológiai adatok (betegszám, prevalencia, incidencia, mortalitás, kísérő betegségek) meghatározása volt. Napjainkra az SM kezelésére használt gyógyszerek számának folyamatos növekedése, a hatásosság és a mellékhatásprofilok különbözősége a terápiás regiszterek használatát is nélkülözhetetlenné tette: egy-egy betegségmódosító kezelés (DMT) monitorozása elkötelezetten vált a korszerű, pontosan vezetett, folyamatosan frissített elektronikus adatbázisok nélkül. A Szegedi Sclerosis Multiplex Regiszter 1993-ban „papíralapon” jött létre, melyet 2012-ben elektronikus, internetes felületről könnyen elérhető és frissíthető adatbázissá alakítottunk. Jelenleg több mint 600 beteg szociodemográfiai és klinikai adatait tartalmazza és a regiszter folyamatosan bővítiük az új betegek adataival és a régiek frissítésével. Lehetőséget nyújt a „klasszikus” klinikai adatok mellett a képalkotó (MRI) és az egyre fontosabbá váló pszichopatológiai és életminőség-vizsgálatok eredményeinek rögzítésére és elemzésére. Az elektronikus regiszter létrejötté nagyban elősegítette mind a terápiák monitorozását, mind az új epidemiológiai és pszichopatológiai vizsgálatok sikereségét.

DOI: 10.18071/isz.70.0301  PMID: 29870621
Alemtuzumab offers a great option as either a first line treatment or as escalation therapy for patients with a highly active disease. The efficacy of alemtuzumab was proven in two phase III trials (CARE-MS I, II), where it was compared to subcutaneous interferon b-1a, administered three times weekly. In both studies alemtuzumab was superior to subcutaneous interferon b-1a in terms of relapse rate reduction, in all scouted MRI parameters. In the CARE-MS II trial it was found superior in terms of progression slowing. In the studies' first 2 years 32% and 39% of the alemtuzumab treated patients managed to achieve the NEDA-3 state (data from CARE-MS II and I respectively). At the end of the 4 year extension of both studies these numbers have increased to 60% and 55% respectively. The aim of our synopsis is to suggest neurologists an evidence based guideline, a therapy algorithm to be used when they give their MS patients the very best, personalised treatment, and also to appoint the recently introduced alemtuzumab to its proper place in the algorithm.

Publisher: A sclerosis multiplex (SM) krónikus, központi idegrendszeri gyulladásal és demyelinisatióval járó autoimmun, neurodegeneratív megbetegedés. Az SM betegség természetes lefolyását tekintve heterogén. Változatos tünettanának köszönhetően megjósolhatatlan formában és mértékben befolyásolja a betegek fizikai és kognitív állapotát. Az SM terápiájában napjainkban zajlik egy paradigmaváltás, melynek kritériumokat; azaz MRI paraméterekben (CARE-MS I, II) szignifikánsan hatásosabbak bizonyult, mint az interferonkészítmény. Az alemtuzumabot. DOI: 10.18071/isz.70.0371  PMID: 29870645

[Experience with natalizumab-treatment at Semmelweis University].

[Article in Hungarian; Abstract available in Hungarian from the publisher]

Gombos B (1)(2), Iljicsov A (1), Barsi P (3), Hegedüs K (1), Simó M (1).
Author information: (1)Semmelweis Egyetem, Neurologiai Klinika, Budapest. (2)Nyíró Gyula Kórház - OPAI, Neurologiai Osztály, Budapest. (3)Semmelweis Egyetem, MR Kutatóközpont, Budapest.

Multiple sclerosis is an autoimmune demyelinating disorder of the central nervous system. During the last two decades, numerous disease modifying drugs have been introduced for the treatment of the relapsing-remitting form of the disease. Since 2010, natalizumab (NTZ) treatment has been used as a second-line therapy for patients with breakthrough disease. In comparison to conventional immunomodulant drugs, NTZ has a more specific effect in that it prevents the entry of immune cells into the central nervous system without interfering with systemic immune response. The efficacy and the safety of NTZ have been confirmed by several studies. The most severe side-effect of NTZ is progressive multifocal leukoencephalopathy, which has been associated with an increased incidence in patients with anti-JCV antibody positivity, and in those who have been undergoing NTZ treatment for over two years and who have received prior immunosuppressive therapy. In the present study, our experience with natalizumab treatment of 37 patients at the Department of Neurology of Semmelweis University during the last 6 years is presented. We have observed a significant decrease of disease activity in our patients; in many cases the disease has become inactive both clinically (36/37) and radiologically (34/37). The patients' quality of life has improved significantly during the treatment. With the literature, we confirm that NTZ is a highly effective treatment in a carefully selected patient group, and can be administered without significant inconvenience to the patient.

Multiple Sklerose: Veröffentlichungen Juni 2018

[Is second-line immunomodulatory treatment effective in multiple sclerosis?]

[Article in Hungarian; Abstract available in Hungarian from the publisher]


Background and purpose: Natalizumab is the first evidence based monoclonal antibody, which was launched for treatment in relapsing remitting multiple sclerosis in Hungary in 2010. Standardized follow-up is required to use it. Methods: Our aim was to evaluate the efficacy and to monitor the safety of natalizumab treatment by using an electronic database established for MS registry. Clinical activity was measured by annual relapse rates, functional status of patients measured by EDSS and MFSC. Radiological activity was evaluated by standard MRI protocol. Data, results of MS patients and side effects of natalizumab treatment were recorded in iMed software. Results: 31 patients started the natalizumab treatment after 6.5±5.8 years from the onset of MS. The efficacy of treatment was evaluated after a mean of 67 (min: 14 max: 128) infusions in December 2016. The drop-out rate was low, due to the presence of neutralising antibodies in one case, pregnancy in two cases and development of malignant disease in one case which was not related to the natalizumab treatment. The treatment was well tolerated with excellent compliance without serious side effects. The annual relapse rate reduced from a mean of 1.7 to 0.03 (p<0.000001) in the first 12 months of treatment compared to the pretreatment 12 month activity, and it stayed at low level during the whole follow up. EDSS was stable or improved with an exception of two cases. In 23 subjects (77%) lack of new/enlarging T2 lesions and lack of gadolineum-enhancing lesions on MRI were observed. 18 patients (60%) had no evidence of disease activity (NEDA-3). PASAT test improved in most of the cases.

Conclusion: The natalizumab therapy was very effective in all cases including those patients who had active disease under the previous immunomodulatory treatment.

A new theory on autoimmunity with reference to multiple sclerosis.

Nexo BA(1).

Author information:  (1)Department of Biomedicine, Aarhus University, Vilhelm Meyers Alle 4, DK-8000, Aarhus C, Denmark. nexo@biomed.au.dk.

Recent genetic evidence points towards endogenous retroviruses as playing a pivotal role in the causation of multiple sclerosis and possibly other autoimmune diseases. We discuss various ways in which this association could be brought about. Specifically, we suggest that two endogenous retroviruses, HERV-Fc1 and HERV-K13, on chromosomes X and 19, respectively, contribute to the development of autoimmune T cells by transforming them in multiple sclerosis. Partially overlapping sets of endogenous retroviruses may play a role in other autoimmune diseases. If this theory holds true, many scientists may have looked for viruses in the wrong tissue. It would also explain why lymphocyte-suppressive agents suppress multiple sclerosis.

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Immunomodulatory function of Treg-derived exosomes is impaired in patients with relapsing-remitting multiple sclerosis.

Azimi M(1), Ghabaei M(2), Moghadasi AN(3), Noorbakhsh F(1), Izad M(4)(5).

Author information:  (1)Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Poorsina St., 16 Azar St., Enghelab Ave., Tehran, Iran. (2)Department of Neurology, Iranian Center of Neurological Research, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran. (3)MS Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran. (4)Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Poorsina St., 16 Azar St., Enghelab Ave., Tehran, Iran. izadm@sina.tums.ac.ir. (5)MS Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran. izadm@sina.tums.ac.ir.

Multiple sclerosis (MS) is an autoimmune disease which is characterized by neuroaxonal degeneration in the central nervous system. Impaired function of regulatory T cells (Tregs) is believed to be an underlying pathogenic mechanism in MS. Tregs is able to release exosomes, which contain a considerable amount of protein and RNA. Exosomes are capable of transporting their content to other cells where the released content exerts biological functions. Here, we investigated whether Tregs exosomes of RRMS patients or healthy controls might regulate the proliferation or survival of T lymphocytes. Regulatory T cells derived from MS patients or healthy controls were cultured for 3 days and exosomes were purified from supernatants. Treg-derived exosomes were co-cultured with conventional T cells (Tconv). The percentages of Tconv proliferation and apoptosis were measured. Our findings showed that the percentage of proliferation suppression induced by exosomes in patients compared to healthy controls was 8.04 ± 1.17 and 12.5 ± 1.22, respectively, p value = 0.035. Moreover, the rate of Tconv apoptosis induced by exosome of MS patient was less than healthy controls (0.68 ± 0.12 vs. 1.29 ± 0.13; p value = 0.015). Overall, Treg-derived exosomes from MS patients and healthy controls suppressed the proliferation and induced apoptosis in Tconv. However, the effect of MS-derived exosomes was significantly less than healthy controls. Our results point to an alternative Treg inhibitory mechanism which might be important in immunopathogenesis of MS. Although, the cause of the exosomal defect in MS patients is unclear, manipulation of patients’ Treg-derived exosomes to restore their suppressive activity might be considered as a potential therapeutic approach.

Graphical abstract  .

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Is there an association between dipeptidyl peptidase-4 inhibitors and autoimmune disease? A population-based study.


Author information:  (1)Department of Dermatology, Rambam Health Care Campus, POB 9602, 31096, Haifa, Israel. dr_kridin@hotmail.com. (2)Department of Dermatology, University of California, Irvine, CA, USA. (3)Internal Medicine D and Institute of Endocrinology, Diabetes and Metabolism, Rambam Health Care Campus, Haifa, Israel. (4)Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel. (5)Department of Quality Measurements and Research, Chief Physician's Office, Clalit Health Services, Tel Aviv, Israel. (6)Siaal Research Center for Family Medicine and Primary Care, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.

The association of dipeptidyl peptidase-4 inhibitors (DPP4is) with autoimmune diseases is controversial. While these agents were proposed as a novel therapeutic approach for several inflammatory diseases by blocking T cell proliferation and cytokine production, they were found to trigger inflammatory bowel disease, inflammatory arthritis and bullous pemphigoid. Our objective is to examine the association between DPP4i and autoimmune diseases. This study was conducted as a cross-sectional study utilizing the database of Clalit Health Services. The prevalence of 15 autoimmune-/immune-mediated diseases was compared between patients on DPP4i treatment and age-, sex-, and ethnicity-matched controls. Univariate analysis was performed using chi-square and the Student t test and multivariate analysis was performed using a logistic regression model. The study included 283 patients treated with DPP4i agents and 5660 age-, sex-, and ethnicity-matched diabetic control subjects. The prevalence of Crohn's disease (1.1 vs. 0.3%; odds ratios (OR), 3.56; 95% CI, 1.04-12.21, P = 0.031), psoriasis (2.5 vs. 1.2%; OR, 2.12; 95% CI, 0.99-4.66; P = 0.050), and Hashimoto's thyroiditis (16.6 vs. 12.6%; OR, 1.38; 95% CI, 1.00-1.91; P = 0.049) was significantly higher in patients on DPP4i treatment than in controls. The prevalence of the remaining autoimmune diseases did not differ significantly between DPP4i-treated patients and their matched control subjects. In conclusion, this population-based study demonstrates an association of DPP4i intake with three autoimmune and inflammatory diseases noted to be part of a distinct autoimmune cluster that includes multiple sclerosis, psoriasis, thyroiditis, bullous pemphigoid, and inflammatory bowel disease. Experimental studies are required to define the role of DPP4i in this autoimmune cluster.

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CD93 regulates CNS inflammation in two mouse models of autoimmune encephalomyelitis.


Author information: (1) BIIG, Brain Inflammation and Immunity Group, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK. (2) Centre for Complement and Inflammation Research, Department of Medicine, Imperial College, London, SW72AZ, UK. (3) Complement Biology Group, Institute of Infection and Immunity, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK. (4) Neuropathology Department, Cardiff University School of Medicine, Cardiff, CF14 4XN, UK. (5) GRI EA4517, Immunopathology and infectious disease grouping, University, CHU, and CYROI of La Réunion, 97400, France. (6) Université de La Réunion, CNRS 9192, INSERM U1187, IRD 249, Unité Mixte, Processus Infectieux en Milieu Insulaire Tropical (PIMIT), Plateforme Technologique CYROI, Sainte-Clotte, La Réunion, France. (7) Laboratoire de Biologie, secteur : Laboratoire d'immunologie clinique et expérimentale ZOI (LICE OI), CHU La Réunion site Félix Guyon, St Denis, La Réunion, France.

Microglia and non-professional immune cells (endothelial cells, neurons) participate in the recognition and removal of pathogens and tissue-debris in the injured CNS through major pro-inflammatory processes. However, the mechanisms involved in regulating these responses remain ill-characterised. We herein show that CD93 also known as complement C1qR/AA4 stem cell marker has an important role in the regulation of inflammatory processes. The role of CD93 was evaluated in two models of neuroinflammation. We used the MOG-experimental autoimmune encephalomyelitis (EAE) model and the antibody-dependent EAE (ADEAE) which were induced in wild type and CD93 knockout mice. We found that CD93 was highly expressed by neurons, endothelial cells and microglia (ramified >> amoeboid). Astrocytes and oligodendrocytes did not express CD93. We further observed that CD93 deficient (CD93/-) mice presented a more robust brain and spinal cord inflammation in EAE and ADEAE. Encephalitis in CD93/- was characterized by increased numbers of infiltrating M1 macrophages (CD11c+ CD206-) and amoeboid microglia exhibiting a more activated phenotype (Tomato Lectinhigh, Cox2high). Damage and leakage of the blood brain barrier was increased in CD93/- animals and was associated with a more robust neuronal injury when compared to wild type EAE mice. We propose that CD93 is an important neuro-immune regulator (NIREG) to control CNS inflammation. This article is protected by copyright. All rights reserved.

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Changes in Th17 cells function after nanocurcumin use to treat multiple sclerosis.


Author information: (1)Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; Student's Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran. (2)Stem Cell and Regenerative Medicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran. (3)Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; Aging Research Institute, Tabriz University of Medical Sciences Tabriz, Iran. (4)Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. (5)Departments of Neurology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran. (6)Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran; Stem Cell and Regenerative Medicine Institute, Tabriz University of Medical Sciences, Tabriz, Iran. Electronic address: Mehdi_yusefi@yahoo.com.

BACKGROUND: MS is a chronic inflammatory disease that causes to brain inflammation and Th17 cells are considered to be important in multiple sclerosis pathogenesis. In the current study, we aimed to identify nanocurcumin effects on Th17 cells frequency, cytokines secretion, and expression of transcription factor of patients with relapsing-remitting multiple sclerosis (RRMS). METHODS: In this study we investigated frequency of Th17 lymphocytes; the expression of transcription factor, associated cytokines and the concentration of them in 35 healthy controls, and from 25 patients at baseline and after 6 months of nanocurcumin treatment and also from 25 patients whose received placebo by flowcytometry, real-time PCR and ELISA, respectively. RESULTS: Our analysis revealed that the proportions of Th17 were increased dramatically, along with increases in the levels of IL-17A, IL-23, and RORγt expression in MS patients in compared with healthy control group. Post-treatment evaluation of the nanocurcumin group revealed a significant decrease in Th17 associated parameters such as Th17 frequency (p = 0.029), expression levels of RORγt (p < 0.0001) and IL-17 (p = 0.0044) and also secretion level of IL-17 (p = 0.0011), but IL-23 mRNA expression levels and IL-23 concentration were not influenced by nanocurcumin. However, in the placebo group there is no significant changes in these factors. CONCLUSION: Our study suggests that the increase in proportion of Th17 cells might contribute to the pathogenesis of RRMS. The results of the current work indicated that nanocurcumin is able to restore the dysregulated of Th17 cells in MS patients.

Low-dose naltrexone (LDN): A promising treatment in immune-related diseases and cancer therapy.

Li Z(1), You Y(2), Griffin N(3), Feng J(4), Shan F(5).

Author information: (1)Department of Neurology, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang, Liaoning 110004, China. Electronic address: zli@cmu.edu.cn. (2)Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang, Liaoning 110004, China. (3)Immune Therapeutics, Inc., 37 North Orange Ave., Suite 607, Orlando, FL 32801, USA. Electronic address: Noreen.Griffin@immunetherapeutics.com. (4)Department of Neurology, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang, Liaoning 110004, China. Electronic address: juanfeng@cmu.edu.cn. (5)Department of Immunology, School of Basic Medical Science, China Medical University, No. 77, Puhe Road, Shenyang, Liaoning 110122, China. Electronic address: fpshan@cmu.edu.cn.

Naltrexone, a non-selective antagonist of opioid receptors, is mainly used as rehabilitation therapy for discharged opiate addicts to eliminate addiction in order to maintain a normal life and prevent or reduce relapse. In recent years, there have been some novel and significant findings on the off-label usage of naltrexone. Within a specific dosage window, LDN can act as an immunomodulator in multiple autoimmune diseases and malignant tumors as well as alleviate the symptoms of some mental disorders. The results of increasing studies indicate that LDN exerts its immunoregulatory activity by binding to opioid receptors in or on immune cells and tumor cells. These new discoveries indicate that LDN may become a promising immunomodulatory agent in the therapy for cancer and many immune-related diseases. In this article, we review the pharmacological functions and mechanisms of LDN as well as its clinical therapeutic potential as revealed by our team and other researchers.

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Low-dose naltrexone (LDN): A promising treatment in immune-related diseases and cancer therapy.

Li Z(1), You Y(2), Griffin N(3), Feng J(4), Shan F(5).

Author information: (1)Department of Neurology, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang, Liaoning 110004, China. Electronic address: zli@cmu.edu.cn. (2)Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang, Liaoning 110004, China. (3)Immune Therapeutics, Inc., 37 North Orange Ave., Suite 607, Orlando, FL 32801, USA. Electronic address: Noreen.Griffin@immunetherapeutics.com. (4)Department of Neurology, Shengjing Hospital of China Medical University, No. 36, Sanhao Street, Shenyang, Liaoning 110004, China. Electronic address: juanfeng@cmu.edu.cn. (5)Department of Immunology, School of Basic Medical Science, China Medical University, No. 77, Puhe Road, Shenyang, Liaoning 110122, China. Electronic address: fpshan@cmu.edu.cn.

Naltrexone, a non-selective antagonist of opioid receptors, is mainly used as rehabilitation therapy for discharged opiate addicts to eliminate addiction in order to maintain a normal life and prevent or reduce relapse. In recent years, there have been some novel and significant findings on the off-label usage of naltrexone. Within a specific dosage window, LDN can act as an immunomodulator in multiple autoimmune diseases and malignant tumors as well as alleviate the symptoms of some mental disorders. The results of increasing studies indicate that LDN exerts its immunoregulatory activity by binding to opioid receptors in or on immune cells and tumor cells. These new discoveries indicate that LDN may become a promising immunomodulatory agent in the therapy for cancer and many immune-related diseases. In this article, we review the pharmacological functions and mechanisms of LDN as well as its clinical therapeutic potential as revealed by our team and other researchers.

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USE OF NEUROFEEDBACK AND MINDFULNESS TO ENHANCE RESPONSE TO HYPNOSIS TREATMENT IN INDIVIDUALS WITH MULTIPLE SCLEROSIS: Results From a Pilot Randomized Clinical Trial.

Jensen MP(1), Battalio SL(1), Chan JF(1), Edwards KA(1), Day MA(2), Sherlin LH(3), Ehde DM(1).

Author information: (1)a University of Washington , Seattle , USA. (2)b The University of Queensland , Brisbane , Australia. (3)c Ottawa University , Phoenix , Arizona , USA.

This pilot study evaluated the possibility that 2 interventions hypothesized to increase slower brain oscillations (e.g., theta) may enhance the efficacy of hypnosis treatment, given evidence that hypnotic responding is associated with slower brain oscillations. Thirty-two individuals with multiple sclerosis and chronic pain, fatigue, or both, were randomly assigned to 1 of 2 interventions thought to increase slow wave activity (mindfulness mediation or neurofeedback training) or no enhancing intervention, and then given 5 sessions of self-hypnosis training targeting their presenting symptoms. The findings supported the potential for both neurofeedback and mindfulness to enhance response to hypnosis treatment. Research using larger sample sizes to determine the generalizability of these findings is warranted.

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Molecular Mechanisms of Oligodendrocyte Regeneration in White Matter-Related Diseases.

Ohtomo R(1)(2), Iwata A(3), Arai K(4).

Author information: (1)Neuroprotection Research Laboratory, Departments of Radiology and Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA. ROHTOMO@mgh.harvard.edu. (2)Department of Neurology, The University of Tokyo Graduate School of Medicine, Tokyo 113-8654, Japan. ROHTOMO@mgh.harvard.edu. (3)Department of Neurology, The University of Tokyo Graduate School of Medicine, Tokyo 113-8654, Japan. Iwata-tky@umin.ac.jp. (4)Neuroprotection Research Laboratory, Departments of Radiology and Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA. karai@partners.org.

Even in adult brains, restorative mechanisms are still retained to maintain the microenvironment. Under the pathological conditions of central nervous system (CNS) diseases, several immature cells in the brain would be activated as a compensative response. As the concept of the neurovascular unit emphasizes, cell-cell interactions play important roles in this restorative process. White matter damage and oligodendrocyte loss are representative characteristics for many neurodegenerative diseases. In response to oligodendrocyte damage, residual oligodendrocyte precursor cells (OPCs) initiate their proliferation and differentiation for the purpose of remyelination. Although mechanisms of oligodendrogenesis and remyelination in CNS diseases are still mostly unknown and understudied, accumulated evidence now suggests that support from neighboring cells is necessary for OPC proliferation and differentiation. In this review, we first overview basic mechanisms of interaction between oligodendrocyte lineage cells and neighboring cells, and then introduce how oligodendrogenesis occurs under the conditions of neurodegenerative diseases, focusing on vascular cognitive impairment syndrome, Alzheimer’s disease, and multiple sclerosis.

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**Metabolic Dysfunction and Peroxisome Proliferator-Activated Receptors (PPAR) in Multiple Sclerosis.**

Ferret-Sena V(1), Capela C(2), Sena A(3).

Author information: (1)Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Instituto Universitário Egas Moniz, Campus Universitário, Quinta da Granja, Monte de Caparica, 2819-511 Caparica, Portugal. versusena@egasmoniz.edu.pt. (2)Centro Hospitalar de Lisboa Central, EPE, Hospital de Santo António dos Capuchos, Departamento de Neurociências, Alameda de Santo António dos Capuchos, 1169-050 Lisboa, Portugal. carlos.capela.trabalho@gmail.com. (3)Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Instituto Universitário Egas Moniz, Campus Universitário, Quinta da Granja, Monte de Caparica, 2819-511 Caparica, Portugal. asena@egasmoniz.edu.pt.

Multiple sclerosis (MS) is an inflammatory and neurodegenerative disease of the central nervous system (CNS) probably caused, in most cases, by the interaction of genetic and environmental factors. This review first summarizes some clinical, epidemiological and pathological characteristics of MS. Then, the involvement of biochemical pathways is discussed in the development and repair of the CNS lesions and the immune dysfunction in the disease. Finally, the potential roles of peroxisome proliferator-activated receptors (PPAR) in MS are discussed. It is suggested that metabolic mechanisms modulated by PPAR provide a window to integrate the systemic and neurological events underlying the pathogenesis of the disease. In conclusion, the reviewed data highlight molecular avenues of understanding MS that may open new targets for improved therapies and preventive strategies for the disease.

DOI: 10.3390/ijms19061639  PMID: 29865151


**Somatic Symptoms of Depression and Anxiety in People with Multiple Sclerosis.**

Jones SMW, Salem R, Amtmann D.

Background: People with multiple sclerosis (MS) are at increased risk for depression and anxiety. The symptoms of MS are often similar to the somatic or physical symptoms of depression and anxiety (fatigue, trouble concentrating). This study examined whether MS symptoms and effects biased the assessment of somatic symptoms of anxiety and depression. Methods: People with MS (n = 513) completed a survey about MS symptoms, treatments, and distress. The Patient Health Questionnaire-9 assessed depression, and the patient-report version of the Primary Care Evaluation of Mental Disorders assessed anxiety. Participants were grouped into low versus high MS symptoms based on self-reported symptoms and as high versus low disability by the Expanded Disability Status Scale (EDSS). Groups were compared using differential item functioning analysis. Results: No bias was found on somatic symptoms of depression comparing high versus low MS symptom groups (P > .15) or comparing groups based on EDSS scores (P > .29). Two anxiety symptoms (fatigue and muscle tension) showed bias comparing high versus low MS symptom groups (P < .01) and comparing high versus low groups based on EDSS scores (P ≤ .01). Intraclass correlations suggested a small effect due to bias in the somatic symptoms of anxiety. Conclusions: Somatic symptoms of depression are unlikely to be biased by MS symptoms. However, the use of certain somatic symptoms to assess anxiety may be biased for those with high MS symptoms.

DOI: 10.7224/1537-2073.2017-069  PMCID: PMC5991508 PMID: 29896052

Conflict of interest statement: Dr. Jones received salary from Pacific Rehabilitation Centers in Puyallup, WA, for conducting psychological evaluations (once weekly, July 2016–August 2017). The other authors have no conflicts of interest to disclose.

Short Report: A Pilot Study of a Group Positive Psychology Intervention for Patients with Multiple Sclerosis.


Background: Positive psychology uses targeted activities to increase the frequency and intensity of positive emotional experiences. Positive psychology interventions that increase positive constructs may facilitate adjustment and improve well-being in patients with multiple sclerosis (MS). The primary goal of this study was to assess the feasibility and acceptability of a 5-week group positive psychology intervention for patients with MS. In addition, we examined the utility of the group intervention to increase positive psychological constructs and health-related quality of life (HRQOL). Methods: 11 patients completed 5 weeks of group positive psychology training, one time per week (session duration, 45-60 minutes). Each week, patients completed one of the following positive psychology exercises: gratitude for positive events, personal strengths, gratitude letter, enjoyable and meaningful activities, and remembering past successes. Patients completed patient-reported outcome measures, including measures of positive affect, optimism, depression, anxiety, and HRQOL, at baseline and after 5 weeks. Results: All the participants completed the 5-week group positive psychology intervention, and 82% attended four or more sessions. Improvements in fatigue (vitality) and depression after the group intervention were significant (P = .016 and .049, respectively). There were no statistically significant changes in positive or negative affect, optimism, anxiety, HRQOL, or cognition. Conclusions: The 5-week group positive psychology intervention was feasible and acceptable to patients with MS. A randomized controlled trial is necessary to further explore the effectiveness of the group intervention.

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Conflict of interest statement: Dr. Healy has served as a consultant for Biogen Idec and receives research support from Merck-Serono, Novartis, and Verily Life Sciences. Dr. Chitnis has received personal compensation for advisory board/consulting from Novartis, Bayer, and Biogen and receives financial support for research activities from Merck-Serono, Novartis, and Verily Life Sciences. Dr. Weiner has served as a consultant for Genentech and Tiziana Life Sciences and has received research support from EMD Serono, Miragen Therapeutics, Sanofi, Teva Pharmaceuticals, and Verily Life Sciences. Dr. Huffman's time for scientific input and editing was supported by grants R01HL113272 and R21DK109313 to him from the National Institutes of Health. Dr. Glanz has received research support from Merck-Serono and Verily Life Sciences. Mss. Leclaire, Cecil, LaRussa, and Stuart and Dr. Hemond have no conflicts of interest to disclose.


Social Cognitive Theory Correlates of Physical Activity in Inactive Adults with Multiple Sclerosis.

Uszynski MK, Casey B, Hayes S, Gallagher S, Purtill H, Motl RW, Coote S.

Background: There is a growing body of evidence that physical activity (PA) improves symptoms of multiple sclerosis (MS). Despite the benefits of PA, people with MS are relatively inactive compared with their healthy counterparts. This study investigated associations between social cognitive theory (SCT) constructs and energy expenditure (EE) as an objective measure of PA in a sample of inactive people with MS. Methods: Participants (n = 65) completed several questionnaires and were assessed using standardized outcome measures as part of a cross-sectional analysis of baseline data from a randomized controlled trial (Step it Up). Results: The bivariate correlation analysis indicated that of all SCT constructs, only exercise self-efficacy was significantly correlated with EE (r = 0.297, P = .022). Multiple linear regression analysis found that exercise self-efficacy independently explained 9% of the variance in EE (R2 = 0.088). A model including exercise self-efficacy, exercise goal setting, exercise planning, and exercise benefits explained 17% of the variance in EE (F4,54 = 2.741, P = .038, R2 = 0.169). In this model, only exercise self-efficacy was significantly associated with EE scores (Exercise Self-Efficacy Scale β = .320, P = .016). Conclusions: The constructs of SCT explained little of the variance of objectively measured PA in a sample of inactive people with MS who volunteered for an exercise trial. The only significant variable was exercise self-efficacy, which confirms the importance of enhancing it through PA interventions.

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Conflict of interest statement: The authors have no conflicts of interest to disclose.
Investigation of the Feasibility of an Intervention to Manage Fall Risk in Wheeled Mobility Device Users with Multiple Sclerosis.

Rice LA, Isaacs Z, Ousley C, Sosnoff J.
Background: Falls are a common concern for wheeled mobility device users with multiple sclerosis (MS); however, no evidence-based fall prevention programs have been developed to meet the specific needs of the population. We examine the preliminary feasibility of a fall management intervention in wheeled mobility device users with MS. Methods: Study participants were exposed to an intervention program targeting risk factors for falls, including transfer skills and seated postural control. The feasibility of the program was evaluated by assessing participant perspectives, cost, recruitment rates, study adherence, participant retention, safety, and the ability to collect primary and secondary outcomes, including fall frequency, concerns about falling, transfer quality, and seated postural control. Results: 16 wheeled mobility device users completed the program, which was found to be feasible and was positively evaluated by participants. No adverse events were experienced. After exposure to the intervention, fall frequency significantly decreased (P < .001) and transfer quality (P = .001) and seated postural control (P = .002) significantly improved. No significant differences were found regarding concerns about falling (P = .728). Conclusions: This study examined the feasibility of an intervention program to manage fall risk in wheeled mobility device users with MS. The program was found to be feasible, and preliminary results showed the intervention to be effective in decreasing fall frequency. Additional testing is needed to further examine the efficacy and long-term impact of the intervention. DOI: 10.7224/1537-2073.2016-097 PMCID: PMC5991503 PMID: 29896048

Conflict of interest statement: The authors have no conflicts of interest to disclose.

Target Coping Strategies for Interventions Aimed at Maximizing Psychosocial Adjustment in People with Multiple Sclerosis.

Grech LB, Kiropoulos LA, Kirby KM, Butler E, Paine M, Hester R.
Background: The experience of psychological distress is prevalent in people with multiple sclerosis (MS), including high levels of stress, anxiety, and depression. It has been shown that people with MS use less adaptive coping compared with healthy individuals. This study examined the ability of coping strategies to predict maladaptive and adaptive psychosocial outcomes across areas of stress, depression, anxiety, and quality of life (QOL) in people with MS. Methods: 107 people with MS completed measures of depression (Beck Depression Inventory-II), anxiety (State-Trait Anxiety Inventory), QOL (Multiple Sclerosis Quality of Life-54), stress (Daily Hassles Scale), and coping (COPE inventory). Results: Consistent with expectations, depression, frequency of stress, trait anxiety, and mental health QOL were predicted by adaptive and maladaptive coping styles. Severity of stressful events was predicted by maladaptive, but not adaptive, coping styles. Depression and mental health QOL were most prominently connected to coping use. Emotional preoccupation and venting showed the strongest relationship with poorer psychosocial outcomes, whereas positive reinterpretation and growth seemed to be most beneficial. Conclusions: The results of this study highlight the importance of intervention programs targeting specific coping strategies to enhance psychosocial adjustment for people with MS. DOI: 10.7224/1537-2073.2016-008 PMCID: PMC5991507 PMID: 29896047

Conflict of interest statement: The authors have no conflicts of interest to disclose.

**Effect of Mindfulness Meditation on Personality and Psychological Well-being in Patients with Multiple Sclerosis.**


**Background:** Varied evidence shows that mindfulness-oriented meditation improves individuals' mental health, positively influencing practitioners' personality profiles as well. A limited number of studies are beginning to show that this type of meditation may also be a helpful therapeutic option for persons with multiple sclerosis (MS).

**Methods:** We evaluated the effects of an 8-week mindfulness-oriented meditation training on the personality profiles, anxiety and depression symptoms, and mindfulness skills of a group of patients with MS. A control group of patients with MS not enrolled in any training was also tested.

**Results:** After mindfulness-oriented meditation training, participants in this group (n = 15) showed an increase in character traits reflecting the maturity of the self at the intrapersonal (self-directedness) and interpersonal (cooperativeness) levels. Moreover, increased mindfulness and conscientiousness and decreased trait anxiety were observed in participants after the training.

**Conclusions:** These data support the utility for patients with MS of therapeutic interventions based on mindfulness meditation that may lead to enhanced character and self-maturity.

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Conflict of interest statement: The authors have no conflicts of interest to disclose.


**Introduction of a palliative approach in the care trajectory among people living with advanced MS: perceptions of home-based health professionals.**

Leclerc-Loiselle J(1), Legault A(2).

**Author information:** (1)Lecturer, Faculty of Nursing, Université de Montréal, Montréal, Canada. (2)Associate Professor, Faculty of Nursing, Université de Montréal, Montréal, Canada.

**BACKGROUND:** Even with the desire of home-based health professionals to provide supportive care, the palliative needs of people living with multiple sclerosis (MS) remain unmet.

**AIM:** To describe the perceptions of home-based health professionals concerning the introduction of a palliative care approach in the care trajectory of people living with advanced MS.

**METHOD:** Based on an exploratory qualitative design, focus groups and individual interviews were conducted with nurses, occupational therapists and social workers (n=13 professionals).

**RESULTS:** A palliative care approach was described as a possibility for opening the discussion between the patient and their caregivers about their needs and desires at the end of life. The approach required professionals to be supportive and to adapt their interventions to people living with MS. However, professionals reported difficulties in introducing a palliative care approach.

**CONCLUSION:** Health professionals reported that they feel a palliative care approach for people living with MS is mandatory; however, they do not feel comfortable integrating it systematically into their care.

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**Novel SPG11 Mutations in a Patient with Symptoms Mimicking Multiple Sclerosis.**


**Author information:** (1)Departments of Neurology and Molecular Life Science, Tokai University School of Medicine, Japan. (2)Department of Neurology, Graduate School of Medical Sciences, University of Yamanashi, Japan. (3)Department of Molecular Life Science, Basic Medical Science and Molecular Medicine, Tokai University School of Medicine, Japan.

We describe the cases of two sisters with spastic paraplegia 11 (SPG11). The younger sister developed relapsing lesions in the brain white matter with enhancement during the acute phase that mimicked multiple sclerosis (MS). The elevation of myelin basic protein in the CSF suggested demyelination, but a normal IgG index, the absence of oligoclonal bands, and the ineffectiveness of steroid treatment indicate that an autoimmune mechanism may not have been involved. In these affected sisters, we identified novel compound heterozygous mutations in the SPG11 gene. Our cases indicate the possible existence of a broader phenotypic spectrum of SPG11 mutations.

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**Outer Retinal Assessment Using Spectral-Domain Optical Coherence Tomography in Patients With Alzheimer's and Parkinson's Disease.**


Author information: (1)Ophthalmic Imaging Center, Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio, United States. (2)Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio, United States. (3)Department of Neurology, Cleveland Clinic, Cleveland, Ohio, United States. (4)Lou Ruvo Center for Brain Health, Cleveland Clinic, Cleveland, Ohio, United States. (5)Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, Ohio, United States. (6)Center for Neurological Restoration, Cleveland Clinic, Cleveland, Ohio, United States. (7)Department of Quantitative Health Sciences, Lerner Research Institute, Cleveland, Ohio, United States. (8)Imaging Institute, Cleveland, Ohio, United States.

Purpose: To investigate outer retinal parameters among patients with various chronic neurodegenerative disorders by using spectral-domain coherence tomography (OCT) in a prospective cross-sectional cohort study. Methods: A total of 132 participants were enrolled following a comprehensive diagnostic evaluation with neurologic, neuropsychology, and magnetic resonance imaging volumetric evaluations. Participants were 50 years or older, either diagnosed with Alzheimer's disease (AD) dementia, amnestic mild cognitive impairment (MCI), non-AD dementia, Parkinson's disease (PD), or age- and sex-matched controls. All participants underwent a macular cube scan for both eyes by using the Cirrus 4000 HD-OCT (Zeiss, Oberkochen, Germany). The OCT image with the best quality was selected for further analysis. Outer retinal parameters including ellipsoid zone mapping and outer nuclear layer metrics were evaluated with a novel software platform. Results: One hundred twenty-four eyes of 124 participants with AD dementia (24 eyes), amnestic MCI (22 eyes), non-AD dementia (20 eyes), PD (22 eyes), and age- and sex-matched controls (36 eyes) were included in the analysis. Eight eyes were excluded either due to the presence of macular disease or poor quality of the OCT image. The mean ages of participants were 65.9 ± 8.9 years. The outer retinal thickness measures did not show any statistical significance between the groups. However, ellipsoid zone to retinal pigment epithelium volume correlated with cognitive testing scores in all study participants. Conclusions: There were no identifiable differences in the outer retinal metrics across neurodegenerative disease groups and controls. The relationship between the degree of cognitive impairment and ellipsoid zone to retinal pigment epithelium volume warrants further study.

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**Engineered MBP-specific human Tregs ameliorate MOG-induced EAE through IL-2-triggered inhibition of effector T cells.**

Kim YC(1), Zhang AH(1), Yoon J(1), Culp WE(2), Lees JR(1), Wucherpfennig KW(3), Scott DW(4).

**Author information:** (1)Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. (2)Office of Research, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. (3)Department of Cancer Immunology and Virology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA. (4)Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. Electronic address: david.scott@usuhs.edu.

Expanded polyclonal T regulatory cells (Tregs) offer great promise for the treatment of immune-mediated diseases. Inhibition by Tregs is under the control of the T-cell receptor (TCR). Therefore, we created Tregs with defined antigen specificity, using a recombinant T-cell receptor isolated from a myelin-basic protein specific T-cell clone of a multiple sclerosis (MS) patient (Ob2F3). We expressed this TCR using a retroviral expression vector in human Tregs from peripheral blood. We observed that transduced Tregs were activated in vitro in response to myelin basic protein (MBP) peptide on DR15 antigen-presenting cells (APC) and upregulated Treg markers, Foxp3, LAP and Helios. These engineered MBP-specific Tregs could suppress MBP-specific T effector cells, and were also able to suppress T cells with other specificities after Tregs had been activated through the TCR. Importantly, we showed that these engineered Tregs were able to function effectively in the presence of strong TLR-induced inflammatory signals, and that MBP-specific Tregs ameliorated EAE in myelin oligodendrocyte glycoprotein (MOG)-immunized DR15 transgenic mice. We further demonstrated in vitro that IL-2 produced by neighboring effector T cells activated MBP-specific Tregs, initiating contact-independent suppression to T effectors in local milieu. Mechanistic studies demonstrated that bystander suppression in vivo may involve transfer of soluble mediators, enhanced by cell contact between Tregs and effectors. Taken together, we show that engineered clonal MBP-specific Tregs are able to suppress autoimmune pathology in EAE. This approach may serve as a cellular therapy for MS patients with the common DR15 haplotype that is associated with disease susceptibility.

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**Effect of sensory-motor latencies and active muscular stiffness on stability for an ankle-hip model of balance on a balance board.**

Chumacero E(1), Yang J(2), Chagdes JR(3).

**Author information:** (1)Human-Centric Design Research Lab, Department of Mechanical Engineering, Texas Tech University, Lubbock, TX 79409, USA. (2)Human-Centric Design Research Lab, Department of Mechanical Engineering, Texas Tech University, Lubbock, TX 79409, USA. Electronic address: james.yang@ttu.edu. (3)Department of Mechanical and Manufacturing Engineering, Miami University, Oxford, OH 45056, USA.

To achieve human upright posture (UP) and avoid falls, the central nervous system processes visual, vestibular, and proprioceptive information to activate the appropriate muscles to accelerate or decelerate the body's center of mass. In this process, sensory-motor (SM) latencies and muscular deficits, even in healthy older adults, may cause falls. This condition is worse for people with chronic neuromuscular deficits (stroke survivors, patients with multiple sclerosis or Parkinson's disease). One therapeutic approach is to recover or improve quiet UP by utilizing a balance board (BB) (a rotating surface with a tunable stiffness and time delay), where a patient attempts to maintain UP while task difficulty is manipulated. While BBs are commonly used, it is unclear how UP is maintained or how changes in system parameters such as SM latencies and BB time delay affect UP stability. To understand these questions, it is important that mathematical models be developed with enough degrees-of-freedom to capture the many responses evoked during the maintenance of UP on a BB. This paper presents an ankle-hip model of balance on a BB, which is used to study the combined effect of SM latencies and active muscular stiffness of the ankle and hip joints, and the BB stiffness and time delay on UP stability. The analysis predicts that people with proprioceptive, visual, vestibular loss, or increased SM latencies may show either leaning postures or larger body-sway. The results show that the BB time delay and the visual and vestibular feedback have the largest impact on UP stability.

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Responsiveness of postural performance measures following balance rehabilitation in multiple sclerosis patients.

Negahban H(1), Monjezi S(2), Mehravar M(3), Mostafaee N(4), Shoeibi A(5).

Author information: (1)Department of Physical Therapy, School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran; Orthopedic Research Center, Mashhad University of Medical Sciences, Mashhad, Iran. Electronic address: honegahban@yahoo.com. (2)Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Electronic address: Saeideh.monjezi@yahoo.com. (3)Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. Electronic address: mohammad.mehravar@gmail.com. (4)Department of Physical Therapy, School of Paramedical Sciences, Mashhad University of Medical Sciences, Mashhad, Iran. Electronic address: neda_mostafaee@yahoo.com. (5)School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. Electronic address: shoeiba@mums.ac.ir.

INTRODUCTION: Evaluating responsiveness has an important role in design and interpretation of the interventional studies. The aim was to estimate the responsiveness and minimally important difference (MID) of postural performance measures following balance rehabilitation in patients with Multiple Sclerosis (MS, n = 38).

METHODS: Postural measures were evaluated at baseline and after 4 weeks intervention. Laboratory-based measures were center of pressure parameters. Clinically-based measures were Activities-specific Balance Confidence (ABC), Berg Balance Scale (BBS), Functional Gait Assessment (FGA); and walking measures 2 Minute Walk (2 MW), 10 Meter Timed Walk (10 MTW) and Timed Up and Go (TUG) performed under single and dual-task conditions. To evaluate responsiveness, we calculated the Receiver Operating Characteristics (ROC) and the Area Under the ROC Curve (AUC). The optimal values for the MID were the cutoffs corresponding to the upper left corner of the ROC curve. RESULTS: The AUCs for mean and standard deviation of sway velocity were above the cutoff of 0.50 in most conditions. For the clinically-based measures, the highest AUCs were found for the ABC, and cognitive-2MW, followed by the BBS and 10 MTW. CONCLUSIONS: In this preliminary study, the most appropriate postural performance measures and the MID values for detecting meaningful changes in MS undergoing balance rehabilitation have been provided.

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Brain Lesion Load and Anatomic Distribution in Patients With Juvenile Clinically Isolated Syndrome Predicts Rapidly Advanced to Multiple Sclerosis.

Menascu S(1), Legarda C(1), Miron S(1), Achiron A(1).

Author information: (1) Multiple Sclerosis Institute, Sheba Medical Center, Sackler Faculty of Medicine, Tel Aviv University Israel, Ramat Gan, Israel.

The aim was to assess brain lesion load and anatomical distribution in patients with juvenile clinically isolated syndrome and define magnetic resonance imaging (MRI) variables associated with rapidly advancing to multiple sclerosis. Patients were followed for one year after disease onset. Patients who experienced a second relapse were defined as those who rapidly advanced to multiple sclerosis. In all, 46 juvenile patients with a clinical presentation suggestive of multiple sclerosis were evaluated; 21 with gadolinium-enhancing lesions on initial brain MRI were excluded as they had already fulfilled the diagnosis criteria for multiple sclerosis. A total of 25 patients, 10 males and 15 females (mean ± SE age at onset 15.6 ± 0.6 years), met the definition of clinically isolated syndrome. The presence of a corpus callosum lesion at onset significantly differentiated between sustained clinically isolated syndrome and patients who rapidly advanced to multiple sclerosis.

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Alemtuzumab-induced thyroid dysfunction exhibits distinctive clinical and immunological features.

Pariani N(1), Willis M(2), Muller I(3), Healy S(2), Nasser T(2), McGowan A(1), Lyons G(1), Jones J(4), Chatterjee K(1), Dayan C(3), Robertson N(2), Coles A(4), Moran C(1).

Author information: (1)University of Cambridge Metabolic Research Laboratories, Wellcome Trust-MRC, Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, United Kingdom. (2)Department of Neurology, Division of Psychological Medicine and Clinical Neuroscience, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, United Kingdom. (3)Thyroid Research Group, Cardiff University, University Hospital of Wales, Heath Park, Cardiff, United Kingdom. (4)Department of Clinical Neurosciences, Addenbrooke's Hospital, Cambridge, United Kingdom.

Context: Alemtuzumab, a highly effective treatment for multiple sclerosis (MS), predisposes to Graves' disease (GD) with a reportedly indolent course. Objective: To determine the type, frequency and course of thyroid dysfunction (TD) in a cohort of alemtuzumab-treated MS patients in the UK. Design: Case records of alemtuzumab-treated patients who developed TD were reviewed. Results: 41.1% (102/248; 80F, 22M) of patients developed TD, principally GD (71.6%). Median onset was 17 months (range 2-107) following last dose; the majority (89%) within 3 years. Follow-up data (range 6-251 months) was available in 71 cases, of whom 52 (73.2%) developed GD: 10 of these (19.2%) had fluctuating TD. All 52 GD patients commenced antithyroid drugs (ATD): 3 required radioiodine (RAI) due to ATD side-effects, drug therapy is ongoing in 2; of those who completed a course, 16 are in remission, 1 developed spontaneous hypothyroidism, and 30 (64%) required definitive or long-term treatment (RAI n=17, thyroidectomy n=5, long-term ATDs n=8). 3 cases of thyroiditis and 16 cases of hypothyroidism were documented; 5 with anti-TPO antibody positivity only, 10 with positive TRAb, 1 hypothyroidism (uncertain aetiology). Bioassay confirmed both stimulating and blocking TRAb in a subset of fluctuating GD cases. Conclusions: Contrary to published literature, we have recorded frequent occurrence of GD that required definitive or prolonged antithyroid drug treatment. Furthermore, fluctuating thyroid status in GD and unexpectedly high frequency of TRAb-positive hypothyroidism suggested changing activity of TRAb in this clinical context; we have documented the existence of both blocking and stimulating TRAb in these patients.

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Applicability of McDonald 2010 and Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) 2016 Magnetic Resonance Imaging Criteria for the Diagnosis of Multiple Sclerosis in Sri Lanka.

Gamage SMK(1), Wijeweera I(2), Wijesinghe P(3), Adikari SB(1), Fink K(4), Sominanda HMA(5).

Author information: (1)Department of Anatomy, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka. (2)Neurology Unit, Teaching Hospital, Kandy, Sri Lanka. (3)Radiology Unit, Sirimavo Bandaranayaka Specialized Children's Hospital, Peradeniya, Sri Lanka. (4)Department of Neurology, Karolinska University Hospital, Stockholm, Sweden. (5)Department of Anatomy, Faculty of Medicine, University of Peradeniya, Peradeniya, Sri Lanka. ajithsomi@yahoo.com.

BACKGROUND AND PURPOSE: The magnetic resonance imaging in multiple sclerosis (MAGNIMS) group recently proposed guidelines to replace the existing dissemination-in-space criteria in McDonald 2010 magnetic resonance imaging (MRI) criteria for diagnosing multiple sclerosis. There has been insufficient research regarding their applicability in Asians. Objective of this study was to determine the sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) of McDonald 2010 and MAGNIMS 2016 MRI criteria with the aim of verifying their applicability in Sri Lankan patients.

METHODS: Patients with clinically isolated syndrome diagnosed by consultant neurologists were recruited from five major neurology centers. Baseline and follow-up MRI scans were performed within 3 months from the initial presentation and at one year after baseline MRI, respectively. McDonald 2010 and MAGNIMS 2016 MRI criteria were applied to all MRI scans. Patients were followed-up for 2 years to assess the conversion to clinically definite multiple sclerosis (CDMS). The sensitivity, specificity, accuracy, PPV, and NPV for predicting the conversion to CDMS were calculated.

RESULTS: Forty-two of 66 patients converted to CDMS. Thirty-seven fulfilled the McDonald 2010 MRI criteria, and 33 converted to CDMS. MAGNIMS 2016 MRI criteria were fulfilled by 29, with 28 converting to CDMS. The sensitivity, specificity, accuracy, PPV, and NPV were 78%, 83%, 64%, 89%, and 69%, respectively, for the McDonald 2010 criteria, and 67%, 96%, 77%, 96%, and 62% for the MAGNIMS 2016 MRI criteria. CONCLUSIONS: MAGNIMS 2016 MRI criteria were superior to McDonald 2010 MRI criteria in specificity, accuracy, and PPV, but inferior in sensitivity and NPV.

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Conflict of interest statement: The authors have no financial conflicts of interest.
Recurrent Optic Neuritis as the Initial Symptom in Demyelinating Diseases.

Falcão-Goñalves AB(1), Bichuetti DB(2), de Oliveira EML(2).

Author information: (1)Department of Neurology and Neurosurgery, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil. alebfalcao@gmail.com, (2)Department of Neurology and Neurosurgery, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil.

BACKGROUND AND PURPOSE: Optic neuritis (ON) is an inflammation of the optic nerve that can be recurrent, with unilateral or bilateral presentation. Diagnosing recurrent cases may be challenging. We aimed to compare patients with recurrent ON as their initial symptom according to their following final diagnoses: multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), or chronic relapsing inflammatory optic neuropathy (CRION). METHODS: The medical records of patients with initial recurrent ON who were followed at the Neuroimmunology Clinic of the Federal University of São Paulo between 2004 and 2016 were analyzed retrospectively. Patients were classified according to their final diagnosis into MS, NMOSD, or CRION, and the characteristics of these groups were compared to identify predictive factors. RESULTS: Thirty-three patients with recurrent ON were included, and 6, 14, and 13 had final diagnoses of MS, NMOSD, and CRION, respectively. Most of the patients were female with unilateral and severe ON in their first episode, and the initial Visual Functional System Score (VFSS) was ≥5 in 63.6%, 85.7%, and 16.7% of the patients with CRION, NMOSD, and MS, respectively. Anti-aquaporin-4 antibodies were detected in 9 of 21 (42.8%) tested patients. Seven of nine (77.8%) seropositive NMOSD patients experienced transverse myelitis episodes during the follow-up period. A multivariate regression analysis showed that the VFSS at the last medical appointment predicted the final diagnosis. CONCLUSIONS: A lower VFSS at the last medical appointment was predictive of MS. Patients with NMOSD and CRION have similar clinical characteristics, whereas NMOSD patients tend to have worse visual acuity.

