MULTIPLE SCLEROSIS
MONITOR and Commentary
Practical Analysis on Today's Findings in Multiple Sclerosis
FALL 2010 www.MonitorAndCommentary.com VOLUME 4, NUMBER 3

From the editor...


ROBERT P. LISAK, MD

We touch on a little bit of everything in this issue of *Multiple Sclerosis Monitor and Commentary*: Practical strategies for considering the risk of accidents while walking or driving, efforts to improve prognosis, and the activity of disease-modifying therapies at the level of immune function. In many cases, our commentators see larger issues introduced by the topic. For example, Dr. Susan Bennett, a physical therapist in the Department of Rehabilitation Science at the State University of New York at Buffalo, uses a study that shows changes in gait among patients asked to perform a cognitive task to encourage measurement of the demands of multitasking in the neurologically impaired. Similarly, Dr. Scott Zamvil from the University of California, San Francisco explains why a study showing that glatiramer acetate upregulates T-regulatory cells in experimental autoimmune encephalomyelitis (EAE) may provide insight on immune function in the central nervous system of patients with MS taking DMTs.

Other than control of MS, one of the most pressing issues for clinicians is better methods of predicting disease course, and two studies on this topic are included. In one case, Dr. Bruce Cree from the University of California, San Francisco examines a study that looks at potential biomarkers for predicting when acute myelitis is an early sign of MS. In another, Dr. Gary Cutter of the University of Alabama at Birmingham critiques an effort to identify surrogate markers for the likelihood of worsening disability.

Not all of our commentators were impressed with the studies they were asked to evaluate, but all have provided a second perspective that typically provides some depth beyond the data discussed. As always, we encourage readers to consult the original sources, but we hope our experts help to broaden the perspective on clinical and research issues in MS. If you have comments or suggestions, please feel free to reach me at msmonitor@delmedgroup.com.

Robert P. Lisak, MD
Parker Webber Chair in Neurology
Professor and Chairman
Department of Neurology
Wayne State University School of Medicine
Detroit, Michigan

This publication is supported by an educational grant from Teva Neuroscience.

IN THIS ISSUE

- Cognition and driving performance
- Walking while talking
- Acute myelitis outcome predictors
- Glatiramer acetate's immunodulatory effects
- Surrogate endpoints for EDSS worsening
- Self-report comorbidity questionnaire

MS MONITOR AND COMMENTARY

Editor
Robert P. Lisak, MD
Parker Webber Chair in Neurology
Professor and Chairman
Department of Neurology
Wayne State University School of Medicine
Detroit, Michigan

Faculty Disclosures:

Robert Lisak has served on an advisory board or panel for MediciNova, Inc. and Teva Neuroscience and has been a consultant to Bayer Healthcare, EMD Serono, Genentech, and Teva Neuroscience. He is also on Speakers' Bureaus for Bayer Healthcare and Teva Neuroscience. He has received grants/research support from Acorda Therapeutics, BioMS Medical Corporation, Ilex Medical Systems, Novartis, and Teva Neuroscience.

Bruce Cree, **Aaron Miller**, and **Kelly Ryan** have no relevant conflicts to report.

Susan Bennett reports receiving speaker honoraria from Acorda Therapeutics, Medtronic, and Teva Neuroscience, and serving on advisory committees for Acorda Therapeutics and Medtronic.

Gary Cutter reports participation on the following Data and Safety Monitoring Committees: Cleveland Clinic, Daichi-Sankyo, Eli Lilly, Genmab Biopharmaceuticals, GlaxoSmithKline Pharmaceuticals, Medivation, Sanofi-Aventis, Teva Neuroscience, Vivus, and the University of Pennsylvania. He reports consulting, speaking, and serving on advisory boards for Alexion, Bayhill, Bayer Healthcare, Consortium of MS Centers (grant), Genzyme, Klein-Buendel Incorporated, Novartis, Peptimmune, Sandoz, Somnus Pharmaceuticals, Teva Neuroscience, UT Southwestern, and Visioneering Technologies, Inc.

