The 14th annual ACTRIMS meeting is jointly sponsored by the University of Maryland School of Medicine and the National Multiple Sclerosis Society.

ACTRIMS meetings are held in collaboration with the National Multiple Sclerosis Society and the MS Society of Canada.

Second Joint Meeting

May 27–30

EnvironmEntal risk Factors in multiplE sclErosis

Basic and Clinical Issues in Multiple Sclerosis Research

Saturday, May 30, 2009

Hyatt Regency Atlanta

Atlanta, Georgia

FUTURE ACTRIMS MEETINGS

2010
San Antonio, Texas — June 5
Offered in cooperation with the Consortium of Multiple Sclerosis Centers, June 2–5

2011
Amsterdam, The Netherlands — October 19–22
Offered jointly with ECTRIMS and LACTRIMS

www.actrims.org
actrims@nmss.org

The 14th annual ACTRIMS meeting is jointly sponsored by the University of Maryland School of Medicine and the National Multiple Sclerosis Society.

ACTRIMS meetings are held in collaboration with the National Multiple Sclerosis Society and the MS Society of Canada.
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Dear Colleague,

Welcome to the 14th annual meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), jointly sponsored by the University of Maryland School of Medicine and the National Multiple Sclerosis Society. We also acknowledge the collaboration of the MS Society of Canada. For the second time, we are meeting together with the Consortium of Multiple Sclerosis Centers (CMSC) and we look forward to that cooperative arrangement next year as well.

Together, with CMSC, we are pleased to offer the fifth annual Donald Paty Memorial Lecture named in honor of Donald W. Paty, MD (1936–2004), a compassionate clinician, distinguished neuroimmunologist, and past winner of the John Dystel Prize and the Charcot Award, each recognizing achievements in MS research.

Our speaker, Dr. Alberto Ascherio, is a worthy recipient of this lectureship. A physician and epidemiologist, Dr. Ascherio is a world-renowned researcher. He has led the application of an interdisciplinary approach and rigorous epidemiology standards to the study of MS, to help identify its cause, risk factors, and biomarkers of susceptibility. We are privileged to hear his interpretation of advancements in these areas of MS research, which may ultimately lead to prevention and early diagnosis of this progressive and disabling disease.

The Steering Committee and I want to express our appreciation to industry sponsors who have helped make these meetings possible over the years. It is remarkable how rapidly basic research in demyelinating diseases has matured to where clinical applications are not only possible but now numerous. We are grateful that the pharmaceutical industry has partnered with the MS community to continue to aggressively seek new means of managing, and hopefully curing, MS and related diseases.

As you know, ACTRIMS was developed to provide a forum where basic scientists, clinical researchers and clinicians interested in the demyelinating diseases could exchange information and network with colleagues to further the science and treatment of MS and related diseases. However, the continued growth and usefulness of ACTRIMS to the MS professional community is dependent upon your support and active participation. I look forward to hearing your suggestions for future meeting themes, and particularly to hearing your ideas on how to make the organization even more valuable in the future.

In the meantime, welcome to today’s timely and thought-provoking program. We look forward to your participation.

Sincerely,

Jerry S. Wolinsky, MD
**ACTRIMS Committees**

**Steering Committee**

Jerry Wolinsky, MD, *Chair*
Houston, Texas

Jack Antel, MD
Montreal, Quebec

Christopher Bever, MD, MBA
Baltimore, Maryland

Peter Calabresi, MD
Baltimore, Maryland

Jeffrey Cohen, MD
Cleveland, Ohio

Suhayl Dhib-Jalbut, MD
New Brunswick, New Jersey

Mark Freedman, MD
Ottawa, Ontario

Nancy Holland, EdD
New York, New York

Kenneth Johnson, MD
Baltimore, Maryland

Samuel Ludwin, MD
Kingston, Ontario

Aaron Miller, MD
New York, New York

Robert Naismith, MD
St. Louis, Missouri

Paul O’Connor, MD
Toronto, Ontario

John Richert, MD
New York, New York

Rhonda Voskuhl, MD
Los Angeles, California

Emmanuelle Waubant, MD, PhD
San Francisco, California

**Program Committee**

Christopher Bever, MD, MBA, *Co-Chair*

Emmanuelle Waubant, MD, PhD, *Co-Chair*

Peter Calabresi, MD

Jeffrey Cohen, MD

Mark Freedman, MD

Robert Naismith, MD

Kristin Summers, PhD

Jerry Wolinsky, MD

**Organizing Committee**

**National Multiple Sclerosis Society**

Kristin Summers, *Chair*

Elaine Ahlers

Barbara Boykin

Todd Culter

Nancy Holland

Kersten Sharrock

Chris Yankee

**Multiple Sclerosis Society of Canada**

Jon Temme

Stuart Wong
It is the policy of the University of Maryland School of Medicine to ensure balance, independence, objectivity, and scientific rigor in all of its educational activities. In accordance with this policy, all persons in control of activity content must disclose their relevant commercial relationships and resolve identified conflicts of interest prior to the activity.

Program Planning

Christopher Bever, MD
No relevant commercial relationships

Peter Calabresi, MD
Grants/Research Support: Biogen Idec, EMD Serono, Genentech, Novartis, Teva Neuroscience
Consultant: Amplimmune, Biogen Idec, Eisai, EMD Serono, Genentech, Novartis, Teva Neuroscience, Vertex Pharmaceuticals

Jeffrey Cohen, MD
Grants/Research Support: Artielle ImmunoTherapeutics, Biogen Idec, BioMS, Genzyme, Orchestra Therapeutics, Novartis, Teva Neuroscience
Consultant: Biogen Idec, Eisai, Eli Lilly and Company, EMD Serono, Genentech, Genzyme, GlaxoSmithKline, IMPAX Laboratories, Inc., Incyte, Novartis, Schering-Plough, Teva Neuroscience, Wyeth

Mark Freedman, MD
Consultant: Bayer HealthCare, BioMS, Biogen Idec, EMD Serono, Eli Lilly and Company, Genentech, Novartis, sanofi-aventis, Teva Neuroscience
Speakers Bureau: Bayer HealthCare, Pfizer Inc

Robert Naismith, MD
Grants/Research Support: Acorda Therapeutics
Consultant: Bayer HealthCare, Biogen Idec, Teva Neuroscience
Speakers Bureau: Bayer HealthCare, Biogen Idec, Elan, Teva Neuroscience

Kristin Summers, PhD
No relevant commercial relationships

Emmanuelle Waubant, MD
No relevant commercial relationships

Jerry Wolinsky, MD
Grants/Research Support: sanofi-aventis
Consultant: Antisense Therapeutics Limited, EMD Serono, Genentech, Novartis, sanofi-aventis, Teva Neuroscience, Teva Pharmaceuticals, UCB
Featured Speakers
Alberto Ascherio, MD, DrPH
No relevant commercial relationships
Philip De Jager, MD, PhD
No relevant commercial relationships
Colleen Hayes, PhD
No relevant commercial relationships
Martin Hewison, PhD
No relevant commercial relationships
Steven Jacobson, PhD
No relevant commercial relationships
Jan Lünemann, MD
No relevant commercial relationships
Jill Norris, MPH, PhD
No relevant commercial relationships
Dessa Sadovnick, PhD
No relevant commercial relationships

Platform Presenters
Dorothee Chabas, MD, PhD
No relevant commercial relationships
Stefan Gold, PhD
No relevant commercial relationships
Judith James, MD, PhD
No relevant commercial relationships
Robyn Lucas, PhD
No relevant commercial relationships
Robert Naismith, MD
Grants/Research Support: Acorda Therapeutics
Consultant: Bayer HealthCare, Biogen Idec, Teva Neuroscience
Speakers Bureau: Bayer HealthCare, Biogen Idec, Elan, Teva Neuroscience
Narendra Singh, PhD
No relevant commercial relationships
Yanming Wang, PhD
No relevant commercial relationships
Emmanuelle Waubant, MD, PhD
No relevant commercial relationships
Program Overview

This day-long session provides a central forum where clinicians, basic scientists, and clinical investigators working in MS can discuss research findings and exchange information.

This knowledge-based course provides important information regarding environmental risk factors associated with MS. A broad overview of the topic will be presented along with recent information concerning the role of Vitamin D, Epstein Barr, and human herpes viruses. Also presented will be information regarding genetic risk factors and gene-environment interactions.

People affected by MS often search for a reason as to why they have developed MS. People affected by MS who have children or are considering having children may have questions regarding risk factors based on a layman’s understanding of scientific literature or the interpretation of this literature by the popular media.

Physicians and other healthcare professionals can help inform their patients about MS risk factors. By being prepared to discuss which risk factors may be important, physicians can help patients allay fears, make informed lifestyle choices, and avoid products or procedures that may be ineffective, harmful, or costly.

Accreditation Statement

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of University of Maryland School of Medicine and the National Multiple Sclerosis Society. The University of Maryland School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Credit Designation Statement

The University of Maryland School of Medicine designates this educational activity for a maximum of 7.5 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Target Audience

- Clinicians with an active practice focused on MS
- Basic scientists with research interests in demyelinating diseases
- Clinical investigators in MS
Learning Objectives

At the conclusion of this course, the participant should be able to:

■ Discuss the substantial evidence for EBV, vitamin D, and other environmental risk factors in MS susceptibility.
■ Describe the effects of various environmental risk factors on the immune system and how these might lead to MS.
■ Describe the role of gene-environment interactions in MS susceptibility.
■ List potential protective strategies to decrease MS incidence.

Sign-In

Please plan to sign into the morning and afternoon sessions of the program. Additionally, if you are claiming credit for the poster session, please sign in to that session as well. Thank you.

Claiming CME Credit

Participants will receive a CME certificate at the activity. The registrant will retain one section of the certificate for their records; the duplicate section will be returned to the University of Maryland School of Medicine. Please leave the duplicate copy at the ACTRIMS registration desk, prior to departure.

Program Evaluation

Participants are asked to complete the program evaluation. Please complete the evaluation form at the conclusion of your participation in the program and return the form to the ACTRIMS registration desk prior to departure. Your comments will be useful in planning future programs. Thank you for your participation and cooperation.
## Schedule of Events

### FRIDAY, MAY 29

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Venue</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00 am – 4:00 pm</td>
<td>CMSC/Whitaker Research Track</td>
<td>International Ballroom South</td>
</tr>
<tr>
<td>6:30 pm – 8:00 pm</td>
<td>Joint CMSC-ACTRIMS Poster Session and Dinner Buffet</td>
<td>Exhibit Hall</td>
</tr>
</tbody>
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### SATURDAY, MAY 30 ACTRIMS MEETING*

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Venue</th>
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</thead>
<tbody>
<tr>
<td>7:00 am – 8:00 am</td>
<td>Continental Breakfast</td>
<td>Centennial Ballroom Foyer</td>
</tr>
<tr>
<td>8:00 am – 9:00 am</td>
<td>CMSC-ACTRIMS Donald Paty Memorial Lecture</td>
<td>Regency Ballroom, VI and VII</td>
</tr>
<tr>
<td>9:00 am – 12:00 pm</td>
<td>ACTRIMS General Session</td>
<td>Regency Ballroom, VI and VII</td>
</tr>
<tr>
<td>12:00 pm – 1:00 pm</td>
<td>Lunch</td>
<td>Centennial Ballroom Foyer</td>
</tr>
<tr>
<td>1:00 pm – 2:00 pm</td>
<td>Poster Session with Authors Present</td>
<td>Regency Ballroom, V</td>
</tr>
<tr>
<td>2:00 pm – 5:00 pm</td>
<td>ACTRIMS General Session</td>
<td>Regency Ballroom, VI and VII</td>
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* The 14th annual ACTRIMS meeting is jointly sponsored by the University of Maryland School of Medicine and the National Multiple Sclerosis Society.
ACTRIMS Agenda

8 – 9 AM  CMSC-ACTRIMS DONALD PATY MEMORIAL LECTURE

1* The environment and multiple sclerosis: causes and consequences
   Alberto Ascherio, MD, DrPH
   Harvard School of Public Health, Boston, Massachusetts, USA

9 – 10:30 AM  SESSION 1: EBV AND OTHER VIRUSES

9 am  2* Epstein-Barr virus-specific immune responses in multiple sclerosis
       Jan Lünemann, MD
       Rockefeller Institute, New York, New York, USA

9:30 am  3* Role of human herpesviruses in multiple sclerosis
         Steven Jacobson, PhD
         National Institute of Neurological Disorders and Stroke, Bethesda, Maryland, USA

10 am  4 Remote EBV, CMV, and HSV-1 and -2 infection and DRB1*1501/1503 status in children with pediatric-onset MS
       Emmanuelle Waubant, MD, PhD
       University of California, San Francisco, San Francisco, California, USA

10:15 am  5 Multiple sclerosis patients make antibodies against a unique sequence of EBNA-1 that cross reacts with myelin basic protein
          Judith James, MD, PhD
          University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

10:30 am  COFFEE BREAK

10:45 AM – 12 PM  SESSION 2: BASIC AND CLINICAL ISSUES IN MS RESEARCH

10:45 am  6 Direct quantification of myelin changes in multiple sclerosis
          Yanming Wang, PhD
          Case Western Reserve University, Cleveland, Ohio, USA

11 am  7 Diffusion tensor imaging predicts severe brain tissue injury in acute MS lesions
       Robert Naismith, MD
       Washington University School of Medicine, St. Louis, Missouri, USA

*Invited Lecture
<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Title</th>
<th>Speaker</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:15 am</td>
<td>8</td>
<td>Flatter diurnal cortisol slope is associated with regional hippocampal atrophy and depressive symptoms in multiple sclerosis</td>
<td>Stefan Gold, PhD</td>
<td>UCLA David Geffen School of Medicine, Los Angeles, California, USA</td>
</tr>
<tr>
<td>11:30 am</td>
<td>9</td>
<td>Combination therapy of resveratrol and retinoic acid suppresses development of EAE by reciprocal differentiation of Th17 cells and regulatory T cells</td>
<td>Narendra Singh, PhD</td>
<td>University of South Carolina School of Medicine, Columbia, South Carolina, USA</td>
</tr>
<tr>
<td>11:45 am</td>
<td>10</td>
<td>Pediatric multiple sclerosis before puberty: a distinct CSF inflammatory profile</td>
<td>Dorothee Chabas, MD, PhD</td>
<td>University of California, San Francisco, San Francisco, California, USA</td>
</tr>
<tr>
<td>12 – 1 pm</td>
<td></td>
<td><strong>LUNCH</strong></td>
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<tr>
<td>1 – 2 pm</td>
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<td><strong>POSTER SESSION WITH AUTHORS PRESENT</strong></td>
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<tr>
<td>2 – 3:15 PM</td>
<td>Session 3: Vitamin D and MS</td>
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</tr>
<tr>
<td>2 pm</td>
<td>11*</td>
<td>Vitamin D and the immune system: from pathological problem to normal physiology</td>
<td>Martin Hewison, PhD</td>
<td>UCLA David Geffen School of Medicine, Los Angeles, California, USA</td>
</tr>
<tr>
<td>2:30 pm</td>
<td>12*</td>
<td>Vitamin D and EAE</td>
<td>Colleen Hayes, PhD</td>
<td>University of Wisconsin-Madison, Madison, Wisconsin, USA</td>
</tr>
<tr>
<td>3 pm</td>
<td>13</td>
<td>Lower vitamin D status at first clinical diagnosis of central nervous system demyelination compared to matched controls</td>
<td>Robyn Lucas, PhD</td>
<td>The Australian National University, Canberra, Australia</td>
</tr>
<tr>
<td>3:15 pm</td>
<td></td>
<td><strong>COFFEE BREAK</strong></td>
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</tbody>
</table>

*Invited Lecture*
ACTRIMS Agenda

3:30 – 5 PM  SESSION 4: GENE-ENVIRONMENT INTERACTIONS AND MS SUSCEPTIBILITY

3:30 pm  14* Gene-environment interactions in diabetes and what it may mean for multiple sclerosis
Jill Norris, MPH, PhD
University of Colorado Denver, Denver, Colorado, USA

4 pm  15* Evidence for an increase in incidence in multiple sclerosis in the female population
Dessa Sadovnick, PhD
University of British Columbia, Vancouver, British Columbia, Canada

4:30 pm  16* Risk alleles and Epstein-Barr virus in susceptibility to multiple sclerosis
Philip De Jager, MD, PhD
Brigham and Women’s Hospital, Harvard Medical School, Boston Massachusetts, USA

5 pm  Closing Remarks

*Invited Lecture
Disease Modifying Therapy

P1 Effect of alemtuzumab on quality of life in patients with relapsing remitting multiple sclerosis
Ann Bass, MD
Neurology Center of San Antonio, San Antonio, Texas, USA

P2 Treatment of aggressive neuromyelitis optica with high-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation
James D. Bowen, MD
Swedish Medical Center, Seattle, Washington, USA

P3 Alemtuzumab improves EDSS functional system scores better than interferon beta-1a in patients with relapsing remitting multiple sclerosis
Edward J. Fox, MD, PhD
University of Texas Medical Branch, Round Rock, Texas, USA

P4 Multiple sclerosis: natalizumab effects on cognitive function
Mark Gudesblatt, MD
Patchogue, New York, USA

P5 Effects of natalizumab on Balo’s sclerosis
Carolina Ionete, MD, PhD
University of Massachusetts, Worcester, Massachusetts, USA