Conflict of interest statement: The authors have no financial conflicts of interest.

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Interleukin-6, S-Nitrosothiols, and Neurodegeneration in Different Central Nervous System Demyelinating Disorders: Is There a Relationship?

Fominykh V(1)(2), Vorobyeva A(3), Onufriev MV(1), Brylev L(1)(4), Zakharova MN(3), Gulyaeva NV(1).

Author information: (1)Institute of Higher Nervous Activity and Neurophysiology Russian Academy of Sciences, Department of Functional Biochemistry of the Nervous System, Moscow, Russia. (2)Bujanov Moscow City Clinical Hospital, Moscow, Russia. hydrohinon@mail.ru. (3)Research Center of Neurology, Volokolamskoe shosse, Moscow, Russia. (4)Bujanov Moscow City Clinical Hospital, Moscow, Russia.

BACKGROUND AND PURPOSE: A few groups have suggested that activated cytokines and nitrosative stress are closely involved in the pathogenesis of different demyelinating disorders induced by the neuroinflammatory destruction of neurons. The purpose of this study was to elucidate the associations of cytokines and S-nitrosothiols (RSNO) with the severity of neurodegeneration during relapse in demyelinating disorders of the central nervous system. METHODS: We measured levels of interleukin-6 (IL-6), erythropoietin, RSNO, and phosphorylated neurofilament heavy chain (pNfh) in cerebrospinal fluid (CSF) samples obtained from patients with different demyelinating disorders: multiple sclerosis (MS, n=52), acute disseminated encephalomyelitis (ADEM, n=9), and neuromyelitis optica spectrum disorders (NMOSD) with aquaporin-4 immunoglobulin G (AQP4-IgG, n=12). We compared these levels with those measured in a control group (n=24). RESULTS: We found that IL-6 in CSF was elevated in NMOSD with AQP4-IgG and ADEM patients as well as in MS patients after the destruction of soluble IL-6. Erythropoietin levels were lower in MS, while RSNO levels were higher in NMOSD with AQP4-IgG and MS patients than in the control group. CSF pNfh levels were elevated in MS and ADEM patients. CONCLUSIONS: These results confirm that IL-6 is activated in different demyelinating disorders, with this elevation being more prominent in the CSF of NMOSD with AQP4-IgG and ADEM patients. Moreover, S-nitrosylation is activated in demyelinating disorders with spinal-cord injury and neurodegeneration in these patients. However, we found no correlation between these biochemical markers, and so we could not confirm whether IL-6-mediated nitric oxide production is involved in spinal-cord lesions.

Conflict of interest statement: The authors have no financial conflicts of interest.
Transcranial direct current stimulation: A glimmer of hope for multiple sclerosis fatigue?

Ayache SS(1), Chalah MA(2).

Author information: (1)Service de Physiologie, Explorations Fonctionnelles, Hôpital Henri-Mondor, AP-HP, Creteil, France; EA 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est-Créteil, Creteil, France; Neurology Division, Lebanese American University Medical Center-Rizk Hospital (LAUMC-RH), Beirut, Lebanon. (2)Service de Physiologie, Explorations Fonctionnelles, Hôpital Henri-Mondor, AP-HP, Creteil, France; EA 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est-Créteil, Creteil, France. Electronic address: moussachalah@gmail.com.

Multiple sclerosis (MS) is a neurological disease of the central nervous system characterized by inflammation, demyelination and neurodegeneration. Throughout the disease process, patients may complain of a panel of sensory, motor, cognitive and behavioral symptoms. Fatigue is a debilitating manifestation of central nervous system diseases with physical, cognitive and psychosocial dimensions. In MS, fatigue could be very frequent concerning up to 90% of patients and may have a drastic impact on their quality of life. Based on neuroimaging studies, a 'cortico-striato-thalamo-cortical' loop seems to underlie this symptom. Despite the availability of pharmacological molecules, the majority of them fail to bring satisfactory outcomes mainly because of the numerous related side-effects. Therefore, finding a safe, easy to implement, and effective alternative therapy is highly needed. These properties appear to match those of noninvasive brain stimulation techniques such as transcranial direct current stimulation (tDCS). tDCS consists of placing two electrodes over cortical sites, such as those that take part in MS fatigue loop. Here, tDCS protocols targeting MS fatigue are revisited. Their short and long-term effects are discussed. The majority of the available protocols have applied 5 consecutive daily 20-min sessions of anodal tDCS over specific cortical sites and yielded beneficial effects on MS fatigue. Finally, the recent emergence of remotely supervised tDCS protocols are also tackled in this work aiming to address the future possibility of translating the current research data into routine clinical practice. This may lead to optimize patients' care and improve their quality of life.

NMO-IgG and AQP4 Peptide Can Induce Aggravation of EAMG and Immune-Mediated Muscle Weakness.

Mizrachi T(1), Brill L(1), Rabie M(2), Nevo Y(2), Fellig Y(1), Zur M(1), Karussis D(1), Abramsky O(1), Brenner T(1), Vaknin-Dembinsky A(1).

Author information: (1)Department of Neurology and The Multiple Sclerosis Center, The Agnes-Ginges Center for Neurogenetics, Hebrew University, Hadassah Medical Center, Ein Karem, Jerusalem 91120, Israel. (2)Schneider Children's Medical Center of Israel, Tel Aviv University, Tel Aviv, Israel.

Neuromyelitis optica (NMO) and myasthenia gravis (MG) are autoimmune diseases mediated by autoantibodies against either aquaporin 4 (AQP4) or acetylcholine receptor (AChR), respectively. Recently, we and others have reported an increased prevalence of NMO in patients with MG. To verify whether coexisting autoimmune disease may exacerbate experimental autoimmune MG, we tested whether active immunization with AQP4 peptides or passive transfer of NMO-Ig can affect the severity of EAMG. Injection of either AQP4 peptide or NMO-Ig to EAMG or to naive mice caused increased fatigability and aggravation of EAMG symptoms as expressed by augmented muscle weakness (but not paralysis), decremental response to repetitive nerve stimulation, increased neuromuscular jitter, and aberration of immune responses. Thus, our study shows increased disease severity in EAMG mice following immunization with the NMO autoantigen AQP4 or by NMO-Ig, mediated by augmented inflammatory response. This can explain exacerbation or increased susceptibility of patients with one autoimmune disease to develop additional autoimmune syndrome.

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NMO-IgG and AQP4 Peptide Can Induce Aggravation of EAMG and Immune-Mediated Muscle Weakness.

Mizrachi T(1), Brill L(1), Rabie M(2), Nevo Y(2), Fellig Y(1), Zur M(1), Karussis D(1), Abramsky O(1), Brenner T(1), Vaknin-Dembinsky A(1).

Author information: (1)Department of Neurology and The Multiple Sclerosis Center, The Agnes-Ginges Center for Neurogenetics, Hebrew University, Hadassah Medical Center, Ein Karem, Jerusalem 91120, Israel. (2)Schneider Children's Medical Center of Israel, Tel Aviv University, Tel Aviv, Israel.

Neuromyelitis optica (NMO) and myasthenia gravis (MG) are autoimmune diseases mediated by autoantibodies against either aquaporin 4 (AQP4) or acetylcholine receptor (AChR), respectively. Recently, we and others have reported an increased prevalence of NMO in patients with MG. To verify whether coexisting autoimmune disease may exacerbate experimental autoimmune MG, we tested whether active immunization with AQP4 peptides or passive transfer of NMO-Ig can affect the severity of EAMG. Injection of either AQP4 peptide or NMO-Ig to EAMG or to naive mice caused increased fatigability and aggravation of EAMG symptoms as expressed by augmented muscle weakness (but not paralysis), decremental response to repetitive nerve stimulation, increased neuromuscular jitter, and aberration of immune responses. Thus, our study shows increased disease severity in EAMG mice following immunization with the NMO autoantigen AQP4 or by NMO-Ig, mediated by augmented inflammatory response. This can explain exacerbation or increased susceptibility of patients with one autoimmune disease to develop additional autoimmune syndrome.

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Is there a link between inflammation and fatigue in multiple sclerosis?

Chalah MA(1)(2), Ayache SS(1)(2)(3).

Author information: (1)EA 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est-Créteil, Créteil, France. (2)Service de Physiologie - Explorations Fonctionnelles, Hôpital Henri Mondor, Assistance Publique - Hôpitaux de Paris, Créteil, France. (3)Neurology Division, Lebanese American University Medical Center, Rizk Hospital, Beirut, Lebanon.

Purpose: Among autoimmune diseases of the central nervous system stands multiple sclerosis (MS), which is characterized by demyelination, synaptopathy, and neurodegeneration. MS fatigue can affect up to 90% of patients and be very disabling, with a drastic impact on their quality of life. To date, the evaluation of MS fatigue has relied mainly on subjective scales, and actual therapeutic interventions are challenged by modest efficacy and numerous undesirable effects. Therefore, finding biomarkers of MS fatigue might help in optimizing evaluation and treatment strategies. The main objective here was to assess the relationship between MS fatigue and inflammatory or other immunomediated markers.

Methods: Research was conducted according to PRISMA guidelines. Computerized databases (ie, PubMed/Medline and Scopus) were consulted until February 2018 aiming to identify articles that addressed inflammation and MS fatigue. Studies in English and French published at any time were considered. Results: A total of 27 studies matched the research criteria. Inconsistency existed regarding the relationship between fatigue and the orexin A system, hypothalamus-pituitary-adrenal axis, and cerebrospinal fluid inflammatory markers. As for peripheral markers, although there was scarcity in the available data, serum proinflammatory cytokines (ie, IL6, TNFα, and IFNγ) seem to be associated with MS fatigue. Finally, no link was found between MS fatigue and T-cell populations (ie, CD3+CD4+ T lymphocytes, regulatory T cells) or other peripheral markers of inflammation (ie, CRP, erythrocyte-sedimentation rate, soluble ICAM1). Conclusion: Future large-scale studies would benefit from comparing the relationship between fatigue and immune measures in patients with different disease phenotypes with and without disease-modifying drugs. With the subjective nature of fatigue scales, finding objective biomarkers for fatigue would be of great help.

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Delayed Hypersensitivity Reaction to Oral Dimethyl Fumarate.

Antolin-Amerigo D(1), Sánchez-González MJ(1), Barbarroja-Escudero J(1), Ayuso-Peralta L(2), Bellón-Heredia T(3), Ortega-Berruezo MA(1), Alvarez-Mon M(1), Rodríguez-Rodríguez M(1).

Author information: (1)Servicio de Enfermedades del Sistema Inmune-Alergia, Hospital Universitario Hospital Príncipe de Asturias, Alcalá de Henares, Spain. (2)Servicio de Neurología, Hospital Universitario Hospital Príncipe de Asturias, Alcalá de Henares, Spain. (3)Instituto de Investigación Hospital La Paz, IDIPAZ, Hospital Universitario La Paz, Madrid, Spain.

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Iron deposition quantification: Applications in the brain and liver.
Yan F(1), He N(1), Lin H(1), Li R(1).
Author information: (1)Department of Radiology, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
Iron has long been implicated in many neurological and other organ diseases. It is known that over and above the normal increases in iron with age, in certain diseases there is an excessive iron accumulation in the brain and liver. MRI is a noninvasive means by which to image the various structures in the brain in three dimensions and quantify iron over the volume of the object of interest. The quantification of iron can provide information about the severity of iron-related diseases as well as quantify changes in iron for patient follow-up and treatment monitoring. This article provides an overview of current MRI-based methods for iron quantification, specifically for the brain and liver, including: signal intensity ratio, R2, R2*, R2’, phase, susceptibility weighted imaging and quantitative susceptibility mapping (QSM). Although there are numerous approaches to measuring iron, R2 and R2* are currently preferred methods in imaging the liver and QSM has become the preferred approach for imaging iron in the brain. LEVEL OF EVIDENCE: 5 Technical Efficacy; Stage 5 J. Magn. Reson. Imaging 2018. © 2018 International Society for Magnetic Resonance in Medicine. DOI: 10.1002/jmri.26161 PMID: 29897645

Economic burden, work, and school productivity in individuals with tuberous sclerosis and their families.
Skalicky AM(1), Rentz AM(1), Liu Z(2), Said Q(2), Nakagawa JA(3), Frost MD(4), Wheless JW(5), Dunn DW(6).
Author information: (1) a Evidera , Seattle , WA , USA. (2) b Novartis Oncology , East Hanover , NJ , USA. (3) c The Tuberous Sclerosis Alliance , Silver Spring , MD , USA. (4) d Minnesota Epilepsy Group , St Paul , MN , USA. (5) e Le Bonheur Children's Hospital and the University of Tennessee, University of Tennessee Health Science Center , Memphis , TN , USA. (6) f Riley Hospital for Children , Indianapolis , IN , USA. AIM S: Tuberous sclerosis complex (TSC) is a multi-organ autosomal-dominant, genetic disorder with incomplete penetrance. The multiple manifestations of TSC and impacts to numerous organ systems represent significant disease, healthcare, and treatment burden. The economic and employment burden of the disease on individuals and their families is poorly understood. This study assessed the cost of illness and work and school productivity burden associated with TSC in a cross-sectional web-survey sample. MATERIALS AND METHODS: Eligible TSC individuals and caregivers were invited through the Tuberous Sclerosis Alliance advocacy group to complete a web-based survey about illness characteristics, treatment, disease burden, direct and indirect healthcare costs, work and school impairment. RESULTS: Data from 609 TSC adults or caregiver respondents with no cognitive impairments were analyzed. TSC adults (>18 years of age) had significantly higher direct out-of-pocket costs for ER visits, expenses for medical tests and procedures, alternative treatments, medications and lifetime cost of surgeries compared to TSC pediatric individuals. Both TSC adults and TSC caregivers reported work and school absenteeism and presenteeism; however, adults reported significantly higher absenteeism and presenteeism and overall activity impairment due to TSC, as might be expected, compared to TSC caregivers. TSC adults had significantly higher absenteeism and presenteeism rates compared to adults with moderate-to-severe plaque psoriasis and muscular sclerosis. CONCLUSIONS: TSC results in considerable direct out-of-pocket medical costs and impairment to work productivity, especially for adults. Future studies should include the comparator group and examine direct cost burden in the US using electronic medical records and insurance databases. DOI: 10.1080/13696998.2018.1487447 PMID: 29890870
When does economic model type become a decisive factor in health technology appraisals? Learning from the expanding treatment options for relapsing-remitting multiple sclerosis.

Noon KM(1), Montgomery SM(2), Adlard NE(3), Kroes MA(4).

Author information: (1)a Costello Medical Consulting Ltd, London, UK. (2)b Costello Medical Consulting Ltd, Cambridge, UK. (3)c Novartis Pharma AG, Basel, Switzerland. (4)d Novartis Pharmaceuticals UK Ltd, Surrey, UK.

OBJECTIVES: Specific economic model types often become de facto standard for health technology appraisal over time. Markov and discrete event simulation (DES) models were compared to investigate the impact of innovative modeling on the cost-effectiveness of disease-modifying therapies (DMTs) in relapsing-remitting multiple sclerosis (RRMS). Fingolimod was compared to dimethyl fumarate (DMF; in highly active [HA] RRMS), alemtuzumab (in HA RRMS) and natalizumab (in rapidly evolving severe RRMS). Comparator DMTs were chosen to reflect different dosing regimens. MATERIALS AND METHODS: Markov and DES models used have been published previously. Inputs were aligned in all relevant respects, with differences in the modeling of event-triggered attributes, such as relapse-related retreatment, which is inherently difficult with a memoryless Markov approach. Outcomes were compared, with and without different attributes.

RESULTS: All results used list prices. For fingolimod and DMF, incremental cost-effectiveness ratios (ICERs) were comparable (Markov: £4206/quality-adjusted life year [QALY] gained versus DES: £3910/QALY gained). Deviations were observed when long-term adverse events (AEs) were incorporated in the DES (Markov: £25,412 saved/QALY lost, versus DES: £34,209 saved/QALY lost, fingolimod versus natalizumab; higher ICERs indicate greater cost-effectiveness). For fingolimod versus alemtuzumab, when relapse-triggered retreatment was included in the DES, large cost differences were observed (difference between incremental cost is £35,410 and QALY is 0.10). LIMITATIONS: UK payer perspective, therefore societal approach was not considered. Resource utilization and utilities for both models were not derived from the subpopulations; as the focus is on model type, input limitations that apply to both models are less relevant. CONCLUSIONS: Whilst no model can fully represent a disease, a DES allows an opportunity to include features excluded in a Markov structure. A DES may be more suitable for modeling in RRMS for health technology assessment purposes given the complexity of some DMTs. This analysis highlights the capabilities of different model structures to model event-triggered attributes.

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Author information: (1)Department of Computer Science, University of Jaén, Campus Las Lagunillas s/n, A3 building, 23071, Jaén, Spain. negrillo@ujaen.es. (2)Department of Computer Science, University of Jaén, Campus Las Lagunillas s/n, A3 building, 23071, Jaén, Spain. (3)Department of Health Sciences, University of Jaén, Jaén, Spain.

The Subjective Visual Vertical (SVV) is a common test for evaluating the perception of verticality. Altered verticality has been connected with disorders in the otolithic, visual or proprioceptive systems, caused by stroke, Parkinson’s disease or multiple sclerosis, among others. Currently, this test is carried out using a variety of specific, mostly homemade apparatuses that include moving planes, buckets, hemispheric domes or a line projected in a screen. Our aim is to develop a flexible, inexpensive, user-friendly and easily extensible system based on virtual reality for the measurement of the SVV and several related visual diagnostic tests, and validate it through an experimental evaluation. Two different hardware configurations were tested with 50 healthy volunteers in a controlled environment; 28 of them were males and 22 females, with ages ranging from 18 to 49 years, being 23 the average age. The Intraclass Correlation Coefficient (ICC) was computed in each device. In addition, a usability survey was conducted. ICC = 0.85 in the first configuration (CI = 0.75-0.92), ICC = 0.76 in the second configuration (CI = 0.61-0.87), both with 95% of confidence, which means a substantial reliability. Moreover, 92.2% of subjects rated the usability of the system as "very good". Our evaluation showed that the proposed system is suitable for the measurement of SVV in healthy subjects. The next step is to perform a more elaborated experimentation on patients and compare the results with the measurements obtained from traditional methods.

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Atrophied Brain Lesion Volume: A New Imaging Biomarker in Multiple Sclerosis.

Dwyer MG(1), Bergslund N(1), Ramasamy DP(1), Jakimovski D(1), Weinstock-Guttman B(2), Zivadinov R(3).

Author information: (1)Buffalo Neuroimaging Analysis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY. (2) Jacobs Multiple Sclerosis Center, Department of Neurology, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, The State University of New York, Buffalo, NY. (3)Center for Biomedical Imaging, Clinical and Translational Science Institute, University at Buffalo, The State University of New York, Buffalo, NY.

BACKGROUND AND PURPOSE: Lesion accrual in multiple sclerosis (MS) is an important and clinically relevant measure, used extensively as an imaging trial endpoint. However, lesions may also shrink or disappear entirely due to atrophy. Although generally ignored or treated as a nuisance, this phenomenon may actually be an important stand-alone imaging biomarker. Therefore, we investigated the rate of brain lesion loss due to atrophy (atrophied lesion volume) in MS subtypes compared to baseline lesion volume and to new and enlarging lesion volumes, and evaluated the independent predictive value of this phenomenon for clinical disability.

METHODS: A total of 192 patients (18 clinically isolated syndrome, 126 relapsing-remitting MS, and 48 progressive) received 3T magnetic resonance imaging at baseline and 5 years. Lesions were quantified at baseline, and new/enlarging lesion volumes were calculated over the study interval. Atrophied lesion volume was calculated by combining baseline lesion masks with follow-up SIENAX-derived cerebrospinal fluid partial volume maps. Measures were compared between disease subgroups, and correlations with disability change (Expanded Disability Status Scale [EDSS]) were evaluated. Hierarchical regression was employed to determine the unique additive value of atrophied lesion volume.

RESULTS: Atrophied lesion volume was different between MS subtypes (P = .02), and exceeded new lesion volume accumulation in progressive MS (298.1 vs. 75.5 mm³). Atrophied lesion volume was the only significant correlate of EDSS change (r = .192 relapsing, r = .317 progressive, P < .05), and explained significant additional variance when controlling for brain atrophy and new/enlarging lesion volume (R² .092 vs. .045, P = .003). CONCLUSION: Atrophied lesion volume is a unique and clinically relevant imaging marker in MS, with particular promise in progressive MS.

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Is Toxoplasma gondii playing a positive role in multiple sclerosis risk? A systematic review and meta-analysis.

Saberi R(1), Sharif M(2), Sarvi S(2), Aghayan SA(3), Hosseini SA(1), Anvari D(1), Nayeri Chegeni T(1), Hosseininejad Z(1), Daryani A(4).

Author information: (1)Toxoplasmosis Research Center, Mazandaran University of Medical Sciences, Sari, Iran; Department of Parasitology and Mycology, School of Medicine, Mazandaran University of Medical Science, Sari, Iran; Student Research Committee, Mazandaran University of Medical Science, Sari, Iran. (2)Toxoplasmosis Research Center, Mazandaran University of Medical Sciences, Sari, Iran; Department of Parasitology and Mycology, School of Medicine, Mazandaran University of Medical Science, Sari, Iran. (3)Laboratory of Zoology, Research Institute of Biology, Yerevan State University, Alex Manoogian 1, Yerevan, Armenia. (4)Toxoplasmosis Research Center, Mazandaran University of Medical Sciences, Sari, Iran; Department of Parasitology and Mycology, School of Medicine, Mazandaran University of Medical Science, Sari, Iran. Electronic address: daryanii@yahoo.com.

Toxoplasmosis is a parasitic disease caused by Toxoplasma gondii with a globally widespread distribution. The aim of this systematic review and meta-analysis was to characterize the association between T. gondii infection and multiple sclerosis (MS). The data were systematically collected from the English electronic databases up to April 2017. The research process resulted in the identification of five studies related to the subject of interest entailing 669 MS patients and 770 controls. The pooled prevalence rates of T. gondii infection in the MS patients and controls were estimated as 32.4% (95% CI: 27.4-38.6) and 39.1% (95% CI: 29.1-50.5), respectively. By random effect model, the combined odds ratio was 0.72 (95% CI: 0.49-1.06) with P = .0961. Although this meta-analysis study showed a lower seroprevalence of T. gondii in the MS patients as compared with that in the control group, no significant association was found between toxoplasmosis and MS disease. Further investigations are recommended to determine the detailed association between MS patients and T. gondii infection.

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Contribution of the macrophage migration inhibitory factor superfamily of cytokines in the pathogenesis of preclinical and human multiple sclerosis: In silico and in vivo evidences.

Fagone P(1), Mazzon E(2), Cavalli E(1), Bramanti A(2), Petralia MC(3), Mangano K(1), Al-Abed Y(4), Bramati P(2), Nicoletti F(5).

Author information: (1)Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy. (2)IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy. (3)Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy; Department of Formative Processes, University of Catania, Catania, Italy. (4)Center for Molecular Innovation, The Feinstein Institute for Medical Research, Manhasset, New York, United States. (5)Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy. Electronic address: ferdinic@unict.it.

Macrophage migration inhibitory factor (MIF) is a cytokine with pleiotropic actions involved in the pathogenesis of autoimmune disorders, including Multiple Sclerosis (MS). We have first evaluated in silico the involvement of MIF, its homologue D-DT, and the receptors CD74, CD44, CXCR2 and CXCR4 in encephalitogenic T cells from a mouse model of MS, the Experimental Allergic Encephalomyelitis (EAE), as well as in circulating T helper cells from MS patients. We show an upregulation of the receptors involved in MIF signaling both in the animal model and in patients. Also, a significant increase in MIF receptors is found in the CNS lesions associated to MS. Finally, the specific inhibitor of MIF, ISO-1, improved both ex vivo and in vivo the features of EAE. Overall, our data indicate that there is a significant involvement of the MIF pathway in MS ethiopathogenesis and that interventions specifically blocking MIF receptors may represent useful therapeutic approaches in the clinical setting.

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Pioglitazone is superior to quetiapine, clozapine and tamoxifen at alleviating experimental autoimmune encephalomyelitis in mice.

Chedrawe MAJ(1), Holman SP(2), Lamport AC(3), Akay T(4), Robertson GS(5).

Author information: (1)Department of Pharmacology, Brain Repair Centre, Faculty of Medicine, 2nd floor, Life Sciences Research Institute, 1348 Summer Street, P.O. Box 15000, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada. Electronic address: ChedraweM@Dal.Ca. (2)Department of Pharmacology, Brain Repair Centre, Faculty of Medicine, 2nd floor, Life Sciences Research Institute, 1348 Summer Street, P.O. Box 15000, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada. (3)Department of Pharmacology, Brain Repair Centre, Faculty of Medicine, 2nd floor, Life Sciences Research Institute, 1348 Summer Street, P.O. Box 15000, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada. Electronic address: aclamport@dal.ca. (4)Department of Medical Neuroscience, Brain Repair Centre, Faculty of Medicine, 3rd floor, Life Sciences Research Institute, 1348 Summer Street, P.O. Box 15000, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada. Electronic address: Turgay.Akay@dal.ca. (5)Department of Pharmacology, Brain Repair Centre, Faculty of Medicine, 2nd floor, Life Sciences Research Institute, 1348 Summer Street, P.O. Box 15000, Dalhousie University, Halifax, Nova Scotia B3H 4R2, Canada; Department of Psychiatry, 5909 Veterans’ Memorial Lane, 8th floor, Abbie J. Lane Memorial Building, QEII Health Sciences Centre, Halifax, Nova Scotia B3H 2E2, Canada. Electronic address: George.Robertson@Dal.Ca.

Recent evidence suggests that clozapine and quetiapine (atypical antipsychotics), tamoxifen (selective-estrogen receptor modulator) and pioglitazone (PPARγ agonist) may improve functional recovery in multiple sclerosis (MS). We have compared the effectiveness of oral administration of these drugs, beginning at peak disease, at reducing ascending paralysis, motor deficits and demyelination in mice subjected to experimental autoimmune encephalomyelitis (EAE). Mice were immunized with an immunogenic peptide corresponding to amino acids 35-55 of the myelin oligodendrocyte glycoprotein (MOG35-55) in complete Freund’s adjuvant and injected with pertussis toxin to induce EAE. Unlike clozapine, quetiapine and tamoxifen, administration of pioglitazone beginning at peak disease decreased both clinical scores and lumbar white matter loss in EAE mice. Using kinematic gait analysis, we found that pioglitazone also maintained normal movement of the hip, knee and ankle joints for at least 44 days after MOG35-55 immunization. This long-lasting preservation of hindleg joint movements was accompanied by reduced white matter loss, microglial and macrophage activation and the expression of pro-inflammatory genes in the lumbar spinal cords of EAE mice. These results support clinical findings that suggest pioglitazone may reduce the progressive loss of motor function in MS by decreasing inflammation and myelin damage.

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The intrathecal polyspecific antiviral immune response (MRZ reaction): A potential cerebrospinal fluid marker for multiple sclerosis diagnosis.

Feki S(1), Gargouri S(2), Mejdoub S(3), Dammak M(4), Hachicha H(3), Hadiji O(4), Feki L(2), Hammami A(2), Mhiri C(4), Karray H(2), Masmoudi H(3).

Author information: (1)Laboratory of Immunology, Habib Bourguiba University Hospital, Faculty of Medicine, University of Sfax, Tunisia. Electronic address: sawsanfeki@yahoo.fr. (2)Laboratory of Microbiology, Habib Bourguiba University Hospital, Faculty of Medicine, University of Sfax, Tunisia. (3)Laboratory of Immunology, Habib Bourguiba University Hospital, Faculty of Medicine, University of Sfax, Tunisia. (4)Department of Neurology, Habib Bourguiba University Hospital, Faculty of Medicine, University of Sfax, Tunisia.

We tested the performance of MRZ-reaction, an intrathecal humoral immune response against-Measles (M), Rubella (R) and Varicella Zoster (Z) viruses, in multiple sclerosis (MS) diagnosis. The MRZ-reaction was significantly more positive in MS than in non-MS group with a specificity of 91.9%. In MS group, the RZ-profile was the most prevalent and the R-specific antibody-index was correlated to the number of oligoclonal bands (OCB) in CSF. Interestingly, the MRZ-reaction was detected in 53% of OCB-negative-MS patients. The MRZ-reaction seems to be a relevant CSF diagnostic marker of MS disease. The likely relation between its positivity and the vaccination status deserves to be investigated.

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Effects of vitamin D on axonal damage during de- and remyelination in the cuprizone model.

Nystad AE(1), Torkildsen Ø(2), Wergeland S(3).

Author information: (1)Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway; Department of Clinical Medicine, University of Bergen, Bergen, Norway. Electronic address: agnes.elisabeth.nystad@helse-bergen.no. (2)Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway; Department of Clinical Medicine, University of Bergen, Bergen, Norway. Electronic address: oivind.torkildsen@helse-bergen.no. (3)Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway. Electronic address: stig.wergeland@helse-bergen.no.

Vitamin D deficiency is a risk factor for multiple sclerosis and associated with higher disease activity. The aim of this study was to investigate the effects of cholecalciferol and calcitriol on axonal damage during de- and remyelination in the cuprizone model. We found significantly less reduction of neurofilament immunopositive axons in the high vs. low cholecalciferol group, while high dose calcitriol, given during remyelination, did not influence axonal regeneration. Our results indicate that high dose vitamin D could protect against axonal loss in an experimental model for demyelination, if given before and during the demyelination.

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Does pregnancy affect women with multiple sclerosis? A prospective study in Western China.

Lai W(1), Kinoshita M(2), Peng A(1), Li W(1), Qiu X(1), Zhu X(1), He S(1), Zhang L(1), Chen L(3).

Author information: (1)Department of Neurology, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu, Sichuan 610041, PR China. (2)Department of Neurology, Utano National Hospital, National Hospital Organization, 8 Onoyama-Cho, Narutaki, Ukyoku, Kyoto 616-8255, Japan. (3)Department of Neurology, West China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu, Sichuan 610041, PR China. Electronic address: leilei_25@126.com.

OBJECTIVES: Pregnancy is considered to be protective for multiple sclerosis (MS) but little is known about Asian MS women. Our study aimed to investigate whether pregnancy affects the course of MS and whether MS affects pregnancy in a Chinese cohort. METHODS: We established a database (2009-2016) of 94 females with MS in the Department of Neurology at West China Hospital. From this database, we enrolled females who had been pregnant before or after the clinical onset of MS and consecutively followed up the patients and their offspring for at least one year after delivery. We registered their demographic, clinical and pregnancy-related information, as well as the annualized relapse rate (ARR) and Expanded Disability Status Scale (EDSS) score. RESULTS: We enrolled 55 females with MS and 126 pregnancies. Among them, 14 females had 15 deliveries after MS onset. In these 15 full-term pregnancies after MS onset, the average ARR decreased from 0.46 ± 0.52 in the year before pregnancy to 0.07 ± 0.26 (P = .034) during pregnancy and no drug exposure were observed during pregnancy. The average EDSS score at one year after delivery (1.50 ± 1.72) was higher than that at conception (0.77 ± 1.35; P = .045). CONCLUSIONS: The natural history of MS during pregnancy suggests that full-term pregnancy protects MS females from relapse. However, the disability of MS females may develop after delivery.

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Author information: (1)Laboratory of Ultrastructure, Aggeu Magalhães Institute (IAM), PE, Brazil; Postgraduate Program in Biosciences and Biotechnology for Health (PPGBBS), Oswaldo Cruz Foundation (FIOCRUZ-PE)/Aggeu Magalhães Institute (IAM), Recife, PE, Brazil. (2)Laboratory of Ultrastructure, Aggeu Magalhães Institute (IAM), PE, Brazil. (3)Postgraduate Program in Biotechnology/Northeast Network in Biotechnology (RENORBIO), Federal University of Pernambuco (UFPE), PE, Brazil. (4)Postgraduate Program in Biological Sciences/Center of Biosciences, Federal University of Pernambuco (UFPE), Recife, PE, Brazil. (5)Department of Structural and Functional Biology, University of Campinas (UNICAMP), Campinas, São Paulo, Brazil. (6)Laboratory of Ultrastructure, Aggeu Magalhães Institute (IAM), PE, Brazil; Institute of Science and Technology on Neuroimmunomodulation (INCT-NIM), Brazil. Electronic address: peixoto.christina@gmail.com.

Apoptosis is one form of cell death that is intimately related to health and pathological conditions. In most neuroinflammatory and/or neurodegenerative diseases, apoptosis is associated with disease development and pathology and inhibition of this process leads to considerable amelioration. It is becoming evident that apoptosis also participates in the pathogenesis of Multiple Sclerosis (MS) and its animal model, Experimental Autoimmune Encephalomyelitis (EAE). Drugs such as Sildenafil, a Phosphodiesterase type 5 Inhibitor (PDE5I), have proven to be neuroprotective in MS models. However, it is not known whether Sildenafil is able to modulate cell death, specifically apoptosis, in EAE mice. Therefore, the aim of this study was to determine the effects of Sildenafil on extrinsic and intrinsic apoptosis pathways in the spinal cord of C57BL/6 mice with EAE. TUNEL analysis showed that EAE mice had elevated number of TUNEL+ cells and that treatment with Sildenafil led to reduced number of dying cells, indicating that Sildenafil was able to inhibit cell death. We observed that both extrinsic and intrinsic pathways of apoptosis were governing the dynamics of EAE progression. We showed that in EAE mice there were increased levels of extrinsic (Caspase-8, -3, TNF-α, FADD) and intrinsic (Caspase-9, Bax and Cytochrome C) apoptosis markers. Bcl-2, an anti-apoptotic protein, was downregulated in EAE mice. We also demonstrated that EAE mice had increased levels of non-caspase mediators of cell survival/cell death (p-IkBα and p-MAPK-p38). Besides, EAE mice presented augmented demyelination. Nevertheless, this is the first research to demonstrate that Sildenafil, when administered concomitant to disease induction, modulated the expression of pro- and anti-apoptotic proteins of the extrinsic and intrinsic pathways, as well as diminished the expression of non-caspase mediators and promoted remyelination in the spinal cord, indicating neuroprotective effects. Thus, the present study demonstrated that Sildenafil inhibits apoptosis by two distinct, although interconnected, mechanisms: directly by modulating caspase expression (through extrinsic and intrinsic pathways) and indirectly by modulating the expression of molecules involved in cell death and/or cell survival.

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**HLA-DRB1 polymorphism and susceptibility to multiple sclerosis in the Middle East North Africa region: A systematic review and meta-analysis.**

Author information: (1)MS Research Centre, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran; Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran. (2)MS Research Centre, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran; Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran. (3)Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. (4)Department of Medical Parasitology and Mycology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. (5)MS Research Centre, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran; Non-Communicable Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran. (6)MS Research Centre, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran. (7)MS Research Centre, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran.  
Electronic address: msahrai@tums.ac.ir.  
This meta-analysis explores association of HLA-DRB1 alleles with MS risk in the Middle-east North Africa (MENA) countries. Divided into two groups of alleles (10 studies, 899 cases/1457 controls) and phenotypes (8 studies, 1,040 cases/1,256 controls), Odds ratios (ORs) of DRB1 distribution in MS subjects were assessed using Cochrane RevMan software. DRB1*15 demonstrated significant association with MS in both groups (OR=1.6 and OR=2.51, respectively). In phenotypes, DRB1*03 and DRB1*04 had predisposing role (OR=1.8 and OR=1.9), while DRB1*07 and DRB1*11 were protective (OR=0.56 and OR=0.67). Similar but non-significant trends were seen among alleles, which in sum coincides with a Caucasian-like pattern.  
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**Immune cell profiling in the cerebrospinal fluid of patients with primary angiitis of the central nervous system reflects the heterogeneity of the disease.**

Strunk D(1), Schulte-Mecklenbeck A(1), Golombeck KS(1), Meyer Zu Hörste G(1), Melzer N(1), Beuker C(1), Schmidt A(1), Wiendl H(1), Meuth SG(1), Gross CC(1), Minnerup J(2).  
Author information: (1)Clinic of Neurology with Institute of Translational Neurology, University Hospital Münster, University Münster, 48149 Münster, Germany. (2)Clinic of Neurology with Institute of Translational Neurology, University Hospital Münster, University Münster, 48149 Münster, Germany. Electronic address: Jens.Minnerup@ukmuenster.de.  
Primary angiitis of the central nervous system (PACNS) is a rare and heterogeneous inflammatory disease of the CNS vasculature with poorly understood pathophysiology. Comprehensive immune-cell phenotyping revealed increased frequencies of leukocytes in the cerebrospinal fluid (CSF) of PACNS patients compared to patients with multiple sclerosis, ischemic stroke, and somatoform disorders (n = 18 per group). Changes in the intrathecal immune-cell profile were heterogeneous in PACNS. While proportions of T-cell subsets remained unaltered, some PACNS patients showed a shift toward NK- or B cells. Intrathecal immunoglobulin synthesis was observed in a subgroup of PACNS patients with an increased frequency of antibody producing plasma cells.  
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Laquinimod protects the optic nerve and retina in an experimental autoimmune encephalomyelitis model.


Author information: (1)Experimental Eye Research Institute, University Eye Hospital, Ruhr-University Bochum, In der Schornau 23-25, 44892, Bochum, Germany. (2)Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Gudrunstrasse 56, 44791, Bochum, Germany. (3)Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, Gudrunstrasse 56, 44791, Bochum, Germany. ingo.kleiter@rub.de. (4)Experimental Eye Research Institute, University Eye Hospital, Ruhr-University Bochum, In der Schornau 23-25, 44892, Bochum, Germany. stephanie.joachim@rub.de.

BACKGROUND: The oral immunomodulatory agent laquinimod is currently evaluated for multiple sclerosis (MS) treatment. Phase II and III studies demonstrated a reduction of degenerative processes. In addition to anti-inflammatory effects, laquinimod might have neuroprotective properties, but its impact on the visual system, which is often affected by MS, is unknown. The aim of our study was to investigate potential protective effects of laquinimod on the optic nerve and retina in an experimental autoimmune encephalomyelitis (EAE) model.

METHODS: We induced EAE in C57/BL6 mice via MOG35-55 immunization. Animals were divided into an untreated EAE group, three EAE groups receiving laquinimod (1, 5, or 25 mg/kg daily), starting the day post-immunization, and a non-immunized control group. Thirty days post-immunization, scotopic electroretinograms were carried out, and mice were sacrificed for histopathology (HE, LFB), immunohistochemistry (MBP, Iba1, Tmem119, F4/80, GFAP, vimentin, Brn-3a, cleaved caspase 3) of the optic nerve and retina, and retinal qRT-PCR analyses (Brn-3a, Iba1, Tmem119, AMWAP, CD68, GFAP). To evaluate the effect of a therapeutic approach, EAE animals were treated with 25 mg/kg laquinimod from day 16 when 60% of the animals had developed clinical signs of EAE.

RESULTS: Laquinimod reduced neurological EAE symptoms and improved the neuronal electrical output of the inner nuclear layer compared to untreated EAE mice. Furthermore, cellular infiltration, especially recruited phagocytes, and demyelination in the optic nerve were reduced. Microglia were diminished in optic nerve and retina. Retinal macroglial signal was reduced under treatment, whereas in the optic nerve macroglia were not affected. Additionally, laquinimod preserved retinal ganglion cells and reduced apoptosis. A later treatment with laquinimod in a therapeutic approach led to a reduction of clinical signs and to an improved b-wave amplitude. However, no changes in cellular infiltration and demyelination of the optic nerves were observed. Also, the number of retinal ganglion cells remained unaltered.

CONCLUSION: From our study, we deduce neuroprotective and anti-inflammatory effects of laquinimod on the optic nerve and retina in EAE mice, when animals were treated before any clinical signs were noted. Given the fact that the visual system is frequently affected by MS, the agent might be an interesting subject of further neuro-ophthalmic investigations.

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The effect of fingolimod on focal and diffuse grey matter damage in active MS patients.

Bajrami A(1), Pitteri M(1), Castellaro M(1)(2), Pizzini F(3), Romualdi C(4), Montemezzi S(3), Monaco S(1), Calabrese M(5).

Author information:  (1)Neurology B, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Policlinico "G.B. Rossi" Borgo Roma, Piazzale L.A. Scuro, 10, 37134, Verona, Italy. (2)Department of Information Engineering, University of Padova, Padua, Italy. (3)Neuroradiology and Radiology Units, Department of Diagnostic and Pathology, University Hospital of Verona, Verona, Italy. (4)Department of Biology, University of Padova, Padua, Italy. (5)Neurology B, Department of Neurosciences, Biomedicine and Movement Sciences, University of Verona, Policlinico "G.B. Rossi" Borgo Roma, Piazzale L.A. Scuro, 10, 37134, Verona, Italy. massimiliano.calabrese@univr.it.

INTRODUCTION: The mechanism of action of fingolimod within the central nervous system and its efficacy in reducing/preventing both focal and diffuse grey matter (GM) damage in active multiple sclerosis (MS) are not completely understood. METHODS: In this longitudinal, 2-year prospective, phase IV, single-blind study, 40 MS patients treated with fingolimod and 39 untreated age, gender, and disability-matched MS patients were enrolled. Each patient underwent a neurological examination every 6 months and a 3T MRI at the beginning of the treatment and after 24 months. The accumulation of new cortical lesions (CLs) and the progression of regional GM atrophy were compared between the two groups. RESULTS: At the end of the study (T24), the percentage of patients with new CLs (13.5 vs. 89%, p < 0.001) and the percentage of GM volume change was lower in the treated group (p < 0.001). The regional analysis revealed that the treated group had also less volume loss in thalamus, caudatus, globus pallidus, cingulate cortex, and hippocampus (p < 0.001), as well as in, cerebellum, superior frontal gyrus, and insular-long gyrus (p < 0.05). Patients with no evidence of disease activity were 60% in the treated group and 10% in the untreated group (p < 0.001). CONCLUSIONS: These results suggest a possible protective effect of fingolimod on focal and diffuse GM damage.

Detection of JC virus archetype in cerebrospinal fluid in a MS patient with dimethylfumarate treatment without lymphopenia or signs of PML.

Motte J(1), Kneiphof J(1), Straßburger-Krogias K(1), Klasing A(1), Adams O(2), Haghiokia A(1), Gold R(3).

Author information:  (1)Department of Neurology, St. Josef-Hospital, Ruhr University Bochum, Gudrunstrasse 56, 44791, Bochum, Germany. (2)Institute for Virology, Medical Faculty, Heinrich-Heine-University, Duesseldorf, Germany. (3)Department of Neurology, St. Josef-Hospital, Ruhr University Bochum, Gudrunstrasse 56, 44791, Bochum, Germany. Ralf.Gold@rub.de.

We report a 76-year-old MS patient, treated with DMF for 3 years. Lymphocytes never showed values below 1240/µl. CSF analysis revealed 1,988,880 copies/ml of JCV-DNA, JCV-DNA was detectable in serum and anti-JCV-antibody in CSF and serum were highly positive. Stratify®-JCV-test was positive. CD8-positive T-lymphocytes were reduced. Therapy with mefloquine, mirtazapine and cidofovir resulted in complete elimination of the virus in serum and 90% reduction of viral load in CSF. This case shows that despite careful monitoring for lymphopenia JCV spreading to the CSF may occur during treatment with DMF.

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Two-year real-life efficacy, tolerability and safety of dimethyl fumarate in an Italian multicentre study.

Mallucci G(1), Annovazzi P(2), Miante S(3), Torri-Clerici V(4), Matta M(5), La Gioia S(6), Cavarretta R(7), Mantero V(8), Costantini G(9), D'Ambrosio V(10), Zaffaroni M(2), Ghezzi A(2), Perini P(3), Rossi S(4), Bertolotto A(5), Rottoli MR(6), Rovaris M(7), Balgera R(8), Cavalla P(9), Montomoli C(11), Bergamaschi R(10).

Author information:  (1)Inter-department Multiple Sclerosis Research Centre, IRCCS Mondino Mondino, Pavia, Italy. giulia.mallucci@mondino.it. (2)Multiple Sclerosis Study Centre, ASST Valle Olona, Gallarate, VA, Italy. (3)Department of Neurosciences, The Multiple Sclerosis Centre, University Hospital of Padova, Padua, Italy. (4)Department of Neuroimmunology and Neuromuscular Diseases, Neurological Institute C, Besta IRCCS Foundation, Milan, Italy. (5)Regional Multiple Sclerosis Centre, San Luigi Gonzaga Hospital, Orbassano, TO, Italy. (6)SS Malattie Autoimmuni USC Neurologia, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy. (7)Multiple Sclerosis Center, IRCCS Santa Maria Nascente, Fondazione Don Carlo Gnocchi, Milan, Italy. (8)Neurological Department, A. Manzoni Hospital, Lecco, Italy. (9)Department of Neuroscience, University of Torino, Turin, Italy. (10)Inter-department Multiple Sclerosis Research Centre, IRCCS Mondino Mondino, Pavia, Italy. (11)Unit of Biostatistics and Clinical Epidemiology, Department of Public Health, University of Pavia, Pavia, Italy.

BACKGROUND: Dimethyl-fumarate (DMF) demonstrated efficacy and safety in relapsing-remitting multiple sclerosis (MS) in randomized clinical trials. OBJECTIVES: To track and evaluate post-market DMF profile in real-world setting. MATERIALS AND METHODS: Patients receiving DMF referred to Italian MS centres were enrolled and prospectively followed, collecting demographic clinical and radiological data. RESULTS: Among the 735 included patients, 45.4% were naïve to disease-modifying therapies, 17.8% switched to DMF because of tolerance, 27.4% switched to DMF because of lack of efficacy, and 9.4% switched to DMF because of safety concerns. Median DMF exposure was 17 months (0-33). DMF reduced the annual relapse rate (ARR) by 63.2%. At 12 and 24 months, 85 and 76% of patients were relapse-free. NEDA-3 status after 12 months of DMF treatment was maintained by 47.5% of patients. 89 and 70% of patients at 12 and 24 months regularly continued DMF. Most frequent adverse events (AEs) were flushing (37.2%) and gastrointestinal AEs (31.1%). CONCLUSION: Our post-market study corroborated that DMF is a safe and effective drug. Additionally, the study suggested that naïve patients strongly benefit from DMF and that DMF improved ARR also in patients who were horizontally switched from injectable therapies due to tolerability and efficacy issues.

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CSF cytokine profile in MOG-IgG+ neurological disease is similar to AQP4-IgG+ NMOSD but distinct from MS: a cross-sectional study and potential therapeutic implications.


Author information: (1)Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan. (2)Department of Neurology, Brain Institute and Hospital Sao Lucas Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil. (3)Department of Neurology, São Paulo University, São Paulo, Brazil. (4)Department of Neurology, Tohoku Medical and Pharmaceutical University, Sendai, Japan. (5)Department of Neurology, Yonezawa National Hospital, Yonezawa, Japan. (6)Department of Neurology, Saitama Medical University, Kawagoe, Japan. (7)Department of Pediatrics, Chiba Kaihin Municipal Hospital, Chiba, Japan. (8)Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, California, USA. (9)Department of Multiple Sclerosis Therapeutics, Fukushima Medical University, Fukushima, Japan. (10)Multiple Sclerosis and Neuromyelitis Optica Center, Tohoku Research Institute for Neuroscience, Koriyama, Japan.

OBJECTIVE: To evaluate cerebrospinal fluid (CSF) cytokine profiles in myelin oligodendrocyte glycospentin IgG-positive (MOG-IgG+) disease in adult and paediatric patients. METHODS: In this cross-sectional study, we measured 27 cytokines in the CSF of MOG-IgG+ disease in acute phase before treatment (n=29). The data were directly compared with those in aquaporin-4 antibody-positive (AQP4-IgG+) neuromyelitis optica spectrum disorder (NMOSD) (n=20), multiple sclerosis (MS) (n=20) and non-inflammatory controls (n=14).

RESULTS: In MOG-IgG+ disease, there was no female preponderance and the ages were younger (mean 18 years, range 3-68; 15 were below 18 years) relative to AQP4-IgG+ NMOSD (41, 15-77) and MS (34, 17-48). CSF cell counts were higher and oligoclonal IgG bands were mostly negative in MOG-IgG+ disease and AQP4-IgG+ NMOSD compared with MS. MOG-IgG+ disease had significantly elevated levels of interleukin (IL)-6, IL-8, granulocyte-colony stimulating factor and granulocyte macrophage-colony stimulating factor, interferon-γ, IL-10, IL-1 receptor antagonist, monocyte chemotactic protein-1 and macrophage inflammatory protein-1α as compared with MS. No cytokine in MOG-IgG+ disease was significantly different from AQP4-IgG- NMOSD. Moreover many elevated cytokines were correlated with each other in MOG-IgG+ disease and AQP4-IgG+ NMOSD but not in MS. No difference in the data was seen between adult and paediatric MOG-IgG+ cases. CONCLUSIONS: The CSF cytokine profile in the acute phase of MOG-IgG+ disease is characterised by coordinated upregulation of T helper 17 (Th17) and other cytokines including some Th1-related and regulatory T cells-related ones in adults and children, which is similar to AQP4-IgG+ NMOSD but clearly different from MS. The results suggest that as with AQP4-IgG+ NMOSD, some disease-modifying drugs for MS may be ineffective in MOG-IgG+ disease while they may provide potential therapeutic targets.

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**MOG antibody disorders and AQP4 antibody NMO spectrum disorders share a common immunopathogenesis.**

Uzawa A(1), Mori M(1), Kuwabara S(1).
Author information: (1)Department of Neurology, Graduate School of Medicine, Chiba University, Chiba, Japan.
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**Less frequent rituximab retreatment maintains remission of neuromyelitis optica spectrum disorder, following long-term rituximab treatment.**

Author information: (1)Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, South Korea.
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Retinal ganglion cell loss in neuromyelitis optica: a longitudinal study.