Scott Zamvill reports serving as Consulting Editor to the *Journal of Clinical Investigation*. He has also served as a consultant for and received speaker honoraria from Biogen Idec, EMD Serono, Inc, and Teva Neuroscience. He has served on Speakers' Bureaus for Advanced Health Media and Health Logix. He receives research support from the Guthy Jackson Charitable Foundation, the Maisin Foundation, the National Institutes of Health (RO1 AI073737 [PI], RO1 NS 063008 [PI], and RO1 AI059709 [PI]), the National Multiple Sclerosis Society (RG 4124 [PI]), and Teva Neuroscience.

Publishing Information
Delaware Media Group, LLC
66 S. Maple Avenue, 3rd Floor
Ridgewood, NJ 07450
Tel: 201-612-7676 • Fax: 201-612-8282
www.delmedgroup.com

Publishers
Joseph D'Onofrio
Frank M. Marino
jdonofrio@delmedgroup.com

Editorial Director
Nancy Monson

Senior Writer
Theodore Bosworth

Art Director
James Ticchio

Examining the relationship between cognition and driving performance in multiple sclerosis.

First Author and Institution:
Maria T. Schultheis, PhD, Drexel University, Philadelphia, Pennsylvania.

Citation:
Archives of Physical Medicine and Rehabilitation. 2010;91:465-473.

Objective:
Identify cognitive tests that predict driving ability.

Type of Study:
Prospective, uncontrolled study in patients with multiple sclerosis (MS).

Result:
Information processing speed on the Symbol Digit Modality Test (SDMT) was the best predictor of driving performance, while visuospatial learning on the 7/24 Spatial Recall Test (SPART 24/7) was the strongest predictor of collisions.

Conclusion:
The SDMT and the SPART 24/7 may be clinically useful tools for cognitive screening to identify patients with deficits that have the potential to adversely affect driving skills.

The progression of MS causes physical and cognitive decline, and can lead to the loss of the ability to drive. To date, there are no well-defined tools for evaluating patients for cognitive skills in this regard.

Sixty-six patients with MS and a valid driver's license were recruited to participate in a series of neuropsychological tests, followed by a behind-the-wheel (BTW) assessment by a trained evaluator. Logistic analysis was used to examine the cognitive predictors of impaired driving behaviors based on the neuropsychological tests.

Of the battery of neuropsychological evaluations employed, information processing speed on the SDMT provided the best prediction of BTW performance. The strongest predictors of violations and collisions as captured in Department of Motor Vehicle (DMV) records from the past 5 years were visuospatial learning and recall on the SPART 7/24. The range of driving skills was narrow, however, limiting the capacity of these tests to show large differences. The SDMT and SPART 7/24 tests had a high specificity but a low sensitivity for identifying patients with impaired driving skills.

Commentary:
Kelly A. Ryan, PhD
Neuropsychologist, Department of Psychology
University of Michigan
Ann Arbor, Michigan

Studies that provide guidance on how to screen patients with MS for the ability to perform daily functions, including driving, are important. We do not have well-validated tools for these assessments, even though the issue of competence to drive is a common concern. The strength of this study is that it correlates specific types of cognitive performance with objective measures of driving. In particular, violations and accidents derived from DMV records offer a hard outcome even if they miss unreported minor accidents and near misses that might be relevant to driving performance. The enrollment of community-based patients with MS is also a strength of this study in that it assesses the types of patients most often seen in daily practice even if it does not represent the full range of MS disability. However, the differences in performance were very narrow and although the authors conclude that the SDMT and SPART 7/24 may be useful for screening, neither test met conventional measures of significance for differentiating driving risk, so the data do not support the conclusion. Despite this flaw, there is a need for these kinds of studies, and this investigation is a step in that direction. M

Walking while talking—Difficulties incurred during the initial stages of multiple sclerosis disease process.

First Author and Institution:
Alon Kalron, MD, Multiple Sclerosis Center, Sheba Medical Center, Tel Hashomer, Israel.

Citation:
Gait and Posture. 2010;33:332-335.

Objective:
Assess ability to walk and perform a simultaneous cognitive task in early multiple sclerosis (MS).

Type of Study:
Prospective analysis, comparison to healthy control group.

Result:
When combined with a cognitive task, patients in the initial stages of MS had a reduced walking velocity when compared with no task. Healthy controls had no change.