P6 Direct comparison of clinical effect of multiple sclerosis immunomodulating agents using a large United States managed care database
Kenneth Johnson, MD
Maryland Center for Multiple Sclerosis, Baltimore, Maryland, USA

P7 Immune reconstitution syndrome in multiple sclerosis patients following cessation of natalizumab therapy
Augusto Miravalle, MD
Beth Israel Deaconess Medical Center, Harvard University, Boston, Massachusetts, USA

P8 An adaptive multiple ascending dose study using lymphocytes as a primary biomarker for early clinical evaluation of a S1P1 receptor modulator for treatment of multiple sclerosis
James Moberly, PhD
Daiichi Sankyo Pharma Development, Edison, New Jersey, USA

P9 WITHDRAWN

Katia Noyes, PhD, MPH
University of Rochester, Rochester, New York, USA
P11  CS-0777, a novel sphingosine 1-phosphate (S1P) receptor modulator, ameliorates experimental autoimmune encephalomyelitis
Wataru Tomisato, PhD
Daiichi Sankyo Co., Ltd., Tokyo, Japan

P12  Breakthrough disease in pediatric patients with multiple sclerosis: a pediatric network experience
Eluen Yeh, MD
The State University of New York at Buffalo, Buffalo, New York, USA

P13  Use of plasmapheresis in pediatric demyelinating disease
Jayne Ness, MD, PhD
University of Alabama at Birmingham, Birmingham, Alabama, USA

Epidemiology/Genetics

P14  Epilepsy in pediatric demyelinating diseases
Jayne Ness, MD, PhD
University of Alabama at Birmingham, Birmingham, Alabama, USA

P15  Serum 25-hydroxyvitamin D level is lower in black patients with multiple sclerosis
Mirela Cerghet, MD, PhD
Henry Ford Health System, Detroit, Michigan, USA

P16  Meta-analysis of genome scans and replication identify rare and common multiple sclerosis susceptibility alleles at TNFRSF1A and other loci
Philip L. De Jager, MD, PhD
Brigham and Women's Hospital, Harvard Medical School, Broad Institute, Boston, Massachusetts, USA

P17  Epidemiology of multiple sclerosis in Mazandaran, Iran, 2007
Reza Habibisaravi, MD
Mazandaran MS Society, Mazandaran Medical University, Sari, Iran

P18  Clinical patterns of multiple sclerosis among Hispanics living in Southern California suggest an earlier onset of disease
Neda Jafarian, BS
Charles Drew University College of Medicine, Los Angeles, California, USA

P19  Baseline characteristics in a Real-World MS Study (ROBUST) compared to the BEYOND Trial
Douglas Jeffery, MD, PhD
Wake Forest University Baptist Medical Center, Winston-Salem, North Carolina, USA
P20  Epidemiology and current treatment trends of multiple sclerosis in Pakistan  
  Abdul Malik, DCN, MD  
  Jinnah Postgraduate Medical Centre, Karachi, Pakistan

P21  The influence of cigarette smoking on brain atrophy in relapsing multiple sclerosis  
  Ellen M. Mowry, MD  
  University of California, San Francisco, San Francisco, California, USA

P22  Residential case-control study of radon and multiple sclerosis  
  John Neuberger, DrPH, MPH, MBA  
  University of Kansas School of Medicine, Kansas City, Kansas, USA

P23  Case-control study of environmental exposures in individuals with multiple sclerosis in three geographic areas  
  Shruti Ramachandran, MPH, MID  
  Centers for Disease Control and Prevention, Atlanta, Georgia, USA

P24  Remote EBV, CMV, and HSV-1 and -2 infection status in children with pediatric-onset multiple sclerosis and age-matched healthy controls  
  Emmanuelle Waubant, MD, PhD  
  UCSF MS Center, San Francisco, California, USA

P25  25(OH) vitamin D levels in children with pediatric-onset multiple sclerosis and controls  
  Emmanuelle Waubant, MD, PhD  
  UCSF MS Center, San Francisco, California, USA

P26  International case control study on risk factors for multiple sclerosis (MS): pilot testing the questionnaire  
  Christina Wolfson, PhD  
  McGill University, Montreal, Quebec, Canada

Experimental Disease Models

P27  1,25-dihydroxyvitamin D3 acts directly on T lymphocytes to mediate protection from experimental autoimmune encephalomyelitis  
  Christopher G. Mayne, PhD  
  University of Wisconsin–Madison, Madison, Wisconsin, USA

Imaging

P28  Comparison of T2-weighted magnetic resonance imaging and retinal nerve fiber layer thickness measurement for detecting prior acute optic neuritis in multiple sclerosis  
  Sheena K. Farrell, BS  
  The Johns Hopkins University, Baltimore, Maryland, USA
P29 Average permeability of the blood-brain-barrier is reduced in patients with multiple sclerosis
Corey C. Ford, MD, PhD
University of New Mexico Health Sciences Center, Albuquerque, New Mexico, USA

P30 Glutathione levels in the brains of patients with secondary progressive multiple sclerosis are reduced by magnetic resonance spectroscopy measures
Sharon Lynch, MD
University of Kansas School of Medicine, Kansas City, Kansas, USA

P31 Magnetic resonance imaging characteristics of the CombiRx cohort at baseline
Flavia Nelson, MD
The University of Texas Medical School at Houston, Houston, Texas, USA

Neuroimmunology

P32 The brain as an effector site of secretory immunity in inflammatory neurological disorders
Dorothee Chabas, MD, PhD
UCSF MS Center, San Francisco, California, USA

P33 Deletion of CD44 induces a protective immune phenotype and suppresses experimental autoimmune encephalomyelitis
H. Guan, PhD
University of South Carolina School of Medicine, Columbia, South Carolina, USA

P34 Pediatric-onset multiple sclerosis patient sera recognize unique regions of Epstein-Barr nuclear antigen 1
Judith A. James, MD, PhD
Oklahoma Medical Research Foundation, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma, USA

P35 Immunoglobulin-like transcript 3 expression on circulating CD14+ cells is low in active remitting relapsing multiple sclerosis and is induced by interferon beta-1b
Mark A. Jensen, PhD
The University of Chicago, Chicago, Illinois, USA

P36 Neuroinflammation in the spinal cord of NG2 null mice
Karolina Kucharova, MD, PhD
Burnham Institute for Medical Research, La Jolla, California, USA

P37 Anti-GAGA4 IgM assay may distinguish primary progressive from relapsing-remitting multiple sclerosis patients
John W. Rose, MD
University of Utah, Salt Lake City, Utah, USA
P38  Immunogenetic predictors of response to glatiramer acetate therapy in multiple sclerosis
Reuben Mari Valenzuela, MD
UMDNJ–Robert Wood Johnson Medical School, Piscataway, New Jersey, USA

Neuropsychology/Neuropsychiatry

P39  Evidence of subtle hippocampal dysfunction is detectable in relapsing-remitting multiple sclerosis
Kyle C. Kern, BS
David Geffen School of Medicine at UCLA, Los Angeles, California, USA

P40  Predicting neurocognitive decline in patients with multiple sclerosis using demographic variables
Ronald Williams, PhD
Fort Wayne Neurological Center, Fort Wayne, Indiana, USA

Rehabilitation and Quality of Life

P41  African Americans with multiple sclerosis: health-related quality of life and psychosocial correlates
Bonnie Chakravorty, PhD, MSW
Tennessee State University, Nashville, Tennessee, USA

P42  Patent foramen ovale as a mechanism for embolic stroke and disability in multiple sclerosis
Robert J. Fallis, MD
St. Thomas Hospital, Nashville, Tennessee, USA

P43  The effects of treadmill training on functional ability, quality of life and fatigue in primary-progressive multiple sclerosis
L. A. Pilutti, BSc
McMaster University, Hamilton, Ontario, Canada

P44  Differences between MS patients with and without self-reported optic neuritis
Amber R. Salter, MPH
University of Alabama at Birmingham, Birmingham, Alabama, USA

Surrogate Markers (Non-MRI)

P45  Serum vitamin D levels are associated with multiple sclerosis disease severity
Allison S. Drake, MSc
Jacobs Neurological Institute, State University of New York at Buffalo, Buffalo, New York, USA
Symptom Management

P46  Symptom clusters in women with relapsing-remitting multiple sclerosis
Pamela Newland, PhD, RN
Southern Illinois University, St. Jacob, Illinois, USA

P47  Assessment of pain in neuromyelitis optica
Peiqing Qian, MD
Washington University School of Medicine, St. Louis, Missouri, USA

P48  Symptom cluster and physical activity in multiple sclerosis
Madeline Weikert, BS
University of Illinois, Urbana, Illinois, USA
ALBERTO ASCHERIO, MD, DRPH

Alberto Ascherio, MD, DrPH, is a Professor of Nutrition and Epidemiology and Associate Professor of Medicine at the Harvard School of Public Health.

Dr. Ascherio’s research is primarily devoted to identifying causes and risk factors for MS and other neurodegenerative diseases, as well as biomarkers that may provide information about susceptibility and that may lead to earlier diagnosis. These investigations are part of an international collaborative effort on the possible etiologic role of the Epstein-Barr virus and other infections, and the protective effect of vitamin D. Since 1997 he has directed the investigation of neurodegenerative diseases in several large cohorts comprising over 400,000 men and women who have provided detailed information on their dietary habits and lifestyle, in addition to blood or cheek cell samples for genetic and other laboratory analyses. Most recently, he has been directing a large prospective seroepidemiologic study based on the Department of Defense Serum Repository to identify pre-diagnostic markers of infection and nutritional status as they relate to the risk of MS.

Dr. Ascherio trained in internal medicine at the University of Milan, and subsequently practiced medicine and public health in Latin America and Africa. He completed his doctoral degree in epidemiology at the Harvard School of Public Health.

PHILIP DE JAGER, MD, PHD

Philip De Jager, MD, PhD, is an Assistant Professor of Neurology at Harvard Medical School and head of the Laboratory of Neurogenetics and Computational Neurology within the Center for Neurologic Disease and the Department of Neurology at Brigham & Women’s Hospital. He is also a member of the Partners Center for Personalized Genetic Medicine and practices neurology at the Partners Multiple Sclerosis Center in Boston.

Dr. De Jager’s research program is focused on understanding how genetic variation affects neuroimmunologic function and susceptibility to MS. He has led or contributed to the discovery of several different genetic loci associated with MS susceptibility, including one in African Americans. Much of this work has been done in the context of the International MS Genetic Consortium, which has been the primary driver of the success of genetic investigations in MS. He and his colleagues have also integrated genetic data with clinical and radiologic data in an effort to develop diagnostic, prognostic and treatment algorithms in MS.

Dr. De Jager received his PhD in neurogenetics at the Rockefeller University and his MD degree from Cornell University Medical College. He completed a neurology residency at the Brigham & Women’s Hospital and Massachusetts General Hospital.
He received additional sub-specialty clinical experience in MS at the partners MS Center, expertise in human genetics at the Broad Institute and training in clinical investigation in the Clinical Investigator Training Program at Harvard and MIT. In 2008, Dr. De Jager received the Harry Weaver Neuroscience Scholar Award from the National MS Society.

COLLEEN HAYES, PhD

Colleen Hayes, PhD, is Professor of Biochemistry at the University of Wisconsin–Madison.

Dr. Hayes and her collaborators study mechanisms by which the sunlight-derived hormone 1,25-dihydroxyvitamin D₃ regulates EAE, the animal model of the autoimmune, neurodegenerative disease multiple sclerosis. They were the first to propose that vitamin D might be a natural inhibitor of MS, due to the immunoregulatory functions of this steroid hormone. For the past fifteen years, her research team has been investigating the mechanisms that govern the metabolism of vitamin D₃ into 1,25-dihydroxyvitamin D₃ in the central nervous system, and the pathways by which this hormone performs anti-inflammatory and neuroprotective functions in EAE.

Dr. Hayes received her PhD in biochemistry from the University of Michigan, and completed postdoctoral training in the Department of Pathology at Harvard Medical School. She has received a fellowship from the National Foundation March of Dimes and a Leukemia Society of America Scholar Award. Dr. Hayes currently serves on a scientific review panel for the National Multiple Sclerosis Society.

MARTIN HEWISON, PhD

Martin Hewison, PhD, is Professor in Residence in the Department of Orthopaedic Surgery at UCLA’s Geffen School of Medicine. He previously held positions in the Department of Medicine at University College London, the University of Birmingham, and Cedars-Sinai Medical Center in Los Angeles.

Dr. Hewison and his colleagues have been involved in a wide variety of studies on the role of vitamin D in human physiology, particular focusing on the interaction between vitamin D and the immune system. These have included the tissue-specific regulation of steroid hormone metabolism and its impact on hormone action, including the role of the vitamin D activating enzyme 1alpha-hydroxylase and the glucocorticoid-metabolising enzymes 11beta-hydroxysteroid dehydrogenase types 1 and 2; the metabolism of vitamin D at barrier sites such as the brain, placenta and colon; and the possible role of vitamin D insufficiency in a number of diseases, including MS.
Dr. Hewison received his PhD from Guy’s Hospital Medical School at the University of London. He subsequently became Professor of Molecular Endocrinology at the University of Birmingham, where he established the UK’s major vitamin D research group.

**STEVEN JACOBSON, PHD**

Steven Jacobson, PhD, is a Senior Investigator in the Viral Immunology Section of the Neuroimmunology Branch at the National Institute of Neurological Disease and Stroke (NINDS) in Bethesda, Maryland.

The focus of his research has been on persistent virus infections, with an emphasis on the virologic, immunologic, and molecular mechanisms of human viruses in the pathogenesis of chronic progressive neurologic disease. In particular, Dr. Jacobson has been interested in the human T lymphotropic virus type I (HTLV-I) as the etiologic agent of the chronic progressive myelopathy HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP), a disease clinically similar to the chronic progressive form of MS. The research premise underlying these studies is that an understanding of the pathogenesis of a neurologic disease with a known viral etiology will aid in defining similar mechanisms of pathogenesis in MS, a disease whose etiology is currently unknown.

Dr. Jacobson received his PhD in virology from the Rensselear Polytechnic Institute. He joined the Neuroimmunology Branch of NINDS as a National Multiple Sclerosis Society Fellow in 1981. In 1993, he formed the Viral Immunology Section within NINDS to study the role of human viruses in the pathogenesis of chronic progressive neurologic disease.

**JAN LÜNEMANN, MD**

Jan Lünemann, MD, is a junior faculty member at Rockefeller University, Laboratory of Viral Immunobiology, in New York.

His research is focused on the immunoregulation of Epstein Barr virus infection in people with MS, and especially the role of Epstein Barr nuclear antigen 1 (EBNA1). It suggests that some individuals’ unusually strong reaction to the virus may trigger MS, which it is hoped could lead to new therapeutic strategies. He has published extensively in the field of translational neuroimmunology on topics that have included the mechanisms of action of IFN-beta therapy in MS, the role of innate immune cells and T cells in inflammatory brain diseases, and Epstein Barr virus-specific immune responses in children and adults with MS.

Dr. Lünemann received his MD degree at the Humboldt University in Berlin, and his residency training in the Department of Neurology at Charite University Hospital in Berlin. He received his doctoral training at the German Rheumatism Research Center in Berlin, and his postdoctoral training at the National Institutes of Health and the Rockefeller University in New York.
JILL NORRIS, MPH, PhD

Jill Norris, MPH, PhD, is Professor in the Department of Epidemiology in the Colorado School of Public Health at the University of Colorado in Denver. She is also Director of the Genetic Epidemiology Program.

Dr. Norris’ research has focused on the relationship between environment and the development of autoimmune diseases, including type 1 diabetes, rheumatoid arthritis, and celiac disease in genetically susceptible individuals. In addition, since 1993 she and her collaborators have conducted a broad-based family study in defined populations that seeks to use what is known about the environmental component in type 2 diabetes to help identify susceptibility genes for the disorder. It is hoped that these studies may shed light on the long-standing issue of the relationship between genes and environment in the development of both metabolic and autoimmune diseases, including MS.

Dr. Norris received her MPH and her PhD in epidemiology from the University of Pittsburgh Graduate School of Public Health. In 2000 she was a visiting scientist and recipient of a Poste Orange Fellowship at INSERM in Paris.

DESSA SADOVNICK, PHD

Dessa Sadovnick, PhD, is a Professor in the Department of Medical Genetics and the Division of Neurology, Faculty of Medicine at the University of British Columbia in Vancouver, Canada. She was also the co-director and academic advisor for the Master’s Degree in the Genetic Counseling Training Program at the University of British Columbia from 1992–2008.

With Dr. G. C. Ebers, Dr. Sadovnick is a principal investigator of the “Canadian Collaborative Project on Genetic Susceptibility to MS” and a co-principal investigator on “Prospective study of the epidemiology, pathobiology, and clinical outcome of Canadian children with clinically isolated demyelinating syndromes (CIS)”. Her research has focused on the role of hereditary and environmental factors and the interaction thereof on the susceptibility and natural history of MS.