Author information: (1)NeuroCure Clinical Research Center, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany. (2)Institute of Clinical Neuroimmunology, Ludwig Maximilians University, Munich, Germany. (3)Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK. (4)Monash School of Medicine, Monash University & The Alfred Hospital, Melbourne, Victoria, Australia. (5)Central Clinical School, Department of Neurosciences, Monash University, Melbourne, Victoria, Australia. (6)Experimental and Clinical Research Center, Max Delbrueck Center for Molecular Medicine and Charité-Universitätsmedizin Berlin, Berlin, Germany. (7)Department of Neurology, Medical Faculty, Heinrich Heine University Düsseldorf, Düsseldorf, Germany. (8)Department of Neurology, Charité-Universitätsmedizin Berlin, Berlin, Germany. (9)Molecular Neuroimmunology Group, Department of Neurology, University of Heidelberg, Heidelberg, Germany. (10)NeuroCure Clinical Research Center, Charité-Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany. friedemann.paul@charite.de. (11)Department of Neurology, University of California, Irvine, Irvine, CA, United States.

OBJECTIVES: Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory conditions of the central nervous system and an important differential diagnosis of multiple sclerosis (MS). Unlike MS, the course is usually relapsing, and it is unclear, if progressive neurodegeneration contributes to disability. Therefore, we aimed to investigate if progressive retinal neuroaxonal damage occurs in aquaporin-4 antibody-seropositive NMOSD. METHODS: Out of 157 patients with NMOSD screened, 94 eyes of 51 patients without optic neuritis (ON) during follow-up (F/U) and 56 eyes of 28 age-matched and sex-matched healthy controls (HC) were included (median F/U 2.3 years). The NMOSD cohort included 60 eyes without (EyeON-) and 34 eyes with a history of ON prior to enrolment (EyeON+). Peripapillary retinal nerve fibre layer thickness (pRNFL), fovea thickness (FT), volumes of the combined ganglion cell and inner plexiform layer (GCIP) and the inner nuclear layer (INL) and total macular volume (TMV) were acquired by optical coherence tomography (OCT). RESULTS: At baseline, GCIP, FT and TMV were reduced in EyeON+ (GCIP p=0.002; FT p=0.040; TMV p=6.1e-06) and in EyeON- (GCIP p=0.002; FT p=0.040; TMV p=6.1e-06) compared with HC. Longitudinally, we observed GCIP thinning in EyeON- (p=0.044) but not in EyeON+. Seven patients had attacks during F/U; they presented pRNFL thickening compared with patients without attacks (p=0.003). CONCLUSION: This study clearly shows GCIP loss independent of ON attacks in aquaporin4-antibody-seropositive NMOSD. Potential explanations for progressive GCIP thinning include primary retinopathy, drug-induced neurodegeneration and retrograde neuroaxonal degeneration from lesions or optic neuropathy. pRNFL thickening in the patients presenting with attacks during F/U might be indicative of pRNFL susceptibility to inflammation.

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Effects of multiple sclerosis disease-modifying therapies on employment measures using patient-reported data.

Chen J(1), Taylor BV(1), Blizzard L(1), Simpson S Jr(1)(2), Palmer AJ(1), van der Mei IAF(3).

Author information: (1)Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia. (2)Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia. (3)Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia

ingrid.vandermei@utas.edu.au.

BACKGROUND: The direct comparative evidence on treatment effects of available multiple sclerosis (MS) disease-modifying therapies (DMTs) is limited, and few studies have examined the benefits of DMTs on employment outcomes. We compared the effects of DMTs used in the previous 5 years on improving the work attendance, amount of work and work productivity of people with MS. METHODS: The Australian MS Longitudinal Study collected data from participants on DMTs usage from 2010 to 2015 and whether DMTs contributed to changes in employment outcomes. We classified 11 DMTs into three categories based on their clinical efficacy (β-interferons and glatiramer acetate as category 1; teriflunomide and dimethyl fumarate as category 2; fingolimod, natalizumab, alemtuzumab and mitoxantrone as category 3). Each DMT used by a participant was treated as one observation and analysed by log-multinomial regression.

RESULTS: Of the 874 participants included, 1384 observations were generated. Those who used category 3 (higher efficacy) DMTs were 2-3 times more likely to report improvements in amount of work, work attendance and work productivity compared with those who used category 1 (classical injectable) DMTs. Natalizumab was associated with superior beneficial effects on patient-reported employment outcomes than fingolimod (RR=1.76, 95% CI 1.02 to 3.03 for increased work attendance and RR=1.46, 95% CI 1.02 to 2.10 for increased work productivity). CONCLUSIONS: Those using the higher efficacy (category 3) DMTs, particularly fingolimod and natalizumab, reported significant increases in amount of work, work attendance and work productivity, suggesting they have important beneficial effects on work life in people with MS. © Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

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Response to screening ability of cognitive function by two measures in patients with multiple sclerosis.

Gromisch ES(1), Portnoy JG(2), Foley FW(3).

Author information: (1)Mandell Center for Multiple Sclerosis, Mount Sinai Rehabilitation Hospital, Trinity Health Of New England, 490 Blue Hills Avenue, Hartford, CT 06112, USA. Electronic address: elizabeth.gromisch@stfranciscare.org. (2)Ferkauf Graduate School of Psychology, Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10468, USA. (3)Ferkauf Graduate School of Psychology, Yeshiva University, 1300 Morris Park Avenue, Bronx, NY 10468, USA; Holy Name Medical Center Multiple Sclerosis Center, 718 Teaneck Road, Teaneck, NJ 07666, USA.

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Screening ability of cognitive function by two measures in patients with multiple sclerosis.

Kawada T(1).

Author information: (1)Department of Hygiene and Public Health, Nippon Medical School, Japan. Electronic address: kawada@nms.ac.jp.

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Post-gadolinium 3-dimensional spatial, surface, and structural characteristics of glioblastomas differentiate pseudoprogression from true tumor progression.


Author information: (1)Neuroinnovation Program, Multiple Sclerosis & Neuroimmunology Imaging Program, Department of Neurology & Neurotherapeutics, UT Southwestern Medical Center, Clinical Center for Multiple Sclerosis, 3923 Harry Hines Blvd., Dallas, TX, 75390-8806, USA. (2)Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Simmons Comprehensive Cancer Center, Dallas, TX, USA. (3)Department of Computer Science, University of Texas at Dallas, Dallas, TX, USA. (4)Department of Statistical Science, Baylor University, Waco, TX, USA. (5)Department of Radiology, Southwestern Medical Center, Dallas, TX, USA. (6)Neuroinnovation Program, Multiple Sclerosis & Neuroimmunology Imaging Program, Department of Neurology & Neurotherapeutics, UT Southwestern Medical Center, Clinical Center for Multiple Sclerosis, 3923 Harry Hines Blvd., Dallas, TX, 75390-8806, USA.

darin.okuda@UTsouthwestern.edu.

PURPOSE: Pseudoprogression is often indistinguishable from true tumor progression on conventional 2-dimensional (2D) MRI in glioblastoma multiforme (GBM) patients. The aim of this study was to determine the association between post-gadolinium 3-dimensional (3D) characteristics and clinical state in GBM patients.

METHODS: Standardized 3D brain MRI studies were performed, and contrast enhancing portions of each tumor were segmented and analyzed, blinded to clinical state, using principal component analysis (PCA), medial axis transformation (MAT), and coverage analysis. Associations between the 3D characteristics of the post-gadolinium enhanced regions and the clinical status of patients were performed. RESULTS: A total of 15 GBM patients [male: 11 (73%); median age (range): 62 years (36-72)] with a median disease duration of 6 months (range 2-24 months) were studied cross-sectionally with 6 (40%) patients identified with tumor progression. Post-gadolinium features corresponding to the group with progressive disease exhibited a more spherical and symmetric shape relative to their stable counterparts (p = 0.005). The predictive value of a more uniformly full post-gadolinium enhanced shell to clinical progression was determined with a sensitivity of 66.7% (95% CI 29.9-92.5), specificity of 100% (54.1-100), and PPV of 100% (p = 0.028, 2-tailed Fisher's exact test). There did not appear to be an association between the thickness of the contrast enhanced shell to clinical state. CONCLUSIONS: The application of 3D technology with post-gadolinium imaging data may inform healthcare providers with new insights into disease states based on spatial, surface, and structural patterns.

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Glia Fibrillary Acidic Protein Antibody: Another Antibody in the Multiple Sclerosis Diagnostic Mix.
Seay M(1), Galetta S.
Author information: (1)Departments of Neurology (MS, SG) and Ophthalmology (SG), New York University School of Medicine, New York, New York.
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Main inherited neurodegenerative cerebellar ataxias, how to recognize them using magnetic resonance imaging?
Heidelberg D(1), Ronsin S(2), Bonneville F(3), Hannoun S(4), Tilikete C(5), Cotton F(6).
Author information: (1)Faculty of Medicine, Claude-Bernard Lyon 1 University, 69000 Lyon, France; Service de radiologie and Laboratoire d'anatomie de Rockefeller, centre hospitalier Lyon Sud, hospices civils de Lyon, 69000 Lyon, France. (2)Neuro-ophtalmology unit and neurology D, Neurological and Neurosurgical Hospital P. Wertheimer, Hospices Civils de Lyon, 69000 Lyon, France. (3)Service de neuroradiologie diagnostique et thérapeutique, Hôpitaux de Toulouse, Hôpital Pierre-Paul-Riquet, 31000 Toulouse, France. (4)Nehme and Therese Tohme Multiple Sclerosis Center, American University of Beirut Medical Center, 1107, 2020 Beirut, Lebanon. (5)Faculty of Medicine, Claude-Bernard Lyon 1 University, 69000 Lyon, France; Neuro-ophtalmology unit and neurology D, Neurological and Neurosurgical Hospital P. Wertheimer, Hospices Civils de Lyon, 69000 Lyon, France; Lyon neuroscience research center, Inserm U1028, CNRS UMR5292, Impact Team, 69000 Lyon, France. (6)Faculty of Medicine, Claude-Bernard Lyon 1 University, 69000 Lyon, France; Service de radiologie and Laboratoire d'anatomie de Rockefeller, centre hospitalier Lyon Sud, hospices civils de Lyon, 69000 Lyon, France; CREATIS, Inserm U1044/CNRS UMR 5220, 69000 Lyon, France. Electronic address: francois.cotton@chu-lyon.fr.
Ataxia is a neurodegenerative disease resulting from brainstem, cerebellar, and/or spinocerebellar tracts impairments. Symptoms onset could vary widely from childhood to late-adulthood. Autosomal cerebellar ataxias are considered as one of the most complex group in neurogenetics. In addition to their genetic heterogeneity, there is an important phenotypic variability in the expression of cerebellar impairment, complicating the genetic mutation research. A pattern recognition approach using brain MRI measures of atrophy, hyperintensities and iron-induced hypointensity of the dentate nuclei, could be therefore helpful in guiding genetic research. This review will discuss a pattern recognition approach that, associated with the age at disease onset, and clinical manifestations, may help neuroradiologists differentiate the most frequent profiles of ataxia.
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**A stable and easily reproducible model of focal white matter demyelination.**

Luo Q(1), Ding L(1), Zhang N(1), Jiang Z(1), Gao C(1), Xue L(1), Peng B(1), Wang G(2).

Author information: (1)Department of Neurophysiology and Neuropharmacology, Institute of Nautical Medicine and Co-Innovation Center of Neuroregeneration, Nantong University, 9 Seyuan Road, Chongchuan District, Nantong, Jiangsu 226019, China. (2)Department of Neurophysiology and Neuropharmacology, Institute of Nautical Medicine and Co-Innovation Center of Neuroregeneration, Nantong University, 9 Seyuan Road, Chongchuan District, Nantong, Jiangsu 226019, China. Electronic address: wgh@ntu.edu.cn.

**BACKGROUND:** Demyelination is the end product of numerous pathological processes, and also is one of the main causes of neurological disability in Multiple sclerosis (MS). Research into the pathogenesis of MS is hampered by the conventional rodent models' inability to produce stable demyelination. **NEW METHOD:** Focal demyelinating lesions were stereotactically targeted to the corpus callosum with a two-point injection of lysophosphatidylcholine (LPC-2) in mice. Three groups were analyzed (n = 8, each) and water maze, sensorimotor test, and compound action potential were included in functional tests. Electron microscopy was used for morphological analyses while western blot and immunohistochemistry were included for molecular detection. **RESULTS:** Ten days after the LPC-2 injection, the expression of myelin basic protein (MBP) was reduced, while non-phosphorylated neurofilament (SMI-32) was increased. The amplitude of the N1 segment decreased and less well-defined myelin sheaths was found. Behavioral tests showed increased latency to escape and reduced time spent in target quadrant. Four weeks later, MBP expression still reduced, SMI-32 expression was increased, both spatial learning (D24-D27) and spatial memory (D28) were still significantly impaired in LPC-2 injection mice. **COMPARISON WITH EXISTING METHOD(S):** Compared with the classic single-point LPC-injection model, our studies showed that the two-point LPC-injection not only could induce demyelination in a short-term manner, but also could cause demyelination in a long-term manner with little remyelination in the mouse corpus callosum. **CONCLUSIONS:** We established a simple, reliable, and inexpensive model of demyelination in the corpus callosum in mice, with functional and morphological reproducibility, and good validity.

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Quantification characteristics of digital spiral analysis for understanding the relationship among tremor and clinical measures in persons with multiple sclerosis.

DelMastro HM(1), Ruiz JA(2), Gromisch ES(1), Garbalosa JC(3), Triche EW(1), Olson KM(1), Lo AC(1). 
Author information: (1)(a)Mandell Center for Multiple Sclerosis, Mount Sinai Rehabilitation Hospital: A Member of Trinity Health Of New England, 490 Blue Hills Avenue, Hartford, CT, USA. (2)(a)Mandell Center for Multiple Sclerosis, Mount Sinai Rehabilitation Hospital: A Member of Trinity Health Of New England, 490 Blue Hills Avenue, Hartford, CT, USA. Electronic address: JFawcett@stfranciscare.org. (3)(b)Motion Analysis Laboratory, Department of Physical Therapy, Quinnipiac University, 275 Mount Carmel Avenue, Hamden, CT, USA.

BACKGROUND: Multiple sclerosis (MS) is a degenerative neurological condition causing demyelination and neuronal loss. Tremor, a symptom of MS, is prevalent in 45.0–46.8% NARCOMS registrants. Although several tools to measure tremor exist, few outcomes are quantitative or regularly utilized clinically. NEW METHOD: Introduction of a novel adaptation of the digital spiral drawing to find a quick, sensitive, and clinically useful technique, to predict tremor in persons with MS (pwMS). Digital spiral measures included: Segment Rate (SEGRT), Standard Deviation (SD) of Radial Velocity (VSD-R), SD of Tangential Velocity (VSD-T), SD of Overall Velocity (VSD-O), Mean Drawing Velocity (MNV-O) and Mean Pen Pressure Acceleration (MNA-P). Digital spiral measures were compared with the manual Archimedes Spiral (AS) drawing and the following clinical measures: Finger-Nose Test (FNT), presence of visually observed intention tremor (VOT), Nine-Hole Peg Test (NHPT), and Box and Block Test (BBT). RESULTS: All clinical measures utilized demonstrated significant relationships with all digital variables, except VSD-R. The forward-stepwise regression revealed BBT accounted for the most variance, followed by SEGRT. Comparison with Existing Methods: SEGRT is more sensitive in detecting VOT and better for quantifying tremor than AS. BBT and SEGRT are optimal predictive measures for tremor. CONCLUSIONS: SEGRT has stronger sensitivity and negative predictive value than AS in detecting VOT. All clinical measures (NHPT, FNT, BBT, and AS) were significantly associated with the digital variables (SEGRT, VSD-T, VSD-O, MNV-O, and MNA-P) except for VSD-R. After controlling for Patient Determined Disease Steps (PDDS), BBT and SEGRT are the best predictive measures for tremor.

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Nutritional modulation of the intestinal microbiota: future opportunities for the prevention and treatment of neuroimmune and neuroinflammatory disease.

Lombardi VC(1), De Meirleir KL(2), Subramanian K(3), Nourani SM(4), Dagda RK(5), Delaney SL(6), Palotás A(7).

Author information: (1)Nevada Center for Biomedical Research, University of Nevada, Reno, 1664 N. Virginia St. MS 0552, Reno, NV, 89557, USA; University of Nevada, Reno, School of Medicine, Department of Pathology, 1664 N. Virginia St. MS 0357, Reno, NV, 89557, USA. Electronic address: vlombardi@med.unr.edu. (2)Nevada Center for Biomedical Research, University of Nevada, Reno, 1664 N. Virginia St. MS 0552, Reno, NV, 89557, USA. Electronic address: de.meirleir@telenet.be. (3)Nevada Center for Biomedical Research, University of Nevada, Reno, 1664 N. Virginia St. MS 0552, Reno, NV, 89557, USA. Electronic address: ksm400@gmail.com. (4)University of Nevada, Reno, School of Medicine, Department of Internal Medicine, 1664 N. Virginia St. MS 0357, Reno, NV, 89557, USA; Advanced Therapeutic, General Gastroenterology & Hepatology Digestive Health Associates, Reno, NV, USA. Electronic address: samnourani@gmail.com. (5)University of Nevada, Reno, School of Medicine, Department of Pharmacology, 1664 N. Virginia St. MS 0318, Reno, NV, 89557, USA. Electronic address: rdagda@med.unr.edu. (6)Columbia University, Department of Psychiatry, New York, NY, USA. Electronic address: sld2158@cumc.columbia.edu. (7)Kazan Federal University, Institute of Fundamental Medicine and Biology, (Volga Region), 18 Kremlyovskaya St., Kazan 420008, Russia; Asklepios-Med (private medical practice and research center), Kossuth Lajos st. 23, Szeged, H-6722, Hungary. Electronic address: palotas@asklepios-med.eu.

The gut-brain-axis refers to the bidirectional communication between the enteric nervous system and the central nervous system. Mounting evidence supports the premise that the intestinal microbiota plays a pivotal role in its function and has led to the more common and perhaps more accurate term gut-microbiota-brain axis. Numerous studies have identified associations between an altered microbiome and neuroimmune and neuroinflammatory diseases. In most cases, it is unknown if these associations are cause or effect; notwithstanding, maintaining or restoring homeostasis of the microbiota may represent future opportunities when treating or preventing these diseases. In recent years, several studies have identified the diet as a primary contributing factor in shaping the composition of the gut microbiota, and in turn, the mucosal and systemic immune systems. In this review, we will discuss the potential opportunities and challenges with respect to modifying and shaping the microbiota through diet and nutrition in order to treat or prevent neuroimmune and neuroinflammatory disease.

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Rapid and Specific Immunomagnetic Isolation of Mouse Primary Oligodendrocytes.

Flores-Obando RE(1), Freidin MM(2), Abrams CK(3).

Author information: (1)Program in Molecular and Cellular Biology, State University of New York Downstate Medical Center. (2)Department of Neurology and Rehabilitation, University of Illinois at Chicago. (3)Department of Neurology and Rehabilitation, University of Illinois at Chicago; cabrams1@uic.edu.

The efficient and robust isolation and culture of primary oligodendrocytes (OLs) is a valuable tool for the in vitro study of the development of oligodendroglia as well as the biology of demyelinating diseases such as multiple sclerosis and Pelizaeus-Merzbacher-like disease (PMLD). Here, we present a simple and efficient selection method for the immunomagnetic isolation of stage three O4+ preoligodendrocytes cells from neonatal mice pups. Since immature OL constitute more than 80% of the rodent-brain white matter at postnatal day 7 (P7) this isolation method not only ensures high cellular yield, but also the specific isolation of OLs already committed to the oligodendroglial lineage, decreasing the possibility of isolating contaminating cells such as astrocytes and other cells from the mouse brain. This method is a modification of the techniques reported previously, and provides oligodendrocyte preparation purity above 80% in about 4 h.

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Wei HJ(1), Letterio JJ(2), Pareek TK(3).

Author information: (1)Department of Biochemistry, School of Medicine, Case Western Reserve University. (2)Department of Pediatrics, Division of Pediatric Hematology/Oncology, Case Western Reserve University; Angie Fowler Cancer Institute, Rainbow Babies & Children's Hospital, University Hospitals, Cleveland. (3)Department of Pediatrics, Division of Pediatric Hematology/Oncology, Case Western Reserve University; Angie Fowler Cancer Institute, Rainbow Babies & Children's Hospital, University Hospitals, Cleveland; tkp5@case.edu.

The immune system operates by maintaining a tight balance between coordinating responses against foreign antigens and maintaining an unresponsive state against self-antigens as well as antigens derived from commensal organisms. The disruption of this immune homeostasis can lead to chronic inflammation and to the development of autoimmunity. Dendritic cells (DCs) are the professional antigen-presenting cells of the innate immune system involved in activating naïve T cells to initiate immune responses against foreign antigens. However, DCs can also be differentiated into TolDCs that act to maintain and promote T cell tolerance and to suppress effector cells contributing to the development of either autoimmune or chronic inflammation conditions. The recent advancement in our understanding of TolDCs suggests that DC tolerance can be achieved by modulating their differentiation conditions. This phenomenon has led to tremendous growth in developing TolDC therapies for numerous immune disorders caused due to break in immune tolerance. Successful studies in preclinical autoimmunity murine models have further validated the immunotherapeutic utility of TolDCs in the treatment of autoimmune disorders. Today, TolDCs have become a promising immunotherapeutic tool in the clinic for reinstating immune tolerance in various immune disorders by targeting pathogenic autoimmune responses while leaving protective immunity intact. Although an array of strategies has been proposed by multiple labs to induce TolDCs, there is no consistency in characterizing the cellular and functional phenotype of these cells. This protocol provides a step-by-step guide for the development of bone marrow-derived DCs in large numbers, a unique method used to differentiate them into TolDCs with a synthetic triterpenoid 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid-difluoro-propyl-amide (CDDO-DFPA), and the techniques used to confirm their phenotype, including analyses of essential molecular signatures of TolDCs. Finally, we show a method to assess TolDC function by testing their immunosuppressive response in vitro and in vivo in a preclinical model of multiple sclerosis.

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Association of Retinal Neurodegeneration on Optical Coherence Tomography With Dementia: A Population-Based Study.


Author information: (1)Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands. (2)Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands. (3)Department of Radiology and Nuclear Medicine, Erasmus Medical Center, Rotterdam, the Netherlands. (4)Department of Neurology, Erasmus Medical Center, Rotterdam, the Netherlands. (5)Department of Psychiatry, Erasmus Medical Center, Rotterdam, the Netherlands. (6)Department of Ophthalmology, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands.

Importance: Retinal structures may serve as a biomarker for dementia, but longitudinal studies examining this link are lacking. Objective: To investigate the association of inner retinal layer thickness with prevalent and incident dementia in a general population of Dutch adults. Design, Setting, and Participants: From September 2007 to June 2012, participants from the prospective population-based Rotterdam Study who were 45 years and older and had gradable retinal optical coherence tomography images and at baseline were free from stroke, Parkinson disease, multiple sclerosis, glaucoma, macular degeneration, retinopathy, myopia, hyperopia, and optic disc pathology were included. They were followed up until January 1, 2015, for the onset of dementia. Exposures: Inner retinal layer thicknesses (ie, retinal nerve fiber layer [RNFL]) and ganglion cell-inner plexiform layer (GC-IPL) thicknesses measured on optical coherence tomography images. Main Outcomes and Measures: Odds ratios and hazard ratios for incident dementia per SD decrease in retinal layer thickness adjusted for age, sex, education, and cardiovascular risk factors. Results: Of 5065 individuals eligible for optical coherence tomography scanning, 3289 (64.9%) (mean [SD] age 68.9 [9.9] years, 1879 [57%] women) were included in the analysis. Of these 3289 individuals, 41 (1.2%) already had dementia. Thinner GC-IPL was associated with prevalent dementia (odds ratio per SD decrease in GC-IPL, 1.37 [95% CI, 0.99-1.90]). No association was found of RNFL with prevalent dementia. During 14,674 person-years of follow-up (mean [SD], 4.5 [1.6] years), 86 individuals (2.6%) developed dementia of whom 68 (2.1%) had Alzheimer disease. Thinner RNFL at baseline was associated with an increased risk of developing dementia (hazard ratio per SD decrease in RNFL, 1.44 [95% CI, 1.19-1.75]), which was similar for Alzheimer disease (hazard ratio, 1.43 [95% CI, 1.15-1.78]). No association was found between GC-IPL thickness and incident dementia (hazard ratio, 1.13 [95% CI, 0.90-1.43]). Conclusions and Relevance: Thinner RNFL is associated with an increased risk of dementia, including Alzheimer disease, suggesting that retinal neurodegeneration may serve as a preclinical biomarker for dementia.

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Monocyte NOTCH2 expression predicts IFN-β immunogenicity in multiple sclerosis patients.

Adriani M(1), Nytrova P(2), Mbogning C(3), Hässler S(3), Medek K(2), Jensen PEH(4), Creeke P(5), Warnke C(6)(7), Ingenhoven K(6), Hemmer B(8), Sievers C(9), Lindberg Gasser RL(9), Fissolo N(10), Deisenhammer F(11), Bocskei Z(12), Mikol V(12), Fogdell-Hahn A(13), Kubala Havrdova E(2), Broët P(3)(14), Dönnes P(15), Mauri C(1), Jury EC(1); ABIRISK Consortium.

Author information: (1)Department of Rheumatology, University College Hospital, London, United Kingdom. (2)Department of Neurology and Center for Clinical Neuroscience, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic. (3)CESP, Fac. De Médecine-Univ. Paris-Sud, Fac. De Médecine-UVSQ, INSERM, Université Paris-Saclay, Villejuif, France. (4)Neuroimmunology Laboratory, DMSC, Department of Neurology, Rigshospitalet, Region H, Copenhagen, Denmark. (5)Neuroimmunology Unit, Centre for Neuroscience and Trauma, Blizard Institute, Queen Mary University of London, London, United Kingdom. (6)Department of Neurology, Medical Faculty, Research Group for Clinical and Experimental Neuroimmunology, Heinrich-Heine-University, Düsseldorf, Germany. (7)University Hospital Koeln, Department of Neurology, Koeln, Germany. (8)Klinikum rechts der Isar, Department of Neurology, School of Medicine, Technical University of Munich, Munich, Germany. (9)Laboratory of Clinical Neuroimmunology, Departments of Biomedicine and Clinical Research, University Hospital Basel and University of Basel, Basel, Switzerland. (10)Centre d'Esclerosi Multiple de Catalunya (Cemcat), Hospital Universitari Vall d'Hebron, Barcelona, Spain. (11)Clinical Department of Neurology, Innsbruck Medical University, Innsbruck, Austria. (12)Translational Sciences Unit, Sanofi R&D, 91385 Chilly-Mazarin, Paris, France. (13)Karolinska Institutet, Department of Clinical Neuroscience, Center for Molecular Medicine (CMM), Karolinska University Hospital, Sweden. (14)Assistance Publique - Hôpitaux de Paris, Hôpital Paul Brousse, Villejuif, France. (15)Scicross AB, Skövde, Sweden.

Multiple sclerosis (MS) is an autoimmune disease characterized by CNS inflammation leading to demyelination and axonal damage. IFN-β is an established treatment for MS; however, up to 30% of IFN-β-treated MS patients develop neutralizing antidrug antibodies (nADA), leading to reduced drug bioactivity and efficacy. Mechanisms driving antidrug immunogenicity remain uncertain, and reliable biomarkers to predict immunogenicity development are lacking. Using high-throughput flow cytometry, NOTCH2 expression on CD14+ monocytes and increased frequency of proinflammatory monocyte subsets were identified as baseline predictors of nADA development in MS patients treated with IFN-β. The association of this monocyte profile with nADA development was validated in 2 independent cross-sectional MS patient cohorts and a prospective cohort followed before and after IFN-β administration. Reduced monocyte NOTCH2 expression in nADA+ MS patients was associated with NOTCH2 activation measured by increased expression of Notch-responsive genes, polarization of monocytes toward a nonclassical phenotype, and increased proinflammatory IL-6 production. NOTCH2 activation was T cell dependent and was only triggered in the presence of serum from nADA+ patients. Thus, nADA development was driven by a proinflammatory environment that triggered activation of the NOTCH2 signaling pathway prior to first IFN-β administration.

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Antineutrophil Cytoplasmic Antibody and Multiple Sclerosis.

George JC(1), Mohan P(1), Ho K(1).

Author information: (1)Department of Nephrology, Geisinger Medical Center, Danville, Pennsylvania, USA.

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Glomerular Filtration Rate in Patients with Multiple Sclerosis Undergoing Stem Cell Transplantation and Treated With Cyclophosphamide.


Author information: (1)Department of Immunology, Laboratorios Clínicos de Puebla. Puebla, México. (2)School of Medicine, Universidad Popular Autónoma del Estado de Puebla. Puebla, México. (3)Centro de Hematología y Medicina Interna. Puebla, México.

Background: Glomerular filtration rate (GFR) is partially impaired in patients with multiple sclerosis (MS). When given chemotherapy before receiving hematopoietic stem-cell transplantation, GFR might be further deteriorated. Objective: To measure the effect of cyclophosphamide on GFR in patients with MS who undergo chemotherapy. Methods: We estimated GFR based on creatinine and cystatin C plasma concentrations in patients undergoing autologous hematopoietic stem-cell transplantation to treat their MS. Results: Baseline GFR values were lower in the 28 patients with MS than in the 20 healthy individuals. Also, according to the Chronic Kidney Disease-Epidemiology Collaborative Group (CKD-EPI) 2012 Creat-CysC equation criteria, 4 of 28 patients were classified as having chronic kidney disease (CKD) before receiving the chemotherapy drugs. After receiving 4 × 50 mg per kg body weight cyclophosphamide, abnormal GFR results were recorded in 12 of 28 patients. Conclusions: Renal function must be monitored in patients with MS undergoing autologous stem-cell transplantation. Also, chemotherapy should be constrained as much as possible to prevent further deterioration of renal function.

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Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants.

Hanlon P(1), Nicholl BI(1), Jani BD(1), Lee D(2), McQueenie R(1), Mair FS(3).

Author information: (1)General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, 1 Horselethill Road, Glasgow, G12 9LX, Scotland, United Kingdom. (2)School of Mathematics and Statistics, University of Glasgow, Glasgow, UK. (3)General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, 1 Horselethill Road, Glasgow, G12 9LX, Scotland, United Kingdom. Electronic address: frances.mair@glasgow.ac.uk.

BACKGROUND: Frailty is associated with older age and multimorbidity (two or more long-term conditions); however, little is known about its prevalence or effects on mortality in younger populations. This paper aims to examine the association between frailty, multimorbidity, specific long-term conditions, and mortality in a middle-aged and older aged population.

METHODS: Data were sourced from the UK Biobank. Frailty phenotype was based on five criteria (weight loss, exhaustion, grip strength, low physical activity, slow walking pace). Participants were deemed frail if they met at least three criteria, pre-frail if they fulfilled one or two criteria, and not frail if no criteria were met. Sociodemographic characteristics and long-term conditions were examined. The outcome was all-cause mortality, which was measured at a median of 7 years follow-up. Multinomial logistic regression compared sociodemographic characteristics and long-term conditions of frail or pre-frail participants with non-frail participants. Cox proportional hazards models examined associations between frailty or pre-frailty and mortality. Results were stratified by age group (37-45, 45-55, 55-65, 65-73 years) and sex, and were adjusted for multimorbidity count, socioeconomic status, body-mass index, smoking status, and alcohol use.

FINDINGS: 493 737 participants aged 37-73 years were included in the study, of whom 16 538 (3%) were considered frail, 185 360 (38%) pre-frail, and 291 839 (59%) not frail. Frailty was significantly associated with multimorbidity (prevalence 18% [4435/25 338] in those with four or more long-term conditions; odds ratio [OR] 27·1, 95% CI 25·3-29·1) socioeconomic deprivation, smoking, obesity, and infrequent alcohol consumption. The top five long-term conditions associated with frailty were multiple sclerosis (OR 15·3; 99·75% CI 12·8-18·2); chronic fatigue syndrome (12·9; 11·1-15·0); chronic obstructive pulmonary disease (5·6; 5·2-6·1); connective tissue disease (5·4; 5·0-5·8); and diabetes (5·0; 4·7-5·2). Pre-frailty and frailty were significantly associated with mortality for all age strata in men and women (except in women aged 37-45 years) after adjustment for confounders.

INTERPRETATION: Efforts to identify, manage, and prevent frailty should include middle-aged individuals with multimorbidity, in whom frailty is significantly associated with mortality, even after adjustment for number of long-term conditions, sociodemographics, and lifestyle. Research, clinical guidelines, and health-care services must shift focus from single conditions to the requirements of increasingly complex patient populations.

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Distinct regional brain atrophy pattern in multiple sclerosis and neuropsychiatric systemic lupus erythematosus patients.


Author information: (1) Division of Neurochemistry and Neuropathology, Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland. (2) Department of Neurology and Cerebrovascular Disorders, Poznan University of Medical Sciences, Poznan, Poland. (3) Department of Neurology, Poznan University of Medical Sciences, Poznan, Poland. (4) Department of Rheumatology and Rehabilitation, Poznan University of Medical Sciences, Poznan, Poland. (5) Department of Rheumatology and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland. (6) Department of Neuroradiology, Poznan University of Medical Sciences, Poznan, Poland.

Differentiation of systemic lupus erythematosus (SLE) from multiple sclerosis (MS) can be challenging, especially when neuropsychiatric (NP) symptoms are accompanied by white matter lesions in the brain. Given the lack of discriminative power of currently applied tools for their differentiation, there is an unmet need for other measures that can aid in distinguishing between the two autoimmune disorders. In this study we aimed at exploring whether brain atrophy measures could serve as markers differentiating MS and SLE. Thirty-seven relapsing-remitting MS and 38 SLE patients with nervous system manifestations, matched according to age and disease duration, underwent 1.5 Tesla magnetic resonance imaging (MRI), including volumetric sequences, and clinical assessment. Voxelwise analysis was performed using ANTS-SyN elastic registration protocol, FSL Randomise and Gamma methods. Cortical and subcortical segmentation was performed with Freesurfer 5.3 pipeline using T1-weighted MPRAGE sequence data. Using MRI volumetric markers of general and subcortical gray matter atrophy and clinical variables, we built a stepwise multivariable logistic diagnostic model to identify MRI parameters that best differentiate MS and SLE patients. We found that the best volumetric predictors to distinguish them were: fourth ventricle volume (sensitivity 0.86, specificity 0.57, area under the curve, AUC 0.77), posterior corpus callosum (sensitivity 0.81, specificity 0.57, AUC 0.68), and third ventricle to thalamus ratio (sensitivity 0.42, specificity 0.84, AUC 0.65). The same classifiers were identified in a subgroup analysis that included patients with a short disease duration. In MS brain atrophy and lesion load correlated with clinical disability, while in SLE age was the main determinant of brain volume. This study proposes new imaging parameters for differential diagnosis of MS and SLE with central nervous system involvement. We show there is a different pattern of atrophy in MS and SLE, and the key structural volumes that are differentially affected include fourth ventricle and posterior section of corpus callosum, followed by third ventricle to thalamus ratio. Different correlation patterns between volumetric and clinical data may suggest that while in MS atrophy is driven mainly by disease activity, in SLE it is mostly associated with age. However, these results need further replication in a larger cohort.

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**Voxel-Wise Logistic Regression and Leave-One-Source-Out Cross Validation for white matter hyperintensity segmentation.**

Knight J(1), Taylor GW(2), Khademi A(3).

Author information:  (1)University of Guelph, 50 Stone Rd E, Guelph, Canada. Electronic address: jesse.x.knight@gmail.com. (2)University of Guelph, 50 Stone Rd E, Guelph, Canada; Vector Institute, 101 College Street, Toronto, Suite HL30B, Canada. (3)Ryerson University, 350 Victoria St, Toronto, Canada.

Many algorithms have been proposed for automated segmentation of white matter hyperintensities (WMH) in brain MRI. Yet, broad uptake of any particular algorithm has not been observed. In this work, we argue that this may be due to variable and suboptimal validation data and frameworks, precluding direct comparison of methods on heterogeneous data. As a solution, we present Leave-One-Source-Out Cross Validation (LOSO-CV), which leverages all available data for performance estimation, and show that this gives more realistic (lower) estimates of segmentation algorithm performance on data from different scanners. We also develop a FLAIR-only WMH segmentation algorithm: Voxel-Wise Logistic Regression (VLR), inspired by the open-source Lesion Prediction Algorithm (LPA). Our variant facilitates more accurate parameter estimation, and permits intuitive interpretation of model parameters. We illustrate the performance of the VLR algorithm using the LOSO-CV framework with a dataset comprising freely available data from several recent competitions (96 images from 7 scanners). The performance of the VLR algorithm (median Similarity Index of 0.69) is compared to its LPA predecessor (0.58), and the results of the VLR algorithm in the 2017 WMH Segmentation Competition are also presented.

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**What about novel pathogenetic mechanisms in Multiple Sclerosis? The emerging role of mitochondria.**

Portaro S(1), Naro A(1), Cimino V(1), Calabrò RS(2).

Author information:  (1)IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy. (2)IRCCS Centro Neurolesi "Bonino-Pulejo", Messina, Italy. Electronic address: salbro77@tiscali.it.

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**Prevalence and predictors of dysphagia in Iranian patients with multiple sclerosis.**

Tarameshlu M(1), Azimi AR(2), Gheilichi L(3), Ansari NN(4).

Author information:  (1)Department of Speech Therapy, School of Rehabilitation, Tehran University of Medical Sciences, Tehran, Iran. (2)MS Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran. (3)Department of Speech and Language Pathology, Rehabilitation Research Center, School of Rehabilitation Sciences, Iran University of Medical Sciences, Tehran, Iran. (4)Department of Physiotherapy, School of Rehabilitation, Sports Medicine Research Center, Tehran University of Medical Sciences, & Neuromusculoskeletal Research Center, Iran University of Medical Sciences, Tehran, Iran.

Background: Dysphagia is frequently observed in patients with multiple sclerosis (MS). Dysphagia and its complications are common causes of morbidity and mortality in final stages of MS disease. This study aimed at determining the prevalence of dysphagia in Iranian patients with MS and identifying predictors associated with dysphagia. Methods: A total of 230 MS patients were enrolled in this cross-sectional study. Dysphagia was evaluated using Mann Assessment of Swallowing Ability (MASA). Demographic characteristics (age and gender), duration of the disease, disease course, and Expanded Disability Status Scale (EDSS) were recorded for all participants. Results: In total, dysphagia was found in 85 participants (37%) with mild to severe dysphagia (mild 50.6%; moderate 29.4%; and severe 20%). The logistic regression model demonstrated that disability status in EDSS (OR= 2.1; 95% CI 0.5-1.2) and disease duration (OR= 2.3; 95% CI 0.4-1.1) predicts a high risk for dysphagia in MS patients. Conclusion: Dysphagia is prevalent in Iranian patients with MS. Disability level and disease duration are significant predictors of dysphagia after MS.

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Role of Inflammasomes in Neuroimmune and Neurodegenerative Diseases: A Systematic Review.

Lang Y(1), Chu F(1), Shen D(1), Zhang W(1), Zheng C(1), Zhu J(1)(2), Cui L(1).

Author information: (1)Department of Neurology and Neuroscience Center, First Hospital of Jilin University, Changchun, Jilin Province, China. (2)Department of Neurobiology, Care Sciences & Society, Division of Neurodegeneration, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden.

Inflammasomes are multiprotein complexes that can sense pathogen-associated molecular patterns and damage-associated molecular signals. They are involved in the initiation and development of inflammation via activation of IL-1β and IL-18. Many recent studies suggest a strong correlation between inflammasomes and neurological diseases, such as multiple sclerosis (MS), Alzheimer's disease (AD), and Parkinson's disease (PD).

Several components of inflammasomes, such as nucleotide-binding oligomerization domain-(NOD-) like receptor, absent in melanoma 2- (AIM2-) like receptors (ALRs), apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC), and caspase-1, as well as the upstream factors and downstream effectors, are associated with the initiation and development of MS and its animal model, experimental autoimmune encephalomyelitis. Additionally, inflammasomes affect the efficacy of interferon-β therapy in patients with MS. Finally, the strong association of inflammasomes with AD and PD needs to be further studied. In this review of latest literatures, we comprehensively tease out diverse roles of different kinds of inflammasomes in neuroimmune and neurodegenerative diseases, especially in the perspective of double roles involved in pathogenesis, and identify future research priorities.

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Turri M(1), Teatini F(2), Donato F(3), Zanette G(4), Tugnoli V(5), Deotto L(6), Bonetti B(7), Squintani G(8).

Author information: (1)Department of Neurology, Central Hospital of Bolzano, 39100 Bolzano, Italy. turrimara@gmail.com. (2)Department of Neurology, Central Hospital of Bolzano, 39100 Bolzano, Italy. francesco.teatini@sabes.it. (3)Department of Neurology, SS Giovanni e Paolo Hospital, 30122 Venice, Italy. donato.fnc@gmail.com. (4)Department of Neuroscience, Casa di Cura Pederzoli, 37019 Peschiera del Garda, VR, Italy. gi.zanette@libero.it. (5)Neurology Unit, Department of Neuroscience and Rehabilitation, S. Anna Hospital, 44124 Ferrara, Italy. v.tugnoli@ospfe.it. (6)Neurology Unit, Department of Neuroscience, AOUI Verona, 37126 Verona, Italy. luciano.deotto@gmail.it. (7)Neurology Unit, Department of Neuroscience, AOUI Verona, 37126 Verona, Italy. bruno.bonetti@univr.it. (8)Neurology Unit, Department of Neuroscience, AOUI Verona, 37126 Verona, Italy. giovannamaddalena.squintani@avvr.veneto.it.

Background. Delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) (nabiximols or Sativex®) is an oromucosal spray formulation containing THC and CBD at an approximately 1:1 fixed ratio. Its administration for the treatment of pain in patients with multiple sclerosis (MS) has been established. MS patients generally complain of different kinds of pain, including spasticity-related and neuropathic pain. In this study, we compared and evaluated pain modulation and thermal/pain threshold of MS patients before and after THC/CBD administration. Methods. 19 MS patients underwent clinical examination, numerical rating scale (NRS), quantitative sensory testing (QST), and laser-evoked potentials (LEPs) before and after 1 month of therapy. Psychophysiological and neurophysiological data were compared to sex- and age-matched controls. Results. Patients reported a significant reduction in pain. We found statistically significant differences in LEP parameters between patients and controls but no significant change in LEP measures after THC/CBD therapy. Cold and heat detection thresholds were altered in patients but did not change after THC/CBD therapy. There was a significant increase in cold pain threshold by hand stimulation and a significant reduction in abnormal cold perception thresholds. Conclusions. Our results indicate that Sativex® therapy provides pain relief in MS patients and suggest that it might modulate peripheral cold-sensitive TRP channels.

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What’s new in multiple sclerosis?

Tillery EE(1), Clements JN(2), Howard Z(3).

Author information: (1)Associate Professor of Pharmacy Practice, Presbyterian College School of Pharmacy, Clinton, South Carolina, ettily2020@gmail.com. (2)Associate Professor of Pharmacy Practice, Presbyterian College School of Pharmacy, Clinton, South Carolina. (3)3 PGY1 Clinical Pharmacy Resident, Catawba Valley Medical Center, Hickory, North Carolina.

Introduction: Multiple sclerosis (MS) is a chronic disease state that affects and disables many people each year. The most common clinical presentation is relapsing-remitting MS (RRMS). In the past 7 years, new medications have been approved for the treatment of RRMS, thereby providing more treatment options for patients and providers. The purpose of this article is to provide an update on medications for the treatment of MS that have been approved since January 2010. Methods: A review was performed utilizing CenterWatch to search for medications approved by the US Food and Drug Administration for the treatment of RRMS between January 2010 and April 2017. The package inserts of medications indicated for RRMS were analyzed, and key points were summarized. PubMed and EBSCOhost were utilized to identify articles relevant to RRMS background and treatment. Results: Seven medications with varying mechanisms of action have been approved to treat RRMS since 2010. Pharmacotherapy options include oral and injectable formulations. Efficacy across the agents is comparable, and each agent has safety data from clinical trials. The safety profile varies between oral and injectable agents, but potential adverse effects are important to consider before initiation. Therapeutic selection is based on patient preference, dosing (frequency and route), and safety considerations. Discussion: Multiple therapeutic options are available for the treatment of RRMS. Health care practitioners should be cognizant of the adverse effects, dosing route, and frequency in order to optimally tailor therapy to meet individual patient needs.

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Impact of a mental health clinical pharmacist on a primary care mental health integration team.

Harms M(1), Haas M(2), Larew J(3), DeJongh B(4).

Author information: (1)Mental Health Clinical Pharmacy Specialist, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin; michelle.harms@va.gov. (2)Mental Health Clinical Pharmacy Specialist, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin. (3)Mental Health Clinical Pharmacy Specialist, Multiple Sclerosis Clinic/Home Base Primary Care Clinical Pharmacy Specialist, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin. (4)Mental Health Clinical Pharmacy Specialist, Clement J. Zablocki Veterans Affairs Medical Center, Milwaukee, Wisconsin; Assistant Professor of Pharmacy Practice, Concordia University Wisconsin School of Pharmacy, Mequon, Wisconsin.

Introduction: Primary care mental health integration (PCMHI) teams function to improve access and quality of integrative physical and mental health (MH) care through a stepped care treatment approach. The project's primary objective was to evaluate the impact a PCMHI clinical pharmacist made on treatment outcomes and interventions. The secondary objective was to assess medication adherence rates. Methods: An electronic medical record was used to identify PCMHI patient referrals for medication management during an 8-month period. Patients were included if they were at least 18 years old and referred for medication management of depression, anxiety, posttraumatic stress disorder, or alcohol use disorder. The scores for the Patient Health Questionnaire (PHQ-9), the Generalized Anxiety Disorder Questionnaire (GAD-7), and the Posttraumatic Stress Disorder Checklist (PCL-C) were recorded at baseline and weeks 4, 8, and 12 during treatment. Results: The analysis included 50 patients, which resulted in a total of 156 contacts between July 2014 and March 2015. The mean change in PHQ-9, GAD-7, and PCL-C scores at week 12 as compared to baseline were a decrease of 10 (95% confidence interval [CI], 6.2-13.8, P < .001), 8 (95% CI, 3.1-12.9, P = .006), and 14.5 (95% CI, -17.3-46.3, P = .109), respectively. A total of 336 treatment interventions were made, and the overall medication adherence rate was 82.9%. Discussion: Medication management, provided by a clinical pharmacist, was associated with a statistically and clinically significant improvement on several MH disorder rating scale scores.

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Evidence for the use of "medical marijuana" in psychiatric and neurologic disorders.

Noel C(1).

Author information: (1)Assistant Professor of Pharmacy Practice, St John Fisher College Wegman's School of Pharmacy, Rochester, New York; Clinical Pharmacist, University of Rochester Medical Center, Rochester, New York, cnoel@sjfc.edu.

Introduction: Cannabis is listed as a Schedule I substance under the Controlled Substances Act of 1970, meaning the US federal government defines it as an illegal drug that has high potential for abuse and no established medical use; however, half of the states in the nation have enacted "medical marijuana" (MM) laws. Clinicians must be aware of the evidence for and against the use of MM in their patients who may consider using this substance. Methods: A PubMed database search was performed using the text string: "Cannabis"[Mesh] OR "Marijuana Abuse"[Mesh] OR "Medical Marijuana"[Mesh] OR "Marijuana Smoking"[Mesh] OR "cannabi*" OR "tetrahydrocannabinol." The search was further limited to randomized clinical publications in English on human subjects to identify articles regarding the therapeutic use of phytocannabinoids for psychiatric and neurologic disorders. Commercially available products (ie, dronabinol, nabilone, nabiximols) and synthetic cannabinoids were excluded from the review. Results: Publications were identified that included patients with dementia, multiple sclerosis, Parkinson disease, Huntington disease, schizophrenia, social anxiety disorder, depression, tobacco use disorder, and neuropathic pain. Discussion: There is great variety concerning which medical conditions are approved for treatment with MM for either palliative or therapeutic benefit, depending on the state law. It is important to keep an evidence-based approach in mind, even with substances considered to be illegal under US federal law. Clinicians must weigh risks and benefits of the use of MM in their patients and should ensure that patients have tried other treatment modalities with higher levels of evidence for use when available and appropriate.

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The m.11778 A > G variant associated with the coexistence of Leber’s hereditary optic neuropathy and multiple sclerosis-like illness dysregulates the metabolic interplay between mitochondrial oxidative phosphorylation and glycolysis.

Uittenbogaard M(1), Brantner CA(2), Fang Z(3), Wong LJ(3), Gropman A(4), Chiaramello A(5).

Author information: (1)Department of Anatomy and Regenerative Biology, George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA. (2)GW Nanofabrication and Imaging Center, Office of the Vice President for Research, George Washington University, Washington, DC 20052, USA. (3)Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX 77030, USA. (4)Children's National Medical Center, Division of Neurogenetics and Developmental Pediatrics, Washington, DC 20010, USA. (5)Department of Anatomy and Regenerative Biology, George Washington University School of Medicine and Health Sciences, Washington, DC 20037, USA. Electronic address: achiaram@gwu.edu.

Little is known about the molecular mechanism of the rare coexistence of Leber’s Hereditary Optic Neuropathy (LHON) and multiple sclerosis (MS), also known as the Harding's syndrome. In this study, we provide novel evidence that the m.11778A > G variant causes a defective metabolic interplay between mitochondrial oxidative phosphorylation and glycolysis. We used dermal fibroblasts derived from a female proband exhibiting clinical symptoms compatible with LHON-MS due to the presence of the pathogenic m.11778A > G variant at near homoplasmic levels. Our mitochondrial morphometric analysis reveals abnormal cristae architecture. Live-cell respiratory studies show stunted metabolic potential and spare respiratory capacity, vital for cell survival upon a sudden energy demand. The m.11778A > G variant also alters glycolytic activities with a diminished compensatory glycolysis, thereby preventing an efficient metabolic reprogramming during a mitochondrial ATP crisis. Our collective results provide evidence of limited bioenergetic flexibility in the presence of the m.11778 A > G variant. Our study sheds light on the potential pathophysiologic mechanism of the m.11778 A > G variant leading to energy crisis in this patient with the LHON-MS disease.

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G-Protein-Coupled Receptor Gpr17 Expression in Two Multiple Sclerosis Remyelination Models.

Nyamoya S(1)(2), Leopold P(1), Becker B(1), Beyer C(1), Hustadt F(3), Schmitz C(2), Michel A(3), Kipp M(4).

Author information: (1)Institute of Neuroanatomy and JARA-BRAIN, Faculty of Medicine, RWTH Aachen University, 52074, Aachen, Germany. (2)Department of Anatomy II, Ludwig-Maximilians-University of Munich, 80336, Munich, Germany. (3)Neurosciences TA Biology, UCB BioPharma, Braine L'Alleud, Brussels, Belgium. (4)Department of Anatomy II, Ludwig-Maximilians-University of Munich, 80336, Munich, Germany. markus.kipp@med.uni-muenchen.de.