Conclusion:
The reduced ability of patients with MS, even at early stages of the disease, to walk and perform an additional task may be an unrecognized deficit that increases the risk of falls.

Disturbances in gait have been observed at very early stages of MS. Although walking is considered to be automatic in healthy individuals, cognitive tasks have been shown to affect walking in other neurological diseases, such as Parkinson's and Alzheimer's diseases.

In this study, gait was evaluated in 52 patients with clinically isolated syndrome (CIS) utilizing a standardized electronic walkway system (GAITrite electronic walkway system) with or without simultaneous performance of a modified word-list generation (WLG) test. Age- and gender-matched healthy subjects were assessed under the same conditions. The average age of the patients with CIS was 33 and the average Expanded Disability Status Scale (EDSS) score was 1.7.

In the absence of the WLG test, patients with CIS had a slower, more asymmetrical gait with a wider base of support than the controls. When the cognitive task was added, patients with CIS but not controls slowed their pace and needed increased prolonged double support.

This study reinforces previous evidence that gait disturbances occur at a very early stage in MS and increase when patients are simultaneously performing a cognitive task. To reduce accidents, the authors suggest identifying gait deficits early and employing specific rehabilitation to initially retrain patients for walking and performing cognitive tasks simultaneously, and to utilize compensatory strategies when retraining cannot be successfully achieved.

Commentary:
Susan Bennett, PT, DPT, EdD, NCS, MSCS
Clinical Associate Professor
Department of Rehabilitation Science
University at Buffalo
State University of New York
Buffalo, New York

This is a well-conducted study that emphasizes an important and emerging issue related to ambulation in individuals with MS. Although disturbances in gait are a common and well-recognized complication of MS, the issue of how multitasking affects gait deserves more attention. As this study demonstrates, simultaneous cognitive tasks do alter gait performance and may pose an important risk for falls or accidents. We have recently completed a study examining gait measures and have also identified that patients with MS have an impaired ability to perform multiple tasks simultaneously to a degree that is likely to be clinically significant.

This specific study provides evidence that it may be beneficial to screen patients for changes that can occur in gait during performance of a cognitive task to identify those who may benefit from rehabilitation designed to provide retraining in ambulation with multitasking. Clearly, more research is needed to determine what specific rehabilitation interventions might best help patients perform physical and cognitive tasks simultaneously, but this study provides a basis for considering this issue in current practice. The fact that this study was conducted in patients with CIS demonstrates that the impairments in multitasking evolve very early in the disease process. At our institution, we have begun to evaluate gait and balance among patients with MS in the context of a cognitive challenge, and are now considering and implementing treatment strategies. M

Assessment of outcome predictors in first-episode acute myelitis.

First Author and Institution:
Alberto Gajofatto, MD, Department of Neurological and Vision Sciences, University of Verona, Verona, Italy.

Citation:
Archives of Neurology. 2010;67:724-730.

Objective:
Identify outcome predictors in acute myelitis.

Type of Study:
Single-center, retrospective analysis.

Result:
A high rate (79%) of conversion of acute myelitis to multiple sclerosis (MS) correlated with traditional risk factors, but also included elevations of cystatin C in the cerebrospinal fluid (CSF).

Conclusion:
Elevated cystatin C in the CSF of patients with first-episode acute myelitis might be useful in the context of other signs and symptoms of progression to MS.

Acute myelitis has a broad array of etiologies, including infections, systemic inflammatory diseases, and MS. Due to the potential for serious consequences, more effective methods of identifying the cause of and the prognosis for this condition would be clinically useful.

In a single-center study of 53 patients with acute myelitis who were followed for a median of 6.2 years, variables, including a panel of CSF molecular markers, were evaluated for their ability to predict recovery and long-term outcome. Fifteen patients recovered from the initial episode, while 32 had mild disability and six had significant residual disability. Forty-three patients had ≥1 relapse during the follow-up period.

