MULTIPLE SCLEROSIS
MONITOR and Commentary
Practical Analysis on Today's Findings in Multiple Sclerosis
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From the editor...


ROBERT P. LISAK, MD

In this issue of *Multiple Sclerosis Monitor and Commentary*, our invited experts have been asked to evaluate studies with data of immediate practical use, as well as studies aimed at questions more basic to the pathophysiology of multiple sclerosis (MS).

On the practical side, Dr. Fred Lublin of Mount Sinai School of Medicine in New York City praises a study that supports evidence that poor recovery from initial attacks of MS is a prognostic sign for progression. He considers the finding useful for clinicians. From another study with immediate practical relevance, Dr. Elliot Frohman from the University of Texas Southwestern Medical Center in Dallas generally agrees with the assertion that early use of high-dose steroids may be even more important for the outcome after optic neuritis in patients with neuromyelitis optica than in those with MS, but he has criticisms about the study that generated this conclusion.

As for studies providing new insight into the mechanisms of MS, Dr. Daniel Pelletier of the University of California, San Francisco, points out a major flaw in a study that concludes patients with benign MS may avoid symptoms because of greater neurologic plasticity than those with conventional MS—even though he likes the general hypothesis. Similarly, Dr. V. Wee Yong of the University of Calgary in Canada likes the theory that ultraviolet B light has neuroprotective activity independent of vitamin D, but he is concerned about several problems with the model used to support this theory. Dr. Amit Bar-Or of the McGill University, also of Canada, supports the efforts to evaluate whether glatiramer acetate or any other disease-modifying therapy affect B cells as well as T cells, but he believes that the study evaluating this concept provides a better path for further discovery rather than hard conclusions.

Our expert commentaries do not provide the final word on the studies evaluated, but they do provide a second perspective. We encourage readers to consult the original sources for a more detailed understanding of the issues. If you have comments or suggestions, please feel free to reach me at msmonitor@delmedgroup.com.

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IN THIS ISSUE

MS MONITOR AND COMMENTARY

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Increased expression of B cell-associated regulatory cytokines by glatiramer acetate in mice with experimental autoimmune encephalomyelitis.

First Author and Institution:
Sakhina Begum-Haque, MD, Dartmouth Medical School, Lebanon, New Hampshire.

Citation:
Journal of Neuroimmunology. 2010;219: 47-53.

Objective:
Evaluate effects of glatiramer acetate (GA) on B-cell activities.

Type of Study:
Prospective study in experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis (MS).

Result:
GA biases B cells towards cytokines associated with beneficial modification of EAE disease activity.

Conclusion:
GA impacts both B-cell survival and cytokine production in a mouse model. Confirmatory studies in patients with MS are needed.

Autoimmune inflammatory diseases have been most closely associated with changes in the activity of T-regulatory cells, but a series of recent clinical studies has suggested that B-cell regulation of immune function also plays an important role in MS pathogenesis.

In this study, the effect of GA on B cells, particularly cytokine expression, was evaluated in mice with EAE relative to mice without EAE.

GA was associated with down-regulation of B-cell expression of several pro-inflammatory cytokines, including interleukin (IL)-6 and IL-12 and up-regulation of B-cell expression of several anti-inflammatory cytokines, including IL-4, IL-10, and IL-13. GA interfered with the expression of B-cell survival factors BAFF (B-cell activating factor of the tumor necrosis family) and APRIL (a proliferation-reducing ligand), and the BAFF receptor. GA also suppressed BAFF mRNA expression in the brain, while it suppressed APRIL mRNA expression in spleen cells.

The suppression of BAFF by GA is noteworthy because preserved B-cell function may be important for preventing inflammatory activity in the central nervous system. According to the authors, this action is not shared by all disease-modifying therapies. For example, interferon beta has been reported to up-regulate BAFF.

Commentary:
Amit Bar-Or, MD
Associate Professor of Neurology
Montreal Neurological Institute
McGill University Health Centre
Montreal, Canada

The potential importance of B cells as targets of therapy in autoimmune diseases has been developing over the past 5 or 6 years. This study provides additional information about B-cell subsets and cytokine activity in the EAE model. The study used appropriate methodology and builds on a growing literature that suggests that B cells are actively involved in mediating autoimmune disease processes.

The recent focus on B cells is an important trend in the efforts to unravel the molecular events in autoimmune pathology. The characterization of MS as a disease solely driven by T-cell activity appears to no longer be valid. However, it should be recognized that EAE, although an important model, is not MS. It is now critical to confirm that the B-cell activity in this model is representative of clinical MS. While the authors show effects on pro-inflammatory cytokines, anti-inflammatory cytokines, and factors that mediate B-cell survival, the relative importance of these for disease modification remains unknown even in this EAE model. The next step is not only to perform studies in humans that confirm the effects of GA on these B-cell activities, but to seek more understanding of B-cell regulatory function as a target for MS control. M

Preserved brain adaptive properties in patients with benign multiple sclerosis.

First Author and Institution:
Maria A. Rocca, MD, Institute of Experimental Neurology, Milan, Italy.

Citation:
Neurology. 2010;74:142-149.

Objective:
Compare functional brain changes in benign and progressive multiple sclerosis (MS).

Type of Study:
Prospective, controlled comparison.

Result:
When performing simple motor tasks, patients with benign MS had limited evidence of network functional impairment on functional magnetic resonance imaging (fMRI).