In multiple sclerosis patients, demyelination is prominent in both the white and gray matter. Chronic clinical deficits are known to result from acute or chronic injury to the myelin sheath and inadequate remyelination. The underlying molecular mechanisms of remyelination and its failure remain currently unclear. Recent studies have recognized G protein-coupled receptor 17 (GPR17) as an important regulator of oligodendrocyte development and remyelination. So far, the relevance of GPR17 for myelin repair was mainly tested in remyelinating white matter lesions. The relevance of GPR17 for gray matter remyelination as well as remyelination of chronic white matter lesions was not addressed so far. Here, we provide a detailed characterization of GPR17 expression during experimental de- and remyelination. Experimental lesions with robust and limited endogenous remyelination capacity were established by either acute or chronic cuprizone-induced demyelination. Furthermore, remyelinating lesions were induced by the focal injection of lysophosphatidylcholine (LPC) into the corpus callosum. GPR17 expression was analyzed by complementary techniques including immunohistochemistry, in situ hybridization, and real-time PCR. In control animals, GPR17+ cells were evenly distributed in the corpus callosum and cortex and displayed a highly ramified morphology. Virtually all GPR17+ cells also expressed the oligodendrocyte-specific transcription factor OLIG2. After acute cuprizone-induced demyelination, robust endogenous remyelination was evident in the white matter corpus callosum but not in the gray matter cortex. Endogenous callosal remyelination was paralleled by a robust induction of GPR17 expression which was absent in the gray matter cortex. Higher numbers of GPR17+ cells were as well observed after LPC-induced focal white matter demyelination. In contrast, densities of GPR17+ cells were comparable to control animals after chronic cuprizone-induced demyelination indicating quiescence of this cell population. Our findings demonstrate that GPR17 expression induction correlates with acute demyelination and sufficient endogenous remyelination. This strengthens the view that manipulation of this receptor might be a therapeutic opportunity to support endogenous remyelination.

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Anti-epileptogenic and Anti-convulsive Effects of Fingolimod in Experimental Temporal Lobe Epilepsy.


Author information: (1)Section for Translational Epilepsy Research, Department of Neuropathology, University of Bonn Medical Center, Sigmund-Freud-Str. 25, 53105, Bonn, Germany. jpitsch@uni-bonn.de. (2)Section for Translational Epilepsy Research, Department of Neuropathology, University of Bonn Medical Center, Sigmund-Freud-Str. 25, 53105, Bonn, Germany. (3)Unit of Epileptology and Experimental Neurophysiology, Fondazione Istituto Neurologico Carlo Besta, 20133, Milan, Italy. (4)Clinic for Neurosurgery, University of Bonn Medical Center, 53105, Bonn, Germany. (5)Clinic for Epileptology, University of Bonn Medical Center, 53105, Bonn, Germany.

Temporal lobe epilepsy (TLE) represents a devastating neurological condition, in which approximately 4/5 of patients remain refractory for anti-convulsive drugs. Epilepsy surgery biopsies often reveal the damage pattern of "hippocampal sclerosis" (HS) characterized not only by neuronal loss but also pronounced astrogliosis and inflammatory changes. Since TLE shares distinct pathogenetic aspects with multiple sclerosis (MS), we have here scrutinized therapeutic effects in experimental TLE of the immunomodulator fingolimod, which is established in MS therapy. Fingolimod targets sphingosine-phosphate receptors (S1PRs). mRNAs of fingolimod target S1PRs were augmented in two experimental post status epilepticus (SE) TLE mouse models (suprahippocampal kainate/pilocarpine). SE frequently induces chronic recurrent seizures after an extended latency referred to as epileptogenesis. Transient fingolimod treatment of mice during epileptogenesis after suprahippocampal kainate-induced SE revealed substantial reduction of chronic seizure activity despite lacking acute attenuation of SE itself. Intriguingly, fingolimod exerted robust anti-convulsive activity in kainate-induced SE mice treated in the chronic TLE stage and had neuroprotective and anti-gliotic effects and reduced cytotoxic T cell infiltrates. Finally, the expression profile of fingolimod target-S1PRs in human hippocampal biopsy tissue of pharmacoresistant TLE patients undergoing epilepsy surgery for seizure relief suggests repurposing of fingolimod as novel therapeutic perspective in focal epilepsies.

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Structure-Activity Relationship of Cannabis Derived Compounds for the Treatment of Neuronal Activity-Related Diseases.

Prandi C(1), Blangetti M(2), Namdar D(3), Koltai H(4).

Author information: (1)Department of Chemistry, University of Turin, 10125 Torino, Italy. cristina.prandi@unito.it. (2)Department of Chemistry, University of Turin, 10125 Torino, Italy. Marco.blangetti@unito.it. (3)ARO, Volcani Center, Rishon LeZion 7505101, Israel. namdardv@gmail.com. (4)ARO, Volcani Center, Rishon LeZion 7505101, Israel. hkolta@agri.gov.il.

Cannabis sativa active compounds are extensively studied for their therapeutic effects, beyond the well-known psychotropic activity. C. Sativa is used to treat different medical indications, such as multiple sclerosis, spasticity, epilepsy, ulcerative colitis and pain. Simultaneously, basic research is discovering new constituents of cannabis-derived compounds and their receptors capable of neuroprotection and neuronal activity modulation. The function of the various phytochemicals in different therapeutic processes is not fully understood, but their significant role is starting to emerge and be appreciated. In this review, we will consider the structure-activity relationship (SAR) of cannabinoid compounds able to bind to cannabinoid receptors and act as therapeutic agents in neuronal diseases, e.g., Parkinson’s disease.

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α-Linolenic acid is associated with MRI activity in a prospective cohort of multiple sclerosis patients.

Bjornevik K(1), Myhr KM(2), Beiske A(3), Bjerve KS(4), Holmøy T(5), Hovdal H(6), Midgard R(7), Riise T(8), Wergeland S(2), Torkildsen Ø(9).

Author information: (1)Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA, USA; Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; The Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway. (2)Department of Clinical Medicine, University of Bergen, Bergen, Norway; Norwegian MS Registry and Biobank, Department of Neurology, Haukeland University Hospital, Bergen, Norway. (3)Multiple Sclerosis Centre Hakadal, Hakadal, Norway. (4)Clinic of Laboratory Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. (5)Department of Neurology, Akershus University Hospital, Lørenskog, Norway; Institute of Clinical Medicine, University of Oslo, Oslo, Norway. (6)Department of Neurology, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway. (7)Department of Neurology, Molde Hospital, Molde, Norway. (8)Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; The Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway. (9)The Norwegian Multiple Sclerosis Competence Centre, Department of Neurology, Haukeland University Hospital, Bergen, Norway; Department of Clinical Medicine, University of Bergen, Bergen, Norway.

BACKGROUND: The plant-based ω-3 fatty acid α-linolenic acid (ALA) has been associated with lower MS risk. It is currently unknown whether ALA affects disease activity. OBJECTIVE: To investigate the association between ALA levels and disease activity. METHODS: We conducted a cohort study including 87 multiple sclerosis (MS)-patients who originally participated in a randomized trial of ω-3 fatty acids (the OFAMS study). We measured serum levels of ALA during follow-up and used random intercept logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CIs) for the association between ALA levels, new magnetic resonance imaging (MRI) lesions, Expanded Disability Status Scale (EDSS) progression and new relapses adjusting for age at inclusion, sex, and use of interferon beta-1a. RESULTS: In continuous (per 1-SD increase) multivariable-adjusted analyses, higher ALA levels were significantly associated with lower odds of new T2-lesions (OR: 0.59, 95% CI: 0.37-0.95) during follow-up. The effect estimates were similar for new T1Gd+ lesions (OR: 0.73, 95% CI: 0.48-1.11), EDSS-progression (OR: 0.62, 95% CI: 0.34-1.16) and new relapses (OR: 0.49, 95% CI: 0.22-1.10), but these estimates did not reach statistical significance. Further adjustment for vitamin D and tobacco use did not materially change the results. CONCLUSION: We found that higher levels of ALA were associated with lower disease activity in MS-patients. DOI: 10.1177/1352458518779925 PMID: 29862891
Detection and clinical correlation of leukocortical lesions in pediatric-onset multiple sclerosis on multi-contrast MRI.

Maranzano J(1), Till C(2), Assemlal HE(1), Fonov V(3), Brown R(1), Araujo D(1), O'Mahony J(4), Yeh EA(4), Bar-Or A(5), Marrie RA(6), Collins L(3), Banwell B(7), Arnold DL(1), Narayanan S(1); Canadian Pediatric Demyelinating Disease Network.

Author information: (1)Departments of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, QC, Canada. (2)Department of Psychology, York University, Toronto, ON, Canada Division of Neurology, Department of Pediatrics, The Hospital for Sick Children Research Institute, University of Toronto, Toronto, ON, Canada. (3)Image Processing Laboratory, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada. (4)Division of Neurology, Department of Pediatrics, The Hospital for Sick Children Research Institute, University of Toronto, Toronto, ON, Canada. (5)Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. (6)Departments of Internal Medicine and Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada. (7)Children's Hospital of Philadelphia, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA Division of Neurology, Department of Pediatrics, The Hospital for Sick Children Research Institute, University of Toronto, Toronto, ON, Canada.

OBJECTIVE: To determine the frequency of cortical lesions (CLs) in patients with pediatric-onset multiple sclerosis (POMS) using multi-contrast magnetic resonance imaging (MRI), and the relationship between frontal CL load and upper limb dexterity assessed with the Nine-Hole Peg Test (9-HPT). METHODS: Participants completed the 9-HPT and were imaged on a 3T MRI scanner to collect T1-weighted three-dimensional (3D) magnetization prepared rapid gradient echo (MPRAGE), proton density-weighted, T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. CLs were manually segmented using all MRI contrasts. RESULTS: We enrolled 24 participants with POMS (mean (standard deviation) age at first symptom: 13.3 (±2.7) years; mean age at scan: 18.8 (±3) years; mean disease duration of 5 (±3.2) years). A total of 391 CLs (mean, 16.3 ± 27.2; median, 7) were identified in 19 of 24 POMS patients (79%). The total number of CLs was positively associated with white matter lesion volume (p = 0.04) but not with thalamic volume, age at the time of the scan, or disease duration. The number of frontal CLs was associated with slower performance on the 9-HPT (p = 0.05). CONCLUSION: Multi-contrast 3T MRI led to a high rate of CL detection, demonstrating that cortical pathology occurs even in pediatric-onset disease. Frontal lobe CL count was associated with reduced manual dexterity, indicating that these CLs are clinically relevant. DOI: 10.1177/1352458518779952 PMID: 29852831
Lifetime exposure to ultraviolet radiation and the risk of multiple sclerosis in the US radiologic technologists cohort study.


Author information: (1)Department of Epidemiology, School of Public Health, Boston University, Boston, MA, USA. (2)Department of Family Medicine and Public Health, University of California, San Diego, San Diego, CA, USA. (3)Department of Neurology, University of Washington, Seattle, WA, USA. (4)Department of Environmental & Occupational Health Sciences, University of Washington, Seattle, WA, USA. (5)Division of Cancer Epidemiology & Genetics, National Cancer Institute and DHHS, NIH, Bethesda, MD, USA. (6)Division of Environmental Health Sciences, School of Public Health, University of Minnesota, Minneapolis, MN, USA. (7)Department of Neurosciences, Department of Family Medicine and Public Health, University of California, San Diego, San Diego, CA, USA.

BACKGROUND: Low exposure to ultraviolet radiation (UVR) from sunlight may be a risk factor for developing multiple sclerosis (MS). Possible pathways may be related to effects on immune system function or vitamin D insufficiency, as UVR plays a role in the production of the active form of vitamin D in the body.

OBJECTIVE: This study examined whether lower levels of residential UVR exposure from sunlight were associated with increased MS risk in a cohort of radiologic technologists.

METHODS: Participants in the third and fourth surveys of the US Radiologic Technologists (USRT) Cohort Study eligible (N = 39,801) for analysis provided complete residential histories and reported MS diagnoses. MS-specialized neurologists conducted medical record reviews and confirmed 148 cases. Residential locations throughout life were matched to satellite data from NASA’s Total Ozone Mapping Spectrometer (TOMS) project to estimate UVR dose. RESULTS: Findings indicate that MS risk increased as average lifetime levels of UVR exposures in winter decreased. The effects were consistent across age groups <40 years. There was little indication that low exposures during summer or at older ages were related to MS risk.

CONCLUSION: Our findings are consistent with the hypothesis that UVR exposure reduces MS risk and may ultimately suggest prevention strategies.

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A framework for measurement and harmonization of pediatric multiple sclerosis etiologic research studies: The Pediatric MS Tool-Kit.

Magalhaes S(1), Banwell B(2), Bar-Or A(3), Fortier I(4), Hanwell HE(5), Lim M(6), Matt GE(7), Neuteboom RF(8), O'Riordan DL(9), Schneider PK(10), Pugliatti M(11), Shatenstein B(12), Tansey CM(13), Wassmer E(14), Wolfson C(15).

Author information: (1)Royal Victoria Hospital, Allan Memorial Institute and Neuroepidemiology Research Unit, Research Institute of the McGill University Health Centre, Montreal, QC, Canada/Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada. (2)Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, USA. (3)Center for Neuroinflammation and Experimental Therapeutics and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. (4)Research Institute of the McGill University Health Centre, Montreal, QC, Canada. (5)Dalla Lana School of Public Health, The University of Toronto, Toronto, ON, Canada. (6)Children's Neurosciences, Evelina London Children's Hospital, Guy's and St Thomas' NHS Foundations Trust, King's Health Partners Academic Health Sciences Centre, London, UK/ Faculty of Life Sciences & Medicine, King's College London, London, UK. (7)Department of Psychology, San Diego State University, San Diego, CA, USA. (8)Department of Pediatric Neurology, Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands. (9)School of Medicine, University of California, San Francisco, San Francisco, CA, USA. (10)Royal Victoria Hospital, Allan Memorial Institute and Neuroepidemiology Research Unit, Research Institute of the McGill University Health Centre, Montreal, QC, Canada. (11)Department of Medicine, McGill University, Montreal, QC, Canada/ Unit of Clinical Neurology, Department of Biomedical and Surgical Sciences, University of Ferrara, Ferrara, Italy. (12)Département de nutrition, Université de Montréal, Montreal, QC, Canada/ Centre de recherche, Institut universitaire de gériatrie de Montréal, CIUSSS du Centre-Sud-de-l'Île-de-Montréal, Montreal, QC, Canada. (13)School of Physical and Occupational Therapy, McGill University, Montreal, QC, Canada. (14)Department of Neurology, Birmingham Children's Hospital, Birmingham, UK. (15)Royal Victoria Hospital, Allan Memorial Institute and Neuroepidemiology Research Unit, Research Institute of the McGill University Health Centre, Montreal, QC, Canada/ Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada/ Department of Medicine, McGill University, Montreal, QC, Canada.

BACKGROUND: While studying the etiology of multiple sclerosis (MS) in children has several methodological advantages over studying etiology in adults, studies are limited by small sample sizes.

OBJECTIVE: Using a rigorous methodological process, we developed the Pediatric MS Tool-Kit, a measurement framework that includes a minimal set of core variables to assess etiological risk factors.

METHODS: We solicited input from the International Pediatric MS Study Group to select three risk factors: environmental tobacco smoke (ETS) exposure, sun exposure, and vitamin D intake. To develop the Tool-Kit, we used a Delphi study involving a working group of epidemiologists, neurologists, and content experts from North America and Europe. RESULTS: The Tool-Kit includes six core variables to measure ETS, six to measure sun exposure, and six to measure vitamin D intake. The Tool-Kit can be accessed online (www.maelstrom-research.org/mica/network/tool-kit). CONCLUSION: The goals of the Tool-Kit are to enhance exposure measurement in newly designed pediatric MS studies and comparability of results across studies, and in the longer term to facilitate harmonization of studies, a methodological approach that can be used to circumvent issues of small sample sizes. We believe the Tool-Kit will prove to be a valuable resource to guide pediatric MS researchers in developing study-specific questionnaire.

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Commentary on Al Hussona et al. 'New-onset seizures as a sole clinical presentation of multiple sclerosis'.

Chard DT(1).

Author information: (1)NMR Research Unit, Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, Institute of Neurology, University College London (UCL), London, UK/ National Institute for Health Research (NIHR), Biomedical Research Centre, University College London Hospitals (UCLH), London, UK.

Despite the now significant contribution of magnetic resonance imaging, the accurate and timely diagnosis of multiple sclerosis (MS) is still clinically challenging. Al Hussona et al., with their case series, highlight the complexities of attributing paroxysmal, and in particular cortical, symptoms such as epileptic seizures to inflammatory demyelinating lesions, and establishing a diagnosis of MS based on them. In such circumstances an MS diagnosis is likely to be more tentative than for more typical MS presentations, and treatment choices should be weighed accordingly.

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New onset seizures as a sole clinical presentation of multiple sclerosis.

Al Hussona M(1), Kearney H(1), Fisher A(2), Lynch J(2), Looby S(3), Delanty N(1).

Author information: (1)Department of Neurology, Beaumont Hospital, Dublin, Ireland. (2)Department of Neurology, University Hospital Galway, Galway, Ireland. (3)Department of Neuroradiology, Beaumont Hospital, Dublin, Ireland.

BACKGROUND AND OBJECTIVES: Epileptic seizures frequently occur in people with multiple sclerosis (MS) and are thought to represent a manifestation of cortical pathology. However, at present, seizures are not considered to be a typical clinical presentation of demyelination. METHODS AND RESULTS: In this case series, we identified four people, who presented with seizures as a sole presenting feature, with demyelinating imaging abnormalities that satisfy current diagnostic criteria for a clinically isolated syndrome (CIS) or early MS. CONCLUSION: Based on this case series, we propose that people presenting with de novo seizures, with concurrent radiological abnormalities suggestive of demyelination could potentially be considered to have a CIS.

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Successful implementation of an automated electronic support system for patient safety monitoring: The alemtuzumab in multiple sclerosis safety systems (AMS3) study.

Reddel SW(1), Barnett MH(2), Rimington S(3), Dugal T(4), Buzzard K(5), Wang CT(6), Fitzgerald F(7), Beadnall HN(8), Erickson D(9), Gahan D(7), Wang D(10), Ackland T(11), Thompson RI(12).

Author information: (1)Department of Neurology, Concord Hospital, The University of Sydney, Concord, NSW, Australia. (2)Sydney Neuroimaging Analysis Centre, Brain and Mind Centre, Sydney, NSW, Australia/Department of Neurology, Royal Prince Alfred Hospital, Sydney, NSW, Australia. (3)Department of Immunology, Concord Hospital, The University of Sydney, Sydney, NSW, Australia. (4)Norwest Medical Imaging, Sydney, NSW, Australia. (5)Department of Neurology, The Royal Melbourne Hospital, Parkville, VIC, Australia. (6)Sydney Neuroimaging Analysis Centre, Brain and Mind Centre, Sydney, NSW, Australia. (7)Medical Safety Systems, Sydney, NSW, Australia. (8)Brain and Mind Centre, Sydney, NSW, Australia. (9)Ryde, NSW, Australia. (10)Converged IT, Singapore. (11)Converged IT, Sydney, NSW, Australia. (12)Converged IT, Auckland, New Zealand.

BACKGROUND: Alemtuzumab is a highly effective treatment for relapsing-remitting multiple sclerosis (MS) but requires ongoing pathology monitoring for autoimmune adverse effects. The Alemtuzumab in MS Safety Systems (AMS3) study evaluated the implementation of an automated pathology-monitoring system.

OBJECTIVES: To develop an efficient automated clinical decision support system (CDSS) to electronically prompt and track pathology collection and to provide prescribers and patients with customised alerts of abnormal results for identified risks. METHODS: A total of 10 patients with relapsing-remitting MS treated with alemtuzumab were enrolled to test the system. Standard care laboratory monitoring was performed and compared to the performance of the CDSS. RESULTS: The automated CDSS, an integrated patient smartphone application and an additional pre-screening tool were all successfully developed. Compliance with pathology monitoring was 96.7%. The automated analysis of pathology results was significantly faster than standard care neurologist review (p < 0.001). The system correctly identified and alerted abnormalities, including one case of immune thrombocytopenia (ITP) while the treating neurologist was on leave, enabling prompt treatment of serious adverse events. During the course of the study, the CDSS was deployed throughout Australia. CONCLUSION: We successfully developed automated pathology monitoring with a CDSS, demonstrating real-world benefits of high compliance and timely alerting of important results.

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Estimating MS-related work productivity loss and factors associated with work productivity loss in a representative Australian sample of people with multiple sclerosis.

Chen J(1), Taylor B(1), Palmer AJ(1), Kirk-Brown A(2), van Dijk P(2), Simpson S Jr(3), Blizzard L(1), van der Mei i(1).

Author information: (1)Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia. (2)Department of Management, Monash University, Narre Warren, VIC, Australia. (3)Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia; Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia.

BACKGROUND: Little is known about the work productivity loss in multiple sclerosis (MS). OBJECTIVES: To quantify the MS-related work productivity loss and to compare factors associated with labour force participation and work productivity loss. METHODS: Participants were from the Australian MS Longitudinal Study. MS-related work productivity loss included absenteeism (time missed from work) and presenteeism (reduced productivity while working). Data were analysed using log-binomial and Cragg hurdle regression.

RESULTS: Among 740 MS employees, 56% experienced any work productivity loss due to MS in the past 4 weeks. The mean total work productivity loss was 2.5 days (14.2% lost productive time), absenteeism 0.6 days (3.4%) and presenteeism 1.9 days (10.8%), leading to AU$6767 (US$4985, EURO€4578) loss per person annually. Multivariable analyses showed that work productivity was determined most strongly by symptoms, particularly 'fatigue and cognitive symptoms' and 'pain and sensory symptoms', while older age, and lower education level were also predictive of not being in the labour force. CONCLUSION: MS-related presenteeism was three times higher than absenteeism, highlighting the importance of presenteeism being included in employment outcomes. The dominance of symptom severity as predictors of both work participation and productivity loss emphasises the need for improved management of symptoms.

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Predicting risk of secondary progression in multiple sclerosis: A nomogram.


Author information: (1)Department of Clinical Neuroscience (CNS), Karolinska Institutet, Stockholm, Sweden. (2)Division of Neurology, UBC Hospital, Faculty of Medicine, The University of British Columbia, Vancouver, BC, Canada. (3)Novartis Pharma AG, Basel, Switzerland.

OBJECTIVES: We aimed at designing a nomogram, a prediction tool, to predict the individual's risk of conversion to secondary progressive multiple sclerosis (SPMS) at the time of multiple sclerosis (MS) onset.

METHODS: One derivation and three validation cohorts were established. The derivation cohort included 8825 relapsing-onset MS patients in Sweden. A nomogram was built based on a survival model with the best statistical fit and prediction accuracy. The nomogram was validated using data from 3967 patients in the British Columbia cohort, 176 patients in the ACROSS and 2355 patients in FREEDOMS/FREEDOMS II extension studies.

RESULTS: Sex, calendar year of birth, first-recorded Expanded Disability Status Scale (EDSS) score, age at the first EDSS and age at disease onset showed significant predictive ability to estimate the risk of SPMS conversion at 10, 15 and 20 years. The nomogram reached 84% (95% confidence intervals (CIs): 83-85) internal and 77% (95% CI: 76-78), 77% (95% CI: 70-85) and 87% (95% CI: 84-89) external accuracy.

CONCLUSIONS: The SPMS nomogram represents a much-needed complementary tool designed to assist in decision-making and patient counselling in the early phase of MS. The SPMS nomogram may improve outcomes by prompting timely and more efficacious treatment for those with a worse prognosis.

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Focal and diffuse cervical spinal cord damage in patients with early relapsing-remitting MS: A multicentre magnetisation transfer ratio study.

Combès B(1), Kerbrat A(1)(2), Ferré JC(1)(3), Callot V(4)(5), Maranzano J(6), Badji A(7), Le Page E(2), Labauge P(8), Ayriugnac X(8), Carra Dalibère C(8), de Champfleur NM(8), Pelletier J(4)(9), Maarouf A(4)(9), de Seze J(10), Collongues N(10), Brassat D(11), Durand-Dubief F(12), Barillot C(1), Bannier E(1)(9), Edan G(1)(2); EMISEP Study Group.

Author information: (1)IRISA, UMR CNRS 6074, VisAGeS U1228, INSERM, INRIA, Université Rennes I, Rennes, France. (2)Neurology Department, Rennes University Hospital, Rennes, France. (3)IUMR CNRS 6074, University of Rennes 1, INSERM, BRM, Université de Rennes 1, Rennes, France. (4)MNI, Montreal, QC, Canada. (5)Montpellier University Hospital, Montpellier, France. (6)AP-HM, Hôpital de La Timone, CEMEREM, Marseille, France. (7)Aix-Marseille Université, CNRS, UMR 7339, CRMBM, Marseille, France. (8)Institut de Biomedical Engineering, Polytechnique Montréal, Montreal, Quebec, Canada. (9)Functional Neuroimaging Unit, CRUGM, Université de Montpellier, Montpellier, QC, Canada. (10)Montpellier University Hospital, Montpellier, France. (11)Institute of Neurology, University of Strasbourg, Strasbourg, France. (12)Lyon University Hospital, Lyon, France.

BACKGROUND: Studies including patients with well-established multiple sclerosis (MS) have shown a significant and disability-related reduction in the cervical spinal cord (SC) magnetisation transfer ratio (MTR).

OBJECTIVES: The objectives are to (1) assess whether MTR reduction is already measurable in the SC of patients with early relapsing-remitting multiple sclerosis (RRMS) and (2) describe its spatial distribution.

METHODS: We included 60 patients with RRMS <12 months and 34 age-matched controls at five centres. Axial T2w, sagittal T2w, sagittal phase-sensitive inversion recovery (PSIR), 3DT1w, and axial magnetisation transfer (MT) images were acquired from C1 to C7. Lesions were manually labelled and mean MTR values computed both for the whole SC and for normal-appearing SC in different regions of interest.

RESULTS: Mean whole SC MTR was significantly lower in patients than controls (33.7 vs 34.9 pu, p = 0.00005), even after excluding lesions (33.9 pu, p = 0.0003). We observed a greater mean reduction in MTR for vertebral levels displaying the highest lesion loads (C2-C4). In the axial plane, we observed a greater mean MTR reduction at the SC periphery and barycentre.

CONCLUSION: Cervical SC tissue damage measured using MTR is not restricted to macroscopic lesions in patients with early RRMS and is not homogeneously distributed.

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Peripheral imbalanced TFH/TFR ratio correlates with intrathecal IgG synthesis in multiple sclerosis at clinical onset.


Author information: (1)Multiple Sclerosis Centre, Department of Neuroscience DNS, Università degli Studi di Padova, via Giustiniani 2, 35128 Padova, Italy. (2)Multiple Sclerosis Centre, Department of Neuroscience DNS, Università degli Studi di Padova, Padova, Padova, Italy. (3)Central Laboratory, Azienda Ospedaliera di Padova, Padova, Padova, Italy. (4)Multiple Sclerosis Centre, Ospedale San Bortolo di Vicenza, Azienda ULSS 8 Berica, Vicenza, Italy. (5)UOC Immunotrasfusionale, Azienda Ospedaliera di Padova, Padova, Italy.

BACKGROUND: Alteration of T-follicular helper (TFH) and regulatory (TFR) subpopulations may contribute to the development of auto-reactive B-cell.

OBJECTIVE: To investigate whether changes in TFH and TFR subsets are associated with abnormal IgG synthesis in blood and cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients.

METHODS: Paired blood and CSF samples were obtained from 31 untreated relapsing-remitting multiple sclerosis (RRMS) patients at diagnosis. Peripheral blood TFH (CD3+CD4+CXCR5+CD25-CD127+), TFR (CD3+CD4+CXCR5+CD25+CD127+), conventional T-Helper (TH, CD3+CD4+CXCR5-CD25-CD127+), and regulatory T-cells (T-Reg, CD3+CD4+CXCR5-CD25+CD127dim) were analyzed in all RRMS patients and in 13 healthy controls (HCs). Qualitative and quantitative intrathecal IgG synthesis was evaluated in RRMS patients, who were then further subclassified according to the presence of IgG oligoclonal bands in blood and/or CSF.

RESULTS: Compared to HC, RRMS had lower TFR percentage (p < 0.01) and higher TFH/TFR ratio (p < 0.001). In RRMS, TFH/TFR ratio correlated with both qualitative (r = 0.56, p < 0.005) and quantitative intrathecal IgG synthesis (IgG Index: r = 0.78; IgGLoc: r = 0.79; IgGIF: r = 0.76, all p < 0.001). Patients with the highest TFH/TFR ratios had higher percentages of circulating B-cells (36.1 ± 35.2%, p < 0.05).

CONCLUSION: In RRMS, increased TFH/TFR ratio associates with abnormal IgG production in blood and CSF, suggesting that antibody-producing cells, derived from deregulated peripheral germinal center reaction, colonize the CNS.

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Linkage analysis and whole exome sequencing identify a novel candidate gene in a Dutch multiple sclerosis family.

Mescheriakova JY(1), Verkerk AJ(2), Amin N(3), Uitterlinden AG(2), van Duijn CM(3), Hintzen RQ(1).

Author information: (1)Department of Neurology, MS Center ErasMS, Erasmus Medical Centre, Rotterdam, The Netherlands. (2)Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands. (3)Department of Epidemiology, Erasmus Medical Centre, Rotterdam, the Netherlands.

BACKGROUND: Multiple sclerosis (MS) is a complex disease resulting from the joint effect of many genes. It has been speculated that rare variants might explain part of the missing heritability of MS.

OBJECTIVE: To identify rare coding genetic variants by analyzing a large MS pedigree with 11 affected individuals in several generations.

METHODS: Genome-wide linkage screen and whole exome sequencing (WES) were performed to identify novel coding variants in the shared region(s) and in the known 110 MS risk loci. The candidate variants were then assessed in 591 MS patients and 3169 controls.

RESULTS: Suggestive evidence for linkage was obtained to 7q11.22-q11.23. In WES data, a rare missense variant p.R183C in FKB6 was identified that segregated with the disease in this family. The minor allele frequency was higher in an independent cohort of MS patients than in healthy controls (1.27% vs 0.95%), but not significant (odds ratio (OR) = 1.33 (95% confidence interval (CI): 0.8-2.4), p = 0.31). CONCLUSION: The rare missense variant in FKB6 was identified in a large Dutch MS family segregating with the disease. This association to MS was not found in an independent MS cohort. Overall, genome-wide studies in larger cohorts are needed to adequately investigate the role of rare variants in MS risk.

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Is the goal of an epigenomic study to determine causality?
De Jager PL(1).
Author information: (1)Center for Translational and Computational Neuro-immunology, Department of Neurology, Columbia University Medical Center, New York, NY, USA/Cell Circuits Program, Broad Institute, Cambridge, MA, USA.
DOI: 10.1177/1352458517750771  PMID: 29889009


Is there an overlooked "window of opportunity" in MS exercise therapy?
Perspectives for early MS rehabilitation.
Riemenschneider M(1), Hvid LG(1), Stenager E(2), Dalgas U(1).
Author information: (1)Department of Public Health, Section of Sport Science, Aarhus University, Aarhus C, Denmark. (2)Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark/Department of Neurology, MS-Clinic of Southern Jutland (Sønderborg, Esbjerg, Kolding), Sønderborg, Denmark.
While early medical treatment has proven effective in MS, early-phase MS rehabilitation has not gained much attention in MS research and clinical practice. Exercise therapy is one of the most promising treatment strategies in MS rehabilitation. Here, we provide a topical review investigating when exercise therapy is initiated in existing MS studies, showing that exercise is initiated at a rather late disease stage, where it predominantly serves as a symptomatic treatment. Recent findings in MS suggest that exercise may have neuroprotective and disease-modifying effects. Such findings along with the findings from medical trials that an early-stage "window of opportunity" exists leads to the proposal that early exercise therapy should be an increased focus in research and clinical practice for persons with MS. A further perspective relates to other rehabilitation interventions that are also initiated at a later disease stage, as these may also take advantage of an early-phase approach.
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Novel computer-based testing shows multi-domain cognitive dysfunction in patients with multiple sclerosis.
Smith AD 3rd(1), Duffy C(2), Goodman AD(2).
Author information: (1)Department of Neurology, Dartmouth-Hitchcock Medical Center, Geisel School of Medicine Dartmouth College, USA. (2)Department of Neurology, University of Rochester Medical Center, USA.
Background: Although cognitive dysfunction is a leading cause of disability and poor quality of life in patients with multiple sclerosis (MS), it is infrequently tested in routine clinical evaluation. Development of a cognitive testing paradigm that captured MS-related cognitive dysfunction and could be obtained in a routine clinical setting may increase surveillance and recognition of cognitive dysfunction. Objectives: This was a pilot study to determine if Cognivue could find cognitive performance differences between patients with MS and healthy controls (HC). Methods: A total of 24 patients with MS and 12 HCs between 18 and 50 years old were enrolled. Baseline testing included an Expanded Disability Scale (EDSS), paced auditory serial additions test (PASAT), symbol digit modalities test (SDMT) and Cognivue. Subjects then had repeat testing every 1-2 months for a maximum of three tests. Results: Significant differences were found between MS and HC on SDMT, PASAT, and Cognivue Total score. Most Cognivue subtests showed significant differences between MS and HC: Cognivue scores correlated with both SDMT and PASAT and had high test-retest reliability in HCs. Conclusion: Cognivue was able to detect multi-domain cognitive dysfunction in MS. Further studies to determine validity of Cognivue in MS with comparison with neuropsychological testing and sensitivity to clinical change are still needed.
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**Relapse Rate and MRI Activity in Young Adult Patients With Multiple Sclerosis: A Post Hoc Analysis of Phase 3 Fingolimod Trials.**

Gärtner J(1), Chitnis T(2), Ghezzi A(3), Pohl D(4), Brück W(5), Häring DA(6), Karlsson G(6), Putzki N(6).

Author information: (1)Department of Pediatrics and Adolescent Medicine, German Centre for Multiple Sclerosis in Childhood and Adolescence, University Medical Center Göttingen, Germany. (2)Partners Pediatric Multiple Sclerosis Center, Massachusetts General Hospital, USA. (3)Centro Studi Sclerosi Multipla, Italy. (4)Division of Neurology, Children's Hospital of Eastern Ontario, University of Ottawa, Canada. (5)Institute of Neuropathology, University Medical Center Göttingen, Germany. (6)Novartis Pharma AG, Switzerland.

Background: Disease activity differs in young patients with multiple sclerosis (MS) compared with the overall adult MS population. Objective: The objective of this paper is to evaluate the effect of fingolimod 0.5 mg on disease activity in young adults with MS from three randomized, double-blind Phase 3 trials. Methods: Annualized relapse rate (ARR), number of new/newly enlarging T2 lesions (neT2), and no evidence of disease activity (NEDA-3) were estimated in the intent-to-treat population at age 20 (youngest) and 30 (young) and compared to the overall population. Models used included a negative binomial regression (ARR/neT2) and a logistic regression (NEDA), with age at baseline as a continuous covariate. Results: ARRs were higher in younger patients (all p < 0.05), and significantly reduced with fingolimod versus placebo or interferon beta-1a (IFN β-1a), with the percentage reduction inversely proportional to age. Fingolimod was significantly associated with a lower number of neT2 lesions versus placebo/IFN in all age groups except versus IFN in the youngest patients. Regardless of age, fingolimod-treated patients were more likely to achieve NEDA-3 versus placebo/IFN β-1a, with strongest benefits in the youngest patients (all p < 0.05).

Conclusions: Young adults show higher levels of MS disease activity, and may particularly benefit from fingolimod treatment compared with the overall study population.

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**Patient-Reported Disease-Modifying Therapy Adherence in the Clinic: A Reliable Metric?**

Conway DS(1), Cecilia Vieira M(2), Thompson NR(3), Parker KN(1), Meng X(2), Fox RJ(1).

Author information: (1)Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic Foundation, USA. (2)Novartis Pharmaceuticals, Division of Health Economics and Outcomes Research, East Hanover, USA. (3)Department of Quantitative Health Sciences, Neurological Institute Center for Outcomes Research and Evaluation, Cleveland Clinic Foundation, USA.

Background: Adherence to multiple sclerosis (MS) disease-modifying therapy (DMT) is commonly assessed through patient reporting, but patient-reported adherence is rarely studied. Objective: To determine rates of DMT adherence reported from patient to clinician, reasons for nonadherence, and relationships between adherence and outcomes. Methods: We identified relapsing-remitting MS patients on DMT for ≥3 months. DMT adherence was defined as taking ≥80% of doses. Linear and logistic regression models were created used to determine the association of baseline adherence with several patient reported outcomes and the timed 25-foot walk at 6 months, 1 year, 2 years, and 3 years after the index visit. Results: The analysis included 1148 patients, of whom 501 had data at 6 months, 544 at 1 year, 331 at 2 years, and 247 at 3 years. Baseline adherence was 94.9% and overall adherence was 93.1%. Forgetting was the most common reason for missed doses. In the adjusted models, adherence was not associated with the outcomes. Conclusions: Higher than expected adherence and a lack of association between adherence and outcomes suggests patient reported adherence may not be reliable. Further research is needed to clarify the relationship between patient-reported adherence and relapses or new lesion formation.

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Disease activity in progressive multiple sclerosis can be effectively reduced by cladribine.


Author information: (1)The Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom; Clinical Board: Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom. (2)The Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom; Department of Neurology, Shenzhen University General Hospital, Shenzhen University, Shenzhen, China; Shenzhen University Clinical Medical Academy, Shenzhen University, Shenzhen, China. (3)Department of Neuroradiology, The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom. (4)The Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom. (5)Clinical Board: Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom. (6)The Blizard Institute, Barts and The London School of Medicine & Dentistry, Queen Mary University of London, London, United Kingdom; Clinical Board: Medicine (Neuroscience), The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom. Electronic address: k.schmierer@qmul.ac.uk.

BACKGROUND: Evidence suggests people with non-relapsing deteriorating ("progressive") multiple sclerosis (pwPMS) may benefit from disease-modifying immune therapy (DMT). However, only one such treatment (ocrelizumab) has been licensed and is highly restricted to pwPMS suffering from the primary progressive phenotype. The difficulties assessing treatment outcome in pwPMS is one important reason for the lack of respective DMT. The concentration of neurofilaments in the cerebrospinal fluid (CSF) provides a biomarker of neuro-axonal damage, and both neurofilament light (NFL) and heavy chain (NFH) levels have been used as outcome indices and to guide treatment choices. METHODS: We report on two pwPMS, who were treated with subcutaneous cladribine undergoing CSF NFL testing, alongside MRI and clinical follow-up, before and after treatment. RESULTS: Cladribine treatment was well tolerated without any side effects. CSF NFL after treatment revealed significant reduction (by 73% and 80%, respectively) corroborating the MRI detectable drop in disease activity. Disability mildly progressed in one, and remained stable in the other pwPMS. CONCLUSIONS: pwPMS with detectable disease activity (MRI, elevated NFL) should be considered for DMT. NFL appears to be a sensitive index of treatment effect in pwPMS, and may be a useful outcome in clinical trials targeting this patient group. Over and above its licensed indication (relapsing MS), cladribine may be an effective treatment option for pwPMS.

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Depression is a predictor for balance in people with multiple sclerosis.

Alghwiri AA(1), Khalil H(2), Al-Sharman A(2), El-Salem K(3).

Author information: (1)The University of Jordan, School of Rehabilitation Sciences, Department of Physical Therapy, Amman 11942, Jordan. Electronic address: alia.alghwiri@gmail.com. (2)Jordan University of Science and Technology, Faculty of Applied Medical Sciences, Department of Rehabilitation Sciences, Irbid, Jordan. (3)Jordan University of Science and Technology, Faculty of Medicine, Department of Neurosciences, Irbid, Jordan.

BACKGROUND: Balance impairments are common and multifactorial among people with multiple sclerosis (MS). Depression is the most common psychological disorder in MS population and is strongly correlated with MS disease. Depression might be one of the factors that contribute to balance deficits in this population. However, the relationship between depression and balance impairments has not been explored in people with MS. OBJECTIVE: To investigate the association between depression and balance impairments in people with MS. METHODS: Cross sectional design was used in patients with MS. The Activities-specific Balance Confidence scale (ABC) and Berg Balance Scale (BBS) was used to assess balance. Beck Depression Inventory (BDI-II) was used to quantify depression and Kurtizki Expanded Disability Status Scale (EDSS) was utilized for the evaluation of MS disability severity. Pearson correlation coefficient was used to examine the association between depression and balance measurements. Multiple linear stepwise regressions were also conducted to find out if depression is a potential predictor for balance deficits. RESULTS: Seventy-five individuals with MS (Female = 69%) with a mean age (SD) of 38.8 (10) and a mean (SD) EDSS score of 3.0 (1.4) were recruited in this study. Depression was present in 53% of the patients. Depression was significantly correlated with balance measurements and EDSS. However, multiple linear stepwise regressions found that only depression and age significantly predict balance. CONCLUSION: Depression and balance were found frequent and associated in people with MS. Importantly depression was a significant predictor for balance impairments in individuals with MS. Balance rehabilitation may be hindered by depression. Therefore, depression should be evaluated and treated properly in individuals with MS.

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Validating the portal population of the United Kingdom Multiple Sclerosis Register.

Middleton RM(1), Rodgers WJ(2), Chataway J(3), Schmiere K(4), Rog D(5), Galea I(6), Akbari A(2), Tuitedalton K(2), Lockhart-Jones H(2), Griffiths D(2), Noble DG(2), Jones KH(2), Al-Din A(7), Craner M(8), Evangelou N(9), Harman P(10), Harrower T(11), Hobart J(12), Husseyin H(13), Kasti M(14), Kipps C(15), McDonnell G(16), Owen C(17), Pearson O(18), Rashid W(19), Wilson H(20), Ford DV(2).

Author information: (1)Swansea University Medical School, Swansea, United Kingdom. Electronic address: r.m.middleton@swansea.ac.uk. (2)Swansea University Medical School, Swansea, United Kingdom. (3)University College London, London, United Kingdom. (4)Queen Mary University of London, Blizard Institute, London, United Kingdom. (5)Salford Royal Hospital, Manchester, United Kingdom. (6)University of Southampton, Clinical Neurosciences, Southampton, United Kingdom. (7)National Health Service, Department of Neurology, North Yorkshire, United Kingdom. (8)University of Oxford, Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom. (9)University of Nottingham, Division of Clinical Neurology, Nottingham, United Kingdom. (10)Southend University Hospital NHS Foundation Trust, Southend, United Kingdom. (11)Exeter Foundation Trust, Department of Neurology Royal Devon, Exeter, United Kingdom. (12)Peninsula College of Medicine and Dentistry, Plymouth, United Kingdom. (13)Luton and Dunstable NHS Foundation Trust, Luton, United Kingdom. (14)Basildon and Thurrock Hospitals NHS Foundation Trust, Basildon United Kingdom. (15)University of Southampton, Faculty of Medicine, Southampton, United Kingdom. (16)Royal Group of Hospitals, Department of Neurology, Belfast, United Kingdom. (17)Shrewsbury and Telford Hospital NHS Trust, Shrewsbury, United Kingdom. (18)Abertawe Bro Morgannwg University Local Health Board, Swansea, United Kingdom. (19)Brighton and Sussex University Hospitals NHS Trust, Department of Neurology, Brighton, United Kingdom. (20)King’s College London, London, United Kingdom.

The UK Multiple Sclerosis Register (UKMSR) is a large cohort study designed to capture 'real world' information about living with multiple sclerosis (MS) in the UK from diverse sources. The primary source of data is directly from people with Multiple Sclerosis (pwMS) captured by longitudinal questionnaires via an internet portal. This population's diagnosis of MS is self-reported and therefore unverified. The second data source is clinical data which is captured from MS Specialist Treatment centres across the UK. This includes a clinically confirmed diagnosis of MS (by Macdonald criteria) for consented patients. A proportion of the internet population have also been consented at their hospital making comparisons possible. This dataset is called the 'linked dataset'. The purpose of this paper is to examine the characteristics of the three datasets: the self-reported portal data, clinical data and linked data, in order to assess the validity of the self-reported portal data. The internet (n = 11,021) and clinical (n = 3,003) populations were studied for key shared characteristics. We found them to be closely matched for mean age at diagnosis (clinical = 37.39, portal = 39.28) and gender ratio (female %, portal = 73.1, clinical = 75.2). The Two Sample Kolmogorov-Smirnov test was for the continuous variables to examine is they were drawn from the same distribution. The null hypothesis was rejected only for age at diagnosis (D = 0.078, p < 0.01). The populations therefore, were drawn from different distributions, as there are more patients with relapsing disease in the clinical cohort. In all other analyses performed, the populations were shown to be drawn from the same distribution. Our analysis has shown that the UKMSR portal population is highly analogous to the entirely clinical (validated) population. This supports the validity of the self-reported diagnosis and therefore that the portal population can be utilised as a viable and valid cohort of people with Multiple Sclerosis for study.

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Analysing the relationship between polysomnographic measures of sleep with measures of physical and cognitive fatigue in people with multiple sclerosis.

Chinnadurai SA(1), Gandhirajan D(2), Pamidimukala V(2), Kesavamurthy B(3), Venkatesan SA(3).

Author information: (1)Institute of Neurology, Madras Medical College, Chennai, India. Electronic address: drsomasundaram_ac@apollohospitals.com. (2)Lalitha Superspecialty Hospital, Kothapet, Guntur, India. (3)Institute of Neurology, Madras Medical College, Chennai, India.

OBJECTIVES: We aimed to determine whether there was a relationship between objective measures of sleep measured by polysomnography and measures of physical and cognitive fatigue in patients with Multiple Sclerosis (MS). METHODS: People with MS of age 18-50 years of any subtype attending the OPDs satisfying the revised 2010 McDonald criteria were recruited. Modified Fatigue Impact Scale (MFIS) and the Fatigue Severity Scale (FSS) were used to assess physical fatigue. Cognitive fatigue was measured with modified versions of the Stroop test, modified Symbol Digit Modalities Test, Serial Addition Test, and with latency and amplitude of the P300 evoked potential. Percentage of N1, N2, N3 and REM sleep stages, Sleep onset latency, Sleep efficiency, Wake after sleep onset, Respiratory event index, Periodic limb movement index were the measures recorded with polysomnography. RESULTS: Among 113 patients, 43 (38.05%) complained of disturbed sleep and 88 (77.88%) complained of increased fatigability and tiredness. Mean MFIS score of the sample was 42.34 ± 9.09. Mean FSS score was 19.12 ± 9.42. Polysomnographic measures of sleep showed a significant correlation with objective measures of cognitive fatigue and did not show any significant correlation with measures of physical fatigue. CONCLUSIONS: Sleep impairment is a very common problem in people with MS justifying routine polysomnographic evaluation. We have found evidence that though sleep impairment is not related to physical fatigue, it is strongly related to cognitive fatigue.

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Natalizumab treatment shows low cumulative probabilities of confirmed disability worsening to EDSS milestones in the long-term setting.

Trojano M(1), Butzkueven H(2), Kappos L(3), Wiendl H(4), Spelman T(5), Pellegrini F(6), Chen Y(7), Dong Q(7), Koendgen H(8), Belachew S(8); Tysabri® Observational Program (TOP) Investigators. Author information: (1)Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari, Bari, Italy. Electronic address: maria.trojano@uniba.it. (2)Department of Neuroscience, Central Clinical School, Alfred Campus, Monash University, Melbourne, Victoria, Australia; Department of Neurology, Box Hill Hospital, Monash University, Box Hill, Victoria, Australia. Electronic address: butz@unimelb.edu.au. (3)Neurologic Clinic and Polyclinic, Departments of Medicine, Clinical Research, Biomedicine and Biomedical Engineering, University Hospital and University of Basel, Basel, Switzerland. Electronic address: ludwig.kappos@usb.ch. (4)Department of Neurology-Inflammatory Disorders of the Nervous System and Neurooncology, University of Münster, Münster, Germany. Electronic address: heinz.wiendl@ukmuenster.de. (5)Department of Neuroscience, Central Clinical School, Alfred Campus, Monash University, Melbourne, Victoria, Australia; Department of Neurology, Box Hill Hospital, Monash University, Box Hill, Victoria, Australia. Electronic address: tim@burnet.edu.au. (6)Biogen, Cambridge, MA, USA. Electronic address: fabio.pellegrini@biogen.com. (7)Biogen, Cambridge, MA, USA. (8)Biogen International GmbH, Zug, Switzerland.

BACKGROUND: Though the Expanded Disability Status Scale (EDSS) is commonly used to assess disability level in relapsing-remitting multiple sclerosis (RRMS), the criteria defining disability progression are used for patients with a wide range of baseline levels of disability in relatively short-term trials. As a result, not all EDSS changes carry the same weight in terms of future disability, and treatment benefits such as decreased risk of reaching particular disability milestones may not be reliably captured. The objectives of this analysis are to assess the probability of confirmed disability worsening to specific EDSS milestones (i.e., EDSS scores ≥3.0, ≥4.0, or ≥6.0) at 288 weeks in the Tysabri Observational Program (TOP) and to examine the impact of relapses occurring during natalizumab therapy in TOP patients who had received natalizumab for ≥24 months. METHODS: TOP is an ongoing, open-label, observational, prospective study of patients with RRMS in clinical practice. Enrolled patients were naive to natalizumab at treatment initiation or had received ≤3 doses at the time of enrollment. Intravenous natalizumab (300 mg) infusions were given every 4 weeks, and the EDSS was assessed at baseline and every 24 weeks during treatment. RESULTS: Of the 4161 patients enrolled in TOP with follow-up of at least 24 months, 3253 patients with available baseline EDSS scores had continued natalizumab treatment and 908 had discontinued (5.4% due to a reported lack of efficacy and 16.4% for other reasons) at the 24-month time point. Those who discontinued due to lack of efficacy had higher baseline EDSS scores (median 4.5 vs. 3.5), higher on-treatment relapse rates (0.82 vs. 0.23), and higher cumulative probabilities of EDSS worsening (16% vs. 9%) at 24 months than those completing therapy. Among 24-month completers, after approximately 5.5 years of natalizumab treatment, the cumulative probabilities of confirmed EDSS worsening by 1.0 and 2.0 points were 18.5% and 7.9%, respectively (24-week confirmation), and 13.5% and 5.3%, respectively (48-week confirmation). The risks of 24- and 48-week confirmed EDSS worsening were significantly higher in patients with on-treatment relapses than in those without relapses. An analysis of time to specific EDSS milestones showed that the probabilities of 48-week confirmed transition from EDSS scores of 0.0-2.0 to ≥3.0, 2.0-3.0 to ≥4.0, and 4.0-5.0 to ≥6.0 at week 288 in TOP were 11.1%, 11.8%, and 9.5%, respectively, with lower probabilities observed among patients without on-treatment relapses (8.1%, 8.4%, and 5.7%, respectively). CONCLUSIONS: In TOP patients with a median (range) baseline EDSS score of 3.5 (0.0-9.5) who completed 24 months of natalizumab treatment, the rate of 48-week confirmed disability worsening events was below 15%; after approximately 5.5 years of natalizumab treatment, 86.5% and 94.7% of patients did not have EDSS score increases of ≥1.0 or ≥2.0 points, respectively. The presence of relapses was associated with higher rates of overall disability worsening. These results were confirmed by assessing transition to EDSS milestones. Lower rates of overall 48-week confirmed EDSS worsening and of transitioning from EDSS score 4.0-5.0 to ≥6.0 in the absence of relapses suggest that relapses remain a significant driver of disability worsening and that on-treatment relapses in natalizumab-treated patients are of prognostic importance. Copyright © 2018 The Authors. Published by Elsevier B.V. All rights reserved. DOI: 10.1016/j.msard.2018.04.020 PMID: 29860197
270. Mortality from Listeria monocytogenes meningoencephalitis following escalation to alemtuzumab therapy for relapsing-remitting Multiple Sclerosis.