At the last follow-up visit, six patients were monophasic (11%), five patients had recurrent myelitis (9%), and 42 patients converted to MS (79%). Significant and persistent disability was observed in 15 of 32 patients with pyramidal symptoms at onset versus two of 21 without (P=0.006) and in 17 of 43 patients with relapses but none of 11 without (P=0.02). Upregulation of cystatin C in the CSF correlated with increased risk of long-term neurological disability in 11 patients (P=0.03).

Since the value of elevated cystatin C as a predictor of disability increased in patients who had at least one relapse during follow-up, the authors conclude that cystatin C is a promising early marker of a neurodegenerative disease in patients with a first episode of acute myelitis, but acknowledge that additional studies are needed.

Commentary:
Bruce Cree, MD
Assistant Professor of Neurology
University of California, San Francisco
San Francisco, California

There is a need for effective methods of distinguishing when a first episode of acute myelitis represents an early sign of MS. This study attempted to look for predictors of disability retrospectively, but the results are somewhat difficult to interpret. Because this study included patients with transverse myelitis and partial myelitis, they were not likely to share the same risk of neurological disability because the leading cause of partial myelitis is MS. The population also included those who had a high probability of MS at the onset based on clinical features such as an abnormal magnetic resonance imaging (MRI) scan. This makes the high rate of conversion from CIS to MS (79%) less surprising.

The suggestion that cystatin C may be a useful early biologic marker of MS is intriguing, but the authors tested a large set of markers simultaneously. The P *value for the association was relatively weak given that multiple comparisons were tested. The authors sent five CSF samples out for serum anti-aquaporin 4 antibody evaluation; however, theses results were not reported in this manuscript.*

While the authors conclude that CSF cystatin C level is a biomarker that helps identify patients with myelitis who are at higher risk for disability, prospective evaluation of myelitis patients in a multicenter cohort will be necessary to better define this potential association. Therefore, this study provides a potential direction for further research in CSF biomarkers in patients with myelitis. M

Glatiramer acetate reduces Th-17 inflammation and induces regulatory T-cells in the CNS of mice with relapsing-remitting or chronic EAE.

First Author and Institution:
Rina Aharoni, MD, The Weizmann Institute of Science, Rehovot, Israel.

Citation:
Journal of Neuroimmunology. 2010;225:100-111.

Objective:
Evaluate effect of glatiramer acetate (GA) on immunoregulatory cell populations.

Type of Study:
Series of prospective studies in animal models with relapsing-remitting and chronic courses of experimental autoimmune encephalomyelitis (EAE).

Result:
In two models of EAE, GA reduced proinflammatory cells and upregulated immune-regulatory cell populations.

Conclusion:
The impact of GA on immune-cell populations in EAE may explain much of the anti-inflammatory effect associated with this disease-modifying therapy (DMT) in the central nervous system (CNS).

In multiple sclerosis (MS), there is increasing interest in the role of a reciprocal pathway that involves the pro-inflammatory activation of Th17 T cells and the anti-inflammatory activation of T-regulatory cells (Tregs). Due to their reciprocal nature, it appears that upregulation of one leads to downregulation of the other. The dysregulation in these cell sets may be important for understanding autoimmune diseases and the activity of MS therapies.

In this study, the impact of GA on the Th17 and Treg cell populations was evaluated in EAE, a commonly used animal model of MS. Studies were conducted in both chronic and relapsing-remitting EAE in the presence and absence of GA.

Even in the absence of treatment, an initial upregulation of T cells with induction of EAE was followed by a downregulation of Th17, suggesting endogenous repair mechanisms. However, the introduction of GA not only reduced a variety of types of inflammatory activity but had a particularly pronounced inhibitory effect on Th17 cells. This was accompanied by a 2- to 3-fold elevation in Treg frequency.

The authors conclude that the benefits of GA in EAE are likely to be explained by parallel suppression of Th17 cells with stimulation of Treg expression. This activity appears to be relevant to both chronic and relapsing-remitting forms of EAE and might be involved in both neuroprotection and repair mechanisms.