Dr. Sadovnick received her MSc in Human Genetics at McGill University in Montreal and her PhD in genetics from the University of British Columbia, and has been affiliated with the Vancouver MS Clinic at UBC since its inception in 1980. She is a member of the Medical Advisory Committee of the MS Society of Canada, a member of several international advisory groups for MS, and a board member of the British Columbia Division of the MS Society of Canada. Dr. Sadovnick is a recipient of the MS Society of Canada Merit award and the Michael Smith Distinguished Scholar Award.
The environment and multiple sclerosis: causes and consequences
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While genetic susceptibility explains the clustering of MS cases within families and the decline in risk with increasing genetic distance, it cannot fully explain the geographical variations in MS frequency and the changes in risk that occur with migration, which support the action of strong environmental factors [1,2]. Epidemiological studies have lead to the discovery that a strong risk factor is infection with the Epstein-Barr virus. As compared with uninfected individuals, the hazard of developing MS is about 10 folds higher among individuals infected with EBV in childhood and at least 20 folds higher among individuals infected in adolescence or later in life [1]. Although rigorous investigations suggest this association is causal, there are no effective tools to prevent or eliminate EBV infection, and a conclusive proof remains thus elusive.

More amenable to immediate intervention are two other risk factors for MS: vitamin D insufficiency and cigarette smoking. Evidence from two longitudinal studies suggests that high levels of vitamin D may decrease MS risk. In the first, a cohort study comprising over 230,000 women, intake of 400 IU/day or more of vitamin D from supplements was found to be associated with a 40% lower risk of developing MS [3]. In the second study, based on a source population of several million young men and women, those individuals in the highest quintile of serum levels of 25(OH)D had a 60% lower risk of developing MS than those in the bottom quintile [4]. Because over 80% of young adults have suboptimal vitamin D levels, if vitamin D was truly protective, supplementation could prevent a large proportion of MS cases. This hypothesis should be tested in a large trial, either in the general population or among individuals at high risk.

Finally, although attributing to cigarette smoke one more adverse health effect may seem redundant, the specific relation between smoking and MS risk [2,5], and possibly MS progression, would provide a strong deterrent for children and sibling of MS patients, whose risk is already 20 to 30 folds higher than among individuals without a family history of MS.

In summary, many MS cases could probably be prevented. Evidence is sufficient to recommend abstinence from smoking, the planning and implementation of a large randomized trial to assess the effectiveness of vitamin D supplementation, and further research on EBV vaccines, drugs, and the mechanisms relating EBV infection to MS.

References:

*Invited Lecture
CNS inflammation in vivo. Data from these studies might lead to concepts of how alterations in EBV immunobiology could be targeted for MS therapy.

References:


*Invited Lecture

3* Role of human herpesviruses in multiple sclerosis

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A major focus of our research is to characterize the extent and distribution of ubiquitous herpesviruses such as the human herpesvirus 6 (HHV-6) in the pathogenesis of MS and other neurological disorders of the central nervous system [1–5]. Studies by a number of other groups have also examined the presence of HHV-6 serum DNA in MS patients. Overall the results from these studies have been supportive. In addition, longitudinal analysis of serum HHV-6 DNA demonstrated that there is a statistically greater likelihood of detecting HHV-6 DNA in the serum of an MS patient during an exacerbation than in remission. These studies further support a role for HHV-6 in the pathogenesis of MS by suggesting that the presence of serum HHV-6 DNA coincides with clinical worsening in a subset of patients [3]. We hypothesize that there may be multiple ‘triggers’ by which foreign antigens, including infectious agents, may be associated with immune attacks on the CNS. We propose that HHV-6 may be one such trigger and if so, the mechanism(s) by which this virus is associated with the pathogenesis of MS will be important to define.

As MS is a disease of the CNS characterized by inflammatory lesions in the brain and spinal cord clinical interventional strategies that inhibit access of these inflammatory cells to the CNS by interference with molecules involved in vascular adhesion (natalizumab) has been an attractive therapeutic target. While natalizumab was shown to be clinically effective in patients with relapsing-remitting MS in two phase III clinical trials it was unexpectedly associated with a JC polyomavirus progressive multifocal leukoencephalopathy (PML). One mechanism suggested to explain the relationship between natalizumab treatment and development of PML is that by blocking a4 integrin and thus decreasing lymphocyte trafficking to the brain, the normal immune surveillance in the brain was reduced, allowing the reactivation of latent viruses present in the nervous system. If impaired immune surveillance in the brain following natalizumab treatment is associated with JCV reactivation, there is no reason to believe, a priori, that such a mechanism would be specific for JCV and thus such impaired surveillance could result in the reactivation of other latent CNS viruses. Therefore, we asked whether HHV-6 might also be reactivated in MS patients treated with natalizumab [4]. Recently, we have reported that HHV-6 was reactivated in MS patients receiving natalizumab therapy, as evidenced by the detection of viral DNA in the CSF of a subset of natalizumab-treated patients but not in samples from controls including untreated MS patients and patients with other neurologic disease [4]. Cell-free HHV-6 DNA is suggestive of active HHV-6 infection. The detection of HHV-6 in natalizumab-treated MS patients was further supported by serologic findings demonstrating statistically higher levels of anti-HHV-6 IgG in serum from MS patients undergoing natalizumab therapy compared to controls. Natalizumab treated MS patients had significantly higher levels of serum HHV-6 IgG than control, untreated MS patients. Increased antibodies to HHV-6 could represent an immune response associated with a more recent exposure to this virus and would be consistent with the hypothesis that natalizumab treatment may be linked with viral reactivation.

We emphasize that only through well-controlled interventional clinical trials with effective and safe antivirals can a causal role be made for any infectious agent in MS. Towards this goal, we continue to investigate the effect of anti-herpesvirus compounds in HHV-6 infected glial cells to ascertain which compounds would be best suited for a clinical trial in MS.
Remote EBV, CMV, and HSV-1 and -2 infection and DRB1*1501/1503 status in children with pediatric-onset multiple sclerosis

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Background: EBV, but not other viruses, appears to be associated with increased susceptibility to pediatric-onset (PO) multiple sclerosis (MS). HLA-DRB1*1501/1503 is the main genetic risk factor in adult MS in white non-Hispanics and African Americans. One report has suggested that this haplotype increases susceptibility to POMS similarly to adult-onset MS. Objectives: To determine whether the rates of remote infection with EBV, CMV, and HSV-1 and -2 in children with POMS are affected by DRB1*1501/1503 status. Methods: Samples were collected from patients with CIS or POMS and controls seen at the six Regional Pediatric MS Clinics sponsored by the National Multiple Sclerosis Society. EBV, CMV, and HSV-1 and -2 IgG seroconversion rates and quantitative responses were measured with normalized ELISAs. Antibody responses against EBNA-1 were detected by standardized ELISA. Results: We identified 117 patients with CIS/POMS (51% white non-Hispanic, mean age at disease onset 12.8±3.4 years, mean age at 15±3.5 years) and 17 pediatric controls (77% white non-Hispanic) for whom MS was excluded. The proportion of individuals positive for HLA DRB1*1501/1503 tended to be higher in POMS than pediatric controls (43% vs. 29.4%; OR=1.85, 95% CI 0.63, 5.38, p=0.27), especially in white non-Hispanics and African Americans (48.8% vs. 30%; OR=2.2, 95% CI 0.54, 8.95, p=0.28). The multivariate analyses showed an independent effect of VCA and DRB1*1501/1503 (respectively, OR=3.73, 95% CI 0.78, 17.7, p=0.09; OR=2.60, 95% CI 0.56, 11.93, p=0.21), and EBNA-1 and DRB1*1501/1503 (respectively, OR=4.65, 95% CI 1.01, 21.3, p=0.04; OR=2.87, 95% CI 0.61, 13.51, p=0.18). Conclusions: HLA-DRB1*1501/1503 tends to be more frequent in POMS than controls. These preliminary findings suggest an independent effect of EBNA-1 and VCA, and HLA-DRB1*1501/1503 in POMS susceptibility. Whether interactions exist between EBV and HLA-DRB1*1501/1503 remains to be determined in a larger prospective cohort.

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Multiple sclerosis patients make antibodies against a unique sequence of EBNA-1 that cross reacts with myelin basic protein

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Background: Strong statistical and temporal relationships between multiple sclerosis (MS) and Epstein-Barr virus (EBV) suggest a role for this virus in the disease. Objectives: This study identifies common MS EBV humoral targets and assesses the capacity of these responses to bind myelin and/or recapitulate features of clinical disease. Methods: Serologic reactivity of adult MS patient and control sera toward common herpes viral antigens (EBV, VCA, CMV, HSV1, HSV2) are treated by ELISA and stet solid phase epitope mapping of unique EBNA1 octapeptides. Common antigenic targets were confirmed and affinity purified anti-peptide responses were tested for binding with myelin basic protein. Inbred mice were immunized with common peptide epitopes and clinical/serologic responses measured. Results: MS patient sera demonstrate higher levels of antibody titers against EBNA1 peptides compared to controls but their titers to other common Herpes viruses (CMV, HSV1 and HSV2), as well as to another common EBV protein, EBV-VCA, were not significantly increased. In order to further characterize this unusual anti-EBNA1 response, we assessed reactivity to individual EBNA1 peptides. Interestingly, MS patients produce antibodies primarily to two unique peptide regions of the EBNA1 protein, epitopes spanning amino acids 143–153 (EBNA72) and 411–427 (EBNA 206), that are not significantly bound by antibodies against EBNA-1. EBNA-1 206 were affinity purified from MS patient sera and were found to cross-react with myelin basic protein (MBP). Furthermore, specific strains of mice immunized with EBNA 206 developed antibodies to MBP as well as clinical symptoms of neurological disease and MRI changes. Conclusions: MS patients produce a unique and fundamentally altered immune response to EBNA1. Select parts of this atypical response may cross-react with myelin basic protein and produce clinical features in animal models.

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Session 2: Basic and Clinical Issues in Multiple Sclerosis Research

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Direct quantification of myelin changes in multiple sclerosis

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Background: Abnormality and changes associated with myelin membranes in the central nervous system play a key role in the pathogenesis of multiple sclerosis and related neurodegenerative disorders. Thus, direct assessment of myelin content in vivo has been an important goal in protection and repair of myelin damage in multiple sclerosis. Objectives: To meet this challenge, a new imaging technique based on positron emission tomography (PET) has been developed that allows for direct quantification of myelin changes in vivo. Methods: For PET imaging studies, a myelin-imaging agent (E,E)-1,4-(4'-aminostyryl-4'-methylaminostyryl)-2-dimethoxy-benzene, termed CIC, has been developed that readily enters the brain and selectively binds to myelin membranes. Here we report the radiosynthesis of [C-11]CIC and its use as a myelin imaging agent for in vivo imaging of myelination. We demonstrate, for the first time, that myelin changes can be directly quantified in the brain in animal models of focal demyelination. Results: In vitro staining showed that CIC selectively stains intact myelinated regions in wild-type mouse brain and lack of CIC staining was observed in brain regions of demyelination. Ex vivo tissue staining demonstrated that CIC readily enters the brain and delineates demyelinating lesions. MicroPET study in a rat model of demyelination showed [C-11]CIC accumulation is proportional to the level of myelination in intact brain regions compared to that in regions of demyelination. Conclusions: A [C-11]CIC-PET has been developed as a direct imaging marker of myelination for MS studies.

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Diffusion tensor imaging predicts severe brain tissue injury in acute MS lesions

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Background: MR DTI quantifies tissue water diffusion, and can serve as a surrogate of tissue integrity. Chronic black holes are indicative of significant tissue destruction, with histopathological correlation to axonal injury and marked demyelination. Gadolinium enhancing (GdE) lesions are associated with pathologic heterogeneity and variable tissue injury. A minority of GdE lesions will become persistent black holes (PBH), defined by a T1 hypointensity 12 months after enhancement. Objectives: Determine whether DTI within an acute GdE lesion can predict those that will become PBH. Methods: Twenty-one subjects underwent 6 monthly MRIs, followed by a 12 month MRI to categorize PBHs. The DTI data were collected in 6 directions at 2.5×2.5×2 mm resolution at 1.5T. After MRIs co-registration, a region of interest (ROI) was drawn to include each GdE lesion, along with a contralateral control ROI. DTI parameters were analyzed by linear mixed repeated measures models. Results: Ninety-five enhancing lesions yielded 27 transient black holes and 30 PBHs. All diffusion parameters, regardless of PBH outcome, became significantly altered with Gd enhancement: Radial diffusivity increased 38%, fractional anisotropy (FA) decreased 34%, mean diffusivity (MD) increased 21%, axial diffusivity increased 6%. All diffusion parameters distinguished GdE lesions that became a PBH vs. a transient black hole (units of μm²/ms): radial diffusivity 1.57 vs. 1.27, MD 1.09 vs. 0.95, axial diffusivity 1.38 vs. 1.27, FA 0.23 vs. 0.28, respectively. A 40% elevation in radial diffusivity during enhancement was associated with a 5-fold increased risk for PBH. Radial diffusivity differentiated PBH outcome 2 months prior to enhancement. Conclusions: DTI becomes abnormal at the time of GdE, or even prior, and may help to distinguish acute lesions associated with the most tissue destruction. An elevated radial diffusivity during enhancement is associated with an increased risk of evolution to a PBH.

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Flatter diurnal cortisol slope is associated with regional hippocampal atrophy and depressive symptoms in multiple sclerosis

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Background: Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and hippocampal atrophy are thought to play a role in the pathogenesis of major depression. Interestingly, HPA axis hyperactivity has also been reported in patients with multiple sclerosis (MS), a patient population with a 25–50% prevalence of depression. Objectives: To determine the association of cortisol levels, hippocampal atrophy and depressive symptoms in relapsing-remitting (RR) MS. Methods: Seventeen RRMS patients (mean age 38.3, mean EDSS 2.1, mean disease duration 8.2 years) and eight matched healthy controls were enrolled. Diurnal salivary cortisol was assessed at awakening, 4 pm and 9 pm on two consecutive days. We obtained high resolution T2-weighted MRI scans of the hippocampus for subregional measurements (CA1, CA23/DG, Subiculum, Entorhinal Cortex) and T1-weighted scans for global atrophy assessment. Patients underwent neurological examination and neuropsychological testing and completed the Beck Depression Inventory (BDI-II). Results: While there were no differences in morning cortisol levels, MS patients showed higher evening levels compared to controls, resulting in a significantly flatter cortisol decline over the diurnal cycle (p=0.04). Within the MS group, flatter cortisol slopes were associated with smaller volumes in the hippocampus (r=-0.63, p=0.01) and most strongly with the CA23/DG subregion (r=-0.71, p=0.001). In addition, flatter cortisol slopes were associated with depressive symptoms (r=0.53, p=0.04) in the MS group. Cortisol slope was not significantly correlated with global atrophy on MRI or disability as measured by EDSS. Conclusions: These results suggest that subtle alterations in diurnal cortisol secretion are associated with regional atrophy in the hippocampus and are linked to depressive symptoms in MS independent of global atrophy or disability. This supports a role of HPA axis dysregulation for depressive symptomatology in MS.

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Combination therapy of resveratrol and retinoic acid suppresses development of experimental autoimmune encephalomyelitis by reciprocal differentiation of Th17 cells and regulatory T cells

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Background: Resveratrol (trans-3,5,4’-trihydroxystilbene; RES), found in red grapes, possesses anticancer, antioxidant, and anti-inflammatory properties. Retinoic acid (RA), a derivative of Vitamin A, participates in differentiation of Th17 cells and regulatory T cells (Tregs). Th17 cells are inflammatory in nature and play important role in the development of autoimmune diseases including multiple sclerosis (MS) whereas Tregs are immunosuppressive and block the development of autoimmune diseases. Objectives: In the current study, we investigated the use of resveratrol in combination with RA as an effective mode of treatment for MS. Methods: Using an animal model of MS, we evaluated the efficacy of resveratrol alone or in combination with RA for the treatment of murine experimental autoimmune encephalomyelitis (EAE). Results: When RES was used alone, we observed a decrease in EAE symptoms but when used in combination with RA, the effects of RES were more pronounced. Upon examination of Th17 and Tregs, we observed significant downregulation in generation of Th17 cells and upregulation of Tregs in mice with EAE and treated with RES and RA when compared to single treatment with RES or RA. In vitro studies on the mechanism of action revealed that T cells in the presence of RES and RA differentiated more into Tregs and less into Th17 cells when compared to RES or RA alone treatments. Also, RES+RA triggered high levels of apoptosis in activated T cells when compared to unactivated T cells. Conclusions: Data from the present study demonstrate for the first time the ability of resveratrol to trigger reciprocal differentiation of Th17 cells and Tregs in vitro as well as in vivo and thus the combined treatment of RES and RA may have potential in clinics to treat autoimmune diseases including MS.

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Pediatric multiple sclerosis before puberty: a distinct CSF inflammatory profile

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Background: The clinical and MRI presentation differs between earlier-onset (EO) and later-onset pediatric multiple sclerosis (LOPMS). The effect of age on the CSF inflammatory profile is unknown in pediatric MS. Objectives: To compare the CSF cellular and IgG profiles between EOPMS and LOPMS. Methods: We queried the databases of 4 Pediatric MS Network Centers of Excellence for EOPMS (age of onset <11 years) and LOPMS patients (11–18 years) with MS or clinically isolated syndrome, who underwent CSF analysis within the first 3 months of disease onset. We compared CSF white blood cell (WBC) count including differential, CSF restricted IgG oligoclonal bands, and IgG index between EOPMS and LOPMS patients. Results: We identified 33 EOPMS (mean age of onset = 7.4±2.63 years, 57.6% females) and 49 LOPMS patients (15.26±1.56 years, 61.2% females). Although WBCs were not significantly different in EOPMS and LOPMS (31.54±67.17 versus 14.66±27.63/mm³, p=0.23), EOPMS patients had higher neutrophil % than LOPMS (20%±25% versus 1±2%, p=0.040). In EOPMS, fewer patients had ≥2 CSF specific oligoclonal bands (24% versus 49% of patients, p=0.037) or an elevated the IgG index (15% versus 47% of patients, p=0.0040) than in LOPMS. Conclusions: Age modifies the CSF profile at onset in pediatric MS. This may mislead diagnosis in younger patients. Our findings argue against a central role of oligoclonal activation of IgG producing B cells in the central nervous system during very early stages of EOPMS pathogenesis.