Canham LJW(1), Manara A(2), Fawcett J(3), Rolinski M(4), Mortimer A(5), Inglis KEA(6), Cottrell DA(7).

Author information: (1)Bristol Brain Centre, Department of Neurosciences, North Bristol NHS Trust, Southmead Road, Westbury-On-Trym, BS10 5NB Bristol, United Kingdom. Electronic address: luke.canham@nbt.nhs.uk. (2)Bristol Brain Centre, Department of Neurosciences, North Bristol NHS Trust, Southmead Road, Westbury-On-Trym, BS10 5NB Bristol, United Kingdom. Electronic address: alex.manara@nbt.nhs.uk. (3)Bristol Brain Centre, Department of Neurosciences, North Bristol NHS Trust, Southmead Road, Westbury-On-Trym, BS10 5NB Bristol, United Kingdom. Electronic address: joanna.fawcett@nbt.nhs.uk. (4)Bristol Brain Centre, Department of Neurosciences, North Bristol NHS Trust, Southmead Road, Westbury-On-Trym, BS10 5NB Bristol, United Kingdom. Electronic address: michal.rolinski@nbt.nhs.uk. (5)Bristol Brain Centre, Department of Neurosciences, North Bristol NHS Trust, Southmead Road, Westbury-On-Trym, BS10 5NB Bristol, United Kingdom. Electronic address: alex.mortimer@nbt.nhs.uk. (6)Bristol Brain Centre, Department of Neurosciences, North Bristol NHS Trust, Southmead Road, Westbury-On-Trym, BS10 5NB Bristol, United Kingdom. Electronic address: kirsty.inglis@nbt.nhs.uk. (7)Bristol Brain Centre, Department of Neurosciences, North Bristol NHS Trust, Southmead Road, Westbury-On-Trym, BS10 5NB Bristol, United Kingdom. Electronic address: david.cottrell@nbt.nhs.uk.

We report the case of a patient who died from the rare complication of Listeriosis in the immediate phase following alemtuzumab administration one month after discontinuing dimethyl fumarate (DMF). There is considerable overlap with typical post-infusion symptoms therefore high surveillance and low threshold for empirical or possible prophylactic antibiotic therapy is advocated.

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Sajedi SA(1).

Author information: (1)Neuroscience Research Center, Golestan University of Medical Sciences, Gorgan, Iran. Electronic address: dr.sajedy@gmail.com.

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McNicholas N(1), Hutchinson M(2), McGuigan C(2), Chataway J(3).

Author information: (1)Department of Neurology, St. Vincent's University Hospital, Dublin 4, Elm park, Ireland. Electronic address: nmcnicholas@svhg.ie. (2)Department of Neurology, St. Vincent's University Hospital, Dublin 4, Elm park, Ireland. (3)Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, UCL Institute of Neurology, University College London, UK.

The diagnosis of Multiple Sclerosis (MS) has continuously evolved, allowing for an earlier and more accurate diagnosis of MS over time. The McDonald Criteria for diagnosis of MS were originally proposed in 2001, with previous revisions in both 2005 and 2010. The International Panel on Diagnosis in MS have recently reviewed the 2010 McDonald Criteria, and made recommendations for the revised 2017 McDonald Criteria. Any revisions made relied entirely on the available evidence, and not expert opinion. In this review, we provide an overview of the recent 2017 revisions to the McDonald Criteria, focusing in particular on the motivating evidence behind the recommendations made. We also review the existing research around misdiagnosis in MS, as well as areas considered to be high priorities of research, currently lacking in sufficient evidence, which may influence future diagnostic criteria in years to come. Finally, we illustrate some clinical examples, to demonstrate the impact of new diagnostic criteria on time to MS diagnosis in a real-world setting. Crown Copyright © 2018. Published by Elsevier B.V. All rights reserved.

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**Progressive visual function impairment as the predominant symptom of the transition phase to secondary progressive multiple sclerosis: A case report.**

Giordano A(1), Colombo B(2), Spinelli EG(2), Gelibter S(2), Guerrieri S(2), Leocani L(2), Comi G(2), Martinelli V(2).

Author information: (1)San Raffaele Scientific Institute and University Hospital, Department of Neurology, Milan, Italy. Electronic address: giordano.antonino@hsr.it. (2)San Raffaele Scientific Institute and University Hospital, Department of Neurology, Milan, Italy.

**BACKGROUND:** No reliable indicators of the transition to the progressive course in multiple sclerosis (MS) have been identified so far. The main clinical feature of the progressive phase of MS is usually impairment of walking. Magnetic resonance imaging and optical coherence tomography have emerged recently as promising tools to assess increasing neurodegeneration and axonal loss in disease progression in MS.

**METHODS:** CASE REPORT: RESULTS: We report a case of progressive visual impairment as the dominant symptom in the transition to secondary progressive MS. CONCLUSIONS: Impairment of vision, together with walking and cognition, should be considered to better define the transition from relapsing/remitting to secondary-progressive MS.

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**Real-life persistence and tolerability with dimethyl fumarate.**

Sejbaek T(1), Nybo M(2), Petersen T(3), Illes Z(4).

Author information: (1)Department of Neurology, Odense University Hospital, Odense, Denmark; Department of Clinical Research, University of Southern Denmark, Odense, Denmark. Electronic address: Tobias.Sejbaek.Mathiesen@rsyd.dk. (2)Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark. (3)Department of Neurology, Aarhus University Hospital, Aarhus, Denmark. (4)Department of Neurology, Odense University Hospital, Odense, Denmark; Department of Clinical Research, University of Southern Denmark, Odense, Denmark.

**BACKGROUND:** Dimethyl fumarate (DMF) has been registered for the treatment of relapsing-remitting multiple sclerosis (RRMS). Differences in tolerability between multiple sclerosis clinics in patients treated with DMF has not been examined. AIM: We examined real-world tolerability to DMF, and also compared adherence data between two MS clinics. METHODS: Adverse events (AE), discontinuation rates, and causes of discontinuation were investigated. RESULTS: 253 patients participated in this retrospective study. In the total cohort, 27.7% of the patients discontinued DMF. Higher rate of discontinuation was associated with higher number of previous disease modifying treatments (p < 0.001). Reasons for discontinuation were primarily flushing (15%) and gastrointestinal AEs (51%). Grade III lymphopenia was detected only in 6 cases (2.4%). We observed differences between the two clinics: discontinuation because of AEs was different (Odds ratio 6.13, 95% CI: 3.0 - 12.7, p < 0.001), the mean treatment duration also differed (305.3 ± 186.3 vs 140.5 ± 114.4 days, p < 0.001), and dissimilarities in adherence were mainly related to flushing, gastrointestinal AEs, and consideration of lymphopenia (p < 0.0001). Better adherence was associated with prospectively planned management of gastrointestinal AEs and flushing. CONCLUSION: Adherence in real-life was similar to pivotal trials. Differences in discontinuation rates at two MS clinics underline importance of AE management.

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Heart rate variability analysis in patients with multiple sclerosis.

Damla O(1), Altug C(2), Pinar KK(3), Alper K(2), Dilek IG(3), Kadiyae A(3).

Author information:  (1)Marmara University School of Medicine, Department of Neurology, Istanbul, Turkey. Electronic address: damlazbek@gmail.com. (2)Marmara University School of Medicine, Department of Cardiology, Istanbul, Turkey. (3)Marmara University School of Medicine, Department of Neurology, Istanbul, Turkey.

BACKGROUND: Multiple sclerosis can cause cardiovascular autonomic dysfunction. It is assumed that is caused by multiple demyelinating plaques localized in the brain stem and spinal cord. Previous studies have determined this using tilt table test, heart rate responses to Valsalva maneuver and deep breathing and heart rate variability analysis with 24 h Holter monitoring. However there is not a consensus regarding the presence of the relationship between autonomic dysfunction and severity of multiple sclerosis, type of multiple sclerosis and expanded disability status scale. The aim of the study is comparison of heart rate variability between recently diagnosed patients with relapsing-remitting multiple sclerosis and healthy controls by using 24 h Holter monitoring. Also we intended to investigate relationship between Expanded Disability Status Scale score, Multiple Sclerosis Functional Composite scores and cranial and spinal magnetic resonance imaging findings and hearth rate variability.

METHOD: Fifty-one patients with newly diagnosed relapsing-remitting multiple sclerosis and 44 age- and sex-matched healthy controls were compared in this study. Patients with multiple sclerosis, who were already under immunomodulatory or immunosuppressive treatment, were excluded from the study. Echocardiography and heart rate variability analysis using 24 h period Holter monitoring were performed in all of the subjects. Echocardiography was used to detect the presence of cardiac pathology. One multiple sclerosis patient with right ventricular dilatation and mobile intratrial septum was excluded from the study. All the patients underwent cranial and cervical spinal magnetic resonance imaging to determine the relationship between autonomic abnormalities and magnetic resonance imaging. RESULTS: Our results showed that hearth rate variability values were significantly lower in patients with multiple sclerosis when compared with healthy controls: SDNN index (the mean of all the 5 min standard deviations of normal RR intervals during the 24 h period) (59.80 ± 17.33 vs. 67.20 ± 21.28, p = 0.044), the root-mean-square successive difference (rMSSD) (34.40 ± 17.50 vs. 38.25 ± 12.95, p = 0.042), spectral heart rate variability total power (3738.84 ± 2085.51 vs. 4427.44 ± 1965.71, p = 0.037), spectral heart rate variability low frequency (852.03 ± 370.06 vs. 1011.75 ± 370.06, p = 0.018). Ten patients (20%) had brainstem lesion, 25 patients (50%) had cervical lesions and 10 patients (20%) had thoracic spinal lesions on magnetic resonance imaging. There was no significant relationship between location of the lesions and heart rate variability analyses. Also there was no significant relationship between hearth rate variability values and Expanded Disability Status Scale score, Multiple Sclerosis Functional Composite scores or number of multiple sclerosis attack (p > 0.05).

CONCLUSION: These findings reveals that our study population with multiple sclerosis had decreased heart rate variability compared to healthy controls. This was reflected by dysfunction of both parasympathetic and sympathetic parameters of heart rate variability analysis. However, there is no significant relationship between hearth rate variability analysis and the findings on cranial, cervical, thoracic spinal magnetic resonance imaging findings, number of attack, Expanded Disability Status Scale score or Multiple Sclerosis Functional Composite scores in patients with multiple sclerosis.

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High intensity interval training for people with multiple sclerosis: A systematic review.

Campbell E(1), Coulter EH(2), Paul L(3).

Author information: (1)School of Medicine, University of Glasgow, Glasgow, United Kingdom. Electronic address: e.campbell.4@research.gla.ac.uk. (2)Division of Dietetics, Nutrition & Biological Sciences, Physiotherapy, Podiatry & Radiography, Queen Margaret University, Edinburgh, United Kingdom; School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, United Kingdom. Electronic address: Elaine.Coulter@gcu.ac.uk. (3)School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, United Kingdom. Electronic address: LornaPaul@gcu.ac.uk.

BACKGROUND: Aerobic high intensity interval training (HIIT) is safe in the general population and more efficient in improving fitness than continuous moderate intensity training. The body of literature examining HIIT in multiple sclerosis (MS) is expanding but to date a systematic review has not been conducted. The aim of this review was to investigate the efficacy and safety of HIIT in people with MS. METHODS: A systematic search was carried out in September 2017 in EMBASE, MEDline, PEDro, CENTRAL and Web of Science Core collections using appropriate keywords and MeSH descriptors. Reference lists of relevant articles were also searched. Articles were eligible for inclusion if they were published in English, used HIIT, and included participants with MS. Quality was assessed using the PEDro scale. The following data were extracted using a standardised form: study design and characteristics, outcome measures, significant results, drop-outs, and adverse events. RESULTS: Seven studies (described by 11 articles) were identified: four randomised controlled trials, one randomised cross-over trial and two cohort studies. PEDro scores ranged from 3 to 8. Included participants (n = 249) were predominantly mildly disabled; one study included only people with progressive MS. Six studies used cycle ergometry and one used arm ergometry to deliver HIIT. One study reported six adverse events, four which could be attributed to the intervention. The other six reported that there were no adverse events. Six studies reported improvements in at least one outcome measure, however there were 60 different outcome measures in the seven studies. The most commonly measured domain was fitness, which improved in five of the six studies measuring aspects of fitness. The only trial not to report positive results included people with progressive and a more severe level of disability (Extended Disability Status Scale 6.0-8.0). CONCLUSION: HIIT appears to be safe and effective in increasing fitness in people with MS and low levels of disability. Further research is required to explore the effectiveness of HIIT in people with progressive MS and in those with higher levels of disability.

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DNA methylation as a mediator of HLA-DRB1*15:01 and a protective variant in multiple sclerosis.


Author information: (1)Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institutet, 171 77, Stockholm, Sweden. (2)Center for Epigenetics, and Departments of Medicine, Biomedical Engineering and Mental Health, Johns Hopkins University, Baltimore, MD, 21205, USA. (3)Key Laboratory of Metabolism and Molecular Medicine, Ministry of Education; Department of Biochemistry and Molecular Biology, Fudan University Shanghai Medical College, 200032, Shanghai, China. (4)Unit of Computational Medicine, Department of Medicine, Solna, Center for Molecular Medicine, Karolinska Institutet, 171 77, Stockholm, Sweden. (5)Max Planck Institute of Psychiatry, 80804, Munich, Germany. (6)Department of Neurology, Klinikum rechts der Isar, School of Medicine, Technische Universität München, 81675, Munich, Germany. (7)German Competence Network Multiple Sclerosis (KKNMS), Klinikum Rechts der Isar, Technische Universität München, 81675, Munich, Germany. (8)Department of Neurology with Institute of Translational Neurology, University of Münster, 48149, Münster, Germany. (9)Department of Neurology, University Medicine Mainz, Johannes Gutenberg University Mainz, 55122, Mainz, Germany. (10)Department of Neurology, St. Josef-Hospital, Ruhr-University Bochum, 44801, Bochum, Germany. (11)Neuroimmunology Center, Marburg University, 35037, Marburg, Germany. (12)Munich Cluster for Systems Neurology (SyNergy), 81377, Munich, Germany. (13)Institute of Genetic Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany and Institute of Medical Informatics, Biometry, and Epidemiology, Chair of Genetic Epidemiology, Ludwig-Maximilians-Universität, 80599, Munich, Germany. (14)Institute of Human Genetics, University Hospital Bonn and Division of Genomics, Life & Brain Research Centre, University of Bonn School of Medicine, 53113, Bonn, Germany. (15)Institute of Epidemiology and Social Medicine, University of Münster, 48149, Münster, Germany. (16)Department of Neurology, University Medicine Greifswald, 17489, Greifswald, Germany. (17)Institute for Community Medicine, University Medicine Greifswald, 17489, Greifswald, Germany. (18)Interfaculty Institute for Genetics and Functional Genomics, Ernst Moritz Arndt University and University Medicine Greifswald, 17489, Greifswald, Germany. (19)Institute of Clinical Molecular Biology, Kiel University, 24105, Kiel, Germany. (20)Department I of Internal Medicine, Kiel University, 24105, Kiel, Germany. (21)Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, OX3 7BN, UK. (22)Institute of Medical Microbiology and Hospital Hygiene Heinrich-Heine-Universität Düsseldorf, 40225, Düsseldorf, Germany. (23)Department of Neurology, Oslo University Hospital, 0372, Oslo, Norway. (24)Institute of Health and Society, Faculty of Medicine, University of Oslo, 0450, Oslo, Norway. (25)Danish Multiple Sclerosis Center, Department of Neurology, Rigshospitalet, University of Copenhagen, 2100, Copenhagen, Denmark. (26)Biological and Environmental Sciences and Engineering Division, Computer, Electrical and Mathematical Sciences and Engineering Division, King Abdullah University of Science and Technology, Thuwal, 23955, Saudi Arabia. (27)Institute of Clinical Medicine, University of Oslo, 0450, Oslo, Norway. (28)deCODE genetics/Amgen Inc, 101, Reykjavik, Iceland. (29)School of Science and Engineering, Reykjavik University, 101, Reykjavik, Iceland. (30)Department of Neurology, Landspitali, The National University of Iceland, 101, Reykjavik, Iceland. (31)Faculty of Medicine, School of Health Sciences, University of Iceland, 101, Reykjavik, Iceland. (32)Department of Immunology, Landspitali, The National University Hospital of Iceland, 101, Reykjavik, Iceland. (33)Center for Epigenetics, and Departments of Medicine, Biomedical Engineering and Mental Health, Johns Hopkins University, Baltimore, MD, 21205, USA. afeinberg@jhu.edu. (34)Department of Clinical Neuroscience, Center for Molecular Medicine, Karolinska Institutet, 171 77, Stockholm, Sweden. Maja.Jagodic@ki.se.

The human leukocyte antigen (HLA) haplotype DRB1*15:01 is the major risk factor for multiple sclerosis (MS). Here, we find that DRB1*15:01 is hypomethylated and predominantly expressed in monocytes among carriers of DRB1*15:01. A differentially methylated region (DMR) encompassing HLA-DRB1 exon 2 is particularly affected and displays methylation-sensitive regulatory properties in vitro. Causal inference and Mendelian randomization provide evidence that HLA variants mediate risk for MS via changes in the HLA-DRB1 DMR that modify HLA-DRB1 expression. Meta-analysis of 14,259 cases and 171,347 controls confirms that these variants confer risk from DRB1*15:01 and also identifies a protective variant (rs9267649, p < 3.32 × 10−8, odds ratio = 0.86) after conditioning for all MS-associated variants in the region. rs9267649...

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http://www.betaferon.de
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is associated with increased DNA methylation at the HLA-DRB1 DMR and reduced expression of HLA-DRB1, suggesting a modulation of the DRB1*15:01 effect. Our integrative approach provides insights into the molecular mechanisms of MS susceptibility and suggests putative therapeutic strategies targeting a methylation-mediated regulation of the major risk gene.

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**Reassessing B cell contributions in multiple sclerosis.**

Li R(1), Patterson KR(1), Bar-Or A(2).

Author information: (1)Center for Neuroinflammation and Experimental Therapeutics (CNET) and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. (2)Center for Neuroinflammation and Experimental Therapeutics (CNET) and Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. amitbar@upenn.edu.

There is growing recognition that B cell contributions to normal immune responses extend well beyond their potential to become antibody-producing cells, including roles at the innate-adaptive interface and their potential to modulate the responses of other immune cells such as T cells and myeloid cells. These B cell functions can have both pathogenic and protective effects in the context of central nervous system (CNS) inflammation. Here, we review recent advances in the field of multiple sclerosis (MS), which has traditionally been viewed as primarily a T cell-mediated disease, and we consider antibody-dependent and, particularly, emerging antibody-independent functions of B cells that may be relevant in both the peripheral and CNS disease compartments.

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Neuroimmune disorders of the central nervous system in children in the molecular era.

Wells E(1), Hacohen Y(2)(3), Waldman A(4), Tillema JM(5), Soldatos A(6), Ances B(7), Benseler S(8), Bielekova B(9), Dale RC(10), Dalmau J(11)(12), Gaillard W(1), Gorman M(13), Greenberg B(14), Hyslop A(15), Pardo CA(16), Tasker RC(17), Yeh EA(18), Bar-Or A(19), Pittock S(5)(20), Vanderver A(4), Banwell B(21).

Author information: (1)Center for Neuroscience and Behavioral Medicine, Children's National Health System, Washington, DC, USA. (2)Department of Neuroinflammation, Queen Square MS Centre, UCL Institute of Neurology, London, UK. y.hacohen@ucl.ac.uk. (3)Paediatric Neurology, Great Ormond Street Hospital, London, UK. y.hacohen@ucl.ac.uk. (4)Department of Neurology and Pediatric Multiple Sclerosis Clinic, Children's Hospital of Philadelphia, Philadelphia, PA, USA. (5)Department of Neurology, Mayo Clinic, Rochester, MN, USA. (6)National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA. (7)Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA. (8)Section of Rheumatology, Department of Pediatrics, Alberta Children's Hospital, Calgary, Alberta, Canada. (9)Neuroimmunological Diseases Unit, National Institute of Neurological Disorders and Stroke, NIH, Bethesda, MD, USA. (10)Institute for Neuroscience and Muscle Research, Kids Research Institute at the Children's Hospital at Westmead, University of Sydney, Westmead, New South Wales, Australia. (11)ICREA-IDIBAPS, Hospital Clinic, University of Barcelona, Barcelona, Spain. (12)Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA. (13)Department of Neurology, Boston Children's Hospital, Boston, MA, USA. (14)Department of Neurology and Neurotherapeutics and Department of Pediatrics, University of Texas Southwestern, Dallas, TX, USA. (15)Department of Pediatric Neurology and Epilepsy, Miami Children's Hospital, Miami, FL, USA. (16)Johns Hopkins Transverse Myelitis Center, Baltimore, MD, USA. (17)Department of Neurocritical Care, Boston Children's Hospital, Boston, MA, USA. (18)Department of Paediatrics, Division of Neurology, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada. (19)Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, McGill University, Montreal, Quebec, Canada. (20)Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA. (21)Department of Neurology and Pediatric Multiple Sclerosis Clinic, Children's Hospital of Philadelphia, Philadelphia, PA, USA. BanwellB@email.chop.edu.

Immune-mediated disorders of the CNS in children are a complex group of demyelinating, inflammatory, parainfectious and postinfectious disorders with heterogeneous pathobiological mechanisms and clinical manifestations, often associated with fundamental derangement in immune regulation. In this Review, we aim to provide an update on our knowledge of neuroimmune disorders and highlight areas of research that are priorities for improving clinical management. We outline the clinical features of neuroimmune disorders, the current approaches to their treatment and new approaches in development. We then consider the pathological features, including biomarkers, pathological mechanisms and genetics, and discuss the value of immune assays in clinical investigation and basic research. On the basis of current knowledge and techniques, we propose four research priorities: rigorous and consistent collection of core clinical data, cooperative investigation of treatments, development of biological assays and genetic studies. These priorities should help us to achieve the shared goal of precision medicine for neuroimmune disorders. However, multicentre research and the creation of clinical consortia for these rare disorders will be necessary, and we hope that this Review serves as a call to action that is timely given current exciting advances in neuroimmune therapeutics.

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[New aspects of immunotherapy in multiple sclerosis].

[Article in German]
Pape K(1), Zipp F(1), Bittner S(2),

Author information:  (1)Klinik und Poliklinik für Neurologie, Universitätsmedizin Mainz, Langenbeckstr. 1, 55131, Mainz, Deutschland. (2)Klinik und Poliklinik für Neurologie, Universitätsmedizin Mainz, Langenbeckstr. 1, 55131, Mainz, Deutschland. stefan.bittner@unimedizin-mainz.de.

The spectrum of therapeutic options for immunotherapy of multiple sclerosis is continuously broadening. After the approval of cladribine and ocrelizumab in Europe, two new drugs are now available with ocrelizumab being the first approved option for treatment of primary progressive multiple sclerosis; however, the increased use of highly effective therapies is accompanied by a rise in severe side effects. During recent months, special attention was paid to the new progressive multifocal leukoencephalopathy (PML) risk assessment in natalizumab-treated patients, cardiac side effects of fingolimod, cases of idiopathic thrombocytopenic purpura and listeria meningitis associated with alemtuzumab and cases of daclizumab-treated patients with liver failure or encephalitis. These case reports highlight the importance of careful monitoring of all patients treated with immunomodulatory therapies.

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[Diagnosis of multiple sclerosis: revision of the McDonald criteria 2017].

[Article in German]
Aktas O(1), Wattjes MP(2), Stangel M(3), Hartung HP(4),

Author information:  (1)Klinik für Neurologie, Medizinische Fakultät, und Zentrum für Neurologie und Neuropsychiatrie, LVR Klinikum Heinrich-Heine-Universität Düsseldorf, Moorenstr. 5, 40225, Düsseldorf, Deutschland. (2)Klinik und Poliklinik für Neurologie, Universitätsmedizin Mainz, Langenbeckstr. 1, 55131, Mainz, Deutschland. hans-peter.hartung@uni-duesseldorf.de.

Multiple sclerosis (MS) is the most common chronic autoimmune disorder of the central nervous system (CNS) largely affecting young adults. The diagnosis of MS is based on two pillars: 1) detection of the spatial and temporal dissemination of focal neurological deficits and 2) exclusion of important differential diagnoses. The current revision of the diagnostic criteria (McDonald 2017) also follows these principles, takes new data on magnetic resonance imaging (MRI) into account and reintroduces the role of cerebrospinal fluid (CSF) diagnostics for relapsing-remitting forms. The main priority is a reliable diagnosis as early as possible with the aim of a timely initiation of course-adapted treatment. Some of the concrete innovations are the consideration of cortical MRI lesions (equivalent to juxtacortical foci), the elimination of a distinction between asymptomatic and symptomatic MRI lesions and consideration of characteristic CSF findings for the criterion of temporal dissemination. Relapsing MS can be diagnosed at the time of the first attack by the detection of CSF-specific oligoclonal bands and the MRI detection of a typical local lesion distribution (even without simultaneous detection of a contrast-enhancing lesion). For the primary progressive course, for which a first treatment option has recently been approved, the known definition remains unaltered. With respect to the differential diagnosis there is a clear demarcation from Devic’s syndrome, now known as neuromyelitis optica spectrum disorders (NMOSD), as recent insights indicate a separate disease entity caused by an autoimmune response against the astrocytic aquaporin 4 (AQP4) water channel. Finally, future studies will have to provide a definition for secondary progressive MS courses and clarify how to handle diseases characterized by antibodies against myelin oligodendrocyte glycoprotein (MOG) or patients with radiologically isolated syndrome (RIS), i. e. incidental MRI-based detection of CNS lesions in the absence of any clinical event. In summary, McDonald 2017 is within the conceptual structure of its predecessor and simplifies an early diagnosis, thus paving the way to early treatment of MS.

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[Article in German]
Jahn M(1)(2), Steinberg H(3).

Author information: (1)Archiv für Leipziger Psychiatriegeschichte, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universität Leipzig, Semmelweisstr. 10, 04103, Leipzig, Deutschland. (2)Neurologisches Rehabilitationszentrum Leipzig, Bennewitz, Deutschland. (3)Archiv für Leipziger Psychiatriegeschichte, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Universität Leipzig, Semmelweisstr. 10, 04103, Leipzig, Deutschland. holger.steinberg@medizin.uni-leipzig.de.

Paul Ferdinand Schilder was born in Vienna in 1886 and died in New York in 1940. He is nowadays remembered predominantly for his contributions to modern psychiatry and psychotherapy; however, he was also a neurologist and neuroscientist and in particular in his early years, he researched and published on neuropathological topics. This paper focuses on his scientific work during his years in Middle Germany (1909-1914), where he worked with Gabriel Anton in Halle and Paul Flechsig in Leipzig. During those years, he laid the foundations for his definition, clinical classification and differentiation of encephalitis periaxialis diffusa. Today, this inflammatory brain disease is known as Schilder's disease and is of some importance as a rare differential diagnosis of multiple sclerosis (MS), especially in children. Schilder's reflections and findings were based on his scrupulous and detailed analysis of only a few medical histories, which also comprised histological neuropathological examinations, as well as on his extensive and critical review of the relevant literature of the time. His aim was to differentiate encephalitis periaxialis diffusa from brain tumors, MS and Heubner's diffuse sclerosis. Schilder's scientific achievement, made in relatively young years, is still impressive even to the present day due to its thoroughness and accuracy as well as the enormous workload and ambition it required. Even though ambitious, Schilder was always prepared to critically review his own ideas.

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Rizzo FR(1), Musella A(2), De Vito F(1), Fresegna D(1), Bullitta S(1), Vanni V(1), Guadalupi L(2), Stampanoni Bassi M(3), Buttari F(3), Mandolesi G(2), Centonze D(1)(3), Gentile A(3).

Author information: (1)Synaptic Immunopathology Lab, Department of Systems Medicine, University of Rome Tor Vergata, 00133 Rome, Italy. (2)Synaptic Immunopathology Lab, IRCCS San Raffaele, Via di Val Cannuta 247, 00166 Rome, Italy. (3)Unit of Neurology and Unit of Neurorehabilitation, IRCCS Istituto Neurologico Mediterraneo (INM) Neuromed, 86077 Pozzilli, Italy.

Cytokines are constitutively released in the healthy brain by resident myeloid cells to keep proper synaptic plasticity, either in the form of Hebbian synaptic plasticity or of homeostatic plasticity. However, when cytokines dramatically increase, establishing a status of neuroinflammation, the synaptic action of such molecules remarkably interferes with brain circuits of learning and cognition and contributes to excitotoxicity and neurodegeneration. Among others, interleukin-1β (IL-1β) and tumor necrosis factor (TNF) are the best studied proinflammatory cytokines in both physiological and pathological conditions and have been invariably associated with long-term potentiation (LTP) (Hebbian synaptic plasticity) and synaptic scaling (homeostatic plasticity), respectively. Multiple sclerosis (MS) is the prototypical neuroinflammatory disease, in which inflammation triggers excitotoxic mechanisms contributing to neurodegeneration. IL-1β and TNF are increased in the brain of MS patients and contribute to induce the changes in synaptic plasticity occurring in MS patients and its animal model, the experimental autoimmune encephalomyelitis (EAE). This review will introduce and discuss current evidence of the role of IL-1β and TNF in the regulation of synaptic strength at both physiological and pathological levels, in particular speculating on their involvement in the synaptic plasticity changes observed in the EAE brain.

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Nogo receptor expression in microglia/macrophages during experimental autoimmune encephalomyelitis progression.

Alrehaili AA(1), Lee JY(2), Bakhrayseh MM(1), Kim MJ(3), Aui PM(3), Magee KA(3), Petratos S(3).

Author information: (1)Department of Neuroscience, Central Clinical School, Monash University, Prahran Victoria, Australia; Department of Clinical Laboratories, College of Applied Medical Sciences, Taif University, Taif, Kingdom of Saudi Arabia. (2)Department of Neuroscience, Central Clinical School, Monash University, Prahran Victoria, Australia; Toolgen Inc., Gasan Digital-Ro, Geumcheon, Seoul, Korea. (3)Department of Neuroscience, Central Clinical School, Monash University, Prahran Victoria, Australia.

Myelin-associated inhibitory factors within the central nervous system (CNS) are considered to be one of the main obstacles for axonal regeneration following disease or injury. The nogo receptor 1 (NgR1) has been well documented to play a key role in limiting axonal regrowth in the injured and diseased mammalian CNS. However, the role of nogo receptor in immune cell activation during CNS inflammation is yet to be mechanistically elucidated. Microglia/macrophages are immune cells that are regarded as pathogenic contributors to inflammatory demyelinating lesions in multiple sclerosis (MS). In this study, the animal model of MS, experimental autoimmune encephalomyelitis (EAE) was induced inngr1+/+ and ngr1-/- female mice following injection with the myelin oligodendrocyte glycoprotein (MOG35-55) peptide. A fate-map analysis of microglia/macrophages was performed throughout spinal cord sections of EAE-induced mice at clinical scores of 0, 1, 2 and 3, respectively (increasing locomotor disability) from both genotypes, using the CD11b and Iba1 cell markers. Western immunoblotting using lysates from isolated spinal cord microglia/macrophages, along with immunohistochemistry and flow cytometric analysis, was performed to demonstrate the expression of nogo receptor and its two homologs during EAE progression. Myelin protein engulfment during EAE progression in ngr1+/+ and ngr1-/- mice was demonstrated by western immunoblotting of lysates from isolated spinal cord microglia/macrophages, detecting levels of Nogo-A and MOG. The numbers of M1 and M2 microglia/macrophage phenotypes present in the spinal cords of EAE-induced ngr1+/+ and ngr1-/- mice, were assessed by flow cytometric analysis using CD38 and Erg-2 markers. A significant difference in microglia/macrophage numbers between ngr1+/+ and ngr1-/- mice was identified during the progression of the clinical symptoms of EAE, in the white versus gray matter regions of the spinal cord. This difference was unrelated to the expression of NgR on these macrophage/microglial cells. We have identified that as EAE progresses, the phagocytic activity of microglia/macrophages with myelin debris, in ngr1-/- mice, was enhanced. Moreover, we show a modulation from a predominant M1-pathogenic to the M2-neurotrophic cell phenotype in the ngr1-/- mice during EAE progression. These findings suggest that CNS-specific macrophages and microglia of ngr1-/- mice may exhibit an enhanced capacity to clear inhibitory molecules that are sequestered in inflammatory lesions.

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Genetic screening in early-onset dementia patients with unclear phenotype: relevance for clinical diagnosis.


Author information: (1)Neurodegenerative Brain Diseases Group, Center for Molecular Neurology, VIB, Antwerp, Belgium; Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. (2)Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; Department of Neurology and Memory Clinic, General Hospitals Middelheim and Hoge Beuken, Hospital Network Antwerp, Antwerp, Belgium. (3)Institute Born-Bunge, University of Antwerp, Antwerp, Belgium; Department of Neurology, Antwerp University Hospital, Edegem, Belgium. (4)Neurodegenerative Brain Diseases Group, Center for Molecular Neurology, VIB, Antwerp, Belgium; Institute Born-Bunge, University of Antwerp, Antwerp, Belgium. Electronic address: christine.vanbroeckhoven@uantwerpen.vib.be.

In a prospective study of dementia in Flanders (Belgium), we observed a substantial fraction of early-onset dementia patients who did not fulfill the criteria for a specific dementia subtype, leaving the patients without a precise clinical diagnosis. We selected 211 of these patients for genetic testing of causal genes linked to neurodegenerative brain diseases. In this group, the onset or inclusion age was 59.9 ± 8.2 years and 27.4% had a positive family history. We used a panel of 16 major genes linked to Alzheimer's disease, frontotemporal dementia, amyotrophic lateral sclerosis, Parkinson's disease, and prion diseases. In addition, we tested for the presence of a pathogenic C9orf72 repeat expansion. We identified 13 rare variants in 15 patients, including a carrier of variants in 2 different genes. Six patients (2.84%), carried a mutation in a Mendelian causal gene, that is, APP, MAPT, SOD1, TBK1, and C9orf72. In the other 7 patients, 7 variants were of uncertain significance, including a frameshift mutation in PSEN2, p.G359Lfs*74, in 2 patients sharing a common haplotype, and in LRRK2, p.L2063fs*. Expression studies showed reduced PSEN2 and a near complete loss of LRRK2, in lymphoblast cells or brain material of these patients. Overall, our study underscores the relevance of genetic testing of known causal genes in early-onset patients with symptomatology of neurodegenerative dementia but an unclear clinical diagnosis. A positive genetic result can help to obtain a precise diagnosis as well as a better understanding of the presence of multiple affected relatives in the family.

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α-Methyl-α-phenylsuccinimide ameliorates neurodegeneration in a *C. elegans* model of TDP-43 proteinopathy.

Wong SQ(1), Pontifex MG(2), Phelan MM(3), Pidathala C(4), Kraemer BC(5), Barclay JW(6), Berry NG(7), O'Neill PM(8), Burgoyne RD(9), Morgan A(10).

Author information: (1)Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK. Electronic address: wongsq@liverpool.ac.uk. (2)Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK. Electronic address: M.Pontifex@uea.ac.uk. (3)Department of Biochemistry, Institute of Integrative Biology, University of Liverpool, Liverpool, UK. Electronic address: Marie.Phelan@liverpool.ac.uk. (4)Department of Chemistry, University of Liverpool, Liverpool, UK. (5)Geriatrics Research Education and Clinical Center, Seattle Veterans Affairs Puget Sound Health Care System, University of Washington Department of Medicine, Seattle, WA 98108, USA. Electronic address: kraemerb@uw.edu. (6)Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK. Electronic address: barclayj@liverpool.ac.uk. (7)Department of Chemistry, University of Liverpool, Liverpool, UK. Electronic address: ngberry@liverpool.ac.uk. (8)Department of Chemistry, University of Liverpool, Liverpool, UK. Electronic address: pmonneill@liverpool.ac.uk. (9)Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK. Electronic address: burgoyne@liverpool.ac.uk. (10)Department of Cellular and Molecular Physiology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK. Electronic address: amorgan@liverpool.ac.uk.

The antiepileptic drug ethosuximide has recently been shown to be neuroprotective in various *Caenorhabditis elegans* and rodent neurodegeneration models. It is therefore a promising repurposing candidate for the treatment of multiple neurodegenerative diseases. However, high concentrations of the drug are required for its protective effects in animal models, which may impact on its translational potential and impede the identification of its molecular mechanism of action. Therefore, we set out to develop more potent neuroprotective lead compounds based on ethosuximide as a starting scaffold. Chemoinformatic approaches were used to identify compounds with structural similarity to ethosuximide and to prioritise these based on good predicted blood-brain barrier permeability and *C. elegans* bioaccumulation properties. Selected compounds were initially screened for anti-convulsant activity in a *C. elegans* pentylenetetrazol-induced seizure assay, as a rapid primary readout of bioactivity; and then assessed for neuroprotective properties in a *C. elegans* TDP-43 proteinopathy model based on pan-neuronal expression of human A315T mutant TDP-43. The most potent compound screened, α-methyl-α-phenylsuccinimide (MPS), ameliorated the locomotion defects and extended the shortened lifespan of TDP-43 mutant worms. MPS also directly protected against neurodegeneration by reducing the number of neuronal breaks and cell body losses in GFP-labelled GABAergic motor neurons. Importantly, optimal neuroprotection was exhibited by external application of 50 μM MPS, compared to 8 mM for ethosuximide. This greater potency of MPS was not due to bioaccumulation to higher internal levels within the worm, based on 1H-nuclear magnetic resonance analysis. Like ethosuximide, the activity of MPS was abolished by mutation of the evolutionarily conserved FOXO transcription factor, daf-16, suggesting that both compounds act via the same neuroprotective pathway(s). In conclusion, we have revealed a novel neuroprotective activity of MPS that is >100-fold more potent than ethosuximide. This increased potency will facilitate future biochemical studies to identify the direct molecular target(s) of both compounds, as we have shown here that they share a common downstream DAF-16-dependent mechanism of action. Furthermore, MPS is the active metabolite of another approved antiepileptic drug, methsuximide. Therefore, methsuximide may have repurposing potential for treatment of TDP-43 proteinopathies and possibly other human neurodegenerative diseases.

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Multiple sclerosis and mixed microbial infections. Direct identification of fungi and bacteria in nervous tissue.

Alonso R(1), Fernández-Fernández AM(1), Pisa D(1), Carrasco L(2).

Author information: (1)Centro de Biología Molecular “Severo Ochoa” (CSIC-UAM), c/Nicolás Cabrera, 1. Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain. (2)Centro de Biología Molecular “Severo Ochoa” (CSIC-UAM), c/Nicolás Cabrera, 1. Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain. Electronic address: lcarrasco@cbm.csic.es.

Multiple sclerosis (MS) is the prototypical inflammatory disease of the central nervous system (CNS), leading to multifocal demyelination and neurodegeneration. The etiology of this incurable disease is unknown and remains a matter of intensive research. The possibility that microbial infections, such as viruses or bacteria, can trigger an autoimmune reaction in CNS tissue has been suggested. However, the recent demonstration that bacteria are present in CNS tissue points to a direct involvement of microbial infections in the etiology of MS. In the present study, we provide the first evidence of fungal infection in CNS tissue of MS patients, and demonstrate that fungal DNA from different species can be detected in the CNS. We used, nested PCR assays together with next-generation sequencing to identify the fungal species in the nervous tissue of 10 patients with MS. Strikingly, Trichosporon mucoides was found in the majority of MS patients, and particularly high levels of this fungus were found in two patients. Importantly, T. mucoides was not detected in the CNS of control subjects. We were also able to visualize fungal structures in CNS tissue sections by immunohistochemistry using specific antifungal antibodies, which also revealed the accumulation of a number of microbial cells in microfoci. Again, microbial structures were not observed in CNS sections from controls. In addition to fungi, neural tissue from MS patients was also positive for bacteria. In conclusion, our present observations point to the novel concept that MS could be caused by polymicrobial infections. Thus, mycosis of the CNS may be accompanied by opportunistic bacterial infection, promoting neuroinflammation and directly causing focal lesions, followed by demyelination and axonal injury.

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Chronic social stress induces peripheral and central immune activation, blunted mesolimbic dopamine function, and reduced reward-directed behaviour in mice.


Author information: (1)Preclinical Laboratory for Translational Research into Affective Disorders, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland. (2)Center for Clinical Studies, Vetsuisse Faculty, University of Zurich, Switzerland. (3)Neuroscience Center Zurich, University of Zurich and ETH Zurich, Switzerland. (4)Warwick Medical School, University of Warwick, Coventry, United Kingdom. (5)Brains On-line, Groningen, The Netherlands. (6)Department of Life Sciences, University of Roehampton, London, UK. (7)Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Switzerland. (8)CNS Diseases Research Germany, Boehringer Ingelheim Pharma GmbH & Co. KG., Biberach, Germany. (9)Neuroimmunology and MS Research, Neurology, and Clinical Research Priority Program Multiple Sclerosis, University Hospital Zurich, University of Zurich, Switzerland.

Psychosocial stress is a major risk factor for depression, stress leads to peripheral and central immune activation, immune activation is associated with blunted dopamine (DA) neural function, DA function underlies reward interest, and reduced reward interest is a core symptom of depression. These states might be inter-independent in a complex causal pathway. Whilst animal-model evidence exists for some specific steps in the pathway, there is currently no animal model in which it has been demonstrated that social stress leads to each of these immune, neural and behavioural states. Such a model would provide important existential evidence for the complex pathway and would enable the study of causality and mediating mechanisms at specific steps in the pathway. Therefore, in the present mouse study we investigated for effects of 15-day resident-intruder chronic social stress (CSS) on each of these states. Relative to controls, CSS mice exhibited higher spleen levels of granulocytes, inflammatory monocytes and T helper 17 cells; plasma levels of inducible nitric oxide synthase; and liver expression of genes encoding kynurenine pathway enzymes. CSS led in the ventral tegmental area to higher levels of kynurenine and the microglia markers Iba1 and Cd11b and higher binding activity of DA D1 receptor; and in the nucleus accumbens (NAcc) to higher kynurenine, lower DA turnover and lower c-fos expression. Pharmacological challenge with DA reuptake inhibitor identified attenuation of DA stimulatory effects on locomotor activity and NAcc c-fos expression in CSS mice. In behavioural tests of operant responding for sucrose reward validated as sensitive assays for NAcc DA function, CSS mice exhibited less reward-directed behaviour. Therefore, this mouse study demonstrates that a chronic social stressor leads to changes in each of the immune, neural and behavioural states proposed to mediate between stress and disruption of DA-dependent reward processing. The model can now be applied to investigate causality and, if demonstrated, underlying mechanisms in specific steps of this immune-neural-behavioural pathway, and thereby to identify potential therapeutic targets.

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Cell- and stage-specific localization of galectin-3, a β-galactoside-binding lectin, in a mouse model of experimental autoimmune encephalomyelitis.


Author information: (1)Laboratory of Histology and Cytology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan; Department of Anatomy, Faculty of Medicine, Hokkaido University, Sapporo, Japan. (2)Division of Molecular Psychoimmunology, Institute for Genetic Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan. (3)Department of Anatomy, Akita University Graduate School of Medicine, Akita, Japan. (4)Laboratory of Histology and Cytology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan. (5)Department of Anatomy, Faculty of Medicine, Hokkaido University, Sapporo, Japan. (6)Laboratory of Histology and Cytology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan. Electronic address: niojun@med.hokudai.ac.jp.

Multiple sclerosis (MS) is an autoimmune disease in which pathogenic T cells play an important role, and an experimental autoimmune encephalomyelitis (EAE) is used as an animal model of MS. Galectins are β-galactoside-binding lectins and involved in various physiological and pathological events. Among fifteen members of galectins, galectin-1, -8, and -9 play immunosuppressive roles in MS and EAE; however, the role of galectin-3 (gal-3) is complex and controversial. We examined expression of gal-3 in the spinal cord and nerve roots of EAE mice. No immunohistochemical signals were detected in naïve mice, whereas gal-3 appeared at lower lumbar levels of the spinal cord and nerve roots in EAE mice. In the spinal cord, gal-3-positive cells were activated microglia and/or infiltrating macrophages, which were round in shape and intensified for the lysosomal enzyme, cathepsin D, indicating elevated phagocytic activity. Gal-3-positive cells in the spinal cord were most abundant during the peak symptomatic period. In the recovery period, they disappeared from the spinal parenchyma but remained at moderate levels in the pia mater. Interestingly, gal-3-positive cells selectively appeared in ventral, but not dorsal, nerve roots running through the spinal canal, with expression peaking during the recovery period. In ventral nerve roots, the major cell type expressing gal-3 was a specific population of Schwann cells that surround unmyelinated axons and express the biosynthetic enzyme for l-serine, a potent neurotrophic amino acid. Gal-3 was also induced in Iba1/F4/80-positive macrophages, which engulf damaged myelin and axon debris. Thus, gal-3 is induced in distinct cell types that are engaged in removal of damaged axons and cell debris and axon regeneration and remyelination, suggesting a potential neuroprotective role of gal-3 in EAE mice. Copyright © 2018 Elsevier Ltd. All rights reserved.

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Kutz CF(1), Dix AL(2).

Author information: (1)Colorado Springs Neurological Associates, 2312 N. Nevada Avenue, Colorado Springs, CO 80907, USA. (2)Kansas City Multiple Sclerosis Center College Park Neurology, 10600 Mastin, Overland Park, KS 66208, USA.

Relapse management is a crucial component of multiple sclerosis care. Acute relapses are defined as new neurological symptoms or worsening of existing symptoms persisting for >24 h that are not attributable to heat, overexertion, or infection. The most commonly used treatment for multiple sclerosis relapse is a 3-5-day course of corticosteroids, primarily intravenous methylprednisolone with or without oral steroid taper. Repository corticotropin injection is also the US FDA-approved option for managing acute relapse, particularly in the patients with inadequate response, intolerability or allergy to corticosteroid treatment; poor venous access; or limited ability to receive home or clinic infusions.

DOI: 10.2217/nmt-2018-0008 PMID: 29869572
Phase III SUNBEAM and RADIANCE PART B trials for Ozanimod in relapsing multiple sclerosis demonstrate superiority versus interferon-β-1a (Avonex®) in reducing annualized relapse rates and MRI brain lesions.

Koscielny V(1).
Author information: (1)Celgene, Boudry, Switzerland.
Biography: Volker Koscielny, MD, is the Vice President, Global Medical Affairs, for Inflammation and Immunology at Celgene. Volker trained as a doctor in his native Germany and worked for several pharmaceutical companies prior to joining Celgene in January 2015.
DOI: 10.2217/nmt-2018-0012  PMID: 29943693

Increases in fatigue do not change spasticity scores in persons with multiple sclerosis.

Karpatkin H(1), Babyar S(1), DiCarrado S(1), McDarby M(1), Narovlianski M(1), Perez B(1), Rimawi I(1).
Author information: (1)Department of Physical Therapy, Hunter College, The City University of New York, New York, NY 10010, USA.
AIM: Fatigue is a common finding in multiple sclerosis (MS) which may result in worsening of gait, function and other MS symptoms, like spasticity. Although the worsening of spasticity with fatigue has been reported by persons with MS, the effect of fatigue on spasticity has not been measured. PURPOSE: The purpose of this study was to compare lower extremity Modified Ashworth Scale (MAS) scores of persons with mild-to-moderate MS symptoms before and after fatigued and unfatigued conditions. METHODS: Using a randomized crossover design, MS subjects underwent 6-min walk to induce fatigue and 6-min supine rests, with lower extremity spasticity measured before and after each condition. Friedman tests gave paired comparisons of MAS before and after each condition. RESULTS: 16 subjects with mild-to-moderate MS completed the study (mean age = 56; standard deviation = 11.7). Friedman tests showed a significant decrease in mean rank for overall average MAS for both lower extremities (p = 0.031) when comparing fatigued to unfatigued conditions. This appeared to be driven by the right lower extremity average MAS (p = 0.002) and, more specifically, in post hoc pre to post-test comparisons for right knee flexor (p = 0.002 fatigued; p = 0.059 unfatigued) and right knee extensor (p = 0.001 fatigued; p = 0.020 unfatigued) MAS mean rank differences. Fatigue did not result in increased spasticity. CONCLUSION: Spasticity in these subjects with MS was not worsened by fatigue suggesting that worsening of gait with fatigue may be due to causes other than spasticity.
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Effect of tetrahydrocannabinol:cannabidiol oromucosal spray on activities of daily living in multiple sclerosis patients with resistant spasticity: a retrospective, observational study.

Mallada Frechín J(1).
Author information: (1)Unidad de Neurología, Hospital General de Elda, Elda (Alicante), Spain.
AIM: To examine evolution in activities of daily living (ADL) in patients with multiple sclerosis spasticity during long-term use of tetrahydrocannabinol (THC):cannabidiol (CBD) oromucosal spray. METHODS: Functional impairment was assessed retrospectively (prior to start of treatment) and at the present moment using a 16-item ADL survey; results were compared. A control group without add-on THC:CBD oromucosal spray was included to investigate possible recall bias. RESULTS: ADL was maintained or slightly improved with THC:CBD oromucosal spray across treatment time (mean 31.9 months) including significant improvement in 'standing up' (p < 0.05) and trends in other items. Significant improvements (p < 0.01) with THC:CBD oromucosal spray were observed in several multiple sclerosis spasticity-related symptoms. Overall, 96.9% of patients using THC:CBD oromucosal spray had a positive global impression of change during treatment. CONCLUSION: In this pilot study, THC:CBD oromucosal spray maintained or improved aspects of daily functioning. Further study in a larger trial is warranted.
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Prevalence of Multiple Sclerosis in Iceland.