Commentary:
Scott S. Zamvil, MD, PhD
Professor of Neurology
Faculty, Program in Immunology
University of California, San Francisco
San Francisco, California

While GA treatment of patients with MS has been associated with elevation of peripheral blood Treg cells, and GA treatment of EAE has led to increased Treg cells and down-regulation of Th17 cells in the peripheral immune compartments, it was not known whether GA treatment had a significant impact on these subsets within the CNS. Using elegant immunohistochemical approaches, these authors demonstrate that anti-inflammatory Treg cells accumulate within the CNS of GA-treated mice with EAE. Conversely, they also demonstrate a reduction in CNS Th17 cells. Thus, the clinical benefit of GA is associated with CNS elevation of both Th2 and Treg cells, and decreased levels of Th1 and Th17 cells.

*These authors also report that the proportion of Treg cells increases during EAE recovery in untreated mice, although presumably much less so than during GA treatment. This finding is consistent with an earlier observation by Korn et al. (*Nature Medicine. *2007), who demonstrated that CNS myelin-specific CD4+Foxp3+ T cells expand during natural recovery. The study by Aharoni and colleagues also demonstrates that GA-reactive T cells do not accumulate in the normal CNS but only in the CNS during EAE. In another study, GA-reactive T cells also accumulated in the gut in experimental inflammatory bowel disease (IBD), which supports previous evidence that GA-reactive T cells accumulate in inflammatory tissues independent of myelin antigen-specificity (Weber MS,* Nature Medicine. *2007), and raises the possibility that GA might have benefit in other autoimmune conditions such as IBD.* M

Surrogate endpoints for EDSS worsening in multiple sclerosis.

First Author and Institution:
Maria Piu Sormani, PhD, Biostatistics Unit, University of Genoa, Genoa, Italy.

Citation:
Neurology. 2010;75:302-309.

Objective:
Evaluate whether treatment effects on surrogate markers predict multiple sclerosis (MS) disability.

Type of Study:
Meta-analysis of randomized, double-blind trials.

Result:
In patients with MS who are taking immunomodulators, common disease outcome markers—particularly rate of relapse—correlate with worsening disability over time.

Conclusion:
Traditional MS outcome endpoints for predicting progression in a population of affected patients is validated by this study at a group level, but relevant markers for the individual patient are needed.

Measuring the efficacy of early interventions for MS has been complicated by the imperfect relationship between measurable changes, such as brain lesions on magnetic resonance imaging (MRI), and the risk of subsequent disability. While a reduction in relapses is considered a marker for effective therapy, there is limited evidence that relapses predict disability over time.

In this meta-analysis, the goal was to evaluate whether there is a correlation between the effects of therapy on surrogate markers, such as a reduction in new MRI lesions or relapses, and the effects on disability as measured by the Expanded Disability Status Scale (EDSS).

The meta-analysis pooled 19 randomized, double-blind trials of various anti-inflammatory disease-modifying therapies for patients with relapsing-remitting MS (RRMS). There were 44 arms evaluated in 10,009 patients. Based on a weighted meta-regression analysis, a worsening rate of relapses correlated with a worsening of the EDSS score in these group-level data (R^2=0.71). There was also a significant correlation between the ability of treatment to prevent new MRI lesions and protect against a worsening of the EDSS score, but this association was weaker (R^2=0.57)

The authors conclude that these findings support the value of common markers of treatment benefit for predicting protection against disability. While these data are relevant when comparing two treatment arms, they are not necessarily accurate for predicting benefit in the individual.

Commentary:

Gary Cutter, PhD
Professor of Biostatistics
Head, Section on Research Methods and Clinical Trials
University of Alabama at Birmingham
Birmingham, Alabama

These data reinforce the clinical impression that relapses in the early phase of RRMS track with risk of disability over time. This is not a perfect relationship, but they do appear to move together in a related way. This relationship was established with studies employing anti-inflammatory agents and may not be relevant to MS agents with a different mechanism of action, such as neuroprotection. For full disclosure, I was a co-author with this same group on another paper, also looking at the relationship between MRI lesions and relapses, and I am supportive of this insightful analysis.