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Session 3: Vitamin D and MS

Vitamin D and the immune system: from pathological problem to normal physiology

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Interaction between vitamin D and the immune system was first recognized over twenty five years when high levels of the active form of vitamin D, calcitriol, were reported in serum from patients with the granulomatous disease sarcoidosis. Subsequent studies showed that the source of elevated calcitriol in these patients is the macrophages that characterize sarcoid granulomata [1]. This coupled with the detection of receptors for calcitriol (vitamin D receptor, VDR) in activated T lymphocytes (T-cells) [2] suggested that vitamin D could act as a paracrine regulator of immune responses. For many years after this, interaction between vitamin D and the immune system was thought to be restricted to pathological scenarios such as sarcoidosis and other inflammatory disorders. However, in recent years it has become clear that vitamin D may play a role in normal innate and adaptive immune activity [3]. Both macrophages [4] and dendritic cells [5] express the enzyme CYP27B1 which catalyzes synthesis of calcitriol from inactive 25-hydroxyvitamin D (25D). In macrophages local conversion of 25D to calcitriol fuels synthesis of cathelicidin a potent antimicrobial protein. Metabolism of 25D in dendritic cells also attenuates innate immunity but in this case the effect occurs at the level of antigen presentation with local synthesis of calcitriol promoting a more tolerogenic dendritic cell phenotype. In this way vitamin D acts to both promote innate immunity in the form of bacterial killing, whilst suppressing adaptive immunity by modulating T-cell function. Recent studies have expanded on these observations by characterizing the mechanisms by which calcitriol regulates cathelicidin [6]. Moreover, it is now clear that calcitriol can affect adaptive immunity through direct effects on T-cells and B-cells. In the case of the former, it appears that key responses to calcitriol are its ability to induce regulatory T-cells (Tregs) whilst suppressing inflammatory Th17 cells [7]. A link between vitamin D and immunity has been further strengthened by recognition that variations in vitamin D (i.e., 25D) status can have profound effects on specific immune responses. Low serum 25D has
been shown to support impaired cathelicidin innate immunity, whilst vitamin D supplementation in vivo does the opposite [8]. Furthermore, it is now clear that optimal serum levels of vitamin D are much higher than previously thought, so that circulating levels of 25D less than 75 nM are currently considered to represent vitamin D ‘insufficiency’. By these parameters a considerable proportion of the US population are likely to have sub-optimal vitamin D status. The questions now being addressed include: 1) what are the immune consequences of vitamin D insufficiency? 2) what are the benefits of vitamin D supplementation? 3) what are the best strategies for implementing vitamin D supplementation? These and other issues will be discussed as part of the symposium, with particular emphasis on how vitamin D deficiency may influence autoimmunity and the merits of vitamin D supplementation as a potential strategy for the treatment and/or prevention of autoimmune disease.

References:

12* Vitamin D in multiple sclerosis and experimental autoimmune encephalomyelitis

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Multiple sclerosis (MS) is a genetically and immunologically complex neurodegenerative disease whose etiology and pathogenesis are poorly understood. Sunlight exposure correlates inversely with MS prevalence indicating that this environmental factor influences MS risk at a population level and may hold the key to preventing ~80% of MS cases [1,2]. The hormone 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3) is unique in that its synthesis requires sunlight exposure [3]. Based on the sunlight-vitamin D relationship and the discovery of vitamin D receptors (VDR) in T lymphocytes, we first proposed that 1,25-(OH)2D3 might regulate the autoimmune T cell responses that are pathogenic in MS [4]. This vitamin D-MS hypothesis has gained significant momentum with data showing that serum 25-hydroxyvitamin D3 levels correlate inversely with MS risk [1,5], MS relapses [6], and MS disability [7,8]. A genetic study showed a strong link between mutations in the Cyp27b1 gene encoding the 25-hydroxyvitamin D3-1α-hydroxylase that produces 1,25-(OH)2D3 and MS in patients with vitamin D-dependent rickets type I [9]. Another study established a genetic link between HLA class II alleles and the vitamin D receptor (VDR) gene in MS patients [10]. A new genetic study confirmed this association, and showed VDR recruitment to a VDR responsive element in the HLA-DRB1*15 promoter implying vitamin D control of this allele [11]. A clinical trial reported that 1,25-(OH)2D3 treatments decreased MS relapses and delayed MS progression [12]. Together, these human studies provide compelling support for the vitamin D-MS hypothesis.

Our studies in experimental autoimmune encephalomyelitis (EAE), an animal model of MS, have also strongly supported the vitamin D-MS hypothesis. Administering 1,25-(OH)2D3 to rodents completely inhibited EAE induction and progression [13]. Additional genetic, nutritional, and biological studies have begun to elucidate the mechanisms. In EAE, the protective functions of the precursor vitamin D2 were female-specific [14] and estradiol dependent (Nashold et al., submitted). In contrast, the active hormone 1,25-(OH)2D3 performed EAE protective functions in male and female mice. Protection depend on regulatory lymphocytes and the cytokine interleukin-10 [15], and involved the activation-induced death of pathogenic T lymphocytes, the cessation of inflammatory cell recruitment, and the enhanced survival of CNS-resident cells [16]. These protective functions required VDR expression in CD4+ T cells (Mayne et al., submitted). In summary, new research on vitamin D, EAE, and MS has supported the view that 1,25-(OH)2D3 is needed to control neural antigen specific T cell-mediated autoimmune responses, revealed mechanisms whereby such control is exerted, and suggested novel approaches to prevent and treat MS.

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References:
Lower vitamin D status at first clinical diagnosis of central nervous system demyelination compared to matched controls

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Background: Rising MS incidence rates and positive latitudinal gradients of MS prevalence suggest a causative role for environmental factor(s). Previous work indicates that higher levels of sun exposure and/or vitamin D may decrease MS risk. Objectives: To examine vitamin D status (assessed by serum 25(OH)D) at first clinical diagnosis of central nervous system demyelination (FCD), compared to unaffected community controls. Methods: The Australian Multicentre Study of Environment and Immune Function (the Ausimmune Study) recruited incident FCD cases and community controls matched on age (18–59 years), sex and study region, between 1 Nov 2003 and 31 Dec 2006 in four Australian centres spanning a latitude range of 27°S to 43°S. 25(OH)D levels were measured by liquid chromatography mass spectrometry and results deseaseasonalised by taking account of blood collection day and month. Results: Analyses draw on a subsample of 259 eligible case participants with FCD and 454 matched controls (this is a majority of the study sample; 25(OH)D levels on most recent cases affected community controls.

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Session 4: Gene-Environment Interactions and MS Susceptibility

14* Gene-environment interactions in diabetes and what it may mean for multiple sclerosis


Supported by: National Multiple Sclerosis Society, National Health and Medical Research Council of Australia, The Royal Australian College of Physicians, Multiple Sclerosis Research Australia.

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14* Gene-environment interactions in diabetes and what it may mean for multiple sclerosis

(e.g., HLA, vitamin D, viruses, etc.), much can be learned by comparing the two diseases.

References:


15* Evidence for an increase in incidence in multiple sclerosis in the female population

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There has long been uncertainty about whether the risk of multiple sclerosis (MS) is truly increasing or only appears to be so because of improved diagnostic techniques and access to specialized health care. In addition, the gender (female:male) ratio in MS has been the subject of speculation since the late 1800s when it was initially believed that there was a male excess among patients and in the 1940s when equality among genders was cited. It was only toward the end of the 1950s that the female preponderance in MS was first recognized and this has been increasing to date (reviewed in [3]). This female preponderance also holds for the pediatric MS population, especially those aged 10–16 years [2].

Recently, the gender ratio has objectively shown that the risk of MS is truly increasing in females but not in males [1]. This has been shown in several North American populations but is still to be documented in migrant populations [3]. MS gender ratio in immigrants to Canada is increasing but variable by region of origin and age at migration [3]. The findings highlight the importance of gender-specific environmental effect(s). The timing of these influences must be at least partially in early life, but appears also to act later in life suggestive of two separable influences of the environment on risk.

Recent data has also shown that gender can influence the transmission of MS genetic risk alleles and that empiric recurrence risk data are higher for sisters of female index cases than male index cases [4]. This increase in MS among females also highlights concerns about the effect of MS therapies (disease modifying, symptom-specific, relapse-specific) and reproduction.

References:


*Invited Lecture
Risk alleles and Epstein-Barr virus in susceptibility to multiple sclerosis
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Multiple sclerosis (MS) now has robust evidence for both genetic and environmental risk factors that increase an individual’s susceptibility for developing inflammatory demyelination of the central nervous system. We have begun to integrate these risk factors to explore their possible redundancy or interaction in an effort to determine the most informative variables to include in a diagnostic algorithm. For example, individuals with high levels of antibodies to the Epstein Barr Virus (EBV) nuclear antigen 1 (EBNA-1) have an increased risk of developing multiple sclerosis (MS), but this association could be confounded by genetic susceptibility conferred by HLA DRB1*1501 since HLA DRB1 is a co-receptor for EBV. We conducted a nested case-control study including 148 women with MS (18 with blood collected before disease onset) and 296 age-matched healthy women that determined that the main effects of the HLA DRB1*1501 allele (DR15) and anti-Epstein Barr Virus (EBV) antibody titers on MS susceptibility are independent [1].

The relative risk of MS among DR15 positive women with elevated (>1:320) anti-EBNA-1 titers was nine fold higher than that of DR15 negative women with low (<1:80) anti-EBNA-1 titers. These results are consistent with those of a similar study in a Swedish population [2]. Nonetheless, in both studies, we see modest evidence of interaction between these two risk factors, and other MS susceptibility alleles may also have an effect on anti-EBV antibody titers [3].

Given the large increase in risk noted between the subjects in the highest and lowest categories of risk, we have extended our assessment to the 16 known MS susceptibility loci that we have catalogued at the conclusion of our recent meta-analysis of whole genome association scans [4]. We have explored whether an aggregate measure of genetic susceptibility to MS has potential for use in a clinical setting as part of diagnostic or prognostic algorithms. To implement this, we have developed a Genetic Risk Score (GRS) measure that takes into account each individual’s allele repertoire at the 16 MS susceptibility loci and weighs the contribution of each locus by the odds ratio observed for the risk allele in that locus in the replication study of our meta-analysis. We then derived a C-statistic to assess the success of our measure in differentiating MS and CIS subjects from healthy subjects in novel subject samples from the Nurses Health Study (NHS) (n=180 subjects) and from therapeutic trials (n=650 subjects with MS/CIS). We also assessed the independent roles of the GRS and two environmental risk factors (smoking and EBV titers) in this predictive model. The C statistic of the GRS for prediction of MS is 0.636 in the NHS data and 0.637 in the pooled CIS and MS subjects of the therapeutic trials. Environmental variables slightly enhance prediction in the NHS data (C=0.684). CIS and MS subjects do not have a significant difference in the distribution of the GRS.

Currently, the predictive power of this GRS for diagnosis of CIS or MS is therefore modest but consistent across two novel, independent collections of subjects. The approach therefore appears to be valid and is enhanced by the addition of environmental susceptibility factors. The contributions of genetic and environmental risk factors appear to be mostly distinct, but it is likely that modest evidence of interaction will emerge from the assessment of larger cohorts.

References:
Disease Modifying Therapy

P1
Effect of alemtuzumab on quality of life in patients with relapsing-remitting multiple sclerosis
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Background: Alemtuzumab, a monoclonal antibody targeting CD52 antigen on lymphocytes, was significantly more effective than interferon beta-1a (IFN-β-1a) at reducing disability progression and relapse rates and improving preexisting disability in a randomized, open-label, rater-blinded, phase 2 study conducted in treatment-naïve patients with relapsing-remitting multiple sclerosis (RRMS) (CAMMS223). Alemtuzumab-related adverse events included infusion reactions, second-ary autoimmunity, and mild to moderate infections, predominantly of the upper respiratory tract. Given the negative impact of RRMS on physical and psychosocial functioning, optimal treatment should be defined by improved quality of life (QoL), alleviation of disease symptoms, and disability. Objectives: Assess the effects of alemtuzumab vs. IFN-β-1a on QoL in early, active, RRMS patients.

Methods: 334 RRMS patients were randomized 1:1:1 to IFN-β-1a (44 mcg SC 3×/week), 24 mg/day alemtuzumab, or 24 mg/day alemtuzumab (alemtuzumab was IV-administered during 2 or 3 brief annual cycles). Key entry criteria: baseline EDSS ≤3.0, ≥2 MS attacks within 2 years, and ≥1 enhancing lesion on MRI. QoL was measured semianu-

Poster Presentations

P2
Treatment of aggressive neuromyelitis optica with high-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation
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Background: Neuromyelitis optica (NMO), an inflammatory disorder of the central nervous system, is associated with auto-antibodies directed against aquaporin-4. It is treated with long-term immunosuppressive medications. High-dose immunosuppressive therapy and autologous hematopoietic stem cell transplantation (HDIT/AHSCT) may induce sustained remission in patients with autoimmune disease and may provide benefit to patients with NMO who are unresponsive to other therapies. Objectives: To evaluate HDIT/AHSCT in NMO.

Methods: Patients with NMO, failing treatment with ≥2 immunosuppressive therapies, with ≥2 relapses in the past five years, and with worsened disability by ≥ one point on the Expanded Disability Status Scale (EDSS) in the past five years are eligible. Stem cells are collected following the administration of rituximab, prednisone and G-CSF. HDIT is then administered including BCNU, VP-16, cytarabine, melphalan and anti-thymocyte globulin followed by AHSCT. Results: Case 1: A 19-year-old male had recurrent attacks of visual loss and myelopathy since age 8. He was diagnosed with NMO-IgG antibody-negative NMO at age 16. His exacerbations continued despite corticosteroids, plasma exchange, additional azathioprine and mycophenolate, and rituximab. She is currently undergoing HDIT/AHSCT without complications and has remained stable for five months. Case 2: A 51-year-old female with attacks of myelopathy, visual and brainstem symptoms since age 30 was treated for multiple sclerosis with corticosteroids, ACTH, azathioprine, three interferons, glatiramer acetate, mycophenolate and mitoxantrone. A longitudinal

P3
Alemtuzumab improves Expanded Disability Status Scale functional system scores better than interferon beta-1a in patients with relapsing-remitting multiple sclerosis
Edward J. Fox, for members of the CAMMS223 Study Group
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Background: Alemtuzumab (monoclonal antibody targeting CD52 antigen on lymphocytes) was more effective than interferon beta-1a (IFN-β-1a) at reducing disability progression, relapse rates and improving pre-existing disability in a randomized, open-label, rater-blinded, phase 2 study conducted in treatment-naïve patients with relapsing-remitting multiple sclerosis (RRMS) (CAMMS223). Alemtuzumab-related adverse events included infusion reactions, secondary autoimmunity, and predominantly mild to moderate infections. Changes in FS scales are important in earlier stages of MS, when disability is evident in areas other than ambulation. Objectives: Assess efficacy of alemtuzumab vs. IFN-β-1a on the 7 Expanded Disability Status Scale (EDSS) Functional System (FS) scores in patients with RRMS.

Methods: 334 patients were randomized 1:1:1 to IFN-β-1a (44 mcg SC 3×/week), 12 mg/day alemtuzumab, or 24 mg/day alemtuzumab (alemtuzumab was IV-administered during 2 or 3 brief annual cycles). Key entry criteria: baseline EDSS ≤3.0, ≥2 MS attacks within 2 years, and ≥1 enhancing lesion on MRI. EDSS assessed quarterly. Proportional odds analyses compared treatment groups for early (6 months), sustained effects (24, 36 months) on: number of improved FSs, and for each FS, proportion of patients that improved or were unchanged from baseline vs. worsened. Results: Alemtuzumab patients were more likely than IFN-β-1a patients to improve on more FSs at Month 6 (p<0.001 both groups), Month 24 (12 mg, p<0.07; 24 mg, p<0.0001), and Month 36 (12 mg, p=0.08; 24 mg, p<0.0001). Similarly, a greater proportion

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of alemtuzumab patients (12 mg and/or 24 mg) improved or remained unchanged from baseline vs. worsened on all but the visual FS scale at 6, 24, and/or 36 months. **Conclusions:** Consistent with positive effects on relapses and disability, alemtuzumab was associated with improvements on more FS scales than IFNβ-1a. All FSs except visual FS were more positively affected by alemtuzumab than IFNβ-1a. EDSS score improvement after alemtuzumab is driven by effects on diverse neurological functions.

**Disclosures:** E. Fox, on behalf of and as a member of the CAMMS223 International Study Group, presents the following disclosures: 1) Several members of the group have received compensation from Genzyme Corporation for participating in a Speaker's Bureau or acting in an advisory capacity; 2) Several members of the group received financial support for their MS research studies from Genzyme Corporation; 3) Several members of the group received compensation (including stock) as employees of Genzyme Corporation.