Eliasdóttir Ö(1)(2), Kjartansson Ö(3), Olafsson E(1)(4).

Author information: (1)University of Iceland, School of Medicine, Reykjavik, Iceland. (2)Sahlgrenska University Hospital, Gothenburg, Sweden. (3)Department of Radiology, Landspitali University Hospital, Reykjavik, Iceland. (4)Department of Neurology, Landspitali University Hospital, Reykjavik, Iceland.

BACKGROUND: In this study, we examined multiple sclerosis (MS) point prevalence in the well-defined island population of Iceland. METHODS: This study included all registered residents of Iceland with MS on the prevalence day, December 31, 2007. All included patients met at least one of the following criteria: McDonald criteria; Poser criteria for clinically definite MS; laboratory-supported definite MS, clinically probable MS; or criteria for primary progressive MS. The patients’ medical records were reviewed, including all available MRI data acquired prior to the prevalence day. RESULTS: We identified 526 patients, of whom 73% (382) were women. The crude point prevalence of MS was 167.1 per 100,000 population on the prevalence day. With age adjustment made to the 2000 U.S. population, the prevalence was 168.5 per 100,000 population. The mean patient age on the prevalence day was 47 years (range 13-89) for both men and women. The mean age at diagnosis was 36 years (range 13-77): 35 years for women and 36 years for men. CONCLUSION: MS prevalence was high in Iceland compared to the prevalence mentioned in reports from most of the world, and was similar to prevalence rates in other Nordic countries.

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Incidental diagnosis of tuberous sclerosis complex by exome sequencing in three families with subclinical findings.


Author information: (1)Department of Pathology and Laboratory Medicine, Children's Mercy Hospitals, Kansas City, MO, 64108, USA. (2)Division of Clinical Genetics, Children's Mercy Hospitals, Kansas City, MO, 64108, USA. (3)Department of Pediatrics, Children's Mercy Hospitals, Kansas City, MO, 64108, USA. (4)Center for Pediatric Genomic Medicine, Children's Mercy Hospitals, 2420 Pershing Rd., Kansas City, MO, 64108, USA. (5)University of Missouri-Kansas City School of Medicine, Kansas City, MO, 64108, USA. (6)Division of Nephrology, Children's Mercy Hospitals, Kansas City, MO, 64108, USA. (7)Division of Dermatology, Children's Mercy Hospitals, Kansas City, MO, 64108, USA. (8)Division of Neurology, Children's Mercy Hospitals, Kansas City, MO, 64108, USA. (9)Department of Pathology and Laboratory Medicine, Children's Mercy Hospitals, Kansas City, MO, 64108, USA. csaunders@cmh.edu. (10)Center for Pediatric Genomic Medicine, Children's Mercy Hospitals, 2420 Pershing Rd., Kansas City, MO, 64108, USA. csaunders@cmh.edu. (11)University of Missouri-Kansas City School of Medicine, Kansas City, MO, 64108, USA. csaunders@cmh.edu.

Tuberous sclerosis complex (TSC) is an autosomal-dominant neurocutaneous disorder characterized by lesions and benign tumors in multiple organ systems including the brain, skin, heart, eyes, kidneys, and lungs. The phenotype is highly variable, although penetrance is reportedly complete. We report the molecular diagnosis of TSC in individuals exhibiting extreme intra-familial variability, including the incidental diagnosis of asymptomatic family members. Exome sequencing was performed in three families, with probands referred for epilepsy, autism, and absent speech (Family 1); epileptic spasms (Family 2); and connective tissue disorders (Family 3). Pathogenic variants in TSC1 or TSC2 were identified in nine individuals, including relatives with limited or no medical concerns at the time of testing. Of the nine individuals reported here, six had post-diagnosis examinations and three met clinical diagnostic criteria for TSC. One did not meet clinical criteria for a possible or definite diagnosis of TSC, and two had only a possible clinical diagnosis following post-diagnosis workup. These individuals as well as their mothers demonstrated limited features that would not raise concern for TSC in the absence of molecular results. In addition, three individuals exhibited epilepsy with normal brain MRIs, and two without seizures or intellectual disability had MRI findings fulfilling major criteria for TSC highlighting the difficulty providers face when relying on clinical criteria to guide genetic testing. Given the importance of a timely TSC diagnosis for clinical management, such cases demonstrate a potential benefit for clinical criteria to include seizures and an unbiased molecular approach to genetic testing.

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Quantitative susceptibility mapping using deep neural network: QSMnet.

Yoon J(1), Gong E(2), Chatnuntawech I(3), Bilgic B(4), Lee J(1), Jung W(1), Ko J(1), Jung H(1), Setsompop K(4), Zaharchuk G(5), Kim EY(6), Pauly J(7), Lee J(8).

Author information: (1)Laboratory for Imaging Science and Technology, Department of Electrical and Computer Engineering, Seoul National University, Seoul, South Korea. (2)Department of Electrical Engineering, Stanford University, Stanford, CA, USA; Department of Radiology, Stanford University, Stanford, CA, USA. (3)National Nanotechnology Center, Pathum Thani, Thailand. (4)Department of Radiology, Harvard Medical School, Boston, MA, USA. (5)Department of Radiology, Stanford University, Stanford, CA, USA. (6)Department of Radiology, Gil Medical Center, Gachon University College of Medicine, Incheon, South Korea. (7)Department of Electrical Engineering, Stanford University, Stanford, CA, USA. (8)Laboratory for Imaging Science and Technology, Department of Electrical and Computer Engineering, Seoul National University, Seoul, South Korea. Electronic address: jonghoyi@snu.ac.kr.

Deep neural networks have demonstrated promising potential for the field of medical image reconstruction, successfully generating high quality images for CT, PET and MRI. In this work, an MRI reconstruction algorithm, which is referred to as quantitative susceptibility mapping (QSM), has been developed using a deep neural network in order to perform dipole deconvolution, which restores magnetic susceptibility source from an MRI field map. Previous approaches of QSM require multiple orientation data (e.g. Calculation of Susceptibility through Multiple Orientation Sampling or COSMOS) or regularization terms (e.g. Truncated K-space Division or TKD; Morphology Enabled Dipole Inversion or MEDI) to solve an ill-conditioned dipole deconvolution problem. Unfortunately, they either entail challenges in data acquisition (i.e. long scan time and multiple head orientations) or suffer from image artifacts. To overcome these shortcomings, a deep neural network, which is referred to as QSMnet, is constructed to generate a high quality susceptibility source map from single orientation data. The network has a modified U-net structure and is trained using COSMOS QSM maps, which are considered as gold standard. Five head orientation datasets from five subjects were employed for patch-wise network training after doubling the training data using a model-based data augmentation. Seven additional datasets of five head orientation images (i.e. total 35 images) were used for validation (one dataset) and test (six datasets). The QSMnet maps of the test dataset were compared with the maps from TKD and MEDI for their image quality and consistency with respect to multiple head orientations. Quantitative and qualitative image quality comparisons demonstrate that the QSMnet results have superior image quality to those of TKD or MEDI results and have comparable image quality to those of COSMOS. Additionally, QSMnet maps reveal substantially better consistency across the multiple head orientation data than those from TKD or MEDI. As a preliminary application, the network was further tested for three patients, one with microbleed, another with multiple sclerosis lesions, and the third with hemorrhage. The QSMnet maps showed similar lesion contrasts with those from MEDI, demonstrating potential for future applications.

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SPG11 mutations cause widespread white matter and basal ganglia abnormalities, but restricted cortical damage.


Author information: (1)Department of Neurology, University of Campinas (UNICAMP), Campinas, Brazil. (2)Department of Neurology, University of São Paulo (USP-RP), Ribeirão Preto, Brazil. (3)Laboratorio di Neurogenetica, Centro Europeo di Ricerca sul Cervello (CERC) - Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Santa Lucia, Rome, Italy. (4)Dipartimento di Scienze Chirurgiche e Biomediche, Università di Perugia, Perugia, Italy. (5)Department of Neurology, Federal University of São Paulo (UNIFESP), São Paulo, Brazil. (6)Department of Medical Genetics, University of Campinas (UNICAMP), Campinas, Brazil.

SPG11 mutations are the major cause of autosomal recessive Hereditary Spastic Paraplegia. The disease has a wide phenotypic variability indicating many regions of the nervous system besides the corticospinal tract are affected. Despite this, anatomical and phenotypic characterization is restricted. In the present study, we investigate the anatomical abnormalities related to SPG11 mutations and how they relate to clinical and cognitive measures. Moreover, we aim to depict how the disease course influences the regions affected, unraveling different susceptibility of specific neuronal populations. We performed clinical and paraclinical studies encompassing neuropsychological, neuroimaging, and neurophysiological tools in a cohort of twenty-five patients and age matched controls. We assessed cortical thickness (FreeSurfer software), deep grey matter volumes (T1-MultiAtlas tool), white matter microstructural damage (DTI-MultiAtlas) and spinal cord morphometry (Spineseg software) on a 3 T MRI scan. Mean age and disease duration were 29 and 13.2 years respectively. Sixty-four percent of the patients were wheelchair bound while 84% were demented. We were able to unfold a diffuse pattern of white matter integrity loss as well as basal ganglia and spinal cord atrophy. Such findings contrasted with a restricted pattern of cortical thinning (motor, limbic and parietal cortices). Electromyography revealed motor neuronopathy affecting 96% of the probands. Correlations with disease duration pointed towards a progressive degeneration of multiple grey matter structures and spinal cord, but not of the white matter. SPG11-related hereditary spastic paraplegia is characterized by selective neuronal vulnerability, in which a precocious and widespread white matter involvement is later followed by a restricted but clearly progressive grey matter degeneration.

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Partial volume-are assessment of multiple sclerosis lesions.


Author information: (1)Advanced Clinical Imaging Technology (HC CMEA SUI DI PI), Siemens Healthcare AG, Lausanne, Switzerland. (2)Department of Radiology, Lausanne University Hospital (CHUV), and University of Lausanne (UNIL), Lausanne, Switzerland. (3)Signal Processing Laboratory (LTS 5), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland. (4)Department of Radiology, Pourtalés Hospital, Neuchâtel, Switzerland. (5)Centre for Advanced Imaging, University of Queensland, Queensland, Australia. (6)Siemens Healthcare Pty. Ltd., Brisbane, Queensland, Australia. (7)Siemens Healthcare Ltd, Zürich, Switzerland. (8)Neurologic Clinic and Polyclinic, Departments of Medicine, Clinical Research and Biomedical Engineering, University Hospital Basel and University of Basel, Basel, Switzerland. (9)Translational Imaging in Neurology (ThINK) Basel, Department of Medicine and Biomedical Engineering, University Hospital Basel and University of Basel, Basel, Switzerland. (10)Medical Image Analysis Laboratory (MIAL), Centre d'Imagerie BioMédicale (CIBM), Lausanne, Switzerland.

White-matter lesion count and volume estimation are key to the diagnosis and monitoring of multiple sclerosis (MS). Automated MS lesion segmentation methods that have been proposed in the past 20 years reach their limits when applied to patients in early disease stages characterized by low lesion load and small lesions. We propose an algorithm to automatically assess MS lesion load (number and volume) while taking into account the mixing of healthy and lesional tissue in the image voxels due to partial volume effects. The proposed method works on 3D MPRAGE and 3D FLAIR images as obtained from current routine MS clinical protocols. The method was evaluated and compared with manual segmentation on a cohort of 39 early-stage MS patients with low disability, and showed higher Dice similarity coefficients (median DSC = 0.55) and higher detection rate (median DR = 61%) than two widely used methods (median DSC = 0.50, median DR < 45%) for automated MS lesion segmentation. We argue that this is due to the higher performance in segmentation of small lesions, which are inherently prone to partial volume effects.

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RANKL/RANK/OPG Axis Is Deregulated in the Cerebrospinal Fluid of Multiple Sclerosis Patients at Clinical Onset.


Author information: (1)Department of Histology and Embryology, University of Zagreb School of Medicine, Zagreb, Croatia. (2)Department of Neurology, Clinical Hospital "Dubrava", Zagreb, Croatia. (3)Department of Neurology, University Hospital "Sestre Milosrdnice", Zagreb, Croatia. (4)Department of Anesthesiology, Reanimatology and Intensive Care, Clinical Hospital "Dubrava", Zagreb, Croatia. (5)Department of Neurosurgery Clinical Hospital "Dubrava", Zagreb, Croatia. (6)Clinic for Neurology, Clinical Hospital Center "Rijeka", Rijeka, Croatia. (7)Department of Physiology and Immunology, and Croatian Institute for Brain Research, University of Zagreb School of Medicine, Zagreb, Croatia.

OBJECTIVES: Our study focused on the RANKL (receptor activator of nuclear factor κB ligand)/RANK/OPG (osteoprotegerin) axis and selected proinflammatory/immunoregulatory upstream mediators in the peripheral blood (PBL) and cerebrospinal fluid (CSF) of multiple sclerosis (MS) patients. METHODS: PBL and CSF were collected from healthy controls (n = 35) and MS patients at the clinical onset of the disease (n = 33). In addition, PBL samples were obtained from relapse-remitting (RR)-MS patients (n = 30). Patients were assessed by means of the expanded disability status scale (EDSS) and routine laboratory parameters. Soluble (s)RANKL and OPG were measured in the CSF and plasma; gene expression was detected for RANKL, RANK, OPG, and selected cytokines/chemokines (interleukin [IL]-4, IL-10, IL-17, CCL2, and CXCL12) in PBL mononuclear cells. RESULTS: The OPG level in the CSF was lower in MS patients at clinical onset than in controls. Moreover, the sRANKL/OPG ratio was higher in the CSF of MS patients at clinical onset and in the plasma of RR-MS patients than in controls. Gene expression of RANKL/RANK/OPG in PBL mononuclear cells was higher only in RR-MS patients. IL-4, CCL2, and CXCL12 were positively correlated and IL-10 was negatively correlated with RANKL/RANK expression. OPG was negatively correlated with EDSS and alkaline phosphatase level. CONCLUSION: Our study revealed that changes of RANKL/RANK/OPG axis are associated with MS, particularly the decreased OPG level in the CSF at disease onset. Therefore, these factors may serve as disease biomarkers and molecular targets of novel therapeutic approaches.

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Rare variants and de novo variants in mesial temporal lobe epilepsy with hippocampal sclerosis.

Wong JKL(1), Gui H(1), Kwok M(1), Ng PW(1), Lui CHT(1), Baum L(1), Sham PC(1), Kwan P(1), Cherny SS(1).

Author information: (1)Centre for Genomic Sciences and Department of Psychiatry (J.K.L.W., H.G., L.B., P.C.S., S.S.C.), Li Ka Shing Faculty of Medicine, The University of Hong Kong; Department of Medicine and Therapeutics (M.K., P.K.), The Chinese University of Hong Kong; Department of Medicine (P.W.N.), United Christian Hospital; Department of Medicine (C.H.T.L.), Queen Elizabeth Hospital, Hong Kong, China; Departments of Medicine and Neurology (P.K.), The University of Melbourne, Royal Melbourne Hospital, Australia; Department of Epidemiology and Preventive Medicine (S.S.C.) and Department of Anatomy and Anthropology (S.S.C.), Sackler Faculty of Medicine, Tel Aviv University, Israel; and The State Key Laboratory of Brain and Cognitive Sciences (P.C.S., S.S.C.).

Objective: We investigated the role of rare genetic variants and de novo variants in the pathogenesis of mesial temporal lobe epilepsy related to hippocampal sclerosis (MTLE-HS). Methods: Whole-exome sequencing (WES) was performed in patients with MTLE-HS and their unaffected parents (trios). Genes or gene sets that were enriched with predicted damaging rare variants in the patients as compared to population controls were identified. Patients and their parents were compared to identify whether the variants were de novo or inherited. Results: After quality control, WES data from 47 patients (26 female), including 23 complete trios, were available for analysis. Compared with population controls, significant enrichment of rare variants was observed in SEC24B. Integration of gene set data describing neuronal functions and psychiatric disorders showed enrichment signal on fragile X mental retardation protein (FMRP) targets. Twenty-one de novo variants were identified, with many known to cause neuropsychiatric disorders. The FMRP-targeted genes also carried more de novo variants. Inherited compound heterozygous and homozygous variants were identified. Conclusions: The genetic architecture underlying MTLE-HS is complex. Multiple genes carrying de novo variants and rare variants among FMRP targets were identified, suggesting a pathogenic role. MTLE-HS and other neuropsychiatric disorders may have shared biology.

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Molecular signature of Epstein-Barr virus infection in MS brain lesions.

Moreno MA(1), Or-Geva N(1), Aftab BT(1), Khanna R(1), Croze E(1), Steinman L(1), Han MH(1).

Author information: (1)Department of Neurology and Neurological Sciences (M.A.M., N.O., L.S., M.H.H.), Stanford University School of Medicine, Multiple Sclerosis Center; Interdepartmental Program in Immunology (M.A.M., N.O., L.S., M.H.H.), Stanford; Atara Biotherapeutics (B.T.A., E.C.), San Francisco, CA; and Queensland Institute of Medical Research (R.K.), Brisbane, Queensland, Australia.

Objective: We sought to confirm the presence and frequency of B cells and Epstein-Barr virus (EBV) (latent and lytic phase) antigens in archived MS and non-MS brain tissue by immunohistochemistry. Methods: We quantified the type and location of B-cell subtypes within active and chronic MS brain lesions in relation to viral antigen expression. The presence of EBV-infected cells was further confirmed by in situ hybridization to detect the EBV RNA transcript, EBV-encoded RNA-1 (EBER-1). Results: We report the presence of EBV latent membrane protein 1 (LMP-1) in 93% of MS and 78% of control brains, with a greater percentage of MS brains containing CD138+ plasma cells and LMP-1-rich populations. Notably, 78% of chronic MS lesions and 33.3% of non-MS brains contained parenchymal CD138+ plasma cells. EBV early lytic protein, EBV immediate-early lytic gene (BZLF1), was also observed in 46% of MS, primarily in association with chronic lesions and 44% of non-MS brain tissue. Furthermore, 85% of MS brains revealed frequent EBER-positive cells, whereas non-MS brains seldom contained EBER-positive cells. EBV infection was detectable by immunohistochemistry and by in situ hybridization, in both MS and non-MS brains, although latent virus was more prevalent in MS brains, while lytic virus was restricted to chronic MS lesions. Conclusions: Together, our observations suggest an uncharacterized link between the EBV virus life cycle and MS pathogenesis.

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**Different clinical response to interferon beta and glatiramer acetate related to the presence of oligoclonal IgM bands in CSF in multiple sclerosis patients.**

Casanova B(1), Lacruz L(2), Villar ML(3), Domínguez JA(4), Gadea MC(5), Gascón F(4), Mallada J(6), Hervás D(7), Simó-Castelló M(1), Álvarez-Cermeño JC(8), Calles C(9), Ólascoaga J(10), Ramió-Torrentà L(11), Alcalá C(1), Cervelló A(5), Boscá l(1), Pérez-Miralles FC(1), Coret F(4).

**Author information:** (1)Neuroimmunology Unit, Hospital Universitari i Politècnic La Fe, Valencia, Spain. (2)Neuroimmunology Unit, Hospital Universitari i Politècnic La Fe, Valencia, Spain. (3)Neuroimmunology Service, Hospital Ramón y Cajal de Madrid, Madrid, Spain. (4)Neuroimmunology Unit, Hospital Clínic Universitari de València, Valencia, Spain. (5)Neurological Service, Hospital General de Valencia, Valencia, Spain. (6)Neurological Service, Hospital de Elda, Alicante, Spain. (7)Biostatistical Unit, Institut d'Investigació Sanitaria La Fe, Valencia, Spain. (8)Neurological Service, Hospital Ramón y Cajal de Madrid, Madrid, Spain. (9)Neurological Service, Hospital Son Espases, Mallorca, Spain. (10)Neurological Service, Hospital de Donostia, San Sebastian, Spain. (11)Neuroimmunology and Multiple Sclerosis Unit, Hospital Dr. Josep Trueta, IDIBGI, Girona, Spain.

**OBJECTIVE:** To study the efficacy of interferon beta (IFNβ) and glatiramer acetate (GA) related to the presence of oligoclonal M bands (OCMB) in the cerebrospinal fluid in relapsing-remitting multiple sclerosis (RRMS). **METHOD:** This is an observational, multicenter and retrospective study with prospectively collected data of patients that started treatment with IFNβ or GA. Treatment decision was made blinded to the OCMB status. Time to first attack after starting therapy was compared by using Kaplan-Meier curves, and adjustment by Cox regression analysis was performed. **RESULTS:** Two hundred and fifty-six patients entered in the study (141-55% received IFNβ; 115-45% received GA). After a mean follow-up of 41 and 65 months, 54.7% of patients remained free from further attacks (RF). The proportion of RF patients was higher in the GA group than in the IFNβ group (72.2 vs. 40.4%, p < 0.001). The IFNβ patients with OCMB+ presented the poorest response, 31.3% RF vs. 48.1% in IFNβ without OCMB, p = 0.03. **CONCLUSION:** OCMB in CSF could be a biomarker of treatment response in multiple sclerosis.

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**Monitoring Progressive Multiple Sclerosis with Novel Imaging Techniques.**

Petracca M(1), Margoni M(1)(2), Bommarito G(3), Inglese M(4)(5).

**Author information:** (1)Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. (2)Multiple Sclerosis Centre, Department of Neurosciences DNS, University Hospital, University of Padua, Padua, Italy. (3)Department of Neuroscience, Rehabilitation, Genetics and Maternal and Perinatal Sciences, University of Genoa, Genoa, Italy. (4)Department of Neuroscience, Rehabilitation, Genetics and Maternal and Perinatal Sciences, University of Genoa, Genoa, Italy. matilde.inglese@mssm.edu. (5)Departments of Neurology, Radiology and Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, USA. matilde.inglese@mssm.edu.

Imaging markers for monitoring disease progression in progressive multiple sclerosis (PMS) are scarce, thereby limiting the possibility to monitor disease evolution and to test effective treatments in clinical trials. Advanced imaging techniques that have the advantage of metrics with increased sensitivity to short-term tissue changes and increased specificity to the structural abnormalities characteristic of PMS have recently been applied in clinical trials of PMS. In this review, we (1) provide an overview of the pathological features of PMS, (2) summarize the findings of research and clinical trials conducted in PMS which have applied conventional and advanced magnetic resonance imaging techniques and (3) discuss recent advancements and future perspectives in monitoring PMS with imaging techniques.

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A Systematic Review and Meta-Analysis of the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS).

Corfield F(1), Langdon D(2).

Author information: (1)Psychology Department, Royal Holloway, University of London, Egham, Surrey, UK. (2)Psychology Department, Royal Holloway, University of London, Egham, Surrey, UK.
d.langdon@rhul.ac.uk.

Multiple sclerosis (MS) is a neurological disease of the central nervous system which can lead to a range of severe physical disabilities. A large proportion of those affected will experience cognitive impairment, which is associated with a worse prognosis. Effective assessment of cognition in MS has been problematic due to a lack of suitable scales. The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) was developed in 2010 as part of an international endeavour to facilitate cognitive assessment. AIM: The aim of this systematic review and meta-analysis was to synthesise the available literature published as part of the BICAMS international validation protocol. METHODS: A literature search conducted using PubMed, PsycINFO and Google Scholar identified 16 studies for inclusion in the systematic review, 14 of which could be included in a meta-analysis. RESULTS: BICAMS has been widely validated across 11 languages and 14 individual cultures and locations. The meta-analysis demonstrated that BICAMS identified significantly reduced cognitive functioning in adults with MS compared to healthy controls. This was true for all three cognitive domains assessed by BICAMS: information processing speed (g = 0.943, 95% CI 0.839, 1.046, g < 0.001), immediate verbal recall memory (g = 0.688, 95% CI 0.554, 0.822, p < 0.001) and immediate visual recall memory (g = 0.635, 95% CI 0.534, 0.736, p < 0.001). CONCLUSION: BICAMS has been widely applied across cultures and languages to assess cognition in MS. BICAMS offers a feasible, cost-effective means of assessing cognition in MS worldwide. Further validation studies are underway to support this project.

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The influence of interferon β-1b on gut microbiota composition in patients with multiple sclerosis.

[Article in English, Spanish]

Castillo Álvarez F(1), Pérez-Matute P(2), Oteo JA(2), Marzo Sola ME(3).

Author information: (1)Servicio de Neurología, Hospital San Pedro, Logroño, La Rioja, España. Electronic address: fcastilloa@riojasalud.es. (2)Servicio de Enfermedades Infecciosas, CIBIR-Hospital San Pedro, Logroño, La Rioja, Spain. (3)Servicio de Neurología, Hospital San Pedro, Logroño, La Rioja, España.

INTRODUCTION: The association between gut microbiota and animal models of multiple sclerosis has been well established; however, studies in humans are scarce. METHODS: We performed a descriptive, cross-sectional study comparing the relative composition of gut microbiota in 30 patients with multiple sclerosis (15 treated with interferon β-1b, 15 not receiving this treatment) and 14 healthy controls using next generation sequencing. RESULTS: Patients with multiple sclerosis and controls showed differences in the proportion of Euryarchaeota, Firmicutes, Proteobacteria, Actinobacteria, and Lentisphaerae phyla and in 17 bacterial species. More specifically, we found significant differences in the proportion of Firmicutes, Actinobacteria, and Lentisphaerae and 6 bacteria species between controls and untreated patients; however, these differences disappeared when compared with treated patients. Untreated patients showed a significant reduction in the proportion of Prevotella copri compared to controls, while the bacteria was significantly more abundant in patients treated with interferon β-1b than in untreated patients, with levels resembling those observed in the healthy control group. CONCLUSION: We observed differences in gut microbiota composition between patients with multiple sclerosis and controls, and between patients treated and not treated with interferon β-1b. In most cases, no differences were observed between treated patients and healthy controls, particularly for P. copri levels. This suggests that the clinical improvements observed in patients with multiple sclerosis receiving interferon β-1b may result from the effect of the drug on gut microbiota. Longitudinal and functional studies are necessary to establish a causal relationship.

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**Quantification of brain atrophy in multiple sclerosis using two-dimensional measurements.**

[Article in English, Spanish]

Pérez-Álvarez Al(1), Suárez-Santos P(2), González-Delgado M(2), Oliva-Nacarino P(2).

Author information:  (1)Servicio de Neurología, Hospital Universitario Central de Asturias, Oviedo, Asturias, España. Electronic address: angelperez@telecable.es.  (2)Servicio de Neurología, Hospital Universitario Central de Asturias, Oviedo, Asturias, España.

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**Delusional parasitosis in multiple sclerosis: An enigmatic manifestation of a multifaceted disease.**

[Article in English, Spanish]

León Ruiz M(1), Mitchell AJ(2), Benito-León J(3).

Author information:  (1)Servicio de Neurología, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, España; Servicio de Neurología, Clínica San Vicente, Madrid, España. Electronic address: pistolpete271285@hotmail.com.  (2)Servicio de Psicooncología, Leicestershire Partnership Trust and University of Leicester, Leicester, Reino Unido.  (3)Servicio de Neurología, Hospital Universitario 12 de Octubre, Madrid, España; Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, España; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, España.

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**Primary cytomegalovirus infection in a patient with relapsing-remitting multiple sclerosis under treatment with alemtuzumab.**

[Article in English, Spanish]


Author information:  (1)Servicio de Neurología, Unidad de Esclerosis Múltiple, Hospital Universitario Virgen Macarena, Sevilla, España.  (2)Servicio de Neurología, Unidad de Esclerosis Múltiple, Hospital Universitario Virgen Macarena, Sevilla, España. Electronic address: Rocí.lopez.ruiz@gmail.com.  (3)Servicio de Enfermedades Infecciosas, Hospital Universitario Reina Sofía, Córdoba, España.  (4)Servicio de Microbiología, Hospital Universitario Virgen Macarena, Sevilla, España.

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Analysis of the diagnostic pathway and delay in patients with amyotrophic lateral sclerosis in the Valencian Community.


Author information: (1)Grupo de investigación en enfermedades neuromusculares y ataxias, Instituto de Investigación Sanitaria La Fe, Valencia, España; Servicio de Neurología, Hospital Universitario y Politécnico La Fe, Valencia, España; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Valencia, España. Electronic address: juan.vazquez.neuro@gmail.com. (2)Servicio de Neurología, Hospital Universitario y Politécnico La Fe, Valencia, España. (3)Unidad de Bioestadística, Instituto de Investigación Sanitaria La Fe, Valencia, España. (4)Grupo de investigación en enfermedades neuromusculares y ataxias, Instituto de Investigación Sanitaria La Fe, Valencia, España; Servicio de Neurología, Hospital Universitario y Politécnico La Fe, Valencia, España. (5)Grupo de investigación en enfermedades neuromusculares y ataxias, Instituto de Investigación Sanitaria La Fe, Valencia, España; Servicio de Neurología, Hospital Universitario y Politécnico La Fe, Valencia, España; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Valencia, España; Departamento de Medicina, Universidad de Valencia, Valencia, España.

INTRODUCTION: Amyotrophic lateral sclerosis (ALS) is an insidious, clinically heterogeneous neurodegenerative disease associated with a diagnostic delay of approximately 12 months. No study conducted to date has analysed the diagnostic pathway in Spain. METHODS: We gathered data on variables related to the diagnostic pathway and delay for patients diagnosed with ALS between October 2013 and July 2017. RESULTS: The study included 143 patients with ALS (57% men; 68% spinal onset). Patients were diagnosed in public centres in 86% of cases and in private centres in 14%. The mean diagnostic delay was 13.1 months (median 11.7). Patients were examined by neurologists a mean time of 7.9 months after symptom onset, with diagnosis being made 5.2 months later. Half of all patients underwent unnecessary diagnostic tests and multiple electrophysiological studies before diagnosis was established. Diagnostic delay was longer in cases of spinal onset (P = .008) due to onset of the disease in the lower limbs. No differences were found between the public and private healthcare systems (P = .897). CONCLUSIONS: The diagnostic delay in ALS in Spain is similar to that of neighboring countries and seems to depend on disease-related factors, not on the healthcare system. Patients with lower-limb onset ALS constitute the greatest diagnostic challenge. Misdiagnosis is frequent, and partly attributable to an incorrect approach or erroneous interpretation of electrophysiological studies. Specific training programmes for neurologists and general neurophysiologists and early referral to reference centers may help to reduce diagnostic delay.

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Current evidence on the potential therapeutic applications of transcranial magnetic stimulation in multiple sclerosis: A systematic review of the literature.

[Article in English, Spanish]
León Ruiz M(1), Sospedra M(2), Arce Arce S(3), Tejeiro-Martínez J(4), Benito-León J(5).

Author information: (1)Servicio de Neurología, Clínica San Vicente, Madrid, España; Servicio de Neurología, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, España. Electronic address: pistolpete271285@hotmail.com. (2)Sección de Neuroinmunología y de Investigación en Esclerosis Múltiple, Departamento de Neurología, Hospital Universitario de Zúrich, Zúrich, Suiza. (3)Servicio de Psiquiatría, Clínica San Vicente, Madrid, España; Departamento de Dirección Médica, Clínica San Vicente, Madrid, España. (4)Servicio de Neurología, Hospital Universitario Príncipe de Asturias, Alcalá de Henares, Madrid, España. (5)Servicio de Neurología, Hospital Universitario 12 de Octubre, Madrid, España; Departamento de Medicina, Facultad de Medicina, Universidad Complutense de Madrid, Madrid, España; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED), Madrid, España.

INTRODUCTION: A growing number of studies have evaluated the effects of transcranial magnetic stimulation (TMS) for the symptomatic treatment of multiple sclerosis (MS). METHODS: We performed a PubMed search for articles, recent books, and recommendations from the most relevant clinical practice guidelines and scientific societies regarding the use of TMS as symptomatic treatment in MS. CONCLUSIONS: Excitatory electromagnetic pulses applied to the affected cerebral hemisphere allow us to optimise functional brain activity, including the transmission of nerve impulses through the demyelinated corticospinal pathway. Various studies into TMS have shown statistically significant improvements in spasticity, fatigue, lower urinary tract dysfunction, manual dexterity, gait, and cognitive deficits related to working memory in patients with MS; however, the exact level of evidence has not been defined as the results have not been replicated in a sufficient number of controlled studies. Further well-designed, randomised, controlled clinical trials involving a greater number of patients are warranted to attain a higher level of evidence in order to recommend the appropriate use of TMS in MS patients across the board. TMS acts as an adjuvant with other symptomatic and immunomodulatory treatments. Additional studies should specifically investigate the effect of conventional repetitive TMS on fatigue in these patients, something that has yet to see the light of day.

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Fingolimod vs dimethyl fumarate in multiple sclerosis: A real-world propensity score-matched study.

Prosperini L(1), Lucchini M(2), Haggiag S(2), Bellantoni P(2), Blanco A(2), Buscarinu MC(2), Buttari F(2), Centonze D(2), Cortese A(2), De Giglio L(2), Fantozzi R(2), Ferraro E(2), Fornasier A(2), Francia A(2), Galgani S(2), Gasperini C(2), Marfia GA(2), Millefiorini E(2), Nociti V(2), Pontecorvo S(2), Pozzilli C(2), Ruggieri S(2), Salvetti M(2), Sgarlata E(2), Mirabella M(2).

Author information: (1)From the Department of Neurosciences (L.P., S.H., S.G., C.G., S.R.), S. Camillo-Forlanini Hospital; Department of Neurology and Psychiatry (A.C., L.D.G., A. Francia, E.M., S.P., C.P., S.R., E.S.), Sapienza University; Fondazione Policlinico Universitario IRCCS “A. Gemelli” (M.L., A.B., V.N., M.M.), Università Cattolica del Sacro Cuore, Rome; Unit of Neurology and of Neurorehabilitation (P.B., F.B., D.C., R.F., M.S.), IRCCS Neuromed, Pozzilli (IS); Center for Experimental Neurological Therapies (M.C.B., A. Fornasiero, M.S.), S. Andrea Hospital, Department of Neurosciences, Mental Health and Sensory Organs, Sapienza University of Rome; Department of Systems Medicine (F.B., D.C., G.A.M.), MS Clinical and Research Center, Tor Vergata University; Neurology Unit (E.F.), S. Filippo Neri Hospital, Rome; and Don Carlo Gnocchi Foundation Onlus (V.N.), Milan, Italy. luca.prosperini@gmail.com. (2)From the Department of Neurosciences (L.P., S.H., S.G., C.G., S.R.), S. Camillo-Forlanini Hospital; Department of Neurology and Psychiatry (A.C., L.D.G., A. Francia, E.M., S.P., C.P., S.R., E.S.), Sapienza University; Fondazione Policlinico Universitario IRCCS “A. Gemelli” (M.L., A.B., V.N., M.M.), Università Cattolica del Sacro Cuore, Rome; Unit of Neurology and of Neurorehabilitation (P.B., F.B., D.C., R.F., M.S.), IRCCS Neuromed, Pozzilli (IS); Center for Experimental Neurological Therapies (M.C.B., A. Fornasiero, M.S.), S. Andrea Hospital, Department of Neurosciences, Mental Health and Sensory Organs, Sapienza University of Rome; Department of Systems Medicine (F.B., D.C., G.A.M.), MS Clinical and Research Center, Tor Vergata University; Neurology Unit (E.F.), S. Filippo Neri Hospital, Rome; and Don Carlo Gnocchi Foundation Onlus (V.N.), Milan, Italy.

OBJECTIVE: To directly compare fingolimod (FNG) and dimethyl fumarate (DMF) on no evident disease activity (NEDA) status in patients with relapsing-remitting multiple sclerosis (RRMS) from 7 multiple sclerosis outpatient clinics in Central Italy. METHODS: We analyzed data of patients with RRMS who started an oral agent, namely DMF or FNG, either as first treatment (naives) or after switching from self-injectable drugs (switchers). We performed a propensity score (PS)-based nearest-neighbor matching within a caliper of 0.05 to select patients with homogeneous baseline characteristics. Pairwise censoring was adopted to adjust for difference in length of follow-up between the 2 treatment groups. Comparisons were then conducted in matched samples with Cox models (stratified by center) with NEDA-3 as the main outcome. NEDA-3 was defined as no relapses, no disability worsening, and no MRI activity. RESULTS: Overall, 483 and 456 patients eligible for analysis started on FNG and DMF, respectively. The PS-matching procedure retained a total of 550 patients (275 per group). After a median on-study follow-up of 18 months, the proportions of patients with NEDA-3 were similar (FNG 73%, DMF 70%; hazard ratio [HR] 0.74, p = 0.078). Subgroup analyses showed a comparable effectiveness of the 2 drugs in naives (n = 170, HR 1.15, p = 0.689), whereas FNG was superior to DMF in the achievement of NEDA-3 status among switchers (n = 380, HR 0.57, p = 0.007). CONCLUSION: We found no significant difference between FNG and DMF on NEDA-3 status, while subgroup analyses suggest the superiority of FNG over DMF in patients switching from self-injectable drugs.

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Tsagkas C(1), Magon S(1), Gaetano L(1), Pezold S(1), Naegelin Y(1), Amann M(1), Stippich C(1), Cattin P(1), Wuerfel J(1), Bieri O(1), Sprenger T(1), Kappos L(1), Parmar K(2).

Author information: (1)From the Department of Neurology (C.T., S.M., L.G., Y.N., M.A., T.S., L.K., K.P.), Division of Diagnostic and Interventional Neuroradiology, Department of Radiology (M.A., C.S.), and Division of Radiological Physics, Department of Radiology (O.B.), University Hospital Basel, University of Basel; Medical Image Analysis Center (MIAC AG) (C.T., S.M., L.G., M.A., J.W.), Basel; Department of Biomedical Engineering (S.P., P.C.), University of Basel, Switzerland; and Department of Neurology (T.S.), DKD HELIOS Klinik Wiesbaden, Germany. (2)From the Department of Neurology (C.T., S.M., L.G., M.A., T.S., L.K., K.P.), Division of Diagnostic and Interventional Neuroradiology, Department of Radiology (M.A., C.S.), and Division of Radiological Physics, Department of Radiology (O.B.), University Hospital Basel, University of Basel; Medical Image Analysis Center (MIAC AG) (C.T., S.M., L.G., M.A., J.W.), Basel; Department of Biomedical Engineering (S.P., P.C.), University of Basel, Switzerland; and Department of Neurology (T.S.), DKD HELIOS Klinik Wiesbaden, Germany. katrin.parmar@usb.ch.

OBJECTIVE: Cross-sectional studies have shown that spinal cord volume (SCV) loss is related to disease severity in multiple sclerosis (MS). However, long-term data are lacking. Our aim was to evaluate SCV loss as a biomarker of disease progression in comparison to other MRI measurements in a large cohort of patients with relapse-onset MS with 6-year follow-up. METHODS: The upper cervical SCV, the total brain volume, and the brain T2 lesion volume were measured annually in 231 patients with MS (180 relapsing-remitting [RRMS] and 51 secondary progressive [SPMS]) over 6 years on 3-dimensional, T1-weighted, magnetization-prepared rapid-acquisition gradient echo images. Expanded Disability Status Scale (EDSS) score and relapses were recorded at every follow-up. RESULTS: Patients with SPMS had lower baseline SCV (p < 0.01) but no accelerated SCV loss compared to those with RRMS. Clinical relapses were found to predict SCV loss over time (p < 0.05) in RRMS. Furthermore, SCV loss, but not total brain volume and T2 lesion volume, was a strong predictor of EDSS score worsening over time (p < 0.05). The mean annual rate of SCV loss was the strongest MRI predictor for the mean annual EDSS score change of both RRMS and SPMS separately, while correlating stronger in SPMS. Every 1% increase of the annual SCV loss rate was associated with an extra 28% risk increase of disease progression in the following year in both groups. CONCLUSION: SCV loss over time relates to the number of clinical relapses in RRMS, but overall does not differ between RRMS and SPMS. SCV proved to be a strong predictor of physical disability and disease progression, indicating that SCV may be a suitable marker for monitoring disease activity and severity.

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Spinal cord atrophy rates: Ready for prime time in multiple sclerosis clinical trials?

Prados F(1), Barkhof F(1).

Author information: (1)From the Centre for Medical Image Computing (CMIC) (F.P., F.B.), Department of Medical Physics and Bioengineering, University College London; UCL Institute of Neurology (F.P., F.B.), London, UK; and Department of Radiology and Nuclear Medicine (F.B.), VU University Medical Centre, Amsterdam, the Netherlands.

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Drug reaction with eosinophilia and systemic symptoms after daclizumab therapy.

Rauer S(1), Stork L(1), Urbach H(1), Stathi A(1), Marx A(1), Süß P(1), Prinz M(1), Brück W(1), Metz I(2).

Author information: (1)From the Departments of Neurology (S.R., A.S., A.M.) and Neuroradiology (H.U.), University Medical Center Freiburg; Institute of Neuropathology (L.S., W.B., I.M.), University Medical Center Goettingen; Institute of Neuropathology, Medical Faculty (P.S., M.P.), and BIOSS Centre for Biological Signalling Studies (M.P.), University of Freiburg, Germany. (2)From the Departments of Neurology (S.R., A.S., A.M.) and Neuroradiology (H.U.), University Medical Center Freiburg; Institute of Neuropathology (L.S., W.B., I.M.), University Medical Center Goettingen; Institute of Neuropathology, Medical Faculty (P.S., M.P.), and BIOSS Centre for Biological Signalling Studies (M.P.), University of Freiburg, Germany. imetz@gwdg.de.

OBJECTIVE: To report on 2 women with multiple sclerosis (MS) who developed severe neurologic deterioration and a drug reaction with eosinophilia and systemic symptoms (DRESS) after treatment with 2 and 4 subcutaneous injections of daclizumab, respectively. METHODS: This report includes clinical, MRI, and histopathologic data. RESULTS: Daclizumab is a humanized monoclonal antibody that binds the interleukin-2 receptor. It was approved for the treatment of relapsing MS. DRESS is an immunologic reaction to various medications that is characterized by eosinophilia as well as cutaneous and visceral manifestations. Following daclizumab treatment, both patients showed fulminant neurologic deterioration along with blood eosinophilia and skin changes, and both fulfilled the clinical criteria for the diagnosis of DRESS. They presented with multiple gadolinium-enhancing supratentorial lesions, with lesions in the basal ganglia, mesencephalon, and cerebellum. Brain biopsies revealed a pronounced inflammatory infiltrate including numerous eosinophils infiltrating demyelinating lesions, a feature that is atypical for MS but compatible with DRESS. In addition, numerous plasma cells and changes reminiscent of vasculitis were evident. CONCLUSIONS: Neurologic deterioration and DRESS occurred as severe adverse drug effects of daclizumab treatment. Early diagnosis and treatment of DRESS are essential because it is associated with complications such as new autoimmune diseases and liver failure, and may even be lethal. Because of its potential serious side effects, daclizumab was recently suspended for use in the European Union.

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Hagens MHJ(1), Burggraaff J(2), Kilsdonk ID(2), de Vos ML(2), Cawley N(2), Sbardella E(2), Andelova M(2), Amann M(2), Lieb JM(2), Pantano P(2), Lissenden-Witte Bl(2), Killestein J(2), Oreja-Guevara C(2), Ciccarelli O(2), Gasperini C(2), Lukas C(2), Wattjes MP(2), Barkhof F(2); MAGNIMS Study Group.

Author information: (1)From the Departments of Neurology (M.H.J.H., J.B., J.K.) and Radiology and Nuclear Medicine (I.D.K., M.L.d.V., M.P.W., F.B.), MS Centre Amsterdam, and Department of Epidemiology and Biostatistics (B.I.L.-W.), VU University Medical Centre; Department of Radiology and Nuclear Medicine (I.D.K.), Onze Lieve Vrouwen Gasthuis, Amsterdam, the Netherlands; Queen Square Multiple Sclerosis Centre (N.C., O.C.) and Institutes of Neurology & Healthcare Engineering (F.B.), UCL Institute of Neurology, London, UK; Department of Neurology and Psychiatry (E.S., P.P.), Sapienza University of Rome, Italy; Department of Neurology (M. Andelova, M. Amann) and Division of Neuroradiology, Department of Radiology (M. Amann, J.M.L.), University Hospital Basel; Medical Image Analysis Centre (M. Amann), Basel, Switzerland; Istituto Neurologico Mediterraneo (P.P.), Neuromed, Pozzilli (IS), Italy; Department of Neurology (C.O.-G.), Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain; National Institute for Health Research (O.C., F.B.), University College London Hospitals (UCLH) Biomedical Research Centre (BRC), UK; Department of Neurosciences (C.G.), San Camillo-Forlanini Hospital, Rome, Italy; and Department of Diagnostic and Interventional Radiology and Nuclear Medicine (C.L.), St. Josef Hospital, Ruhr University, Bochum, Germany. m.hagens1@vumc.nl. (2)From the Departments of Neurology (M.H.J.H., J.B., J.K.) and Radiology and Nuclear Medicine (I.D.K., M.L.d.V., M.P.W., F.B.), MS Centre Amsterdam, and Department of Epidemiology and Biostatistics (B.I.L.-W.), VU University Medical Centre; Department of Radiology and Nuclear Medicine (I.D.K.), Onze Lieve Vrouwen Gasthuis, the Netherlands; Queen Square Multiple Sclerosis Centre (N.C., O.C.) and Institutes of Neurology & Healthcare Engineering (F.B.), UCL Institute of Neurology, London, UK; Department of Neurology and Psychiatry (E.S., P.P.), Sapienza University of Rome, Italy; Department of Neurology (M. Andelova, M. Amann) and Division of Neuroradiology, Department of Radiology (M. Amann, J.M.L.), University Hospital Basel; Medical Image Analysis Centre (M. Amann), Basel, Switzerland; Istituto Neurologico Mediterraneo (P.P.), Neuromed, Pozzilli (IS), Italy; Department of Neurology (C.O.-G.), Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain; National Institute for Health Research (O.C., F.B.), University College London Hospitals (UCLH) Biomedical Research Centre (BRC), UK; Department of Neurosciences (C.G.), San Camillo-Forlanini Hospital, Rome, Italy; and Department of Diagnostic and Interventional Radiology and Nuclear Medicine (C.L.), St. Josef Hospital, Ruhr University, Bochum, Germany.

OBJECTIVE: In the work-up of patients presenting with a clinically isolated syndrome (CIS), 3T MRI might offer a higher lesion detection than 1.5T, but it remains unclear whether this affects the fulfilment of the diagnostic criteria for multiple sclerosis (MS). METHODS: We recruited 66 patients with CIS within 6 months from symptom onset and 26 healthy controls in 6 MS centers. All participants underwent 1.5T and 3T brain and spinal cord MRI at baseline according to local optimized protocols and the MAGNIMS guidelines. Patients who had not converted to MS during follow-up received repeat brain MRI at 3-6 months and 12-15 months. The number of lesions per anatomical region was scored by 3 raters in consensus. Criteria for dissemination in space (DIS) and dissemination in time (DIT) were determined according to the 2017 revisions of the McDonald criteria. RESULTS: Three-Tesla MRI detected 15% more T2 brain lesions compared to 1.5T (p < 0.001), which was driven by an increase in baseline detection of periventricular (12%, p = 0.015), (jux)ta-cortical (21%, p = 0.005), and deep white matter lesions (21%, p < 0.001). The detection rate of spinal cord lesions and gadolinium-enhancing lesions did not differ between field strengths. Three-Tesla MRI did not lead to a higher number of patients fulfilling the criteria for DIS or DIT, or subsequent diagnosis of MS, at any of the 3 time points. CONCLUSION: Scanning at 3T does not influence the diagnosis of MS according to McDonald diagnostic criteria.
Exercise-induced changes in neurotrophic factors and markers of blood-brain barrier permeability are moderated by weight status in multiple sclerosis.

Mokhtarzade M(1), Motl R(2), Negaresh R(3), Zimmer P(4), Khodadoost M(5), Baker JS(6), Patel D(7), Majdinasab N(8), Ranjbar R(9).  Author information:  (1)Department of Sport Physiology, Tarbiat Modares University, Tehran, Iran. (2)Department of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL, USA. (3)Department of Sport Physiology, Tarbiat Modares University, Tehran, Iran. Electronic address: Raoof.negaresh@modares.ac.ir. (4)Department for Molecular and Cellular Sports Medicine, German Sport University Cologne, Cologne, Germany; Division of Physical Activity, Prevention and Cancer, German Cancer Research Center, Heidelberg, Germany. (5)Department of Physical Education, Abadan branch, Islamic Azad University, Abadan, Iran. (6)Institute of Clinical Exercise and Health Sciences, School of Science and Sport, University of the West of Scotland, Hamilton, Lanarkshire, Scotland, United Kingdom. (7)School of Nursing, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. (8)Musculoskeletal Rehabilitation Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; Department of Neurology, Golstan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. (9)Department of Sport Physiology, Shahid Chamran University of Ahvaz, Ahvaz, Iran.

Blood-brain barrier (BBB) and neurotrophic factors seemingly have an important role in multiple sclerosis pathology. Physical activity may influence blood-brain barrier function and levels of neurotrophic factors, and such effects might be moderated by body weight status. This study investigated the effect of exercise training on markers of blood-brain barrier permeability and neurotrophic factors as a function of weight status in multiple sclerosis patients. Sixty three persons with relapsing remitting multiple sclerosis who were normal weight (n: 33) or overweight (n: 33) were randomly assigned into groups of exercise (normal weight training, n: 18; overweight training group, n: 18) or no exercise (normal weight control, n: 15; overweight control group, n: 15). The intervention consisted of 8 weeks (3 days per week) of cycling undertaken at 60-70% peak power. Resting blood concentrations of s100 calcium-binding protein B (s100b) and neuron-specific enolase as BBB permeability markers, neurotrophic factors and cytokines (Interleukin-10 and tumor necrosis factor alpha) were evaluated before and after the intervention. There were significant weight, training, and interaction effects on brain-derived neurotrophic factor and platelet-derived growth factor; however, ciliary neurotrophic factor and nerve growth factor did not demonstrate any effect. Brain-derived neurotrophic factor and platelet-derived growth factor were significantly increased from pre-post in normal weight exercise. Significant weight, training, and interaction effects were found for s100b. In detail, s100b was significantly increased from pre-post in normal weight exercise. In contrast, neuron-specific enolase and cytokines did not demonstrate any effect. Generally, Exercise training may alter markers of BBB permeability and neurotrophic factor status in normal weight persons with multiple sclerosis; however, overweight participants may be more resistant to these effects of exercise.

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Schmidt SL(1)(2), Santos da Silva M(2), Schmidt JJ(2), Carvalho ALN(3), Vasconcelos CCF(2), Paes RA(2), Boechat YE(4), Neder R(2), Alvarenga RP(2).