Although we still do not know whether patients treated and untreated end up at the same point in 10 or more years, these data may provide support for current beliefs. We want more studies to confirm patients are better off long term, but these results are consistent with studies suggesting anti-inflammatory agents can delay disease progression for 8 or more years. Even though these data do not predict a reduction in disability from a reduction in relapses in the individual patient, they are not necessarily irrelevant to clinical practice. We often make decisions based on aggregate rather than individual benefit. Use of seatbelts that may never benefit the individual driver is an example. These data are useful for supporting our current assumptions about therapy. For those who argue that relapses do not matter for prognosis, these results would argue against that notion. Certainly, a relapse is not unimportant to the patient with MS who has one. M

Validation of a self-report comorbidity questionnaire for multiple sclerosis.

First Author and Institution:
Myles Horton, MD, University of Manitoba, Winnipeg, Canada.

Citation:
Neuroepidemiology. 2010;35:83-90.

Objective:
Validate a self-report method of identifying comorbidities in patients with multiple sclerosis (MS).

Type of Study:
Prospective, two-center study.

Result:
Agreement between the questionnaire and medical records was good for a broad array of major diseases and was considered a valid way to capture comorbidities in patients with MS.

Conclusion:
Less expensive and time-consuming than a review of medical records, self-report questionnaires to capture comorbidities may be useful for clinical care, particularly in patients with incomplete records.

Comorbidities are common in patients with MS. They can complicate or be complicated by the presence of MS and should, therefore, be considered in MS management. Evaluating medical records is one approach to establishing the presence of comorbidities, but this is time-consuming and may not be wholly accurate for patients who consult with multiple specialists or have incomplete records for another reason.

Self-report questionnaires have the potential to be more efficient and more accurate. They can be designed to elicit the information most important to clinicians and avoid both time-consuming history-taking or medical-records review. In this study, two participating MS centers collaborated to validate a self-report questionnaire by comparing correlations with medical records.

After a development phase and pilot testing, the 36-item questionnaire was administered to 404 patients. The mean age of the participants was around 45 years, more than 90% were white, and approximately 2/3 had at least a high school diploma, while 1/3 had less education. The questionnaire covered a broad array of comorbidities. Of the participants, 35% reported no comorbidities, 29% one comorbidity, 16% two comorbidities, and 20% three or more comorbidities on the questionnaire.

Agreement between the questionnaire and the medical records was very good for many major illnesses or conditions, such as diabetes and hypertension, was moderate for most serious but non-life threatening disorders such as migraine and osteoporosis, and was poor for several minor disorders. The authors conclude that the questionnaire is a reasonable method for capturing major comorbidities important to an MS population.

Commentary:
Aaron Miller, MD
Medical Director, Corinne Goldsmith Dickinson Center for Multiple Sclerosis
Mount Sinai School of Medicine
New York, New York

Being aware of comorbidities is an important part of optimal management in MS. This study showed that a questionnaire can provide a good correlation between self-reports and medical records for the major comorbidities that hold the most interest for clinicians. Although the correlation was weaker for many disorders less likely to influence MS management, this mismatch was often due to better recall from patients relative to the limitations of isolated medical records. However, there were also some mismatches produced by patients recounting comorbidities they did not have, such as vitamin B deficiency.

Relative to the type of history-taking a clinician might perform in a single visit, the questionnaire appears to be a useful tool for identifying significant comorbidities, but I am not certain that this is a tool that will be coming soon to clinical practice. The article was published in a neuroepidemiology journal, which is an appropriate place to raise this issue, but its clinical importance relates more strongly to the need to consider comorbidities in the treatment of MS than the need for a more efficient tool to perform this task.

This study may best serve as a wake-up call for clinicians to establish a consistent approach to inquiring about comorbidities, and for considering any relationship or influence that they have on MS and its treatment. M

Delaware Media GROUP

66 South Maple Avenue
Ridgewood, NJ 07450
201-612-7676

PRSRT STD
US POSTAGE
PAID
PERMIT 135
MIDLAND MI

Fall 2010

MULTIPLE SCLEROSIS MONITOR and Commentary

Practical Analysis on Today's Findings in Multiple Sclerosis

IN THIS ISSUE

- Cognition and driving performance
- Walking while talking
- Acute myelitis outcome predictors
- Glatiramer acetate's immunodulatory effects
- Surrogate endpoints for EDSS worsening
- Self-report comorbidity questionnaire

MS Monitor and Commentary is now available on the web at www.MonitorAndCommentary.com