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**P4**

**Multiple sclerosis: natalizumab effects on cognitive function**

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**Background:** Natalizumab effects on cognition are not well described.

**Objectives:** Evaluate natalizumab effects on MS cognitive function using computerized cognitive assessment. **Methods:** 22 MS patients (age: 45.1±7.5 years; education: 15.4±2.5 years; 18 female; EDSS: 4.1±2.4; disease duration: <5 years N=1; 5-10 years N=10; >10 years N=8) were tested with a 30-minute computerized cognitive assessment battery for mild impairment (Mindstrokes, NeuroTrax Corp., NJ). Patients completed the battery twice (inter-test interval: 13.1±3.0 months), once prior to or early in natalizumab treatment (0-3 infusions) and again after extended treatment (>9 infusions). Repeated measures analysis of variance evaluated improvement in EDSS, age- and education-adjusted cognitive domain scores (memory, executive function, visual spatial, attention), and raw outcome parameters from individual tests (Go-NoGo, Stroop, Verbal Memory, Non-Verbal Memory, Visual Spatial Processing, Catch Game). Cohen’s d was computed as a measure of effect size. Given the directional hypothesis of improvement with treatment, p<0.05 (1-tailed) was considered significant. **Results:** Natalizumab-related improvement was identified for the attention domain score (p=0.02, d=0.39). Associated with this improvement was: greater Go-NoGo test (p=0.03, d=0.32) response time consistency, faster Stroop non-interference response time (color: p=0.03, d=0.44; meaning: p=0.004; d=0.43) and better overall performance (color: p=0.006, d=0.55; meaning: p=0.01; d=0.48). Greater accuracy was identified for the third (p=0.04, d=0.32) and fourth (p=0.03, d=0.45) immediate repetitions of the Verbal Memory test. Group means reflected small improvements in EDSS as well as memory and executive function domain scores, but these changes did not reach significance. **Conclusions:** Natalizumab treatment improvement appears evident mainly for attention/response time and learning of new verbal material. Computerized cognitive testing detected small treatment effects not apparent from EDSS alone. The obtained response time effects detected with computerized response time measures (milliseconds timescale) remain undetected with traditional paper-based methods. Larger studies evaluating natalizumab effects on cognition are required.

**Disclosures:** G. Doniger and E. Simon are employed by the NeuroTrax Corporation.

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**P5**

**Effects of natalizumab on Balo’s sclerosis**

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**Background:** Balo’s concentric sclerosis (BCS) is a rare demyelinating disorder usually considered a variant of multiple sclerosis (MS) with usually poor prognosis. However, its pathogenesis, and its therapeutic options remain unclear and controversial. **Objectives:** To explore the use of natalizumab, an alpha4 integrin monoclonal antibody, in the treatment of a refractory case of MS and BSC. **Methods:** Here we report a case of BCS in a 36-year-old Caucasian woman with a previous history of relapsing-remitting MS. She has had 3-4 severe relapses annually despite immunomodulatory agents and pulse steroids. MRI evaluation during the last severe relapse showed multiple “onion-like” enhancing lesions, typical for BCS, along with previous typical lesions of MS. She deteriorated neurologically despite methylprednisolone therapy (reaching EDSS of 7) and developed mania followed by severe depression, presumably secondary to the corticosteroids treatment. She was treated with natalizumab 300 mg IV every four weeks for more than 12 months. **Results:** Patient has had no clinical relapses since natalizumab therapy was initiated. Her physical disability improved significantly. Twelve months after first treatment her EDSS was 4. Her MRI evaluation at six months and 12 months showed absence of new or enhancing lesions and disappearance of some of the previous T2/FLAIR lesions. **Conclusions:** To our knowledge, this is the first case demonstrating a benefit of natalizumab in a case of Balo’s disease and co-existing with MS-like lesions.

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**Supported by:** No outside sources of funding reported.

**P6**

**Direct comparison of clinical effect of multiple sclerosis immunomodulating agents using a large US managed care database**

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**Background:** For over a decade the relative clinical benefit of marketed therapies for multiple sclerosis (MS) have been debated. This US managed care market outcomes analysis focuses on this issue. **Objectives:** To compare the relative clinical benefit of glatiramer acetate (GA) and the three beta interferons (IFN) on MS activity. **Methods:** From over 20 million deidentified enrollees in a major U.S. managed care insurance database, intent-to-treat (ITT) cohorts of MS patients prescribed GA or any of the three IFNs between 2001 and 2006 were identified. To ensure that all were in the database for the duration of the study, they had to show continuous insurance coverage for 6 months before to 24 months after they began taking the disease-modifying therapy. The data included demographic characteristics, impatient, outpatient and prescription drug services. MS activity was defined as either hospitalization with a primary MS diagnosis or an office visit with an MS diagnosis and a prescription for steroids within 7 days. **Results:** Enrollees came from physician practices in all regions of the U.S. There were no significant differences in use of immunomodulators across regions. Demographic profiles of the cohorts using the various immunomodulators were similar. Comparison of the 2-year risk of MS activity between the GA and IFNβ1b cohorts (n=842) was 5.3% vs. 13.5% p=0.0006; between the GA and IFNβ1a IM cohorts (n=1228) was 5.3% vs. 10.0% p=0.0034; and between the GA and IFNβ1a SC cohorts (n=845) was 5.9% vs. IFN 10.9% p=0.0305. **Conclusions:** In this recent comparison of immunomodulators for MS, the 2-year risk of MS activity was significantly lower for GA than for any of the three IFN’s. Nationwide outcomes came from community
P7

Immune reconstitution syndrome in multiple sclerosis patients following cessation of natalizumab therapy
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Background: Six cases of progressive multifocal leukoencephalopathy (PML) were reported in multiple sclerosis (MS) patients receiving natalizumab therapy. Evidence suggests a higher risk of developing PML with prolonged immunosuppression. In an attempt to restore immune surveillance and decrease the risk of PML, we instituted a 3-month drug holiday in our patients. Objectives: Understand the clinical consequences of natalizumab therapy discontinuation in patients with secondary-progressive (SP) MS and relapsing-remitting (RR) MS.

Methods: 32 patients (SP=8; RR=24) receiving natalizumab therapy for a period longer than 12 consecutive months received a 3-month drug holiday. Immune reconstitution syndrome (IRS) was prospectively defined as a clinical documented exacerbation with objective findings and/or the development of multiple new enhancing lesions on MRI.

Results: 61% of the patients (4 SP and 16 RR) reported a significant return of symptoms. Clinically defined exacerbation occurred in nine (RR) and two (SP) patients. The mean time period between the last infusion and the onset of exacerbation was shorter in relapsing patients (82.8 days versus 124). Spinal fluid analysis was done in 3 patients. This revealed a lymphocytic pleocytosis, with normal glucose, protein and cultures, and negative PCR for JC virus.

Conclusions: Our cohort of 33 consecutive patients experienced near complete cessation of MRI and clinical disease activity, as well as significant improvement in daily symptoms, during natalizumab therapy. Over 60% of the patients reported a significant return of MS related symptoms, especially fatigue, beginning 60 days into their drug holiday. One third of our patients developed an objectively defined exacerbation during their drug holiday, often associated with multiple cranial enhancing lesions and, in three cases tested, a CSF pleocytosis. This rapid return of inflammatory disease activity despite long term therapy in a significant proportion of patients shortly after cessation of VLA-4 blockade suggests a phenomenon akin to IRS.

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P8

An adaptive multiple ascending dose study using lymphocytes as a primary biomarker for early clinical evaluation of a S1P1 receptor modulator for treatment of multiple sclerosis
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Background: CS-0777 is a selective S1P1 receptor (S1P1R) modulator in clinical development for multiple sclerosis (MS). In a first-in-human (FIH) study in healthy subjects, single oral doses of CS-0777 produced a dose-dependent reduction in lymphocyte counts (20-80% at 0.1–2.5 mg) and B- and T-cell subsets. Due to the lymphocyte reduction potential, CS-0777 may have efficacy in MS or other autoimmune diseases. However, lymphocyte suppression may increase the risks of infections and, therefore, necessitates a conservative approach in early clinical studies. To address this concern, an adaptive dosing approach has been implemented to investigate the safety, tolerability, and pharmacokinetics/pharmacodynamics of CS-0777 when administered once weekly or biweekly for 12 weeks in MS patients. Objectives: The aim of the design is to implement individual dose adjustments to allow investigation of a broader dose range without pronounced and/or prolonged CD4 suppression (<100 cells/μL for 2 weeks or <200 cells/μL for 4 weeks). Methods: Individual dose adjustment will be done based on the model prediction of each subject’s pharmacodynamic response (CD4 cells) over a 12-week treatment period. An indirect response model developed with FIH data will be updated based on emerging pharmacodynamic data from MS subjects. Each subject’s pharmacodynamic response after the first dose of the default dosing regimen will be utilized to predict their response following multiple doses. Protocol defined default dosing regimens include 0.1, 0.3 and 0.6 mg administered once weekly or biweekly.

Results: This multiple ascending dose study in MS patients is currently ongoing in six US centers (ClinicalTrials.gov registration number NCT00616733). Conclusions: Results of the study will be used in the design and dose selection for a phase 2 study in relapsing-remitting MS patients.


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P9

Cost-effectiveness of disease-modifying therapy for multiple sclerosis: a population-based evaluation
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Background: Costly disease modifying therapies (DMTs; interferon beta-1a, beta-1b and glatiramer acetate) were introduced in the 1990s to reduce the frequency of relapses and to slow disease progression in patients with multiple sclerosis (MS). At the same time, these therapies are characterized by uncomfortable side effects and high costs.

Objectives: This study examines data from a 2000–2005 population-based survey of MS patients from the Sonya Slifka Study to evaluate the cost-effectiveness (CE) of DMTs in the US compared to no DMT.

Methods: We generated 10-year disease progression paths using first-order Markov models to estimate transitional probabilities and logistic models to estimate relapse rates based on published estimates of DMT treatment effects. To estimate costs, we used Medicare rates for reported utilization events. Outcomes were measured as gains in quality-adjusted life years (QALY) and relapse-free years, differences in the number of disease progressions (as measured by disability status), and gains in years spent in lower disability states. Monte Carlo (n=50) simulations, resampling (n=250) methods, and sensitivity analyses were conducted to evaluate uncertainty.

Results: Using DMT for 10 years resulted in significant health gains. The choice of the optimal therapy depends on the outcome, with interferons generating the highest QALY gain (0.187 QALY), fewer disease progressions (by 0.91), fewer years spent in higher disability states (by 0.81 year), and leading to more relapse-free years (by 1.12 year) compared to glatiramer acetate or no DMT. The CE of all DMTs exceeded $1,000,000/QALY, with glatiramer acetate being the most cost-ineffective ($5,209,524/QALY).

As the cost of DMT decreases, DMTs become more cost-effective.

Conclusions: The health insurance industry and policy makers should fund DMTs to improve health and quality of life.

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P11

CS-0777, a novel sphingosine 1-phosphate receptor modulator, ameliorates experimental autoimmune encephalomyelitis

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Background: CS-0777 is an oral prodrug, phosphorylated in vivo to an active compound, M-1, which acts as a S1P1 modulator. FTY720P (phosphorylated FTY720), another S1P1 modulator, sequesters peripheral lymphocytes in secondary lymphoid organs and has been shown to be effective in experimental autoimmune encephalomyelitis (EAE) and in patients with relapsing-remitting multiple sclerosis. Objectives: The current investigation aimed to determine both in vitro and in vivo activity of CS-0777/M-1, including effect on peripheral lymphocytes and EAE score in mice and rats.

Methods: The agonistic activity of M-1 to both human S1P1 and S1P3, was evaluated using a GTPγS binding assay. The effect on peripheral lymphocytes and EAE score in mice and rats.

Results: CS-0777 significantly decreased the cumulative EAE score (23.9, 5.6, 3.3 and 0.4 for the vehicle- and 0.1, 0.3 and 1 mg/kg CS-0777-treated groups, respectively) and delayed the onset of EAE at all doses. Furthermore, the rate of increase in the EAE score for CS-0777-administered groups was dose-dependent and more gradual relative to the vehicle-administered group. Similar results were obtained in the rat EAE model. Conclusions: CS-0777 has relatively low S1P1 agonist activity and potently ameliorates EAE.

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P12

Breakthrough disease in pediatric patients with multiple sclerosis: a pediatric network experience

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Results: Almost one-fourth of our cohort experienced breakthrough disease requiring therapeutic modifications. Although IFN dose escalation or therapeutic changes may be partially effective, a subset of patients may require more aggressive therapeutic interventions.

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P13

Use of plasmapheresis in pediatric demyelinating disease

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Background: While high dose steroid therapy, intravenous immune globulin (IVIG) and plasmapheresis (PLEX) have all been utilized in treatment of acute CNS demyelinating events, there are no controlled trials comparing these treatments in children and adolescents. There is limited experience in use of PLEX for pediatric demyelinating disease, including acute disseminated encephalomyelitis (ADEM), transverse myelitis (TM), optic neuritis (ON), neuromyelitis optica (NMO) and MS. Objectives: Assess indications and outcomes for plasmapheresis (PLEX) in pediatric CNS demyelinating disorders. Methods: Database of Pediatric MS Network Centers of Excellence were queried for patients treated with PLEX. Results: PLEX was used in 19 patients.
Epidemiology/Genetics

P14

Epilepsy in pediatric demyelinating diseases

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Background: In the pediatric population, seizures can occur as part of acute disseminated encephalomyelitis (ADEM) and other CNS demyelinating disorders such as MS, transverse myelitis (TM), optic neuritis (ON) or neuromyelitis optica (NMO) but it is unknown how many children later develop epilepsy. Objectives: Characterize children and adolescents with CNS demyelinating diseases who experience seizures during an initial demyelinating event (IDE) or who later develop epilepsy (defined as 2 or more unprovoked seizures). Methods: Databases from Pediatric MS Centers of Excellence were queried. Conclusions: ADEM (mean age 11.4±1.1 years; 73% female; 52% Caucasian, 26% African-American; 11% Hispanic; 11% other) for the following indications: MS relapse (10), NMO (4), 2 each of ADEM and TM and 1 with recurrent ON. Seventeen of 18 patients had failed prior treatments with high-dose methylprednisolone and 50% also failed treatment with IVIG. Patients underwent 2 to 13 PLEX treatments at a time (mean 5±0.6, median 5.0). Half the patients (n=9) improved in one or more functional systems following PLEX; the remainder experienced minimal or no improvement in their deficits. Only 2 (11%) returned to their normal baseline although some required additional rounds of PLEX (n=2) due to breakthrough disease. Two-thirds of patients continue to require disease modifying therapy, including interferon-beta or cycloxyan for MS or retuximab, azathioprine or mycophenolate or steroids for NMO. Three patients developed central line infections. Conclusions: PLEX benefited a sub-group of children and adolescents with severe demyelinating events unresponsive to high-dose methylprednisolone and/or IVIG but 50% did not appear to benefit from PLEX, perhaps because of the severity of their disease. For most part, PLEX was well tolerated although line infection remains a significant complication.

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P15

Serum 25-hydroxyvitamin D level is lower in black patients with multiple sclerosis

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Background: Vitamin D deficiency has been shown to be a risk factor for multiple sclerosis (MS). Higher serum vitamin D level was associated with lower incidence of MS and MS-related disability in women. Few studies have shown a more aggressive course with increased disability among black patients. Yet, knowledge of vitamin D deficiency by race is not known. Objectives: To evaluate serum vitamin D status in a cohort of patients with multiple sclerosis in southeastern Michigan. Methods: We prospectively obtained serum 25-hydroxy (OH) vitamin D levels in 65 patients with MS between January 2008–2009. 25 OH vitamin D level were obtained at routine clinic visits as an exploratory evaluate. Kruskall-Wallis and Fisher’s exact tests were used to assess the relationship of vitamin D level with sociodemographic variables. Results: 65 patients (30 black, 35 white) had serum 25OH vitamin D levels measured. 91% (59) had an insufficient level of vitamin D (<30 ng/ml). Black patients had lower level of 25OH vitamin D (median 9 vs. 12 ng; p<0.001). Similarly, lower levels of vitamin D were found in younger patients (p=0.006). There were no statistical significant seasonal differences in patients with vitamin D insufficiency. Conclusions: Vitamin D insufficiency is common in patients with MS, however a more profound vitamin D insufficiency was found in black patients and in younger patients. Further, larger studies are needed to confirm racial discrepancies and assess relationship with disease severity.

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P16

Meta-analysis of genome scans and replication identify rare and common multiple sclerosis susceptibility alleles at TNFRSF1A and other loci

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Background: Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system that has a genetic component. Here, we have extended the initial MS genome scan by performing a meta-analysis of two existing and a third, novel whole genome scan of subjects with MS. Objectives: Discover alleles associated with susceptibility for MS by performing a meta-analysis of three existing and a third, novel whole genome genome scan of subjects with MS. Methods: We used the MACH algorithm to impute a common panel of 2.56 million SNPs in each of the 2624 subjects with MS and 7220 control subjects that are considered in this study. We then applied a meta-analysis method and subsequently replicated a selection of its results in an additional 2215 subjects with MS and 2189 control subjects. We examined the functional consequences of these alleles in a set of RNA data from 241 subjects with MS using associated with an increased subsequent risk of epilepsy. Prospectively studies are needed to identify risk factors for developing intractable epilepsy in this population.