Author information: (1)Department of Neurophysiology, State University of Rio de Janeiro, RJ, Brazil. (2)Neurology Department, Federal University of the State of Rio de Janeiro, RJ, Brazil. (3)Department of Psychology, Fluminense Federal University, Niteroi, Brazil. (4)Department of Internal Medicine, Fluminense Federal University, Niteroi, Brazil.

Background: In the early phases of multiple sclerosis (MS), patients exhibit slight neuropsychiatric deficits that can only be detected using reliable tools. Aim: The present investigation aimed to examine neuropsychological performance in 35 patients with incipient MS. Patients and methods: For the MS group, the inclusion criteria included time of disease <3 years and low disability. The neuropsychological battery consisted of Rey Auditory Learning Test, Controlled Oral Word Association Test, Hooper Visual Organization Test, and Symbol Digit Modalities Test (SDMT). Results: After correction for the educational level, no significant effect of MS on performance was found for all the tests except for the number of errors of the SDMT (NE-SDMT). Higher levels of education were associated with better performances in all tests, except for the NE-SDMT. MS patients made more errors than the controls. Conclusion: The effect on the NE-SDMT may reflect difficulties in the ability to inhibit inadequate responses. Patients may exhibit impulsive control disorders in incipient MS, independent of their educational level.

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Majdinasab N(1), Namjoyan F(2), Taghizadeh M(3), Saki H(4).

Author information: (1)Department of Neurology, Ahvaz Jundishapur University of Medical Sciences, Musculoskeletal Rehabilitation Research Center, Ahvaz, Iran. (2)Department of Pharmacognosy, Marine Natural Pharmaceutical Research Center, School of Pharmacy, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. (3)Department of Nutrition, Research Center for Biochemistry & Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran. (4)Department of Neurology, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

Background: Multiple sclerosis (MS) is a chronic progressive and inflammatory disease of the central nervous system that is characterized by demyelination in the central nervous system. In regard to the prevalence of diseases and enormous costs imposed on society and the health system, finding a way to stop the progression of the disease using drugs with fewer side effects seems a serious sanitation issue to the health of the international community. This study aimed to evaluate the effect of evening primrose oil (EPO) on fatigue and quality of life in patients with MS. Materials and methods: In this double-blind randomized clinical trial, 52 patients with MS were chosen and categorized into 2 groups which received 2 doses of EPO and placebo. In addition, the quality of life and fatigue scale in these patients were investigated before the treatment and again 3 months after therapy. The findings were then compared between the 2 groups. Result: EPO consumption significantly increased cognitive function, vitality, and overall life satisfaction and also reduced pain and fatigue compared to placebo (P<0.05). Conclusion: Our findings indicated that EPO consumption had no impact on the quality of life in general; however, it had a significant effect on several important aspects of life quality such as the increase of cognitive function, vitality, and overall life satisfaction. It also reduced the pain and fatigue in comparison to the placebo consumption. Herbal medicines are brittle and have fewer side effects than chemical drugs. With use of this plant, reduced fatigue and improved quality of life were observed in MS patients. But the drug did not prevent the progression of the disease.

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Cognition in older patients with multiple sclerosis compared to patients with amnestic mild cognitive impairment and healthy older adults.

Roth AK(1), Denney DR(1), Burns JM(2), Lynch SG(2).

Author information: (1)Department of Psychology, University of Kansas. (2)Department of Neurology, University of Kansas Medical Center.

OBJECTIVE: Progress in the treatment of multiple sclerosis (MS) has resulted in larger numbers of patients living to an advanced age, but little is known about the cognitive status of these individuals. The primary purpose of this study was to identify differences in the cognitive performance between elderly individuals with MS and those with amnestic mild cognitive impairment (aMCI). METHOD: Three groups ranging in age from 60 to 80 were compared: patients with MS (n = 64), patients with aMCI (n = 58), and healthy adults (n = 70). All participants completed a standard neuropsychological test battery that evaluated domains of attention, processing speed, executive function, memory, language, and visual spatial function. RESULTS: Compared to age- and gender-matched healthy controls, elderly MS patients exhibited a pattern of cognitive impairment centered on information processing speed and memory that was consistent with the deficits observed in other studies of MS patients regardless of age. Compared to aMCI patients, the MS patients exhibited worse performance on measures of processing speed, but better performance on a measure of memory under cued conditions (Selective Reminding Test), a nonspeeded measure of language (Boston Naming Test), and measures of executive function with processing speed statistically controlled (Trail Making Test, Stroop Test). CONCLUSIONS: Differences on neuropsychological measures can serve to distinguish aMCI from MS-related cognitive impairment in older patients, but it is essential that these measures control for the deficit in processing speed that is such a primary feature of MS.

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Thalamus volume change and cognitive impairment in early relapsing-remitting multiple sclerosis patients.

Rojas JI(1), Murphy G(2), Sanchez F(1)(3), Patrucco L(1), Fernandez MC(2), Miguez J(1), Funes J(4), Golimstok A(2), Cristiano E(1).

Author information: (1) Multiple Sclerosis Center of Buenos Aires, Italian Hospital of Buenos Aires, Argentina. (2) Department of Neurology, Italian Hospital of Buenos Aires, Argentina. (3) Laboratory of Tumor Immunopharmacology, University of Buenos Aires, Argentina. (4) Department of Neuroradiology, Italian Hospital of Buenos Aires, Argentina.

Aims The objective of the study was to assess whether changes in the volume of the thalamus during the onset of multiple sclerosis predict cognitive impairment after accounting for the effects of brain volume loss. Methods A prospective study included patients with relapsing-remitting multiple sclerosis less than 3 years after disease onset (defined as the first demyelinating symptom), Expanded Disability Status Scale of 3 or less, no history of cognitive impairment and at least 2 years of follow-up. Patients were clinically followed up with annual brain magnetic resonance imaging and neuropsychological evaluations for 2 years. Measures of memory, information processing speed and executive function were evaluated at baseline and follow-up with a comprehensive neuropsychological test battery. After 2 years, the patients were classified into two groups, one with and the other without cognitive impairment. Brain dual-echo, high-resolution three-dimensional T1-weighted magnetic resonance imaging scans were acquired at baseline and every 12 months for 2 years. Between-group differences in thalamus volume, total and neocortical grey matter and white matter volumes were assessed using FIRST, SIENA, SIENAX, FIRST software (logistic regression analysis P < 0.05 significant). Results Sixty-one patients, mean age 38.4 years, 35 (57%) women were included. At 2 years of follow-up, 17 (28%) had cognitive impairment. Cognitive impairment patients exhibited significantly slower information processing speed and attentional deficits compared with patients without cognitive impairment (P < 0.001 and P = 0.02, respectively). In the cognitive impairment group a significant reduction in the percentage of thalamus volume (P < 0.001) was observed compared with the group without cognitive impairment. Conclusion We observed a significant decrease in thalamus volume in multiple sclerosis-related cognitive impairment.

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Now is the Critical Time for Engineered Neuroplasticity.


Author information:  (1)Division of Physical Therapy, Department of Rehabilitation Medicine, University of Washington, Seattle, WA, USA. ctmoritz@uw.edu. (2)Department of Physiology & Biophysics, University of Washington, Seattle, WA, USA. ctmoritz@uw.edu. (3)Graduate Program in Neuroscience, University of Washington, Seattle, WA, USA. ctmoritz@uw.edu. (4)UW Institute of Neuroengineering (UWIN), University of Washington, Seattle, WA, USA. ctmoritz@uw.edu. (5)Washington Spinal Cord Injury Consortium, University of Washington, Seattle, WA, USA. ctmoritz@uw.edu. (6)Center for Sensorimotor Neural Engineering, Seattle, WA, USA. ctmoritz@uw.edu. (7)Department of Electrical Engineering, University of Washington, Box 356490, Seattle, WA, 98195, USA. ctmoritz@uw.edu.

Recent advances in neuroscience and devices are ushering in a new generation of medical treatments. Engineered biodevices are demonstrating the potential to create long-term changes in neural circuits, termed neuroplasticity. Thus, the approach of engineering neuroplasticity is rapidly expanding, building on recent demonstrations of improved quality of life for people with movement disorders, epilepsy, and spinal cord injury. In addition, discovering the fundamental mechanisms of engineered neuroplasticity by leveraging anatomically well-documented systems like the spinal cord is likely to provide powerful insights into solutions for other neurotraumas, such as stroke and traumatic brain injury, as well as neurodegenerative disorders, such as Alzheimer's, Parkinson disease, and multiple sclerosis. Now is the time for advancing both the experimental neuroscience, device development, and pioneering human trials to reap the benefits of engineered neuroplasticity as a therapeutic approach for improving quality of life after spinal cord injury.

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Tornic J(1), Sartori AM(1)(2), Gajewski JB(3), Cox A(3), Schneider MP(1)(2)(4), Youssef NA(1), Mordasini L(5), Chartier-Kastler E(6), Bachmann LM(7), Kessler TM(1).

Author information:  (1)Neuro-Urology, Spinal Cord Injury Center and Research, University of Zürich, Balgrist University Hospital, Zürich, Switzerland. (2)Brain Research Institute, University of Zürich and Department of Health Sciences and Technology, Swiss Federal Institute of Technology Zürich, Zürich, Switzerland. (3)Department of Urology, Dalhousie University, Halifax, Nova Scotia, Canada. (4)Department of Urology, Inselspital, Bern University Hospital, Bern, Switzerland. (5)Department of Urology, Cantonal Hospital Lucerne, Lucerne, Switzerland. (6)Department of Urology, Groupe Hospitalier Pité-Salpêtrière, Medical School Sorbonne University, Paris, France. (7)Medigation Inc., Research Consultants, Zürich, Switzerland.

AIM: To systematically assess all available evidence on efficacy and safety of catheterization for treating neurogenic lower urinary tract dysfunction (NLUTD) in patients with multiple sclerosis (MS). METHODS: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were identified by electronic search of Embase, Medline, Scopus, Cochrane register (last search March 3, 2018) and by screening of reference lists and reviews. RESULTS: After screening 7,015 articles, we included four studies (one prospective and two retrospective cohort studies, one retrospective cross-sectional study), in which a total of 445 patients were enrolled. No randomized controlled trial was available. Catheterization substantially increased quality of life, post void residual, and incontinence episodes in all included studies. Pooling of data for meta-analysis was not possible due to the heterogeneity of reported outcomes. Adverse events were reported in two studies only. Risk of bias and confounding was intermediate. CONCLUSIONS: Preliminary data suggests beneficial effects of catheterization on the urological outcome in patients with MS. However, although intermittent and indwelling catheterization is used frequently in daily clinical practice in the MS population, the evidence base is very limited and well-designed, properly sampled, and powered studies are urgently needed.

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**Impact of Dietary Cholesterol on the Pathophysiology of Infectious and Autoimmune Disease.**

Andersen CJ(1).
Author information: (1)Department of Biology, Fairfield University, Fairfield, CT 06824, USA. candersen@fairfield.edu.

Cellular cholesterol metabolism, lipid raft formation, and lipoprotein interactions contribute to the regulation of immune-mediated inflammation and response to pathogens. Lipid pathways have been implicated in the pathogenesis of bacterial and viral infections, whereas altered lipid metabolism may contribute to immune dysfunction in autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. Interestingly, dietary cholesterol may exert protective or detrimental effects on risk, progression, and treatment of different infectious and autoimmune diseases, although current findings suggest that these effects are variable across populations and different diseases. Research evaluating the effects of dietary cholesterol, often provided by eggs or as a component of Western-style diets, demonstrates that cholesterol-rich dietary patterns affect markers of immune inflammation and cellular cholesterol metabolism, while additionally modulating lipoprotein profiles and functional properties of HDL. Further, cholesterol-rich diets appear to differentially impact immunomodulatory lipid pathways across human populations of variable metabolic status, suggesting that these complex mechanisms may underlie the relationship between dietary cholesterol and immunity. Given the Dietary Guidelines for Americans 2015–2020 revision to no longer include limitations on dietary cholesterol, evaluation of dietary cholesterol recommendations beyond the context of cardiovascular disease risk is particularly timely. This review provides a comprehensive and comparative analysis of significant and controversial studies on the role of dietary cholesterol and lipid metabolism in the pathophysiology of infectious disease and autoimmune disorders, highlighting the need for further investigation in this developing area of research.

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**Changes of Colonic Bacterial Composition in Parkinson's Disease and Other Neurodegenerative Diseases.**

Gerhardt S(1), Mohajeri MH(2).
Author information: (1)Departement of human medicine, University of Zurich, Winterthurerstrasse 190, 8057 Zürich, Switzerland. sara.gerhardt@uzh.ch. (2)Departement of human medicine, University of Zurich, Winterthurerstrasse 190, 8057 Zürich, Switzerland. Mhasan.Mohajeri@Uzh.Ch.

In recent years evidence has emerged that neurodegenerative diseases (NDs) are strongly associated with the microbiome composition in the gut. Parkinson's disease (PD) is the most intensively studied neurodegenerative disease in this context. In this review, we performed a systematic evaluation of the published literature comparing changes in colonic microbiome in PD to the ones observed in other NDs including Alzheimer's disease (AD), multiple system atrophy (MSA), multiple sclerosis (MS), neuromyelitis optica (NMO) and amyotrophic lateral sclerosis (ALS). To enhance the comparability of different studies, only human case-control studies were included. Several studies showed an increase of Lactobacillus, Bifidobacterium, Verrucomicrobiaceae and Akkermansia in PD. A decrease of Faecalibacterium spp., Coprococcus spp., Blautia spp., Prevotella spp. and Prevotellaceae was observed in PD. On a low taxonomic resolution, like the phylum level, the changes are not disease-specific and are inconsistent. However, on a higher taxonomic resolution like genus or species level, a minor overlap was observed between PD and MSA, both alpha synucleinopathies. We show that standardization of sample collection and analysis is necessary for ensuring the reproducibility and comparability of data. We also provide evidence that assessing the microbiota composition at high taxonomic resolution reveals changes in relative abundance that may be specific to or characteristic of one disease or disease group, and might evolve discriminative power. The interactions between bacterial species and strains and the co-abundances must be investigated before assumptions about the effects of specific bacteria on the host can be made with certainty.

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Sizemore G(1), Lucke-Wold B(2), Rosen C(2), Simpkins JW(3), Bhatia S(2), Sun D(4).

Author information: (1) Department of Clinical and Translational Science, West Virginia School of Medicine, Morgantown, WV. (2) Department of Neurosurgery, West Virginia School of Medicine, Morgantown, WV. (3) Center for Basic and Translational Stroke Research, West Virginia School of Medicine, Morgantown, WV. (4) Department of Neurology, University of Pittsburgh, Pittsburgh, PA.

The brain is an integrated network of multiple variables that when compromised create a diseased state. The neuropathology of temporal lobe epilepsy (TLE), stroke, and traumatic brain injury (TBI) demonstrate both similarity and complexity that reflects this integrated variability; TLE with its live human tissue resection provides opportunity for translational science to demonstrate scale equivalent experimentation between the macroscopic world of clinical disease and the microscopic world of basic science. The extended value of this research is that the neuroinflammatory abnormalities that occur throughout astrocytes with hippocampal sclerosis and damaged or even reversed signaling pathways (inhibition to excitation such as with gaba-aminobutyric acid) are similar to those seen in post-stroke and TBI models. In evaluation of the epilepsy population this interconnectedness of pathology warrants further evaluation with collaborative efforts. This review summarizes patterns that could shift experimentation closer to the macro level of humanity, but still represent the micro world of genetics, epigenetics, and neuro-injury across etiologies of physiologic dysfunction such as TLE, stroke, and TBI with evaluation of cell function using electrophysiology. In conclusion we demonstrate the plausibility of electrophysiologic voltage and current measurement of brain tissue by patch clamp analysis to specify actual electrophysiologic function for comparison to electroencephalography in order to aid neurologic evaluation. Finally, we discuss the opportunity with multiscale modeling to display integration of the hyperpolarization cyclic-nucleotide gated channel, the depolarized calcium channels, and sodium-potassium-chloride-one/potassium-chloride-two co-transporter channels as potential mechanisms utilized as tri-coordinate biomarkers with these three forms of neurologic disease at a molecular scale of electrophysiologic pathology.

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A Cognitive Occupation-Based Programme for People with Multiple Sclerosis: A Study to Test Feasibility and Clinical Outcomes.

Reilly S(1), Hynes SM(1).

Author information: (1) Discipline of Occupational Therapy, National University of Ireland Galway, Galway, Ireland.

Cognitive impairments are common in MS and affect personal, social, and occupational functioning. There is a developing body of evidence highlighting the role of cognitive rehabilitation, but there is still no evidence for a validated holistic approach. The aim of this study was to assess the effectiveness of Cognitive Occupation-Based Programme for People with Multiple Sclerosis (COB-MS) for improving daily life and cognitive impairment. This study used an experimental pretest/posttest design with eight-week follow-up. Participants were recruited from MS networks using convenience sampling. The primary outcome measure was the GAS. Secondary outcomes included the OSA-DLS, CVLT-II, BVMT-R, SDMT, TMT, BRIEF-A, and EMQ-R. Twelve participants were recruited, aged 39-73 years (mean: 55.08; SD: 9.61). There were statistically significant improvements in the GAS (p < .002), CVLT-II: total free recall (p < .000), short delay free recall (p < .018), long delay free recall (p < .008), BVMT-R total recall (p < .000), TMT part B (p < .044), and EMQ-R (p < .006). Except for the BRIEF-A, clinically significant improvements were observed in secondary outcome measures at posttest and follow-up. Limitations include selection bias and subtle practice effects in cognitive measures. Results suggest that a larger scale study is justified considering improvements seen in daily life and cognitive measures.

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*Mycobacterium avium* subspecies *paratuberculosis*: A possible causative agent in human morbidity and risk to public health safety.

Garvey M(1).

Author information:  (1)Cellular Health and Toxicology Research Group, Institute of Technology, Sligo, Ash Lane, Sligo, Ireland.

*Mycobacterium avium* subspecies *paratuberculosis* is a bacterial parasite and the causative agent of *paratuberculosis*, a disease predominately found in cattle and sheep. Infection with this microorganism results in substantial farming economic losses and animal morbidity. The link between infection with this pathogen and human disease has been theorised for many years with Crohn's disease being one of many suspected resultant conditions. *Mycobacterium avium* may be spread from animal to human hosts by water and foodborne transmission routes, where the foodborne route of exposure represents a significant risk for susceptible populations, namely children and the immune-compromised. Following colonisation of the host, the parasitic organism evades the host immune system by use of molecular mimicry, displaying peptide sequences similar to that of the host cells causing a disruption of self-versus non self-recognition. Theoretically, this failure to recognise the invading organism as distinct from host cells may result in numerous autoimmune conditions. Here, the author presents current information assessing the link between numerous diseases states in humans such inflammatory bowel disease, Type 1 diabetes, rheumatoid arthritis, Hashimoto's thyroiditis, multiple sclerosis and autism following infection with *Mycobacterium avium* *paratuberculosis*. The possibility of zoonotic transmission of the organism and its significant risk to public health safety as a consequence is also discussed.

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**Potential Effect of Cyclophosphamide on Bleb Survival in Five Patients with Multiple Sclerosis Who Underwent Glaucoma Surgery.**

Giudiceandrea A(1), Toro ME(2), Scupola A(1), Caporossi A(1), Nociti V(3)(4), Mirabella M(3), Salgarello T(1).

Author information:  (1)Ophthalmology Division - Department of Head and Neck Surgery of Catholic University of "Sacro Cuore", Fondazione Policlinico Universitario "A. Gemelli", Rome, Italy.
(2)Ophthalmology Division - Department of Head and Neck Surgery of Catholic University of "Sacro Cuore", Fondazione Policlinico Universitario "A. Gemelli", Rome, Italy. emanuelotoro@tiscali.it. (3)Catholic University of "Sacro Cuore", Fondazione Policlinico Universitario "A. Gemelli", Rome, Italy. (4)Don C. Gnocchi Foundation Onlus, Milan, Italy.

INTRODUCTION: The purpose of this case series was to report the potential role of cyclophosphamide (CY) on bleb survival and to evaluate the safety of the trabeculectomy procedure under immunosuppressant systemic therapy. CASE SERIES: Five eyes of five patients with unresponsive to intraocular pressure (IOP) lowering medication, progressive glaucoma, underwent mytomycin C (MMC) augmented phaco-trabeculectomy, performed by the same surgeon, A.G., during the period from May 2015 to January 2016. All patients were treated with low doses of systemic CY at the time of surgery, to control their relapsing progressive multiple sclerosis (MS) form. RESULTS: During a mean follow-up period of 20.6 ± 8.1 months, for cases of "complete success" (when the IOP was < 15 mmHg without glaucoma therapy) were observed, while one case was classified as a "qualified success" since the IOP was ≤ 15 mmHg with β-blocker drops. There were no bleb infections, nor bleb-related complications. CONCLUSION: This study reports the safety of performing the filtration surgical procedure under immunosuppressant systemic therapy and provides a possible explication of CY anti-fibrotic mechanism and its possible role on bleb survival. Our findings may suggest new perspectives of study in this field.

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**Sensory Function and Chronic Pain in Multiple Sclerosis.**

Scherder RJ(1), Kant N(2), Wolf ET(1), Pijnenburg BCM(3), Scherder EJA(1).

Author information: (1)Department of Clinical Neuropsychology, Vrije Universiteit, Amsterdam, Netherlands. (2)Department of Neuropsychology, Reade, Amsterdam, Netherlands. (3)Acibadem International Medical Center, Amsterdam, Netherlands.

Objective: To examine whether hypoesthesia and chronic pain are related in patients with MS. Methods: Sixty-seven MS patients with pain and 80 persons without MS were included. Sensory functioning was tested by bedside neurological examination. Touch, joint position (dorsal column-medial lemniscus pathway), temperature sense, and pain (spinothalamic tract) were tested. Pain intensity was measured by the Colored Analogue Scale (CAS Intensity) and the Faces Pain Scale (FPS); pain affect was also measured by CAS Affect and Number of Words Chosen-Affective (NWC-A). Mood was assessed with the SCL-90 anxiety and depression subscales and the Beck Depression Inventory (BDI). Results: A significant negative relationship was found between pain intensity and the function of the dorsal column-medial lemniscal pathway, but not with the spinothalamic tract. Conclusion: In addition to the already known relation between hyperesthesia and pain, hypoesthesia for touch and joint position also seems to be related to chronic pain in MS patients.

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**Computerized adaptive testing with decision regression trees: an alternative to item response theory for quality of life measurement in multiple sclerosis.**

Michel P(1)(2), Baumstarck K(1), Loundou A(1), Ghattas B(2), Auquier P(1), Boyer L(1).

Author information: (1)Aix-Marseille Univ, School of Medicine, CEReSS - Health Service Research and Quality of Life Center, Marseille, France. (2)Mathematics Institute of Marseille, Aix-Marseille University, Marseille, France.

Background: The aim of this study was to propose an alternative approach to item response theory (IRT) in the development of computerized adaptive testing (CAT) in quality of life (QoL) for patients with multiple sclerosis (MS). This approach relied on decision regression trees (DRTs). A comparison with IRT was undertaken based on precision and validity properties. Materials and methods: DRT- and IRT-based CATs were applied on items from a unidimensional item bank measuring QoL related to mental health in MS. The DRT-based approach consisted of CAT simulations based on a minsplit parameter that defines the minimal size of nodes in a tree. The IRT-based approach consisted of CAT simulations based on a specified level of measurement precision. The best CAT simulation showed the lowest number of items and the best levels of precision. Validity of the CAT was examined using sociodemographic, clinical and QoL data. Results: CAT simulations were performed using the responses of 1,992 MS patients. The DRT-based CAT algorithm with minsplit = 10 was the most satisfactory model, superior to the best IRT-based CAT algorithm. This CAT administered an average of nine items and showed satisfactory precision indicators (R = 0.98, root mean square error [RMSE] = 0.18). The DRT-based CAT showed convergent validity as its score correlated significantly with other QoL scores and showed satisfactory discriminant validity. Conclusion: We presented a new adaptive testing algorithm based on DRT, which has equivalent level of performance to IRT-based approach. The use of DRT is a natural and intuitive way to develop CAT, and this approach may be an alternative to IRT.

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Mékiès C(1), Heinzle O(2), Jenny B(3), Ramelli AL(4), Clavelou P(5).


Background: The development of oral treatments for relapsing-remitting multiple sclerosis (RRMS) may alter patient satisfaction and quality of life (QoL). The aim of this survey was to evaluate treatment satisfaction and QoL in patients treated with fingolimod in everyday clinical practice in France. Methods: Neurologists treating MS in France were invited to participate in the survey by telephone. Each physician was expected to recruit up to six patients with RRMS currently being treated with fingolimod. Enrolled patients were asked to complete the Treatment Satisfaction Questionnaire for Medication (TSQM), the 3-level 5-dimension EuroQoL instrument, as well as specific questions on change in QoL since starting fingolimod. Factors associated with the TSQM score were evaluated using multiple logistic regression analysis. Results: Two hundred and fourteen patients were recruited by 54 neurologists. The mean age of the patients was 41.6±10.0 years, and 73.4% of them were women. During the hospitalization for initiation of fingolimod treatment, 70.1% of patients had received information on MS, 76.6% had received information on fingolimod, and 20.7% had participated in a therapeutic education program. The two variables with the strongest associations with high TSQM scores (≥75) were a positive perception of initial hospitalization (hazard ratio: 10.27) and receiving information on MS during hospitalization (hazard ratio: 5.70). The mean EQ-visual analog scale score was 71.6±16.8. The mean EQ-visual analog scale score was significantly higher in patients satisfied with their treatment (75.8±15.2) compared to those unsatisfied with treatment (66.6±17.2). The proportion of patients who reported an improvement in their capacity to plan for the future was higher in satisfied (72.6%) than in unsatisfied patients (49.5%). Conclusion: The majority of patients treated with fingolimod are satisfied with their treatment. Treatment satisfaction is associated with better self-rated QoL and an improvement of QoL since starting treatment.

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Author information: (1)Department of Dermatology, Rabin Medical Center - Beilinson Hospital, Petach Tikva, Israel. (2)Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. (3)The Laboratory for Molecular Dermatology, Felsenstein Medical Research Center, Rabin Medical Center - Beilinson Hospital, Petach Tikva, Israel. (4)Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer, Israel.

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B cells are capable of independently eliciting rapid reactivation of encephalitogenic CD4 T cells in a murine model of multiple sclerosis.

Parker Harp CR(1), Archambault AS(1), Sim J(2), Shlomchik MJ(3), Russell JH(2), Wu GF(1)(4).

Author information: (1)Department of Neurology, Washington University School of Medicine, St. Louis, MO, United States of America. (2)Department of Developmental Biology, Washington University School of Medicine, St. Louis, MO, United States of America. (3)Department of Immunology, University of Pittsburgh, Pittsburgh, PA, United States of America. (4)Department of Pathology & Immunology, Washington University School of Medicine, St. Louis, MO, United States of America.

Recent success with B cell depletion therapies has revitalized efforts to understand the pathogenic role of B cells in Multiple Sclerosis (MS). Using the adoptive transfer system of experimental autoimmune encephalomyelitis (EAE), a murine model of MS, we have previously shown that mice in which B cells are the only MHCII-expressing antigen presenting cell (APC) are susceptible to EAE. However, a reproducible delay in the day of onset of disease driven by exclusive B cell antigen presentation suggests that B cells require optimal conditions to function as APCs in EAE. In this study, we utilize an in vivo genetic system to conditionally and temporally regulate expression of MHCII to test the hypothesis that B cell APCs mediate attenuated and delayed neuroinflammatory T cell responses during EAE. Remarkably, induction of MHCII on B cells following the transfer of encephalitogenic CD4 T cells induced a rapid and robust form of EAE, while no change in the time to disease onset occurred for recipient mice in which MHCII is induced on a normal complement of APC subsets. Changes in CD4 T cell activation over time did not account for more rapid onset of EAE symptoms in this new B cell-mediated EAE model. Our system represents a novel model to study how the timing of pathogenic cognate interactions between lymphocytes facilitates the development of autoimmune attacks within the CNS.

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The long-term costs for treating multiple sclerosis in a 16-year retrospective cohort study in Brazil.


Author information: (1)SUS Collaborating Centre for Technology Assessment & Excellence in Health, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil. (2)Programa de Pós-Graduação em Medicamentos e Assistência Farmacêutica, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil. (3)Programa de Pós-Graduação em Saúde Pública, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil. (4)Departamento de Gestão e Incorporação de Tecnologias em Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Ministério da Saúde, Esplanada dos Ministérios Bloco G, Brasília, Distrito Federal, Brazil. (5)Programa de Pós-Graduação em Saúde Baseada em Evidências, Universidade Federal de São Paulo, São Paulo, São Paulo, Brazil. (6)Strathclyde Institute of Pharmacy & Biomedical Sciences, Pharmacoepidemiology, Strathclyde University, Glasgow, United Kingdom. (7)Division of Clinical Pharmacology, Karolinska Institute, Stockholm, Sweden. (8)Division of Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden.

BACKGROUND: Multiple Sclerosis (MS) is a disease that appreciably impacts on the quality of life of patients and is associated with high expenditure. MS is a chronic multifactorial disease, characterized by inflammation, demyelination and axonal loss. The Brazilian public health system provides pharmacological treatment as well as hospital and outpatient care for patients with relapsing-remitting and secondary progressive multiple sclerosis. However, we are not aware of any previous publications assessing total direct medical costs in patients with a long follow-up within the Brazilian healthcare system. Consequently, the objective is to analyze public spending on patients with MS to guide stakeholders in future investment and disinvestment decisions.

METHODS AND FINDINGS: We retrospectively analyzed public Brazilian spending on patients with MS between 2000 and 2015 using the patient-centered registry of all patients in the public health system (SUS) obtained through deterministic-probabilistic record linkage of the Outpatient Information System, Hospital Information System and Mortality Information Systems in Brazil. Descriptive data analysis and a multiple linear regression model was performed to evaluate the associations between the mean annual cost per patient and the clinical and demographic variables. The suitability of the model was verified from a residue analysis and the level of significance adopted was 5%.

RESULTS: 28,401 patients were identified and subsequently 23,082 patients were analyzed. The majority of the patients were female (73.3%), lived in the southeast region (58.9%), had a mean age of 36.8 (± 12.2) years and started treatment using one of the interferons beta (78.9%). The total direct medical cost spending in the sixteen years of the follow-up was US $2,308,393,465.60, and the mean annual expenditure per patient was US $13,544.40 (± 4,607.05). In the best fit model (p <0.001), approximately 40% of the variability of the mean annual cost per patient was explained by the region of residence; medication used (intention to treat); if the patient was a non-exclusive user of medicines, i.e., used SUS for other procedures other than high-cost medicines; year of treatment start; and presence of events (death; Relapse; change of treatment and/or comorbidity).

CONCLUSIONS: In the public health system of Brazil, disease modifying therapies currently represent almost all of the total direct costs of multiple sclerosis treatment. Around the world, new and emerging health technologies to treat of MS impose a challenge to health budgets, highlighting the need for cost-effectiveness studies comparing these technologies to those already available. Our regression model may help in this process, and calls attention to the need to access the real world performance of new therapies available in SUS, with the potential for disinvestment and/or price reductions if needed.

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Tolerogenic β2-glycoprotein I DNA vaccine and FK506 as an adjuvant attenuates experimental obstetric antiphospholipid syndrome.

Chao YH(1), Chen DY(2), Lan JL(2), Tang KT(3), Lin CC(1)(4)(5).

Author information: (1)Institute of Biomedical Science, National Chung-Hsing University, Taichung, Taiwan. (2)Division of Immunology and Rheumatology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan. (3)Division of Allergy, Immunology and Rheumatology, Taichung Veterans General Hospital, Taichung, Taiwan. (4)Department of Biotechnology, Asia University, Taichung, Taiwan. (5)Department of Medical Research, China Medical University Hospital, Taichung, Taiwan.

DNA vaccines have recently emerged as a therapeutic agent for treating autoimmune diseases, such as multiple sclerosis. Antiphospholipid antibody syndrome (APS) is an autoimmune disease characterized by β2-glycoprotein I (β2-GPI)-targeting antiphospholipid antibodies (APAs) and vascular thrombosis or obstetrical complications. To examine the therapeutic potential of a β2-GPI DNA vaccine, we administered a vaccine mixed with FK506 as an adjuvant to a mouse model of obstetric APS. First, the pCMV3-β2-GPI DNA vaccine, which encodes the full-length human β2-GPI gene, was constructed. Then, we administered the β2-GPI DNA vaccine in 0.1 ml of saline, mixed with or without 100 μg of FK506, intramuscularly to the mice on days 28, 35 and 42. Blood titers of the anti-β2-GPI antibody, platelet counts, activated partial thromboplastin times (aPTTs), and the percentage of fetal loss were measured. We also stimulated murine splenic T cells ex vivo with β2-GPI and determined the T helper cell proportion and cytokine secretion. The administration of the β2-GPI DNA vaccine mixed with FK506 reduced the blood IgG anti-β2-GPI antibody titers and suppressed APS manifestations in mice. The combination also suppressed interferon-γ and interleukin (IL)-17A secretion but increased the Treg cell proportion and IL-10 secretion in murine splenic T cells following ex vivo stimulation with β2-GPI. Our results demonstrated the therapeutic efficacy of a β2-GPI DNA vaccine and FK506 as an adjuvant in a murine model of obstetric APS. Possible mechanisms include the inhibition of Th1 and Th17 responses and the up-regulation of Treg cells.

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The association of fatigue, pain, depression and anxiety with work and activity impairment in immune mediated inflammatory diseases.

Enns MW(1)(2), Bernstein CN(3), Kroeker K(4), Graff L(5), Walker JR(5), Lix LM(2)(4), Hitchon CA(3), El-Gabalawy R(5)(6), Fisk JD(7), Marrie RA(2)(3); CIHR Team in Defining the Burden and Managing the Effects of Psychiatric Comorbidity in Chronic Immunoinflammatory Disease.

Author information:  (1)Department of Psychiatry, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada. (2)Department of Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada. (3)Department of Internal Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada. (4)George & Fay Yee Centre for Healthcare Innovation, Winnipeg, Manitoba, Canada. (5)Department of Clinical Health Psychology, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada. (6)Department of Anesthesia and Perioperative Medicine, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada. (7)Department of Psychiatry, Faculty of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.

Impairment in work function is a frequent outcome in patients with chronic conditions such as immune-mediated inflammatory diseases (IMID), depression and anxiety disorders. The personal and economic costs of work impairment in these disorders are immense. Symptoms of pain, fatigue, depression and anxiety are potentially remediable forms of distress that may contribute to work impairment in chronic health conditions such as IMID. The present study evaluated the association between pain [Medical Outcomes Study Pain Effects Scale], fatigue [Daily Fatigue Impact Scale], depression and anxiety [Hospital Anxiety and Depression Scale] and work impairment [Work Productivity and Activity Impairment Scale] in four patient populations: multiple sclerosis (n = 255), inflammatory bowel disease (n = 248, rheumatoid arthritis (n = 154) and a depression and anxiety group (n = 307), using quantile regression, controlling for the effects of sociodemographic factors, physical disability, and cognitive deficits. Each of pain, depression symptoms, anxiety symptoms, and fatigue individually showed significant associations with work absenteeism, presenteeism, and general activity impairment (quantile regression standardized estimates ranging from 0.3 to 1.0). When the distress variables were entered concurrently into the regression models, fatigue was a significant predictor of work and activity impairment in all models (quantile regression standardized estimates ranging from 0.2 to 0.5). These findings have important clinical implications for understanding the determinants of work impairment and for improving work-related outcomes in chronic disease.

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Turning is an important marker of balance confidence and walking limitation in persons with multiple sclerosis.

Adusumilli G(1), Lancia S(1), Levasseur VA(2), Amblee V(3), Orchard M(1), Wagner JM(4)(5), Naismith RT(1).

Author information: (1)Department of Neurology, Washington University in Saint Louis School of Medicine, St. Louis, Missouri, United States of America. (2)School of Medicine, University of Missouri, Columbia, Missouri, United States of America. (3)School of Medicine, University of Illinois, Chicago, Illinois, United States of America. (4)Department of Physical Therapy and Athletic Training, Saint Louis University, St. Louis, Missouri, United States of America. (5)Acorda Therapeutics, Ardsley, New York, United States of America.

The standard functional tool for gait assessment in multiple sclerosis (MS) clinical trials has been the 25-Foot Timed Walk Test, a measure of gait speed. Straight-line gait assessment may not reflect adequately upon balance and coordination. Walking tests with turns may add additional information towards understanding gait and balance status, and be more reflective of ambulation in the community. Understanding the impact of turn parameters on patient-reported outcomes of balance and walking would help MS clinicians better formulate treatment plans for persons with gait limitations. In this study, ninety-one persons with MS (Expanded Disability Status Score; EDSS, range: 0-6.5) were enrolled in an initial cross-sectional study. Twenty-four subjects (EDSS, range:1.0-6.0) completed a follow-up visit an average of 12 months later. Spatiotemporal gait analysis was collected at both visits using APDM Opal wireless body-worn sensors while performing the Timed-Up-and-Go (TUG) and 6-Minute Walk Test (6MWT). For both cross-sectional and longitudinal data, regression analyses determined the impact on the addition of turning parameters to stride velocity (SV), in the prediction of self-reported balance confidence (Activities-Specific Balance Confidence Scale (ABC)) and walking limitation (12-item Multiple Sclerosis Walking Scale (MSWS-12)). The addition of 6MWT peak turn velocity (PTV) to 6MWT SV increased the predictive power of the 6MWT for the ABC from 20% to 33%, and increased the predictive power from 28% to 41% for the MSWS-12. TUG PTV added to TUG SV also strengthened the relationship of the TUG for the ABC from 19% to 28%, and 27% to 36% for the MSWS-12. For those with 1 year follow-up, percent change in turn number of steps (TNS%Δ) during the 6MWT added to 6MWT SV%Δ improved the modeling of ABC%Δ from 24% to 33%. 6MWT PTV%Δ added to 6MWT SV%Δ increased the predictive power of MSWS-12%Δ from 8% to 27%. Conclusively, turn parameters improved modeling of self-perceived balance confidence and walking limitations when added to the commonly utilized measure of gait speed. Tests of longer durations with multiple turns, as opposed to shorter durations with a single turn, modeled longitudinal change more accurately. Turn speed and stability should be qualitatively assessed during the clinic visit, and use of multi-faceted tests such as the TUG or 6MWT may be required to fully understand gait deterioration in persons with MS.

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Advising patients seeking stem cell interventions for multiple sclerosis.


Author information:  (1)Clinical Neurosciences, Translational Health Sciences, University of Bristol, Bristol, UK. (2)School of Medicine, Vita-Salute san Raffaele University, Milan, Italy. (3)Bristol and Avon MS Unit, Bristol Brain Centre, North Bristol NHS Trust, Southmead Hospital, Bristol, UK. (4)Department of Haematology, University Hospitals Bristol NHS Foundation Trust. Bristol, UK.

Conflict of interest statement: Competing interests: Not declared.

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Caspase-1 inhibition prevents glial inflammasome activation and pyroptosis in models of multiple sclerosis.

McKenzie BA(1), Mamik MK(2), Saito LB(1), Boghazian R(2)(3), Monaco MC(4), Major EO(4), Lu JQ(5)(6), Branton WG(2), Power C(7)(2)(6).

Author information:  (1)Department of Medical Microbiology and Immunology, University of Alberta, Edmonton, AB T6G 2R3, Canada. (2)Division of Neurology, Department of Medicine, University of Alberta, Edmonton, AB T6G 2R3, Canada. (3)Department of Immunology, Tehran University of Medical Sciences, Tehran 1417653761, Iran. (4)National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892. (5)Department of Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB T6G 2R3, Canada. (6)Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB T6G 2R3, Canada. (7)Department of Medical Microbiology and Immunology, University of Alberta, Edmonton, AB T6G 2R3, Canada; chris.power@ualberta.ca.

Multiple sclerosis (MS) is a progressive inflammatory demyelinating disease of the CNS of unknown cause that remains incurable. Inflammamsec-associated caspases mediate the maturation and release of the proinflammatory cytokines IL-1β and IL-18 and activate the pore-forming protein gasdermin D (GSDMD). Inflammatory programmed cell death, pyroptosis, was recently shown to be mediated by GSDMD. Here, we report molecular evidence for GSDMD-mediated inflammasome activation and pyroptosis in both myeloid cells (macrophages/microglia) and, unexpectedly, in myelin-forming oligodendrocytes (ODCs) in the CNS of patients with MS and in the MS animal model, experimental autoimmune encephalomyelitis (EAE). We observed inflammasome activation and pyroptosis in human microglia and ODCs in vitro after exposure to inflammatory stimuli and demonstrate caspase-1 inhibition by the small-molecule inhibitor VX-765 in both cell types. GSDMD inhibition by siRNA transduction suppressed pyroptosis in human microglia. VX-765 treatment of EAE animals reduced the expression of inflammasome- and pyroptosis-associated proteins in the CNS, prevented axonal injury, and improved neurobehavioral performance. Thus, GSDMD-mediated pyroptosis in select glia cells is a previously unrecognized mechanism of inflammatory demyelination and represents a unique therapeutic opportunity for mitigating the disease process in MS and other CNS inflammatory diseases.

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Conflict of interest statement: The authors declare no conflict of interest.
The Association Between Septicemia and the Risk of Multiple Sclerosis: a Nationwide Register-based Retrospective Cohort Study in Taiwan.

Tsai CL(1)(2), Lee JT(1)(2), Lien LM(3)(4), Lin CC(1), Tsai IJ(5), Sung YF(1), Chou CH(1)(2), Yang FC(1), Tsai CK(1)(2), Wang IK(6)(7)(8), Tseng CH(9), Hsu CY(6).

Author information: (1)Department of Neurology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, Republic of China. (2)Graduate Institute of Medical Sciences, National Defense Medical Center, Taipei, Taiwan, Republic of China. (3)Department of Neurology, Shin-Kong WHS Memorial Hospital, Taipei, Taiwan, Republic of China. (4)School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan, Republic of China. (5)Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, College of Medicine, China Medical University, Taichung, Taiwan, Republic of China. (6)Graduate Institute of Clinical Medical Science, China Medical University, Taichung, Taiwan, Republic of China. (7)Department of Internal Medicine, College of Medicine, China Medical University, Taichung, Taiwan, Republic of China. (8)Division of Kidney Disease, China Medical University Hospital, Taichung, Taiwan, Republic of China. (9)Department of Neurology, China Medical University Hospital, Taichung, Taiwan, Republic of China.

Background: Multiple sclerosis (MS) is the most common inflammatory demyelinating disease of the central nervous system. Few studies focused on the relationship between septicemia and MS. Aim: To evaluate the potential impact of septicemia on risk for MS. Design: Two cohorts of patients with septicemia and without septicemia were followed up for the occurrence of MS. Methods: 482,790 patients with septicemia was enrolled from the National Health Insurance Research Database between 2001 and 2011 as the study group to match the 1,892,820 individuals, as the control group, by age and gender. Incidence of MS in both groups were calculated. Cox proportional-hazards regressions were performed for investigating hazard ratios (HR) for MS between groups. Results: Septicemia patients had a 3.06-fold (95% CI: 2.16-4.32, p < 0.001) greater risk of developing MS than the matched group. In addition, higher severity of septicemia was associated with higher risk of developing MS (moderate: HR = 4.03, 95% CI: 2.53-6.45, p < 0.001; severe: HR = 11.1, 95% CI: 7.01-17.7, p < 0.001). Similar results also occurred in both male and female patients with septicemia (male: HR = 4.06, 95% CI: 2.17-7.58, p < 0.001; female: HR = 2.72, 95% CI: 1.79-4.11, p < 0.001). Patients without counterpart comorbidities had a significantly higher risk of MS than the controlled group (HR = 3.02, 95% CI: 2.10-4.35, p < 0.001). Conclusion: The results indicated septicemia is linked to an increased risk for multiple sclerosis. Aggressively preventing and treating septicemia may be warranted for one of precautionary strategies of MS.

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Adherence in Youth With Multiple Sclerosis: A Qualitative Assessment of Habit Formation, Barriers, and Facilitators.

Yeh EA(1)(2), Chiang N(3), Darshan B(3), Nejati N(1)(2), Grover SA(1), Schwartz CE(4)(5), Slater R(1), Finlayson M(3); Pediatric MS Adherence Study Group.

Author information: (1)1 The Hospital for Sick Children, Toronto, Ontario, Canada. (2)2 The University of Toronto, Toronto, Ontario, Canada. (3)3 School of Rehabilitation Therapy, Queen's University, Kingston, Ontario, Canada. (4)4 DeltaQuest Foundation, Concord, Massachusetts, USA. (5)5 Tufts University, Boston, Massachusetts, USA.

Rates of medication nonadherence in youth with multiple sclerosis (MS) range from 10% to 60%. Qualitative studies of adherence can provide insight into children's own perspectives about barriers and facilitators to their adherence and inform future interventions. This qualitative longitudinal descriptive study included children with MS (n = 28) participating in a randomized controlled trial focused on medication adherence (clinicaltrials.gov : NCT02234713). Following established methods, three independent reviewers coded transcripts of motivational interviewing (MI) sessions (three interviews per subject, performed monthly over a 3-month period) for relevant themes. They were subsequently categorized using inductive content analysis. Youth described medication adherence as being dependent on the ability to build and maintain healthy habits related to medication use, including embodiment of these habits. Barriers and facilitators included remembering/forgetting, experiences with fatigue, and experiences with medication. These themes were maintained through the second and third interviews. Future research focus on barriers and facilitators to habit maintenance in this population.

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Evaluation of the Effect of α-L-Guluronic Acid (G2013) on COX-1, COX-2 Activity and Gene Expression for Introducing this Drug as a Novel NSAID with Immunomodulatory Property.

Mortazavi-Jahromi SS(1), Taeb M(1), Cuzzocrea S(2), Esposito E(2).

Author information: (1)Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. (2)Department of Chemical, Biological, Pharmacological and Environmental Sciences, University of Messina, Messina, Italy.

BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) are used to treat the pathological pain and inflammation through inhibition of cyclooxygenase (COX) enzyme and disruption of the synthesis of prostaglandins (PGs). The α-L-guluronic acid (G2013) patented (PCT/EP2017/067920), as a novel NSAID with the immunomodulatory property, has been shown its positive effects in experimental models of multiple sclerosis and anti-aging. OBJECTIVE: This study was aimed to investigate the effects of G2013 on the gene expression and activity of COX-1/COX-2 enzymes in order to introduce a novel NSAID for the treatment of inflammatory diseases. METHOD: The mRNA expression levels of COX-1/COX-2 were measured by qRT-PCR. The PGE2 concentration in culture media was determined using ELISA method. RESULTS: Our results demonstrated that the low and high dose of G2013 could significantly reduce the gene expression of COX-1 and COX-2, as compared to the control treated with LPS (p < 0.05). In addition, data showed that 5, 50, and 500 mMol/ml doses of this drug can significantly the reduce activities of COX-1 and COX-2, as compared to the control treated with LPS and AA (p < 0.0001). CONCLUSION: This study revealed that G2013, as a novel NSAID with the immunomodulatory property, is able to reduce the gene expression and activity of COX-1/COX-2 enzymes. According to the findings, this agent might be categorized and introduced as a novel NSAID for the treatment of inflammatory diseases.

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Psychological symptoms and perceived cognitive impairment in multiple sclerosis: The role of rumination.

Malivoire BL(1), Hare CJ(1), Hart TL(1).

Author information: (1)Department of Psychology, Ryerson University.

PURPOSE/OBJECTIVE: Perceived cognitive impairment is a common concern among individuals with multiple sclerosis (MS) and is associated with prevalent psychological symptoms, namely depression and anxiety. The mechanisms by which these psychological symptoms are associated with perceived cognitive impairment among people diagnosed with MS have been unexplored. A possible mechanism is rumination, a maladaptive form of self-reflection that is commonly associated with anxiety and depression. The purpose of this study was to examine the associations of symptoms of anxiety and depression with perceived cognitive impairment, and to examine whether anxiety and depression indirectly affect cognitive impairment through rumination.

Research Method/Design: The study utilized a cross-sectional observational design. People diagnosed with MS (N = 111) were recruited from an MS clinic in Toronto, and through the community. Participants completed self-report questionnaires that included the Multiple Sclerosis Neuropsychological Screening Questionnaire (MSNQ), the Hospital Anxiety and Depression Scale (HADS), and the Rumination-Reflection Questionnaire (RRQ). Two indirect effect statistical analyses were conducted using bootstrapping techniques.

RESULTS: We found a positive association between both symptoms of depression and anxiety and perceived cognitive impairment. Moreover, psychological symptoms were related to perceived cognitive impairment indirectly through rumination, indicating ruminative thinking style may be implicated in the relationship between anxiety, depression, and perceived cognitive impairment.

CONCLUSIONS/IMPLICATIONS: These findings provide additional support for previous research examining the relationship between psychological symptoms (e.g., anxiety and depression) and perceived cognitive impairment, and enrich our understanding of a potential mechanism driving these relationships.

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Assessing everyday life functional activity using actual reality in persons with MS.

Goverover Y(1), DeLuca J(2).

Author information: (1)Department of Occupational Therapy, New York University. (2)Kessler Foundation.

BACKGROUND: Multiple sclerosis (MS) can have dramatic effects on performance of everyday life activity. However, the ability to assess everyday functional activity remains elusive. The purpose of this study was to establish validity and reliability to a performance-based assessment of everyday life activities called actual reality (AR). AR involves utilization of the Internet to perform three actual everyday life activities: purchasing (a) an airline ticket, (b) cookies, and (c) pizza.

METHOD: A repeated measure design was used to examine 30 adults with MS who were recruited from a nonprofit rehabilitation research institution and 30 healthy controls (HC) living in the community. Participants were administered the 3 AR tasks twice, 3 weeks apart. Additionally, neuropsychological tests and self-report functional questionnaires were administered.

RESULTS: This study supported moderate to large Interrater Reliability of the AR assessment. Additionally, the 3 AR tasks did not differ in the number of errors made, and number and quality of cues required to complete the AR tasks. Participants with MS committed more errors, and required significantly more cues to perform the 3 AR tasks successfully compared with HC, supporting discriminant validity of the AR. Concurrent validity was supported by moderate to large associations between AR performance and neuropsychological test scores. Practice effect was observed for cognitive processes and the time it took participants to perform the task.

CONCLUSIONS: Data support the use of actual, real-life, performance-based approach to measuring functional cognition outcomes. However, the observed practice effects for AR-cognitive capacity and AR-latency should be noted.

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Multiple Sklerose: Veröffentlichungen Juni 2018


Sexual communication, sexual satisfaction, and relationship quality in people with multiple sclerosis.

Valvano AK(1), Rollock MJD(2), Hudson WH(3), Goodworth MR(4), Lopez E(5), Stepleman L(5).