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a quantitative trait analysis. Results: We report the discovery and validation of new MS susceptibility loci at TNFRSF1A (P=2.0×10^{-12}), ICSBP1/IRF8 (P=7.6×10^{-16}), and CD6 (P=8.6×10^{-16}). Both rare and common TNFRSF1A alleles demonstrate association with MS and affect gene function. In addition, we demonstrate that the susceptibility allele of ICSBP1/IRF8, a transcription factor, is associated with higher RNA expression of one of its known target genes, TLR4, a molecule that may be involved in breaking tolerance to auto-antigen. This allele is also correlated with broader changes in gene expression: the susceptibility variant correlates with higher expression of interferon-response pathway genes. Conclusions: With the associations to genes of the TNF and the interferon pathways found in this study, we implicate dysregulation of the innate immune system in the onset of MS, which is consistent with its known immunopathology and observations of disease exacerbation with anti-TNFα treatment.

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P17
Epidemiology of multiple sclerosis in Mazandaran, Iran, 2007
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Background: Despite epidemiologic similarity of multiple sclerosis (MS) worldwide, its prevalence shows considerable variability. Accord-
ing to Kurtzke, Iran is considered to have a low prevalence. Objectives: In this study we wanted to estimate the period prevalence and in-
dicate epidemiologic aspects of MS in Mazandaran province, in northern Iran. Methods: A cross-sectional case register study was conducted in 2007 on all definite MS patients who were alive and resident within Mazandaran as well as being a member of the Mazan-
daran MS Society. 582 definite MS patients (161 men and 421 women) have been identified. The disease was confirmed using clinical in-
formation and MRI findings by a neurologist and radiologist. The patients were evaluated by interview and a questionnaire to record demo-
graphic and case-related information. According to the national cen-
tral reports, the population of Mazandaran was 2,893,087 (male: 1,447,978 and female: 1,445,109). Results: The mean (SD) age of the participants was 34.3 (9.4) years. The MS period prevalence was 20.1 per 100,000 [95% confidence interval (CI) 18.7–22.1], with a higher rate in women than men [29.1 (95% CI: 27.9–30.3) for women and 11.1 (95% CI: 9.9–12.3) for men]. The mean (SD) age of disease onset was 26.9 (8.3) years and mean (SD) disease duration was 7.4 (5.8) years. The female/male ratio was 2.6 and MS rates were highest among 3rd decade. Visual and sensory disturbances were the most common initial presentations with prevalence of 40.1% (95% CI: 38.5–42.9) and 14.2% (95% CI: 32.8–36.1), respectively. Only 5.3% of cases reported MS disease in first or second degree relatives. Conclusions: Mazan-
daran is in high medium MS prevalence area. This is in clear contrast with the background hypothesis, but other epidemiologic indices were almost pursuant previous information. Transmission and genetic pat-
terns of MS were unclear and we need more studies.

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P18
Clinical patterns of multiple sclerosis among Hispanics living in Southern California suggest an earlier onset of disease
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Background: Studies of the epidemiology of multiple sclerosis (MS) among Hispanics are very limited and is made even more difficult given their presumed different genetic admixture and environmental exposures, as compared to non-Hispanic Caucasians. Objectives: Describing the phenotypic expression of MS in a large population of Hispanic patients with well defined demographic data may enable us to identify those factors that correlate with the development of MS, presentation of disease and level of disability in this population. Methods: A retrospective analysis of clinical measures, coupled with collection of thorough demographic data through patient interview, of a large cohort of Hispanic patients enrolled in two MS clinics served by the Department of Neurology at USC. Results: A preliminary analysis of 126 Hispanic patients was recently completed. The female to male was 2.1 ratio with approximately 86% of patients following a relapsing remitting pattern. The most common presenting signs of disease included optic neuritis and sensory disturbance with a mean age of presentation distinctly earlier than that reported in many other epidemiological studies. Disease progression however appears to be slow; of those patients with MS for more than 10 years only half had an EDSS of greater than 6. Conclusions: Preliminary analyses suggest that the initial expression of MS in Hispanics is earlier in onset and has features suggestive of Asian MS. In contrast, disease progression has more similarity to classical MS. Thus we could hypothesize that the European and Asian genetic admixture may influence disease phe-
notype in this population. Studies assessing the correlates of genetic heterogeneity and environmental exposure to disease phenotype are currently underway.

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P19
Baseline characteristics in a real-world MS study (ROBUST) com-
pared to the BEYOND trial
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Background: A US prospective, multi-center, observational study (ROBUST) evaluated outcomes reported from multiple sclerosis (MS) patients and their physicians via web-based tool. BEYOND is a recently completed Phase III trial in MS. Objectives: To compare baseline data between the ROBUST observational study and the BEYOND clinical trial. Methods: Descriptive statistics were generated for demographic and baseline variables in ROBUST (n=226), and the results are compared to baseline results of F subjects in BEYOND (n=532). Results: Compared to the U.S. BEYOND population, ROBUST is more female (80% vs. 74%); more racially diverse with smaller per-
centages of Asian and mixed race, albeit a larger percentage of white (87% vs. 81%; p=0.477); older (mean age 42.0 vs. 38.9 years, p<0.0001), with more patients above 50 years (22% vs. 11%; p=0.0022 overall), yet slightly younger at onset (33.7 vs. 35.1 years, p=0.0886). Disease duration was similar between the two populations (4.8 vs. 4.4 years; p=0.4910), as were mean EDSS scores (2.5 vs. 2.4). ROBUST had a wider range of EDSS vs. BEYOND: EDSS≤5% vs. 14%; 1.5 to 3: 48% vs. 62%; 3.5 to 5: 17% vs. 24%; EDSS>5: 10% vs. <0.1%, respectively (overall p<0.0001) and had 8% EDSS=vs. excluded EDSS>5.5. ROBUST had
20% (vs. 0%) without relapses in the past year; but fewer with two relapses (17% vs. 39%); and similar percentages with only one relapse (55% vs. 54%) and with three or more relapses (8% vs. 7%) (overall p<0.0001). In addition, ROBUST had 31% who were diagnosed with relapse at baseline. Conclusions: The broader range of baseline characteristics and EDSS scores in a real-world observational study constitute a more heterogeneous population in terms of disease and demographic characteristics than those seen in controlled clinical trials such as documented in BEYOND.

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P20
Epidemiology and current treatment trends of multiple sclerosis in Pakistan
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Background: Multiple sclerosis (MS) is a complex demyelinating disorder. Limited data is available regarding epidemiology as well as kind of practices regarding MS treatment in different parts of Pakistan

Objectives: Aim of this study was to describe epidemiology of multiple sclerosis (MS) and treatment trends of the disease from different cities of Pakistan.

Methods: This was a cross-sectional study conducted over a period of 12 months. We collected information regarding newly diagnosed cases of MS, MS subtype, frequency of visits to neurologists and type of therapy initiated. We send standard survey questionnaires to all major cities in Pakistan. We analyzed the received data using SPSS.

Results: We received reply from thirty three neurologists from seven major cities of Pakistan. There were 245 newly diagnosed cases of MS during one year period (July 2004 till June 2005). We found 40% (n=98) had relapsing remitting MS, 30% (n=74) had secondary progressive MS, 20% (n=49) had primary progressive MS and 10% (n=24) had benign course of the disease. Only 45% (n=110) patients visited there neurologists >5 times per year, rest of the patients visited there neurologists between 2-4 times. Majority of the neurologists 82% advised IV methylprednisolone as 1st line-therapy for MS. 82% advised IV methylprednisolone and interferon, at the time of diagnosis. Total of 25% (n=63) patients received Interferon therapy.

Conclusions: We conclude that frequency of newly diagnosed cases is less than the Western World, and awareness regarding the disease resulted in less number of patient visits to neurologists. Treatment trends are comparable to western population. We speculate that infrequent use of interferon would be linked to socioeconomic status of the patients. We feel low frequency of MS may require further study.

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P21
The influence of cigarette smoking on brain atrophy in relapsing multiple sclerosis
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Background: Cigarette smoking reduces susceptibility to Parkinson’s disease, a predominantly neurodegenerative disorder, but likely increases susceptibility to multiple sclerosis (MS).

Objectives: To determine if cigarette smoking influences the rate of brain atrophy in relapsing MS.

Methods: Patients with relapsing-remitting MS or clinically isolated syndrome in a prospective cohort study at UCSF were evaluated. Subjects were categorized according to baseline smoking status; the number of pack-years smoked was recorded. Multivariate regression was used to assess smoking as a three-level predictor (never-smokers, quitters, and baseline smokers) on percent change of brain volume over three years (SIENA). Covariates included gender, age at onset, disease duration, and baseline treatment status; interaction with the number of pack-years smoked was assessed.

Results: Of 440 subjects, 56 (13%) were baseline smokers and 135 (31%) were quitters; the number of pack-years smoked was not different between groups (p=0.577). Baseline smokers, and to a lesser extent quitters, developed more brain atrophy over three years compared to never-smokers (respectively, −0.49% brain volume, 95% CI [−0.96%, −0.03%], p=0.039; −0.19% brain volume, 95% CI [−0.52%, +0.14], p=0.25). However, this effect was modified strongly by the number of pack-years smoked (p value for interaction term=0.038). Among baseline smokers, brain volume loss was less likely as the number of pack-years increased (per pack-year, OR for brain volume loss: 0.79, 95% CI [0.61, 1.03], p=0.078), whereas the number of pack-years smoked did not predict brain volume loss in quitters.

Conclusions: The deleterious effects of smoking on brain volume may be offset in patients with multiple sclerosis who have more recently smoked or have had a greater overall exposure to smoking. The biological mechanisms underlying these results are unknown. Investigations in larger cohorts of multiple sclerosis patients are needed to explore these findings further.

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P22
Residential case-control study of radon and multiple sclerosis
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Background: The prevalence of multiple sclerosis (MS) increases in temperate climates. Objectives: A case control study investigated the hypotheses that MS is associated with either reduced exposure to sunlight or increased residential radon exposure. Methods: We compared 97 MS patients with 51 other patients with non-autoimmune neurological diseases, all of whom had been diagnosed less than five years. The interview included sunlight related variables. We placed radon detectors in the homes of 25 MS and 21 control patients who had lived in their home for at least five years prior to diagnosis. Results: For sunlight related variables, the odds-ratios were: Skin Cancer 0.16, Severe Sunburn 0.38, SIR for brain VS7, Sunscreen Use 0.65, and Tanning Bed Use, not calculated but not statistically significant. There was no statistically significant increase in risk for hobbies or outdoor sports (OR=1.06, 95% CI=0.49–2.29). For vitamin D related variables, the odds-ratios were 2.24 for Drinks Milk and 0.65 for Vitamin Pill Use. Males had significantly more years of exposure to outdoor jobs than females (45.8 versus 6.8 years, p<0.0001). The weekly cumulative radon values averaged 373.04 pCi/L-hours for cases and 253.22 pCi/L-hours for controls (p=0.1719). Using the log of exposure, the p value decreased to 0.1015. Cumulative weekly hours spent in the home were similar for cases and controls (p=0.4842). The unadjusted odds-ratio for radon exposure was 1.62 (95% CI=0.50–5.28). When the analysis was adjusted for severe sunburn, the odds-ratio was virtually unchanged. Conclusions: We found minimal or
no evidence that sunlight exposure is protective against multiple sclerosis. There was a non-significant trend towards higher levels of radon in homes of MS patients. A larger study using radon measurements in more homes might reveal differences not detectable in this relatively small sample.

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P23
Case-control study of environmental exposures in individuals with multiple sclerosis in three geographic areas
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Background: Although the cause of multiple sclerosis (MS) is unknown, evidence suggests that exposure to certain environmental factors may play a role in disease onset. A number of environmental exposures have been investigated as possible etiologic factors for MS including metals, solvents, ultraviolet radiation, and diet, but with no consistent findings. Objectives: The goal of this multisite case control study was to examine whether exposure to heavy metals or other toxic chemicals is associated with increased risk of MS. Methods: This study was conducted in Lorain County, Ohio; the cities of Independence and Sugar Creek, Missouri; and Lubbock, Texas. Individuals who were diagnosed with MS and reside in the study areas were eligible to participate. Controls were population-based, identified by random digit dialing methods, and matched to a case on gender, age, and race. Each participant was asked to complete a questionnaire which included history of non-occupational environmental exposures and activities or hobbies that resulted in potential exposure to specific agents. Results: Information was available for 421 participants (n=185 cases and 236 controls). Preliminary results suggest that exposure to insecticides (crude odds ratio [COR]=2.24; 95% confidence interval [CI]=1.44–3.52), fungicides (COR=2.53; 95% CI=1.02–6.67) paint strippers (COR=3.37; 95% CI=1.50–8.17), varnishes (COR=3.10; 95% CI=1.35–7.57), and gas, diesel fuel, motor or fuel oil (COR=2.16; 95% CI=1.30–3.61) increased the risk of having MS. Conclusions: These preliminary findings support a strong role for remote EBV infection in POMS susceptibility. It remains to be determined whether the effect of EBV is mediated through molecular mimicry or other biological mechanisms.

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P24
Remote EBV, CMV, and HSV-1 and -2 infection status in children with pediatric-onset of multiple sclerosis and age-matched healthy controls
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Background: Two reports suggest EBV is associated with increased susceptibility to pediatric-onset (PO) multiple sclerosis (MS). Objectives: To determine whether POMS patients have higher rates of remote infection with EBV, CMV, and HSV-1 and -2 than age-matched controls. Methods: EBV, CMV, and HSV-1 and -2 genome seroconversion rates and quantitative responses were measured with normalized ELISAs. Antibody responses against EBNA-1 were detected by standardized ELISA. Samples were collected from pediatric patients with clinically isolated syndromes (CIS) or POMS seen at the six Regional Pediatric MS Clinics sponsored by the National Multiple Sclerosis Society (University of California San Francisco, State University of New York at Stony Brook, Harvard Medical School, University of Alabama at Birmingham, Mayo Clinic, State University of New York at Buffalo). Age-matched healthy controls were collected for 1/3 in New York, 1/3 in California, 1/3 in Oklahoma. Results: Sera were available from 112 patients with CIS/POMS (51% white non-Hispanic, disease onset 12.8 years, age at sampling 15 years) and 118 healthy children (age 14.6 years). Proportions of individuals positive for VCA and EBNA-1 were substantially higher in POMS compared to controls (VCA: 91.3% vs. 69.5%; OR=4.47; 95% CI 2.01, 10.67; p<0.0001; EBNA-1: 90.3% vs. 56.7%; OR=6.98; 95% CI 3.27, 15.84; p<0.0001). In contrast the proportion of HSV-2 positive was lower in POMS (21.9% vs. 38.1%; OR=0.47; 95% CI 0.25, 0.86; p=0.009). No significant differences were found for HSV-1 (43.3% vs. 49.1%; OR=0.80; 95% CI 0.46, 1.39; p=0.41) or CMV (28.1% vs. 34.7%; OR=0.75; 95% CI 0.41, 1.36; p=0.32). Quantitative antibody responses were higher in positive subjects in the POMS group compared to the healthy group for EBNA-1 (0.87±0.18 vs. 0.75±0.24, p=0.13) but not against other viruses. Conclusions: These preliminary findings support a strong role for remote EBV infection in POMS susceptibility. It remains to be determined whether the effect of EBV is mediated through molecular mimicry or other biological mechanisms.

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P25
25(OH) vitamin D levels in children with pediatric-onset of multiple sclerosis and controls
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Background: There are a few reports that suggest that low vitamin D levels in adults are associated with increased susceptibility to multiple sclerosis (MS). Whether this stands in pediatric-onset (PO) MS is unknown. Objectives: To determine whether children affected by POMS have lower 25(OH) vitamin D levels than age-matched controls. Methods: Serum 25(OH) vitamin D levels were measured with a chemiluminescent immunoassay on samples collected from patients with POMS and controls seen at the UCSF and Stony Brook pediatric MS clinics. Results: Sera were available from 117 patients with clinically isolated syndrome (CIS) or POMS (51% white non-Hispanic, mean age at disease onset 12.8±4.3 years, mean age at sampling 15±5.5 years) and 23 pediatric controls who were healthy or had other neurological diseases (77% white non-Hispanic). Vitamin D levels were within nor-
nal range (30–80 ng/ml) in only 18.8% of the POMS group and 17.4% of the control group. Mean 25(OH) vitamin D serum levels were similar in POMS and pediatric controls (22.2±9.6 ng/ml versus 22.5±9.6 ng/ml respectively; p=0.89). Conclusions: These preliminary findings do not support that children with MS have more vitamin D deficiency than pediatric controls, raising the question as to whether it is a true susceptibility factor in POMS. These levels were measured after disease onset and were not adjusted for season; further, supplementation with vitamin D after MS onset (e.g., at the time of sample collection) was not measured and may confound these findings. Further studies in a larger cohort of POMS patients and healthy controls are required.

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P26

International case control study on risk factors for multiple sclerosis (MS): pilot testing the questionnaire

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Background: The largest international case-control study ever conducted in multiple sclerosis (MS) will be launched in 2009 and will include over 4000 MS-patients and 16,000 healthy subjects. The study focuses on independent and joint effects of early life infections, vitamin D exposure (sun and food) and on smoking habits. Data will be collected using self administered questionnaires that were pre-tested on MS patients and healthy subjects in 2008. Based on the results we performed a second pilot of revised questionnaire on 115 healthy subjects from 3 countries. Objectives: To examine the ease of understanding and perceived difficulty of completing the modified version of the questionnaire. Methods: In addition to completing the questionnaire the subjects were asked to evaluate each question using scores of 1 ("easy to understand, easy to answer"), 2 ("easy to understand, difficult to answer"), 3 ("easy to understand, impossible to answer") to 4 ("difficult to understand"). Results: The subjects were aged 23–76 years: 59 from Italy; 27 from Norway; 30 from Serbia. Overall the questions were found easy to understand and to answer (score 1). Mean evaluation scores were 1.01 (SD 0.01) for general background questions, 1.13 (0.08) for recall of past sun exposure, 1.27 (0.17) for diet questions, 1.14 (0.04) for medical history, 1.02 (0.02) for smoking habits, and 1.05 (0.04) for weight, height, body shapes and physical activity. For all modified items the mean scores were lower compared to the previous pilot study. Conclusions: The ease of understanding and the perceived difficulty of completing the risk factor questionnaire improved after modification of the questionnaire. The questionnaire is cross-culturally acceptable and is likely to be an appropriate tool to gather information to assess the association between MS risk and past environmental exposures in large international case-control studies.

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Experimental Disease Models

P27

1,25-dihydroxyvitamin D3 acts directly on T lymphocytes to mediate protection from experimental autoimmune encephalomyelitis

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Background: Multiple sclerosis (MS) is an autoimmune disease that results in demyelination of the central nervous system. Genetic susceptibility, infectious agents, and environmental factors all contribute to MS etiology. One environmental risk factor for MS is lack of vitamin D3. Vitamin D3 is converted into the biologically active hormone 1,25-dihydroxyvitamin D3 (1,25-(OH)2D3). This hormone binds to the vitamin D receptor (VDR) to mediate downstream anti-inflammatory and neuroprotective functions. Supporting the role of vitamin D3 in MS, 1,25-(OH)2D3 has been shown to inhibit the onset of experimental autoimmune encephalomyelitis (EAE), a mouse MS model. Objectives: Though 1,25-(OH)2D3 is known to inhibit EAE, it is unknown how this occurs. We sought to determine if this protective effect occurs through direct modulatory effects of 1,25-(OH)2D3 on the immune system. In particular, since T lymphocytes play both protective and pathogenic roles in EAE, we hypothesized 1,25-(OH)2D3 may act directly on these cells to protect from disease. Methods: The contribution of immune and non-immune cells to 1,25-(OH)2D3 protection was determined by bone marrow adoptive transfer between wild-type mice and mice with a targeted VDR mutation (VDR−/−). Conditional T cell specific ablation of VDR was accomplished via a mouse strain with a floxed VDR locus and CD4-Cre transgene. Results: Mice with VDR−/− immune cells were unable to be protected from EAE by 1,25-(OH)2D3, regardless of their non-immune cell genotype. Conversely, 1,25-(OH)2D3 inhibited EAE in mice whose immune cells expressed wild-type VDR, whether their non-immune tissues were VDR−/− or wild-type. T cell-specific deletion of VDR eliminated the ability of 1,25-(OH)2D3 to protect mice from EAE. Conclusions: Direct effects of 1,25-(OH)2D3 on the immune system are necessary to confer protection from EAE. Specifically, 1,25-(OH)2D3 must act directly on T lymphocytes to inhibit the onset of EAE.

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Imaging

P28

Comparison of T2-weighted magnetic resonance imaging and retinal nerve fiber layer thickness measurement for detecting prior acute optic neuritis in multiple sclerosis

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Background: Orbital MRI has high sensitivity for detecting acute optic neuritis (AON) although its sensitivity for optic neuropathy (ON) is unknown. While optical coherence tomography (OCT) is sensitive for detection of optic nerve damage, it has not been directly compared to MRI for detecting ON in the absence of a history of AON (HxAON).

Objectives: To determine the relative sensitivity and specificity of MRI and OCT for detecting abnormalities associated with HxAON or ON in multiple sclerosis (MS).

Methods: 84 participants with MS (56 women, Age 43±12 years (mean±SD), EDSS 3.5±2.2), 18 with HxAON >6 weeks prior to scanning, underwent T2-weighted 3T MRI of the optic nerves (Phillips) and retinal nerve fiber layer thickness (RNFL) measurement (Zeiss OCT-3). The eye with lower RNFLT was analyzed.

Results: 16 participants, 6 with HxAON, had T2-weighted abnormalities along the optic nerve (sensitivity: 33%; specificity: 85%). In the HxAON group, the mean±SD length of T2-weighted abnormality was 4.8±7.4 mm. In the other patients, the length of abnormality was significantly less (1.5±3.8 mm; p=0.007). HxAON was associated with length of T2-weighted signal abnormality in a logistic regression (OR 1.13, 95% CI=1.03–1.26, p=0.014). 31 participants, 11 with HxAON, had RNFLT below the 5th percentile for age (sensitivity: 61%; specificity: 70%). HxAON was not associated with RNFLT (OR 0.96, 95% CI=0.93–1.00, p=0.08).

Conclusions: Compared to RNFLT measurement, T2-weighted MRI is less sensitive to, but more specific for, HxAON associated with MS. MRI may be more useful for confirming HxAON, as a marker for dissemination in space and time, key elements of the MS diagnosis. The lower specificity of RNFLT measurement for HxAON likely reflects its ability to detect subclinical ON in addition to AON.

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P29

Average permeability of the blood-brain barrier is reduced in patients with multiple sclerosis

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Background: Although damage to the blood-brain barrier (BBB) in multiple sclerosis (MS) has been demonstrated with conventional gadolinium-enhanced MRI, the permeability of the BBB has not been quantified in a voxel-based approach. Objectives: To quantify the BBB permeability in MS patients by employing a Dynamic Contrast Enhanced MR imaging (D-CEMRI) technique. Methods: Ten subjects with MS were recruited for this preliminary study. Twenty normal, age-matched controls with normal neurological exam and normal brain MRI were recruited for comparison. MS subjects had conventional gadolinium enhanced MRI 2 to 7 days prior to the permeability study. Patients and controls underwent D-CEMRI with a fast T1 mapping technique and a reduced dose of Gd-DTPA to obtain a Time Activity Curve for each voxel in 6 supraventricular brain slices. A multi-compartmental modeling technique based on the Patlak method was used to derive voxel-based permeability within each slice. Permeability data were subjected to statistical analyses for inferences with methods from the R-Project computing environment to establish cutoff probabilities for control data. Results: We quantified the BBB permeability in the 6 brain slices imaged from 10 MS patients and 17 controls. A threshold of 3×10−4 ml/g-min for classifying abnormal BBB leakage from normal control white matter was established. We observed a reduced 6 slice average brain permeability in MS patients compared to controls. All lesions seen in conventional Gad-enhanced images were confirmed in a voxel-based approach.

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P30
Glutathione levels in the brains of patients with secondary-progressive multiple sclerosis are reduced by magnetic resonance spectroscopy measures
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Background: Oxidative stress has been implicated by many investigators in multiple sclerosis (MS). Glutathione (GSH), a powerful antioxidant, plays a key role in the first line of antioxidant defense against free radicals. A reduction in GSH indicates the presence of oxidative stress in the brain. Patients with secondary-progressive (SP) MS will often worsen despite a stable T2 lesion burden in MRI. Increased cell death associated with oxidative stress in the absence of measurable inflammation could explain this phenomenon. Recently, we and a few others were able to detect GSH in the human brain using H MRS. We demonstrated a reduction in GSH in patients with Alzheimer’s disease compared to normal controls. Objectives: To compare the levels of GSH in 3 brain regions of SPMS patients with normal controls Methods: We recruited 18 SPMS patients and 18 age- and gender-matched normal controls with EDSS ranging from 4.0–7.5. A specially designed MRS chemical shift imaging of GSH, was performed on all subjects. GSH levels were measured in an axial slab (3 cm thickness) placed just superior to the ventricle covering front-parietal regions of the brain. Glutathione levels in 3 brain regions, frontoparietal, mainly frontal, and mainly parietal regions were compared between SPMS subjects and controls. Results: Glutathione levels were reduced in the SPMS patients in the frontoparietal region, frontal region, and parietal region at 12.5%, 18.5% and 7.7%, respectively. The largest reduction was in the frontal regions at 18.5% (p<0.001). Conclusions: The reduction in GSH levels in these patients indicates the presence of oxidative stress in SPMS. This could partially explain the ongoing decline in function in patients with SPMS. Further study is needed to evaluate GSH in other types of MS and to correlate the changes in GSH levels with alterations in function in MS.

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P31
Magnetic resonance imaging characteristics of the CombiRx cohort at baseline
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Background: The CombiRx trial is a three year, double blind, multicenter randomized clinical trial studying relapsing-remitting multiple sclerosis (RRMS), to compare patients on interferon beta 1a and glatiramer acetate versus single agent arms with matching placebo; recruitment should close early 2009. Subject entry criteria include: EDSS<5.5, RRMS diagnosed by Poser or McDonald criteria, 18-60 years of age, at least 2 relapses in prior 3 years, and no prior use of either medication. Objectives: We will describe the entire baseline cohort by demographic (age, race, ethnicity, and sex) and MRI characteristics, including diagnosis criteria (Poser or McDonald). Methods: Comparisons of demographic and MRI criteria, including number of Gd lesions, T2 lesion number, overall plaque volume or burden of disease (BOD) including its T2 and T1-hypointense component volumes, and measures of atrophy, and by diagnosis criteria will be presented. Results: As of January 2009, 946 subjects were at trial entry: mean age 37.7±9.7 years; 72% female; 88% white; 7% AA; 6% Hispanic/Latino; with 3.7±3.5 years disease duration. MRI characteristics: 78.0% Poser criteria, 60% of subjects CEL lesion free, 1.8±4.3 CEL lesions, 86.6±59.3 T2 lesions, 12.3±13.4 BOD. McDonald subjects have significantly lower lesion numbers and atrophy with nominally lower gad lesions, BOD and time since diagnosis. Conclusions: The CombiRx cohort is a unique treatment naive RRMS cohort with 22% diagnosed using McDonald criteria. This study provides opportunities to further define the MRI differences and similarities between types of RRMS subjects using a modern cohort. All results will be updated to the full subject cohort upon completion of study recruitment.

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P32
The brain as an effector site of secretory immunity in inflammatory neurological disorders
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Background: Secretory IgAs (SIgAs) are released via mucosal epithelia (effector sites) into human body fluids where they mediate the first line of immune defense against outside pathogens. IgAs but not SIgAs have been detected in the brain and CSF in patients with multiple sclerosis (MS). The choroid plexus (CP) secretes CSF and is the only epithelial structure in the CNS. Objectives: To evaluate whether SIgAs are secreted into the CSF by CP in MS patients versus controls. Methods: Patients with MS and controls that had CSF, serum or brain tissue available for research were identified. IgA, SIgA and IgG levels were measured in the CSF and serum by asymmetrical ELISA. CP paraffin embedded sections were stained for IgA, and IgG using immunofluorescence and for SIgA using immunohistochemistry. Results: We analyzed the CSF of 40 MS patients and 200 controls. CSF SIgA was detected in 57.5% of MS patients (median=13.5 ng/mL, range [0-954]), 11.1% of 18 healthy controls (p=0.001) (median=0 ng/mL,
Deletion of CD44 induces a protective immune phenotype and suppresses experimental autoimmune encephalomyelitis
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Background: Experimental autoimmune encephalomyelitis (EAE) is commonly used as an animal model of human multiple sclerosis. Th1 and Th17 effector cells play a critical role in the disease initiation and development. Objectives: Here we report that deletion of CD44 in T cells has dramatically decreased, but Th2 cells significantly increased in CD44KO mice. Also, CD44 deficiency significantly increased regulatory T cells in comparison to WT controls. Accordingly, occurrence of the disease was delayed and severity was constrained in CD44KO mice as well as these mice were eventually cured and did not show any relapse of the disease. In CD44KO mice, inflammatory cell infiltration particularly transmigration of ependymalogenic CD4+ T cells in the brain and spinal cords was dramatically inhibited and no significant demyelination was observed. The results demonstrated that deletion of CD44 caused immune cell phenotype shifting from pathogenic to protective status, or from Th1 response to Th2 response. CD44 deficiency rendered polarization of CD4+ T cells preferentially towards Th2 and inhibition of Th1 and Th17 polarization with stimulation of MOG35–55 peptide or anti-CD3 antibody. In adoptive cell transfer studies, we show that MOG35–55 peptide or anti-CD3 antibody can induce Th2 and inhibition of Th1 and Th17 polarization. Inhibitors of Th1 and Th17 responses were only recognized by a few patients, three unique EBNA1 regions are commonly targeted by POMS which are not bound by healthy POMS parents or SLE patients. Only one of these regions was recognized by healthy POMS parents; however, patients demonstrated significantly greater serologic reactivity. The two unique POMS epitopes are EADYFEHYQEG and DVPPGAIE of the carboxyl region of EBNA1.

Conclusions: These data support the proposition that POMS patients mount unique humoral immune responses to EBNA1 compared to their parents, healthy controls or SLE patients. They are also consistent with the hypothesis that the risk of MS is related to the immune response to EBV.

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P34
Pediatric-onset multiple sclerosis patients sera recognize unique regions of Epstein-Barr nuclear antigen 1
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Background: Growing serologic (temporal and cross-sectional), DNA and pathogenic mechanism information supports a function for Epstein-Barr virus in some aspect of multiple sclerosis etiology and/or pathogenesis. However, without animal models and with high seroconversion rates by adulthood, dissecting the role(s) of this common human infection in autoimmune disease is difficult. Objectives: This study uses a unique collection of pediatric-onset multiple sclerosis (POMS) patient sera to understand the human, humoral immune response in POMS patients compared to matched controls to help identify potential molecular mimicry specificities between EBNA1 and self antigens in MS.

Methods: Overlapping octapeptides spanning all of the unique sequences of EBNA1 were constructed to evaluate the fine specificity of these immune differences. Sera from POMS, POMS controls, pediatric-onset SLE (n=10), pediatric-onset IPEX (n=10), healthy parents, and SLE patients were tested for anti-EBNA1 by ELISA and EBNA1 fine specificity was tested for 10 POMS, 10 healthy parents, 10 SLE patients and 10 unaffected pediatric controls. Results: POMS sera recognize up to 20 unique regions of EBNA1, compared to the relatively restricted anti-EBNA1 response seen in healthy controls and parents against the glycine-alanine rich region. Although many of these responses were only recognized by a few patients, three unique EBNA1 regions are commonly targeted by POMS which are not bound by healthy controls or SLE patients. Only one of these regions was recognized by healthy POMS parents; however, patients demonstrated significantly greater serologic reactivity. The two unique POMS epitopes are EADYFEHYQEG and DVPPGAIE of the carboxyl region of EBNA1.

Conclusions: These data support the proposition that POMS patients mount unique humoral immune responses to EBNA1 compared to their parents, healthy controls or SLE patients. They are also consistent with the hypothesis that the risk of MS is related to the immune response to EBV.

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P38
Immunoglobulin-like transcript 3 expression on circulating CD14+ cells is low in active remitting-relapsing multiple sclerosis and is induced by interferon-β-1b
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Background: Immunoglobulin-like transcript 3 (ILT3) expression on circulating CD14+ monocytes may have implications not only for MS but also for other CNS diseases especially in patients with relapsing disease, and during relapses. This study is the first to report that ILT3 expression on circulating CD14+ cells is low in active relapsing-remitting multiple sclerosis and is induced by interferon-β-1b.

Objectives: To determine if ILT3 and ILT4 expression on CD14+ monocytes in MS are altered compared to controls, and if interferon-β-1b treatment induces ILT3 expression.

Methods: We collected blood from 10 POMS patients, 10 healthy parents, 10 SLE patients and 10 unaffected pediatric controls. We measured ILT3 expression on circulating CD14+ cells of freshly isolated peripheral blood mononuclear cells (PBMC) and of PBMC cultured with or without IFN-β-1b. IFN-β-1b induces ILT3 expression on donor APCs. ILT3+ APCs suppress CD4+ T cell activation directly and help induce Tregs and CD4+ CD25+ Tregs. Tg function is decreased in active relapsing-relapsing multiple sclerosis (RRMS), persistently subnormal in secondary-progressive MS, and increased by interferon-β-1b (IFN-β-1b). ILT3+ APCs may have potential roles in the therapeutic activity of IFN-β-1b in MS.

Results: This study was approved by The University of Chicago Institutional Review Board. ILT3 expression on CD14+ cells of freshly isolated peripheral blood mononuclear cells (PBMC) and of PBMC cultured with or without IFN-β-1b was analyzed using immunocytochemistry. Parallel PBMC cultures were activated with anti-CD3 antibody with or without blocking antibodies to ILT3 and ILT4 and proliferative responses measured 72 hours later. Results: Monocytes in active RRMS (n=10) express lower ILT3 levels than in stable RRMS (p=0.003; n=10) and IFNβ-treated RRMS (p<0.05; n=15). IFNβ-1b (10 U/ml) treatment quadruples monocyte ILT3 expression in MS (n=7) and controls (n=5) (p<0.05 for both groups vs untreated controls). Blocking ILT3 doubles T cell proliferation (p=0.05 for MS and controls).