Author information: (1)Department of Neuropsychology, Baylor Institute for Rehabilitation. (2)Department of Psychiatry and Health Behavior, Georgia Regents University/East Central Regional Hospital. (3)Graduate Department of Clinical Psychology, George Fox University. (4)Graduate Department of Clinical Psychology, George Fox University. (5)Department of Psychiatry and Health Behavior, Georgia Regents University.

OBJECTIVE: This study sought to explore relationships between sexual satisfaction, sexual communication and relationship satisfaction in people living with multiple sclerosis (MS). Specifically, sexual satisfaction was evaluated as a moderator between sexual communication and relationship satisfaction. DESIGN: Individuals diagnosed with MS and being treated in a hospital-based MS clinic in the southeastern United States (n = 58) completed measures of sexual satisfaction, sexual communication, sexual dysfunction, relationship quality, depression, level of disability, and frequency of sex-related communication and behaviors in a cross-sectional survey design. RESULTS: Sexual satisfaction moderated the relationship between quality of sexual communication and relationship quality, controlling for depression and frequency of sexual behavior and sexual communication. Directionality was examined in a 2nd regression analysis, in which the predictor and outcome variables were switched, which was also significant. Additionally, depression most strongly predicted relationship dissatisfaction. CONCLUSIONS: Findings help to establish sexual satisfaction as a moderator between sexual communication and relationship satisfaction, although directionality cannot be supported. Results also highlight the role of depression in overall relationship functioning and support the biopsychosocial model of care for treatment of sexual dysfunction in people living with MS. (PsycINFO Database Record (c) 2018 APA, all rights reserved).

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[Retinal vasculitis and systemic diseases].

[Article in French]

Gascon P(1), Jarrot PA(2), Matonti F(1), Kaplanski G(3).

Author information: (1)Service d'ophtalmologie, Aix-Marseille université, CHU Nord, 13015 Marseille, France. (2)Service de médecine interne et immunologie clinique, hôpital de la Conception, Aix-Marseille université, 147, boulevard Baille, 13005 Marseille, France. (3)Service de médecine interne et immunologie clinique, hôpital de la Conception, Aix-Marseille université, 147, boulevard Baille, 13005 Marseille, France. Electronic address: gilles.kaplanski@ap-hm.fr.

Retinal vasculitis (RV) is an inflammation of retinal blood vessels that can be associated with uveitis or be isolated, and can induce vascular occlusion and retinal ischemia. Visual acuity can be severely affected in case of macular involvement or neovessel formation. The diagnosis relies on fundoscopy and fluorescein angiography. Systemic diseases may be associated with RV, the most frequently encountered are Behçet's disease, sarcoidosis or multiple sclerosis, all predominantly associated with venous involvement, whereas systemic lupus erythematosus and necrotizing vasculitis are less frequently observed and predominantly associated with arterial or mixed vasculitis. Treatments are usually aggressive in order to preserve a good visual acuity and to reduce retinal inflammation and chronic ischemia. Steroids, immunosuppressive drugs, retinal laser photocoagulation, intravitreal anti-VEGF injections are usual treatments and more recently, anti-TNFalpha monoclonal therapeutic antibodies have been shown to be very successful.

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Ocrelizumab: its efficacy and safety in multiple sclerosis.

Juanatey A(1), Blanco-Garcia L(1), Tellez N(1).

Author information:  (1)Hospital Clinico Universitario, 47005 Valladolid, Espana.

INTRODUCTION: Ocrelizumab is a humanised monoclonal antibody that targets the CD20 antigen on B cells. It has recently been approved by the US (Food and Drug Administration) and European health agencies (European Medicines Agency) for the treatment of multiple sclerosis (MS) and is the first drug marketed for both relapsing-remitting MS (RRMS) and primary progressive MS (PPMS). The clinical trials conducted for both the relapsing forms (OPERA I/II) and the progressive forms of the disease (ORATORIO) have demonstrated its efficacy. The aim of this review is to address the main aspects of the efficacy and safety of ocrelizumab in MS.

DEVELOPMENT: Using PubMed, a literature review was conducted of studies published at the ECTRIMS 2017 Congress and of active studies in ClinicalTrials. In order to evaluate the efficacy and safety of ocrelizumab in MS, both randomised clinical trials and their extension and follow-up studies were reviewed, and information about its safety obtained from monitoring programmes of the Food and Drug Administration and European Medicines Agency was included.

CONCLUSIONS: Ocrelizumab is the first drug that has been shown to be able to significantly slow disability progression at 12 and 24 weeks in patients with PPMS. It is also effective in controlling clinical and radiological activity in patients with RRMS forms, and it is approved and indicated for both phenotypes of the disease. To date, the safety profile of ocrelizumab matches that observed in clinical trials, without any unexpected alerts.

Publisher: Ocrelizumab: eficacia y seguridad en la esclerosis multiple. Introduccion. El ocrelizumab es un anticuerpo monoclonal humanizado contra el antigeno CD20 de las celulas B. Ha sido aprobado recientemente por las agencias sanitarias estadounidense (Food and Drug Administration) y europea (European Medicines Agency) para el tratamiento de la esclerosis multiple (EM), y supone el primer farmaco comercializado tanto para la EM remitente recurrente (EMRR) como para la EM primariamente progresiva (EMPP). Los ensayos clinicos, tanto pa-ra formas recurrentes (OPERA I/II) como para las formas progresivas de la enfermedad (ORATORIO), han demostrado su eficacia. El objetivo de esta revision es abordar los principales aspectos de eficacia y seguridad del ocrelizumab en la EM. Desarrollo. Se ha realizado una revision bibliografica a traves de PubMed de trabajos publicados en el congreso ECTRIMS 2017 y de estudios activos en ClinicalTrials. Con el fin de evaluar la eficacia y seguridad del ocrelizumab en la EM, se han revisado ensayos clinicos aleatorizados, asi como sus estudios de extension y de seguimiento, y se ha incluido informacion sobre seguridad de los programas de monitorizacion de la Food and Drug Administration y la European Medicines Agency. Conclusiones. El ocrelizumab es el primer farmaco que ha demostrado poder frenar de forma significativa la progresion de la discapacidad en 12 y 24 semanas en pacientes con EMPP. Es tambien eficaz en el control de la actividad clinica y radiologica en pacientes con formas de EMRR, y su aprobacion e indicacion engloban ambos fenotipos de la enfermedad. Hasta ahora, el perfil de seguridad del ocrelizumab se ajusta a lo observado en los ensayos clinicos, sin alertas inesperadas.

PMID: 29897610
[Review of the novelties from the 2017 ECTRIMS Congress, presented at the 10th Post-ECTRIMS Meeting (I)].

[Article in Spanish; Abstract available in Spanish from the publisher]

Fernandez O(1), Tintore M(2), Saiz A(3), Calles-Hernandez MC(4), Comabella M(2), Ramio-Torrenta L(5), Oterino A(6), Izquierdo G(7), Tellez N(8), Garcia-Merino JA(9), Brieva L(10), Arnal-Garcia C(11), Aladro Y(12), Mendibe-Bilbao MM(13), Meca-Lallana JE(14), Romero-Pinel L(15), Gines MLC(17), Arroyo R(18)(19), Rodriguez-Antiguedad A(13).


The Post-ECTRIMS Meeting is an emblematic event in the field of multiple sclerosis in Spain. Its chief aim is to bring together the country’s leading specialist neurologists to analyse the main advances made in multiple sclerosis and to review the most important topics addressed at the ECTRIMS Congress. The tenth Post-ECTRIMS Meeting was held in November 2017. Over the years this event has firmly established itself as an important meeting point where experts from all over the country get together to foster communication, establish synergies and promote and enhance research ultimately aimed at improving the prognosis and quality of life of patients with multiple sclerosis. This first part reports on the publication of the new European and American clinical guidelines on the use of disease-modifying treatments and the new diagnostic criteria. It also discusses the strategies for following up patients treated with disease-modifying therapies, reviews cerebral atrophy and biomarkers of neurodegeneration and neuroinflammation, and analyses the role of neuroglia in pathogenesis and treatment. The study examines the natural history of the disease, with the evidence provided by registers, and we anticipate the future thanks to the progress being made in genetics and immunology.

Publisher: Revision de las novedades del Congreso ECTRIMS 2017, presentadas en la X Reunion Post-ECTRIMS (I). La reunion Post-ECTRIMS es una reunion emblematica en el ambito de la esclerosis multiple en Espana, con el claro objetivo de analizar, de la mano de reconocidos neurologos especialistas nacionales, los principales avances en esclerosis multiple y revisar los temas mas importantes del congreso ECTRIMS. En noviembre de 2017, la reunion Post-ECTRIMS celebro su decima edicion, y se ha consolidado como un importante foro de encuentro de expertos en nuestro pais para favorecer la comunicacion, establecer sinergias, y promover y potenciar la investigacion para mejorar, en ultima instancia, el pronostico y la calidad de vida de los pacientes con esclerosis multiple. En esta primera parte se avanza la publicacion de las nuevas guias clinicas europea y americana para el uso de los tratamientos modificadores de la enfermedad, y los nuevos criterios diagnosticos. Se discuten las estrategias para el seguimiento de los pacientes tratados con terapias modificadoras de la enfermedad, se revisan la atrofia cerebral y los biomarcadores de neurodegeneracion y neuroinflamacion, y se analiza el papel de la neuroglia en la patogenia y el tratamiento. Se hace un recorrido por la historia natural de la enfermedad, con la evidencia que aportan los registros, y nos adelantamos al futuro gracias a los avances en genetica e immunologia.

PMID: 29923596
Multiple Sclerosis over the last 25 years: an introduction.  
Edan G(1).  
Author information: (1)Department of neurology, CIC-P 02-03 Inserm, INCR, CHU de Rennes, 2, rue Henri-le-Guilloux, 35000 Rennes, France. Electronic address: gilles.edan@chu-rennes.fr.  
DOI: 10.1016/j.neurol.2018.04.008  PMID: 2990397

Multiple sclerosis pathogenesis: missing pieces of an old puzzle.  
Rahmanzadeh R(1), Brück W(2), Minagar A(3), Sahraian MA(1)(4).  
Author information: (1)MS Research Center, Neuroscience Institute, Tehran University of Medical Science, Department of Neurology, Sina Hospital, 1136746911 Tehran, Iran. (2)Institute of Neuropathology, University Medical Center, D-37075 Göttingen, Germany. (3)Department of Neurology, LSU Health Sciences Center, Shreveport, LA 71130, USA. (4)Iranian Center for Neurological Research, Neuroscience Institute, Tehran University of Medical Science, 1136746890 Tehran, Iran.  
Traditionally, multiple sclerosis (MS) was considered to be a CD4 T cell-mediated CNS autoimmunity, compatible with experimental autoimmune encephalitis model, which can be characterized by focal lesions in the white matter. However, studies of recent decades revealed several missing pieces of MS puzzle and showed that MS pathogenesis is more complex than the traditional view and may include the following: a primary degenerative process (e.g. oligodendrogial pathology), generalized abnormality of normal-appearing brain tissue, pronounced gray matter pathology, involvement of innate immunity, and CD8 T cells and B cells. Here, we review these findings and discuss their implications in MS pathogenesis.  
DOI: 10.1515/revneuro-2018-0002  PMID: 29883325

Ongoing clinical trials and treatment options for patients with systemic sclerosis-associated interstitial lung disease.  
Author information: (1)Division of Rheumatology, Department of Medicine, University of Michigan, Ann Arbor, MI. (2)Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California at Los Angeles, Los Angeles, CA, USA. (3)Centre for Rheumatology, Division of Medicine, University College London, London, UK. (4)Global Clinical Development, EMD Serono Inc., Billerica, MA, USA.  
SSc is a rare CTD that affects multiple organ systems, resulting in substantial morbidity and mortality. Evidence of interstitial lung disease (ILD) is seen in ~80% of patients with SSc. Currently there is no approved disease-modifying treatment for ILD and few effective treatment options are available. CYC is included in treatment guidelines, but it has limited efficacy and is associated with toxicity. MMF is becoming the most commonly used medication in clinical practice in North America and the UK, but its use is not universal. Newer agents targeting the pathogenic mechanisms underlying SSc-ILD, including fibrotic and inflammatory pathways, lymphocytes, cell-cell and cell-extracellular membrane interactions, hold promise for better treatment outcomes, including improved lung function, patient-related outcomes and quality of life. Here we review ongoing trials of established and novel agents that are currently recruiting patients with SSc-ILD.  
DOI: 10.1093/rheumatology/key151  PMID: 29893938
**Morphofunctional changes in distribution of pressure center in multiple sclerosis.**
Neamţu MC(1), Neamţu OM, Enescu Bieru D, Marin MI, Rusu MR, Tudorache Ş, Brâila AD, Poiană C, Rusu L.
Author information: (1)Department of Sports Medicine and Kinesiology, University of Craiova, Romania; oanacristi_neamtu@yahoo.com.
INTRODUCTION: Gait evaluation and assessment of motor performance are of utmost importance in the clinical management of multiple sclerosis (MS). A new approach to the analysis of static and dynamic balance of MS patients is the use of complex biomechanical analysis that includes an analysis of the distribution of the center of pressure (DCP) and loading, measured by using the pressure and force platforms. PATIENTS AND METHODS: The study was conducted on a total of 18 patients with MS, with the mean age of 41.2 years old, divided into two groups, according to the presence of clinically detectable gait disturbances. The biomechanical analysis that included the assessment of the loading and DPC was performed using the platform of force distribution. DPC represented the center of all the forces applied and its value could appreciate the mediolateral stability, hence the pronation or, respectively, the supination.
Group 1, consisting of 12 patients with MS with clinically detectable gait disorders, including six men and six women, and group 2, of six MS patients without clinically detectable gait disorders, including two men and four women. RESULTS: For group 1, the center of pressure had a left-right asymmetric distribution, and also an anterior-posterior one. There was a predominant distribution at the medial heel, at metatarsals 1-3 and at the hallux. For group 2, the analysis of the plantograms recorded in our study indicated a tendency of the distribution of the pressure center in the metatarsals 2, 3 and less in the heel. CONCLUSIONS: The analysis of the loading and distribution of the pressure center was important not only to appreciate the static equilibrium disorders but also to appreciate how these disorders affected the gait initiation, since the patients suffered from anterior-posterior and mediolateral disorders, which produced spatial and temporal distortion preventing gait initiation. In the study of pressure and force, we noticed a predominant distribution on the lateral region of the heel, explained by an attempt of the body to compensate the disorders of balance and orientation of the reaction force of the ground to normalize the gait.
PMID: 29940631

**Glatiramer acetate-specific antibody titres in patients with relapsing/remitting multiple sclerosis and in experimental autoimmune encephalomyelitis.**
[No authors listed]
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National guidelines for evaluating pain-Patients' legal right to prioritised health care at multidisciplinary pain clinics in Norway implemented 2009.

Hara KW(1), Borchgrevink P(1).

Author information: (1)Department of Pain and Complex Disorders, St Olav's Hospital and the University of Trondheim, Trondheim, Norway.

Background All nations are posed with the challenge of deciding how to allocate limited health care resources. A Patients' Rights Law from 1999 gives patients in Norway with a serious health condition, for which there is efficacious and cost-effective treatment, a legal right to receive health care from the National Health Care system. Methods Recently national guidelines have been produced for implementing these legal rights within 32 fields of specialist health care. One of these fields deals with serious chronic pain conditions. A task force established by the Directorate of Health, comprising pain specialists, primary care and patient representatives, have produced guidelines for pain conditions. The newly published guidelines seek to answer the difficult questions of which patients should be prioritised at pain clinics and what is a medically acceptable waiting time. Results The guidelines deal with non-acute pain conditions that are too complex for primary care and organ- or disease-specific fields of specialist care. The guidelines state that if health-related quality of life is severely affected by the pain condition and efficacious and cost-effective treatment is available, then patients have a legal right to receive prioritised specialist health care in multidisciplinary pain clinics. The guidelines describe 5 categories of complex pain disorders that as a main rule should be given the right to prioritised health care in pain clinics. The 5 categories are Category 1 Sub-acute (≤6 months) pain conditions with reason to fear chronification. Maximum waiting time 2 weeks, e.g., progressing complex regional pain syndrome (CRPS) 5 months after an ankle-fracture. Category 2 Chronic complex pain condition, with or without known initiating cause, combined with substance abuse and/or psychiatric illness. These patients need concomitant follow-up by psychiatric and/or addiction medicine department(s) and a multidisciplinary pain clinic approach. Maximum waiting time 16 weeks, e.g., CRPS of an arm combined with depression and addiction to heroin. Category 3 Chronic complex pain condition WITH known initiating cause (that can no longer be treated with a curative approach). Maximum waiting time 16 weeks, e.g., Post-herpetic neuralgia. Category 4 Chronic complex pain condition WITHOUT known initiating cause. Maximum waiting time 2 weeks, e.g., advanced cancer, COLD, heart failure, end stage multiple sclerosis. The maximum medically accepted waiting time is set at either 2 or 16 weeks depending on the condition. The full version of the guidelines describes pain categories in detail and gives information on cases that do not qualify to be prioritised for care in a pain clinic. Conclusions Norwegian national guidelines for prioritising among pain conditions are in the process of being implemented. Epidemiologic data and expert opinion suggest that in order to meet the chronic pain patient's legal claim to prioritised specialist health care, the national health care system in Norway will have to establish new pain clinics and increase capacity at existing pain clinics.

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High-Dimensional Immunology for Schizophrenia Research: A Short Perspective.

Lewis GK(1).

Author information: (1)Division of Vaccine Research, Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD.

There is evidence that many diseases are accompanied by immunological perturbations and even when the perturbations are not directly pathogenic, they can provide correlative signatures of pathology that can be useful diagnostically. For example, the neuromuscular disease, multiple sclerosis, has a pathophysiology that is immunologically mediated, evinced by the use of increasingly sophisticated immunosuppression therapy and by animal studies in which many of the symptoms can be reproduced by breaking immunological tolerance to myelin basic protein. By contrast, immunological correlates exist for other diseases, such as schizophrenia, but it is not clear which, if any, are causative. The problem is compounded in that genome-wide association studies have shown strong genetic correlation between schizophrenia and bipolar disorder, moderate correlation with schizophrenia and major depressive disease, and low correlation with autism spectrum disorders, yet schizophrenia and autism spectrum disorders share immunological signatures. This example illustrates the problem of ferreting out specific, and hopefully causal, immunological correlates with schizophrenia that differentiate it from genetically or immunologically related psychiatric disorders. Fortunately, recent advances in systems immunology provide potent tools to tackle this problem. This review will illustrate these tools by recent examples and sketch out possible pathways to use them for identification of schizophrenia-specific immunological correlates.

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Interactome analyses revealed that the U1 snRNP machinery overlaps extensively with the RNAP II machinery and contains multiple ALS/SMA-causative proteins.

Chi B(1), O'Connell JD(1)(2), Yamazaki T(1), Gangopadhyay J(1), Gygi SP(1), Reed R(3).

Author information: (1)Department of Cell Biology, Harvard Medical School, 240 Longwood Ave, Boston, MA, 02115, USA. (2)Department of Microbiology and Immunology, Stanford University School of Medicine, 291 Campus Drive, Stanford, CA, 94305, USA. (3)Department of Cell Biology, Harvard Medical School, 240 Longwood Ave, Boston, MA, 02115, USA. reed@hms.harvard.edu.

Mutations in multiple RNA/DNA binding proteins cause Amyotrophic Lateral Sclerosis (ALS). Included among these are the three members of the FET family (FUS, EWSR1 and TAF15) and the structurally similar MATR3. Here, we characterized the interactomes of these four proteins, revealing that they largely have unique interactors, but share in common an association with U1 snRNP. The latter observation led us to analyze the interactome of the U1 snRNP machinery. Surprisingly, this analysis revealed the interactome contains ~220 components, and of these, >200 are shared with the RNA polymerase II (RNAP II) machinery. Among the shared components are multiple ALS and Spinal muscular Atrophy (SMA)-causative proteins and numerous discrete complexes, including the SMN complex, transcription factor complexes, and RNA processing complexes. Together, our data indicate that the RNAP II/U1 snRNP machinery functions in a wide variety of molecular pathways, and these pathways are candidates for playing roles in ALS/SMA pathogenesis.

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Development of a Novel Backbone Cyclic Peptide Inhibitor of the Innate Immune TLR/IL1R Signaling Protein MyD88.


Author information: (1)Institute of Dental Sciences, Hebrew University-Hadassah Faculty of Dental Medicine, Ein Kerem, 91120, Jerusalem, Israel. (2)Institute for Drug Research, School of Pharmacy, Faculty of Medicine, The Hebrew University of Jerusalem, Ein Kerem, 91120, Jerusalem, Israel. (3)Institute of Chemistry, The Hebrew University of Jerusalem, Safra Campus, Givat Ram, Jerusalem, 91904, Israel. (4)Department of Neurology and Laboratory of Neuroimmunology, Hadassah-Hebrew University Medical Center, Ein Kerem, 91120, Jerusalem, Israel. (5)Institute of Dental Sciences, Hebrew University-Hadassah Faculty of Dental Medicine, Ein Kerem, 91120, Jerusalem, Israel. gabrieln@ekmd.huji.ac.il.

MyD88 is a cytoplasmic adaptor protein that plays a central role in signaling downstream of the TLRs and the IL1R superfamily. We previously demonstrated that MyD88 plays a critical role in EAE, the murine model of multiple sclerosis, and showed that the MyD88 BB-loop decoy peptide RDVLPGT ameliorates EAE. We now designed and screened a library of backbone cyclized peptides based on the linear BB loop peptide, to identify a metabolically stable inhibitor of MyD88 that retains the binding properties of the linear peptide. We identified a novel cyclic peptide protein mimic that inhibits inflammatory responses to TLR ligands, and NFκB activation in response to IL-1 activation. The inhibitor, c(MyD 4-4), is metabolically stable in comparison to the linear peptide, blocks MyD88 in a specific manner, and inhibits MyD88 function by preventing MyD88 dimerization. Finally, treatment of mice with c(MyD 4-4) reduced the severity of clinical disease in the murine EAE model of multiple sclerosis. Thus, modulation of MyD88-dependent signaling using c(MyD 4-4) is a potential therapeutic strategy to lower innate immune inflammation in autoimmune CNS disease.

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Human IgM antibody rHIgM22 promotes phagocytic clearance of myelin debris by microglia.

Zorina Y(1), Stricker J(2), Caggiano AO(3), Button DC(4).

Author information: (1)Gene Editing and Screening Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY, USA. (2)Translational Medicine, Celgene Corporation, Summit, NJ, USA. (3)Research and Development, Acorda Therapeutics Inc., Ardsley, NY, USA. (4)PharmAble, San Francisco, CA, USA. donb@fastmail.com.

In multiple sclerosis (MS), demyelinated CNS lesions fail to sufficiently remyelinate, despite the presence of oligodendrocyte precursor cells (OPCs) capable of differentiating into mature oligodendrocytes. MS lesions contain damaged myelin debris that can inhibit OPC maturation and hinder repair. rHIgM22 is an experimental human recombinant IgM antibody that promotes remyelination in animal models and is being examined in patients with MS. rHIgM22 binds to CNS myelin and partially rescues OPC process outgrowth on myelin. Since rHIgM22 does not affect OPC process outgrowth in vitro on permissive substrate, we examined the possibility that it acts by enhancing phagocytic clearance of myelin debris by microglia. In this study, we tested if rHIgM22 binding could tag myelin for microglial phagocytosis. A mouse microglial cell line and primary rat microglia were treated with myelin and rHIgM22 and assayed for myelin phagocytosis. We found that: 1) rHIgM22 binding could tag myelin for microglial phagocytosis. A mouse microglial cell line and primary rat microglia were treated with myelin and rHIgM22 and assayed for myelin phagocytosis. We found that: 1) rHIgM22 binding could tag myelin for microglial phagocytosis; 2) rHIgM22-mediated myelin phagocytosis requires actin polymerization; and 3) rHIgM22-stimulation of myelin phagocytosis requires activity of rHIgM22 Fc domain and activation of Complement Receptor 3. Since myelin inhibits OPC differentiation, stimulation of phagocytic clearance of damaged myelin may be an important means by which rHIgM22 promotes remyelination.

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Calcification in cerebral parenchyma affects pharmacoresistant epilepsy in tuberous sclerosis.

Zhang MN(1), Zou LP(2), Wang YY(1), Pang LY(1), Ma SF(1), Huang LL(3), Gao Y(1), Lu Q(4), Franz DN(5).

Author information: (1)Department of Pediatrics, Chinese PLA General Hospital, Beijing, China. (2)Department of Pediatrics, Chinese PLA General Hospital, Beijing, China; Center for Brain Disorders Research, Capital Medical University, Beijing Institute for Brain Disorders, Beijing, China. Electronic address: zouliping21@hotmail.com. (3)Department of Pediatrics, Chinese PLA General Hospital, Beijing, China; School of Medicine, Nankai University, Tianjin, China. (4)Department of Pediatrics, Chinese PLA General Hospital, Beijing, China; Center for Brain Disorders Research, Capital Medical University, Beijing Institute for Brain Disorders, Beijing, China. (5)Department of Pediatrics and Neurology, University of Cincinnati, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA. Electronic address: franz@tsdev.org.

PURPOSE: Tuberous sclerosis (TSC) is an autosomal dominant inherited disease caused by mutations in the TSC1 or TSC2 gene and results in the over-activation of the mammalian target of the rapamycin (mTOR) signaling pathway. Rapamycin, an mTOR inhibitor, is clinically used to treat hamartomatous lesions in TSC and its effect on controlling epilepsy is also reported in many studies. This study aims to evaluate the risk factors of pharmacoresistant epilepsy in patients with TSC receiving long-term rapamycin treatment.

METHOD: A total of 108 patients with TSC taking rapamycin for over 1 year were enrolled in this study. Factors that might influence seizure control were statistically analyzed by multiple factor analysis. A subgroup analysis was also conducted to access the relationship between calcified epileptic foci and pharmacoresistant epilepsy. (Clinical trial registration number: ChiCTR-OOB-15006535(2015-05-29)).

RESULTS: Seizure was controlled in 53 patients but was not managed in 55 patients considered to be drug resistant. Logistic regression analysis showed that calcification in the cerebral parenchyma was a risk factor of pharmacoresistant epilepsy [P = 0.006, odds ratio (OR) = 4.831 (1.577, 14.795)]. Fifteen of 17 patients with calcified epileptic foci suffered from pharmacoresistant epilepsy (88.2%). Seizures in patients with calcified epileptic foci were probably pharmacoresistant (P = 0.010).

CONCLUSION: Calcification in epileptic foci strongly indicates pharmacoresistant epilepsy in patients with TSC even when treated with appropriate anti-epilepsy drugs (AEDs) and rapamycin. Calcification can be used to evaluate pharmacoresistant epilepsy in patients with TSC.

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Rasch analysis of the University of Washington Self-Efficacy Scale short-form (UW-SES-6) in people with long-standing spinal cord injury.

Post MWM(1)(2), Adriaansen JJE(3), Peter C(4)(5).

Author information: (1)Center of Excellence for Rehabilitation Medicine, Brain Center Rudolf Magnus, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, The Netherlands. m.post@dehoogstraat.nl. (2)University of Groningen, University Medical Center Groningen, Department of Rehabilitation Medicine, Groningen, The Netherlands. m.post@dehoogstraat.nl. (3)Center of Excellence for Rehabilitation Medicine, Brain Center Rudolf Magnus, University Medical Center Utrecht and De Hoogstraat Rehabilitation, Utrecht, The Netherlands. (4)Swiss Paraplegic Research (SPF), Nottwil, Switzerland. (5)Department of Health Sciences and Health Policy, University of Lucerne, Lucerne, Switzerland.

STUDY DESIGN: Cross-sectional psychometric study. OBJECTIVES: The University of Washington Self-Efficacy Scale (UW-SES) is a measure of self-efficacy regarding managing challenges related to multiple sclerosis or spinal cord injury (SCI) that can be used across disabling conditions. The objective of this study was to examine the psychometric properties of its short form, the UW-SES-6, using the Rasch model.

SETTING: Community, The Netherlands. METHODS: Secondary analysis of data from the ALLRISC study. Participants were 261 individuals with a time since onset of SCI (TSI) for at least 10 years, 18-35 at the onset of SCI, and used a wheelchair in everyday life. Rasch analyses were conducted to examine stochastic ordering (fit), unidimensionality, local dependency, reliability, response scale structure, targeting, and item bias. RESULTS: Median age was 47.8 years (Inter-Quartile Range (IQR) 41.9-55), median TSI was 22 years (IQR 16.8-30.3). 73.6% were male, 90.4% had a traumatic SCI, 39.8% had tetraplegia, and 81.6% had motor complete SCI. After merging the middle three response categories of item 4, the UW-SES-6 showed satisfactory item fit without local dependence. The PSI was high (0.87). Comparison of the person and item threshold distributions showed satisfactory targeting of the UW-SES-6 to the study group. No differential item functioning was seen with respect to sex, age, level of education, level and completeness of lesion, and TSI. CONCLUSIONS: This study showed the UW-SES-6 to be a scale with sound psychometric properties that can be used as a quick and easy self-report measure of self-efficacy in people with SCI. DOI: 10.1038/s41393-018-0166-z PMID: 29895882

Long term outcome of treatment of vertebral body hemangiomas with direct ethanol injection and short segment stabilization.

Chandra PS(1), Singh P(2), K R(2), Agarwal D(2), Tandon V(2), Kale SS(2), Sarkar C(3).

Author information: (1)Dept of Neurosurgery, All India Institute of Medical Sciences, New Delhi (110029). (2)Dept of Neurosurgery, All India Institute of Medical Sciences, New Delhi (110029). (3)Dept of Neuropathology, All India Institute of Medical Sciences, New Delhi (110029). (5)Department of Health Sciences and Health Policy, University of Lucerne, Lucerne, Switzerland.

BACKGROUND: Vertebral body (VH) hemangiomas with myelopathy are difficult to manage. OBJECTIVE: To evaluate the role of intra-operative ethanol embolization, surgical decompression and instrumented short segment fusion in VH with myelopathy and long-term outcome (>24 months). METHODS: Prospective study: Symptomatic VH with cord compression with myelopathy. Excluded: pathologic fractures, and/or deformity or multi-level pathologies. Surgery consisted of intra-operative bilateral pedicular absolute alcohol (<1% hydrated ethyl alcohol) injection, laminectomy and cord decompression at the level of pathology followed by a short segment instrumented fusion using pedicle screws. RESULTS: 33 patients (Mean 26.9+13.2, range: 10-68 years, 18 females). CLINICAL FEATURES: myelopathy all (5 paraplegic), sphincter involvement (13), and mid back/ lower pain (7). Pre-operative American Spinal Injury Association (ASIA) scores: A(7), B(11), C(6), D(8) and E(1). Majority had single vertebral involvement (30), 3 multiple level. Six underwent surgery earlier (1 alcohol embolization here). Mean surgical time: 124+39 minutes, average blood: 274+80 cc. Mean amount of absolute alcohol injected: 14.6+5.7 cc. (2 requiring 20 & 25 cc). Immediate embolization achieved in all, allowing laminectomy and soft-tissue hemangioma removal easily. Post-surgery, 1 patient had transient deterioration, rest all patients improved (sphincters improved in 9) at a follow up ranging 28-103 months (mean 47.6+22.3). Follow-up ASIA scores: E(26), D(4), B(2) & C(1). All patients showed evidence of bone sclerosis and relief of cord compression on follow-up imaging. CONCLUSIONS: This is largest study in literature showing excellent improvement, low re-operation rates following ethanol embolization and short segment fixation. Copyright © 2018. Published by Elsevier Inc. DOI: 10.1016/j.spinee.2018.05.015 PMID: 29890263
A Comparison of Implicit and Explicit Motor Sequence Learning in Patients with Relapsing-Remitting Multiple Sclerosis.

Sarabandi M(1).

Author information: (1)Department of Physical Training, Faculty of Human Sciences, University of Zabol, Zabol 009854, Iran. maliheh.sarabandi@gmail.com.

This study tends to assess implicit and explicit types of motor learning in patients with Multiple Sclerosis (MS) and normal peers by means of a serial reaction time. Sample size was 15 for each group and samples included 30 patients with MS and 30 normal peers and were assigned to implicit and explicit learning groups. A repeated measures ANOVA was used for measuring reaction time and response error, and a paired samples t-test was used to compare regular and irregular sequence data in each group. Comparison of these two types of learning in speed (response time) and accuracy (number of errors) showed the number of errors (P = 0.012) and response time (P = 0.012) in the implicit motor learning group of MS patients and the number of errors (P = 0.096) and response time (P = 0.954) in the explicit motor learning group of MS patients. Moreover, comparison showed the number of errors (P = 0.008) and response time (P = 0.05) in the implicit group of normal peers and the number of errors (P = 0.011) and response time (P = 0.442) in the explicit group of normal peers. The results showed that explaining and describing the task is less effective at training the motor sequence of MS patients and that these patients benefit more from implicit learning.

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Wang CK(1), Lin CK(1), Wang TJ(1), Wang CY(1), Hsu PC(1), Su HY(2).

Author information: (1)Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. (2)Department of Obstetrics and Gynecology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan. Electronic address: su108868@gmail.com.

OBJECTIVE: Multiple sclerosis (MS) preferentially affects females of reproductive age, making reproduction an important issue for women with MS. An increased incidence of poor labor progress often results in assisted vaginal delivery or a cesarean section. However, with good pre-pregnancy counseling and management, women with MS can conceive and give birth safely. Here, we present a case of pregnancy with MS, which was carried to term uneventfully and ended with unassisted vaginal delivery. CASE REPORT: A 36-year-old woman was treated for MS for three years before she conceived. Because of her mild clinical presentation, medication was discontinued when her pregnancy was confirmed. Counseling was completed, and she had a smooth pregnancy course and gave birth vaginally at 38 weeks and two days. CONCLUSION: Based on this case report, women with mild clinical presentation of MS before pregnancy can conceive and carry successfully to term with no or improved disease presentation.

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Tryptophan immunoadsorption during pregnancy and breastfeeding in patients with acute relapse of multiple sclerosis and neuromyelitis optica.

Hoffmann F(1), Kraft A(2), Heigl F(3), Mauch E(4), Koehler J(5), Harms L(6), Kümpfel T(7), Köhler W(8), Ehrlich S(8), Bayas A(9), Weinmann-Menke J(10), Beuker C(11), Hennek KH(12), Ayzenberg I(13), Elrichmann G(13), Hellig K(13), Klingel R(14), Fassbender CM(14), Fritz H(15), Slowinski T(16), Weihprecht H(17), Brand M(18), Stiegler T(19), Galle J(20), Schimrigk S(21).

Author information: (1)Department of Neurology, Martha-Maria Hospital, Halle/Saale, Academic, Hospital of University, Halle-Wittenberg, Röntgenstraße 1, D-06120 Halle (Saale), Germany. (2)Department of Neurology, Martha-Maria Hospital, Halle/Saale, Academic Hospital of University Halle-Wittenberg, Germany. (3)Medical Care Center Kempten-Allgäu, Kempten, Germany. (4)Clinic for Neurology Dietzenbrough, Academic Hospital of University of Ulm, Schwendi, Germany. (5)Marianne-Strauss-Hospital, Multiple Sclerosis Center Kempfenhausen, Berg, Germany. (6)Departments of Neurology Charité University Medicine Berlin, Germany. (7)Institute of Clinical Neuroimmunology, University Hospital and Biomedical Center, Ludwig-Maximilians University Munich, Munich, Germany. (8)Clinic for Neurology and Neuromedical Intensive Care Medicine, Hubertusburg Hospital, Wermersdorf, Germany. (9)Department of Neurology, General Hospital Augsburg, Germany. (10)Department of Nephrology, Medical Center of the Johannes-Gutenberg University, Mainz, Germany. (11)Department of Neurology, University of Münster, Germany. (12)Department of Neurology and Sana Clinic, Offenbach, Germany. (13)Department of Neurology, St. Josef Hospital, Ruhr University, Bochum, Germany. (14)Apheresis Research Institute, Köln, Germany. (15)Department of Anaesthesiology and Intensive Care Medicine, Martha-Maria Hospital, Halle/Saale, Germany. (16)Department of Nephrology, Charité University Medicine, Berlin, Germany. (17)Department of Nephrology, General Hospital Augsburg, Germany. (18)Department of Nephrology, University of Münster, Germany. (19)Clinic of Internal Medicine III, Sana Clinic, Offenbach, Germany. (20)Department of Nephrology, General Hospital Lüdenscheid, Märkische Kliniken GmbH, Germany. (21)Department of Neurology, General Hospital Lüdenscheid, Märkische Kliniken GmbH, Germany.

Background: Up to every fourth woman with multiple sclerosis (MS) or neuromyelitis optica spectrum disorder (NMOSD) suffers a clinically relevant relapse during pregnancy. High doses of steroids bear some serious risks, especially within the first trimester of pregnancy. Immunoadsorption (IA) is an effective and more selective treatment option in disabling MS relapse than plasma exchange. Data on the use of IA during pregnancy and breastfeeding are scarce. Methods: In this retrospective multicenter study, we analyzed the safety and efficacy of IA treatment in acute relapses during pregnancy or breastfeeding. The primary outcome parameter - change of acute relapse-related disability after IA - was assessed using Expanded Disability Status Scale (EDSS) and visual acuity (VA) measurements for patients with optic neuritis (ON).

Results: A total of 24 patients were analyzed, 23 with relapsing-remitting MS, and 1 with NMOSD. Twenty patients were treated with IA during pregnancy. Four patients received IA postnatally during the breastfeeding period. Treatment was started at a mean 22.5 [standard deviation (SD) 13.9] days after onset of relapse. Patients were treated with a series of 5.8 (mean, SD 0.7) IA treatments within 7-10 days. Sixteen patients received IA because of steroid-refractory relapse, eight were treated without preceding steroid pulse therapy. EDSS improved clinically relevant from 3.5 [median, interquartile range (IQR) 2] before IA to 2.5 (median, IQR 1.1) after IA, p < 0.001. In patients with ON, VA improved in four out of five patients. Altogether, in 83% of patients, a rapid and marked improvement of relapse-related symptoms was observed after IA with either a decrease of ≥1 EDSS grade or improvement in VA ≥20%. No clinically relevant side effect was reported in 138 IA treatments. Conclusions: Tryptophan-IA was found to be effective and well tolerated in MS/NMOSD relapses, both as an escalation option after insufficient response to steroid pulse therapy and as first-line relapse treatment during pregnancy and breastfeeding.

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Botulinum Toxin for Central Neuropathic Pain.

Park J(1), Chung ME(2).

Author information: (1)Department of Rehabilitation Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222, Banpo-daero, Seocho-gu, Seoul 06591, Korea. sophia@catholic.ac.kr. (2)Department of Rehabilitation Medicine, St. Paul's Hospital, College of Medicine, The Catholic University of Korea, Wangsan-ro 180, Dongdaemoon-Gu, Seoul 02559, Korea. coltrane@catholic.ac.kr.

Botulinum toxin (BTX) is widely used to treat muscle spasticity by acting on motor neurons. Recently, studies of the effects of BTX on sensory nerves have been reported and several studies have been conducted to evaluate its effects on peripheral and central neuropathic pain. Central neuropathic pain includes spinal cord injury-related neuropathic pain, post-stroke shoulder pain, multiple sclerosis-related pain, and complex regional pain syndrome. This article reviews the mechanism of central neuropathic pain and assesses the effect of BTX on central neuropathic pain.

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**Epigenetic Regulation in Neurodegenerative Diseases.**

Berson A(1), Nativio R(2), Berger SL(3), Bonini NM(4).

Author information:  (1)Department of Biology, University of Pennsylvania, Philadelphia, PA 19104, USA. (2)Epigenetics Institute, Department of Cell and Developmental Biology, University of Pennsylvania, Philadelphia, PA 19104, USA. (3)Department of Biology, University of Pennsylvania, Philadelphia, PA 19104, USA; Epigenetics Institute, Department of Cell and Developmental Biology, University of Pennsylvania, Philadelphia, PA 19104, USA. (4)Department of Biology, University of Pennsylvania, Philadelphia, PA 19104, USA; Epigenetics Institute, Department of Cell and Developmental Biology, University of Pennsylvania, Philadelphia, PA 19104, USA. Electronic address: nbonini@sas.upenn.edu.

Mechanisms of epigenetic regulation, including DNA methylation, chromatin remodeling, and histone post-translational modifications, are involved in multiple aspects of neuronal function and development. Recent discoveries have shed light on critical functions of chromatin in the aging brain, with an emerging realization that the maintenance of a healthy brain relies heavily on epigenetic mechanisms. Here, we present recent advances, with a focus on histone modifications and the implications for several neurodegenerative diseases including Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). We highlight common and unique epigenetic mechanisms among these situations and point to emerging therapeutic approaches.

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**Dietary approaches to treat MS-related fatigue: comparing the modified Paleolithic (Wahls Elimination) and low saturated fat (Swank) diets on perceived fatigue in persons with relapsing-remitting multiple sclerosis: study protocol for a randomized controlled trial.**

Wahls T(1), Scott MO(2), Alshare Z(2), Rubenstein L(2), Darling W(2), Carr L(2), Smith K(2), Chenard CA(2), LaRocca N(3), Snetselaar L(2).

Author information:  (1)University of Iowa, Iowa City, Iowa, USA. terry-wahls@uiowa.edu. (2)University of Iowa, Iowa City, Iowa, USA. (3)National Multiple Sclerosis Society, New York, New York, USA.

BACKGROUND: Fatigue is one of the most disabling symptoms of multiple sclerosis (MS) and contributes to diminishing quality of life. Although currently available interventions have had limited success in relieving MS-related fatigue, clinically significant reductions in perceived fatigue severity have been reported in a multimodal intervention pilot study that included a Paleolithic diet in addition to stress reduction, exercise, and electrical muscle stimulation. An optimal dietary approach to reducing MS-related fatigue has not been identified. To establish the specific effects of diet on MS symptoms, this study focuses on diet only instead of the previously tested multimodal intervention by comparing the effectiveness of two dietary patterns for the treatment of MS-related fatigue. The purpose of this study is to determine the impact of a modified Paleolithic and low saturated fat diet on perceived fatigue (primary outcome), cognitive and motor symptoms, and quality of life in persons with relapsing-remitting multiple sclerosis (RRMS).

METHODS/DESIGN: This 36-week randomized clinical trial consists of three 12-week periods during which assessments of perceived fatigue, quality of life, motor and cognitive function, physical activity and sleep, diet quality, and social support for eating will be collected. The three 12-week periods will consist of the following: 1. OBSERVATION: Participants continue eating their usual diet. 2. INTERVENTION: Participants will be randomized to a modified Paleolithic or low saturated fat diet for the intervention period. Participants will receive support from a registered dietitian (RD) through in-person coaching, telephone calls, and emails. 3. FOLLOW-UP: Participants will continue the study diet for an additional 12 weeks with minimal RD support to assess the ability of the participants to sustain the study diet on their own. DISCUSSION: Because fatigue is one of the most common and disabling symptoms of MS, effective management and reduction of MS-related fatigue has the potential to increase quality of life in this population. The results of this study will add to the evidence base for providing dietary recommendations to treat MS-related fatigue and other symptoms associated with this disease. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02914964.

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Fetal cardiac tumors: fetal echocardiography, clinical outcome and genetic analysis in 53 cases.

Chen J(1), Wang J(2), Sun H(1), Gu X(1), Hao X(1), Fu Y(1), Zhang Y(1), Liu X(1), Zhang H(3), Han L(4), He Y(1).

Author information: (1)Maternal-Fetal Consultation Center of Congenital Heart Disease, Department of echocardiography, Beijing Anzhen Hospital, Capital Medical University, Beijing, China. (2)College of life science, Tsinghua University, Beijing, China. (3)Department of cardiac surgery, Beijing Anzhen Hospital, Capital Medical University, Beijing, China. (4)Department of Pediatrics, Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

OBJECTIVE: To analyse the imaging and clinical features of fetal cardiac tumours, and to explore the relationship between tuberous sclerosis complex (TSC) and cardiac rhabdomyoma in fetuses. METHODS: In total, 53 pregnant women with fetal cardiac tumour(s) were examined by standardized fetal echocardiography (FE) and familial TSC genetic testing, and relevant pathological features were also collected. RESULTS: Of the 53 fetuses, 37 cases exhibited multiple cardiac tumours and 16 exhibited a single cardiac tumor by FE. All 53 fetuses and their families successfully received TSC genetic testing. In total, 37 of 53 fetuses had TSC1 or TSC2 mutations, which were pathogenic or suspected pathogenic mutations. Of the above 37 mutations, 25 were sporadic mutations and 12 were familial mutations. In addition, 6 mutations were located in TSC1 and 31 mutations were located in TSC2. The results of gene detection were negative in 16 fetuses. In total, 45 pregnant women and their families eventually decided to terminate the pregnancy, and 8 fetuses were liveborn. Autopsy was performed in 38 fetuses, revealing 36 cases of pathologically confirmed cardiac rhabdomyoma, 1 case of haemangioma and 1 case of fibroma. CONCLUSION: No significant difference was noted between single cardiac tumours and multiple tumours regarding the degree of fetal heart damage. Cardiac rhabdomyoma is the most common cardiac tumour in fetus. The correlation between cardiac rhabdomyoma and TSC is high regardless of the presence of single or multiple tumours. This article is protected by copyright. All rights reserved.

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Therapeutic failure in trigeminal neuralgia: from a clarification of trigeminal nerve somatotopy to a targeted partial sensory rhizotomy.


Author information: (1)Department of Neurosurgery, CHRU de Tours, 37044, Tours, FRANCE; UMR Inserm U1253, iBrain, Université de Tours, Tours, FRANCE; Laboratory of Anatomy - Faculté de Médecine - 10 bd Tonnellé - 37032 Tours - FRANCE. Electronic address: lmterrier14@gmail.com. (2)Assistance Publique-Hopitaux de Paris, Department of Neurosurgery, La Pitié-Salpêtrière, Paris, France; Sorbonne-University, Pierre et Marie Curie School of Medicine, Paris, France. (3)Department of Neurosurgery, CHRU de Tours, 37044, Tours, FRANCE; UMR Inserm U1253, iBrain, Université de Tours, Tours, FRANCE. (4)Department of Neurosurgery, CHRU de Tours, 37044, Tours, FRANCE; UMR Inserm U1253, iBrain, Université de Tours, Tours, FRANCE; Laboratory of Anatomy - Faculté de Médecine - 10 bd Tonnellé - 37032 Tours - FRANCE. (5)Department of Neurosurgery, CHRU de Tours, 37044, Tours, FRANCE.

BACKGROUND: Trigeminal Neuralgia (TN) is a severe unilateral facial pain involving one or more branches of the trigeminal nerve (CNV). Microvascular decompression is a standard curative treatment of pharmacoresistant classical TN. Alternative procedures used for secondary or idiopathic TN usually lead to a high rate of pain recurrence and sensitive deficits. Partial sensory rhizotomy (PSR) is one of these ablative procedures. However the lack of anatomical knowledge about the somatotopy of CNV lead to variable results in pain relief and hypoesthesia. OBJECTIVE: To refine the somatotopy of CNV and bring new anatomical landmarks for PSR. Study a cohort of patients treated by a targeted partial sensory rhizotomy (TPSR). METHODS: Retrospective and consecutive cases of adult patients treated in our institution between March 2000 and June 2015 for pharmacoresistant TN without vascular compression were collected. Our surgical procedure was performed using a precision map of the somatotopy of CNV. We compared our results to other surgical and non-surgical therapies. RESULTS: Twenty-two patients had undergone TPSR. Fourteen had an idiopathic TN without compression of the nerve root, 6 had a secondary TN due to multiple sclerosis and 2 had a trigeminal conflict by inoperable tumor. Complete pain relief was achieved in 86.4% of the patients. Postoperative hypoesthesia was partial and focalized (22.7%). TN recurrence rate at 5 years was 31.5% (SD 10.9%). CONCLUSION: We clarified the functional somatotopy of CNV in its juxtapontine portion. TPSR is a very interesting alternative to other ablative procedures to treat pharmacoresistant TN without vascular compression.

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[Experience of the use of gasserian ganglion balloon compression in patients with trigeminal neuralgia associated with multiple sclerosis].

Rzaev DA(1), Denisova NP(1), Moisak GI(1), Rogov DY(1), Kulikova EV(1).

Author information: (1)Federal Center of Neurosurgery, Novosibirsk, Russia.

AIM: To evaluate the efficacy of gasserian ganglion balloon compression in patients with trigeminal neuralgia associated with MS. MATERIAL AND METHODS: Eight patients (3 men, 5 women), aged from 46 to 66 years (mean age 55 years), with trigeminal neuralgia associated with MS underwent surgery. An average duration of the pain syndrome was 8.4 years. Six patients had previous surgeries due to facial pain. Percutaneous balloon compression of gasserian ganglion was performed to all patients. Follow up period was from 2 to 24 months. RESULTS: Six patients (75%) reported 100% of pain relief right after the surgery, 2 patients (25%) reported a significant decrease of pain (2-3 points on VAS). Pain recurrence occurred in 3 patients: in 4 months, in 12 months and in 6 months. All of them were operated repeatedly. After the surgery, hypoesthesia on the side of surgery was observed in all patients with a trend towards regression. There was no keratopathy or any complications. CONCLUSION: Percutaneous balloon compression of gasserian ganglion is an effective and minimally invasive method which can be performed repeatedly in patients with trigeminal neuralgia associated with MS.

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Effect of CD4(+) T cell surface CD1d molecules on progression of multiple sclerosis in mouse experimental autoimmune encephalomyelitis model.

Wang KH(1), Zang WZ, Li YL, Zhou LH.

Author information: (1)Department of Neurology, Xinxiang Central Hospital of Henan, Xinxiang 453000, China.

Objective: To investigate the effect of CD1d molecules on the surface of CD4(+) T cells on the progression of experimental autoimmune encephalomyelitis (experimental, allergic, encephalomyelitis, EAE) mouse models. Methods: EAE model of C57BL/6 mice was established, Splenic cells were isolated at different stages of the progression of the disease. The proportion of CD1d(+) cells on the surface of activated and non activated CD4(+) T cells was detected by flow cytometry. Results: The proportion of CD1d(+) cells in the control group (normal group and complete Freund's adjuvant (CFA) group), in the peak and recovery period of disease in the EAE group were compared. The proportion of CD1d(+) cells in the control group was (8.98 ±0.36)% and the proportion of CD1d(+) cells in the peak and recovery period of disease in the EAE group were respectively (2.14±0.15)% and (13.80±0.84)%. The differences were statistically significant difference (P<0.05). Conclusion: The trend of the proportion of CD4(+) T cells expressing CD1d molecules during the course of EAE pathogenesis is verified, which lays a foundation for further study on the interaction between CD4(+) T cells and NKT cells in the progression of EAE models.

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