Conclusions: ILT3 expression on circulating monocytes is lower in active RRMS than in stable RRMS and IFNβ-treated RRMS. IFNβ-1b induces ILT3 expression. IFNβ-1b induced ILT3 may be therapeutically beneficial.
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P36
Neuroinflammation in the spinal cord of NG2 null mice
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Background: Understanding factors that influence demyelination/remyelination will be important for developing new treatments for demyelinating diseases such as multiple sclerosis. Objectives: The loss of myelin basic protein (MBP)-positive fibers and responses of cell types expressing NG2 (oligodendrocyte progenitors, pericytes, and macrophages/microglial cells) were evaluated 7 and 14 days after lyssolecithin injection. Methods: To investigate the role of the NG2 proteoglycan in these processes, we induced neuroinflammation by microinjection of 1% lyssolecithin into the lumbar spinal cords of wild type and NG2 null mice. Results: Seven days after lyssolecithin injection, both the loss of MBP-positive fibers and the extent of cellular infiltration at the injection site were greater in wild type animals than in NG2 null animals. The expanded site of demyelination/cellular infiltration in the wild type mouse correlated with a region in which NG2 expression was up-regulated. In addition to PDGFβR-immunoreactive (IR) oligodendrocyte progenitors, OX-42-IR macrophages/microglial cells and PDGFRβ-IR pericytes also appear to contribute to this NG2 up-regulation. Fourteen days after lyssolecithin injection, we observed a decrease in the size of the demyelinated region in wild type mice, so that the areas of demyelination were similar in wild type and NG2 null mice. Compared to the 7th postgery day, fewer OX-42-IR macrophages/microglial cells and more PDGFβ-IR oligodendrocyte progenitors were seen in the 14 day postsurgery lesion site. Conclusions: Our study suggests a role for NG2 in cell proliferation/infiltration after spinal cord injury and in the inflammatory processes that lead to spinal cord demyelination.

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P37
Anti-GAGA4 IgM assay may distinguish primary progressive from patients with relapsing-remitting multiple sclerosis
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Background: The gMS®DX test have a specificity of 92.3% and a sensitivity of 59% for the detection of GAGA4 IgM measurements were at the equivocal cutoff level [52.7 and 54.4 EU/(mg/mL)0.5]. Mann Whitney U revealed only a trend (p=0.1) difference in the level of anti-GAGA4 IgM level between PPMS patients [median; range, 30.7; 9.7 to 54.4 EU/(mg/mL)0.5] and RRMS patients [median; range, 36.8; 6.6 to 422.2 EU/(mg/mL)0.5], most likely because of the low number of PPMS patients. Conclusions: This pilot study revealed that MS patients who are positive for the gMS®DX test have a clinical course that is more likely to be RRMS and not PPMS. In order to confirm these results further studies will be performed.

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P38
Immunogenetic predictors of response to glatiramer acetate therapy in multiple sclerosis
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Background: A goal of immunotherapy in multiple sclerosis (MS) is to develop predictive biomarkers of treatment response. Glatiramer acetate (GA), used in the treatment of relapsing-remitting MS (RRMS) involves binding to MHC class II molecules and induction of regulatory IL-10 producing Tr1 cells. Objectives: To determine whether the HLA background and GA induced serum IL-10 levels can differentiate GA responders (GA-R) from hypo/non-responders (GA-HR/NR). Methods: Seventy RRMS patients treated with GA were classified clinically as GA-R (n=44) or GA-HR/NR (n=26) based on EDSS and relapse rate after 2 years of treatment. Intermediate HLA analysis (DR and DQ) was performed. Serum IL-10 levels were measured by ELISA pre-treatment and at 3 and 6 months. HLA association with response was tested using Fisher’s Exact Test followed by permutation testing. Change from IL10 after 2 years of treatment. Intermediate HLA analysis (DR and DQ) was performed. Serum IL-10 levels were measured by ELISA pre-treatment and at 3 and 6 months. HLA association with response was tested using Fisher’s Exact Test followed by permutation testing. Change from IL10 baseline at 6 months (Delta-IL10) was added to form a predictive model. Results: 64% of subjects were responders. Only DQ6 was associated with response (multiple-testing adjusted p=0.02). 86% of DQ6-positive patients were GA-R versus 50% of DQ6-negative patients. Delta-IL10 had a median of 9 and interquartile range 22. Higher Delta-IL10 and IL-10-negative were each associated with GA-R (p=0.0001 and p=0.0451, respectively). A 22 unit increase in Delta-IL10 predicts a 5.3-fold (95% confidence interval: 1.7–26.3) increase in odds of GA-R. The area under the ROC curve (AUC) was 0.85. A simplified model, using (Delta-IL10>0 AND DQ6 positive) as sole predictor, had AUC of 0.74; positive subjects were 91% GA-R while negative subjects were 45% GA-R. Conclusions: The combined measures of change in serum IL-10 at 6 months during GA-treatment and the presence of the DQ6 allele predict a clinical response to GA with 89% specificity and 59% sensitivity.

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Evidence of subtle hippocampal dysfunction is detectable in relapsing-remitting multiple sclerosis
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Background: Widespread cognitive impairments are common in multiple sclerosis (MS) and there is evidence for subcortical and cortical gray matter involvement at the earliest stages of MS. Objectives: Determine the pattern of performance in relapsing-remitting MS (RRMS) using a previously validated sequential learning paradigm sensitive to dysfunction in deep gray matter structures. Methods: et al (2007) have developed a simple computer based paradigm that tests distinct aspects of spatial learning. Initially a sequential learning (chaining) task, thought to be mediated by basal ganglia input, is performed. This is followed by a probe phase, thought to be mediated by mesial temporal lobe structures including the hippocampus, in which previously learned associations are tested in novel contexts. Poor performance during the chaining task has been reported in patients with Parkinson’s disease, while individuals with mild amnestic cognitive impairment have poor performance in the probe phase. We used a version of this sequential learning paradigm, “Kilroy” in a group of RRMS patients and controls. Results: Seventeen RRMS patients (mean age 38.3, mean EDSS 2.1, mean disease duration 8.2 years) and seven RRMS patients and controls.

Results: RRMS patients showed difficulties of life and psychosocial correlates

Evidence of subtle hippocampal dysfunction is detectable in relapsing-remitting multiple sclerosis

Predicting neurocognitive decline in patients with multiple sclerosis using demographic variables
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Background: Multiple sclerosis (MS) is a debilitating demyelinating disorder, which has been shown to lead to associated cognitive deficits. Research to date suggests that cognitive decline can occur early in the disease before salient physical markers are present. Additionally, physical health problems and EDSS scores appear to be poor predictors of the level of cognitive decline. The relationship between demographic variables such as education and cognitive decline has been underexplored in patients with MS. Objectives: The purpose of this study was to evaluate the relationship between demographic variables and cognitive decline in patients with MS as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Randolph, 1998). Methods: Participants were 50 individuals diagnosed with MS (mean age 45.49 years, standard deviation 9.13 years). The mean time since diagnosis was 7.76 years with a standard deviation of 8.92 years. The mean level of education was 13.44 years with a standard deviation of 2.21 years. Results: Linear regression analysis indicated that time since diagnosis was a poor predictor of overall neurocognitive impairment (R²=0.018; p=0.358) as was age (R²=0.006; p=0.606). However, level of education was a strong predictor of delayed memory (R²=0.103; p=0.023) and immediate memory, but not overall neurocognitive impairment (R²=0.048; p=0.126). Conclusions: The results of this study were consistent with some research that shows that length of education is not a reliable predictor of cognitive impairment. This is an important finding, especially when compared to other progressive neurological disorders which usually show a high correlation between disease progression and cognitive impairment. Interestingly, level of education appeared to be a resiliency factor for memory problems. However, the protective relationship was not present across neurocognitive domains (e.g., language, visual-spatial processing, attention). The implications will be discussed in regards to practitioners and researchers.

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Rehabilitation and Quality of Life

African Americans with multiple sclerosis: health-related quality of life and psychosocial correlates
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Background: Five percent of people with multiple sclerosis (MS) in the US are African American. Almost all previous studies of African Americans with MS have focused on the clinical or epidemiologic aspects of MS in this population. Assessing health related quality of life and other psychosocial aspects of MS in African Americans may be useful in identifying and tailoring mental health and social services for this group. Objectives: The purpose of this pilot study was to describe selected psychosocial characteristics of African Americans with MS including health-related quality of life and perceptions of MS-related stigmatization. Methods: Invitations to participate in a computer assisted telephone interview were sent to the 720 African Americans active in the North American Research Registry on MS. 137 people completed the 63 item survey (response rate 19%). Among others, survey items included the SF-8 Health Survey, which provides a health-related quality of life profile; questions about use of mental health services, and perceptions of MS-related stigmatization. Descriptive statistics and chi square tests of association were calculated, and a multiple regression analysis was also performed to quantify identified associations. Results: Among other findings, most respondents feel that others treat them differently because of MS, that they have more worries than people their age because of MS, and that MS affects their chances for career advancement. Over a third agree that MS may negatively impact their romantic prospects, marriages, long-term relationships, and social lives. Conclusions: In this sample of African Americans with MS, concerns about the potentially negative impacts of MS on career, social life, and relationships suggest that mental health and social services for African Americans are essential for health management and improved quality of life.

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The effects of treadmill training on functional ability, quality of life and fatigue in primary-progressive multiple sclerosis


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Background: Exercise therapy has been shown to improve both physical and psychosocial outcomes in individuals with multiple sclerosis (MS). However, there is a paucity of data on whether exercise is equally effective for those with primary-progressive MS (PPMS) as it is for those with relapsing-remitting MS. Many exercise studies have also excluded individuals with high disability levels (EDSS>6.0). Objectives: This study was undertaken to investigate the effects of exercise using body-weight supported treadmill training (BWSTT) in individuals with PPMS of high disability level (EDSS>5.0–8.0).

Methods: Six patients (5 PPMS, 1 SPMS; mean EDSS=6.92±1.07) were recruited to participate in 50 min sessions of BWSTT with manual assistance, 3×/wk for 12 weeks. Training intensity, as determined by treadmill speed and % body weight support, increased gradually over time. Outcome measures included functional ability assessed by EDSS and Multiple Sclerosis Functional Composite (MSFC), Quality of Life and fatigue were assessed using the MSQOL-54 and Modified Fatigue Impact Scale (MFIS), respectively. All tests were administered at baseline and following 12 weeks of training. Results: Treadmill training was very well tolerated and a 98% adherence rate was recorded. Following training, treadmill walking speed significantly increased (34%, p=0.01), and percent body-weight support was significantly reduced (42%, p=0.00). A significant improvement in both physical and mental subscales of the MSQOL-54 (p=0.02; p=0.01) was found, together with a non-significant reduction in fatigue (p=0.18; ES=−0.93). Functional ability remained stable with small, non-significant improvements in EDSS and MSFC. Conclusions: BWSTT appears to be an effective therapeutic strategy to improve quality of life and potentially reduce fatigue in PPMS patients of high disability level. BWSTT may also produce improvements in functional ability. Larger trials will be required to confirm these findings and to further evaluate the effects of BWSTT in MS.

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**Surrogate Markers (Non-MRI)**

**P45**

Serum vitamin D levels are associated with multiple sclerosis disease severity

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Background: Vitamin D deficiency has been implicated as a risk factor for multiple sclerosis (MS). Higher circulating levels of 25(OH)D are associated with a decreased risk of developing MS. In vivo studies have demonstrated that 25(OH)D inhibits experimental autoimmune encephalomyelitis (EAE) induction in mice and also prevents disease progression. However, the association between 25(OH)D and MS disease severity in humans has yet to be elucidated. Objectives: To evaluate whether 25-hydroxyvitamin D (25(OH)D) levels are associated with disease severity in patients with multiple sclerosis. Methods: Clinical, demographic and 25(OH)D data from 228 MS patients enrolled in the New York State Multiple Sclerosis Center (NYSMSC) were analyzed (mean age 50.5±9.5 yr). The Expanded Disability Status Scale (EDSS) was used to measure MS disease severity (median 3.0); serum 25(OH)D level results were obtained from the same commercial laboratory. Serum 25(OH)D levels <32 ng/mL were considered less than sufficient. Ordinal regression was performed to assess the impact of several factors on EDSS score. Results: Mean serum 25(OH)D level was 29.8 ng/mL, with 63.4% of patients considered 25(OH)D deficient/insufficient. The ordinal regression model contained the following variables: sex, age, age at symptom onset, season and 25(OH)D (Chi-square = 49.9, p<0.001). Correcting for sex, season, age and age of onset, 25(OH)D levels were found to be significantly predictive of EDSS scores (Wald parameter = 4.9, p<0.05).

Conclusions: The results of this study indicate that 25(OH)D levels are significantly associated with MS disease severity. While further studies regarding the role of 25(OH)D in MS are warranted, these results support a potential disease modifying effect of high levels of 25(OH)D.

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**Symptom Management**

**P46**

Symptom clusters in women with relapsing-remitting multiple sclerosis

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Background: Multiple sclerosis (MS) is a chronic neurological disease, and many patients develop various sets of symptoms. Much of the research in MS is focused on a single symptom in isolation rather than examining the relationships among symptoms. Objectives: To investigate the relationships among a set of symptoms (fatigue, depression, impaired cognitive function, and sleep disturbance) with pain severity in women with relapsing-remitting (RR) MS and to determine if the differences between symptoms clusters (pain severity, fatigue, depression, impaired cognitive function, and sleep disturbance) are related to age, marital status, or education level in women with RRMS. Methods: Secondary analysis was conducted using a convenience sample of 40 women with RRMS and healthy women. Women completed the Brief Pain Inventory, McGill Pain Questionnaire, Lee Fatigue Scale, Beck Depression Inventory, and General Sleep Disturbance Scale. The Paced Auditory Serial Addition test also was administered in the original study. Results: Analysis of clusters was completed using factor analysis and regression. There was a relationship between fatigue and sleep in one group, and pain and depression in another group. Race and marital status were statistically significant in predicting cluster membership. Conclusions: These women must be educated on these symptoms in a way that will assist them in assessing their symptoms to ultimately guide their treatment plans. Women with RRMS also need to be communicated to healthcare providers in order to facilitate assessment and timely interventions.

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**P47**

Assessment of pain in neuromyelitis optica

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Background: Pain is a frequent and disabling symptom among demyelinating diseases. The characteristics of pain in patients with neuromyelitis optica (NMO) have not been defined. Objectives: To characterize pain in NMO, along with its relationship to depression, fatigue, sleepiness, cognition, CNS medication usage, physical and cognitive functions. Methods: A cross-sectional study was conducted of those who meet NMO research criteria. Measures included the McGill Pain Score (MPS), the Short Form 36 QOL Scale (SF36), the Center for Epidemiologic Studies Depression Scale (CES-D), Modified Fatigue Impact Scale (MFS), Epworth Sleepiness Scale (ESS), characterization of pain medications, Expanded Disability Status Score (EDSS), Multiple Sclerosis Functional Composite (MSFC), and Symbol Digit Modality Test (SDMT). Results: Pain syndromes of the spinal cord are frequent in NMO. These include: repetitive tonic spasms, tingling and burning in the limbs, a squeezing sensation around the trunk, and radiating sharp pain throughout the body. The average McGill pain score was markedly elevated at 49.5 out of a maximum 78. This was associated with decreases in both the mental (41.8±11.3) and physical components (25.3±9.7) of the SF36. Fatigue was also noted (MFS = 43.7±14.0). Polyparmacy for pain was common, with frequent use of opioid derivatives, anti-epileptics, and tricyclic antidepressants. Depression was also common (CES-D = 22.3±13.0), as was use of antidepressants. Many patients would describe their pain as one of the most disabling symptoms of NMO. Treatment of pain and other symptoms can be effective, and deserves special attention in clinic visits. Despite the use of multiple medications for pain, very few would characterize the response as excellent.

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Symptom cluster and physical activity in multiple sclerosis
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Background: We previously reported that a symptom cluster of fatigue, depression, and pain was inversely associated with physical activity in persons with multiple sclerosis (MS). Importantly, our research was limited by the consideration of a narrow range of symptoms as part of the symptom cluster and lack of control for exercise history and neurological impairment.

Objectives: The present study examined the symptom cluster of fatigue, pain, depression, cognitive impairment, and sleep insufficiency as a correlate of physical activity behavior controlling for exercise history and neurological impairment in a sample of individuals with MS.

Methods: The sample included 166 individuals with relapsing-remitting MS (RRMS). The participants completed self-report measures of fatigue, depression, pain, cognitive impairment, sleep insufficiency, neurological impairment, exercise history, and physical activity. The data were primarily analyzed using confirmatory factor analysis and structural equation modeling in Mplus 3.0.

Results: Our results indicated that (1) fatigue, depression, pain, cognitive impairment, and sleep insufficiency represented a single symptom cluster based on confirmatory factor analysis ($\chi^2=9.47$, df=5, p=0.09, CFI=0.98); (2) the symptom cluster had a strong and negative predictive relationship with physical activity (path coefficient = −0.49); and (3) the relationship between the symptom cluster and physical activity was attenuated (path coefficient = −0.34), but still significant, after controlling for exercise history and neurological impairment.

Conclusions: Such findings provide stronger support for the importance of considering a broadly-defined symptom cluster as a correlate of physical activity in persons with RRMS.

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