Conclusion:
Although the extent of pathology is often similar in benign and progressive MS of similar duration, adaptation in the brain tissue of patients with benign MS may explain their preserved neurologic function.

The extent of T2 lesions in benign MS, a designation based on preserved neurologic function 15 years after the diagnosis of disease, has been reported to be similar to that observed in patients with secondary-progressive MS (SPMS). One hypothesis is that patients with benign MS have adaptive signaling to counteract the effects of damage to brain tissue.

In this study, motor network function was monitored during the performance of simple motor tasks with (fMRI). The study included 17 patients with benign MS, 15 patients with SPMS, and 17 healthy controls. The two groups of patients were matched for age, gender, and disease duration. In addition to fMRI, histograms of the normal-appearing white and gray matter were evaluated with diffusion tensor MRI.

Relative to healthy controls, patients with benign MS and SPMS had increased activation of the left primary sensorimotor cortex when performing tasks with the right upper limb. Patients with SPMS also showed increased activation of the left middle occipital gyrus, right hippocampus, right fusiform gyrus, left secondary sensorimotor cortex, left middle temporal gyrus, and left inferior frontal gyrus. In comparison to the other two groups, SPMS subjects also demonstrated reduced activation of the left supplementary motor area, left putamen, and the right cerebellum. Finally, compared with patients with SPMS, those with benign MS had increased activation of the anterior lobe of the right cerebellum, left supplementary motor area, and left putamen.

The results suggest that patients with benign MS have an adaptive capacity not shared by those with SPMS.

Commentary:
Daniel Pelletier, MD
Associate Professor of Neurology and Radiology
Andy and Debbie Rachleff Distinguished Professor of Neurology
Director, Advanced Imaging in Multiple Sclerosis (AIMS) Laboratory
University of California, San Francisco
San Francisco, California

This is the first head-to-head comparison of benign to secondary progressive MS with functional brain imaging and is, in that sense, a novel study. The authors conclude that the increased sensorimotor activation in patients with benign MS may demonstrate a sign of plasticity or adaptation that explains the preservation of neurologic function. However, there is a fundamental problem with this and other studies focused on this same issue. The association of greater white matter injury (T2 lesions) with greater fMRI changes may reflect a significant disconnection between cerebral hemispheres. In MS, increased ipsilateral activation may be the result of a lack of normal inhibitory signal generated from the contralateral hemisphere. However, it is a difficult task to overcome with current fMRI methods. One potential approach is to perform a multivariate analysis and use covariates to correct for the influence of T2 white matter lesion volume on the degree of activation.

Whether or not there is brain adaptation in patients with benign MS is a crucial question and would be useful to better understand the disease. Even in this exploratory analysis with a small sample size, it would have been important to introduce and discuss this potential confounder. Controlling for inhibitory signaling will be important for any study attempting to look at fMRI activation as a sign of brain plasticity. M

Comprehensive follow-up of the first genome-wide association study of multiple sclerosis identifies *KIF21B* and *TMEM39A* as susceptibility loci.

First Author and Institution:
The International Multiple Sclerosis Genetics Consortium (IMSGC).

Citation:
Human Molecular Genetics. 2010;19:953-962.

Objective:
Expand genetic associations of multiple sclerosis (MS) beyond those already identified.

Type of Study:
Genotyping of >30,000 single-nucleotide polymorphisms (SNPs) in patients with MS and controls.

Result:
Many loci beyond those originally identified in previous studies, including KIF21B and TMEM39A, have highly significant associations with MS, suggesting a complex genetic determination of risk.

Conclusion:
The large and expanding genetic associations for MS suggest that familial risk factors for this disease are complex and that the understanding of genetic risk factors may be at an early stage.

A couple of years ago, a study that screened more than 300,000 SNPs identified several strong associations between specific genes and the risk of MS. In a new study by the same group, a more comprehensive screening was undertaken with the goal of expanding the number of associations, including those with mild to moderate significance.

In the new study, conducted in stages, genotype data on 29,561 SNPs from 1,343 MS cases and 3,577 controls were evaluated. In the first stage, many of the top hits from the first study were replicated, but a second stage was conducted to evaluate SNPs with a more modest association.

Of 19 new SNPs of interest, five met conservative estimates of genome-wide significance. When data from this most recent set of cases and controls were combined with data generated by the set of cases and controls used in the previous study, four remained significant. Of these, one SNP was within or in proximity of KIF21B on chromosome 1, another was associated with TMEM39A on chromosome 3, and two, on C16orf75 and PRM1, were found on chromosome 16.

With a more detailed evaluation of SNPs associated with MS, this study has identified new loci potentially important in determining genetic susceptibility to MS. The identification of other loci associated with significant increased risk of MS suggests that the top hits previously reported are not likely to fully explain genetic susceptibility to MS. The authors characterize these new loci as functionally interesting, citing evidence, for example, that KIF21B is implicated in a direct neurodegenerative role.

Commentary:
Daniela Galimberti, PhD
Department of Neurological Sciences
Dino Ferrari Center
University of Milan
Milan, Italy

This was a well-planned study with good methodology, but the impact of this information on how we understand MS is likely to be relatively modest. The odds ratio for developing MS in the presence of the loci identified was quite small, suggesting that these are not strong predictors of risk. In addition, the cases were not stratified by the subtype of MS, which is likely to be important in understanding how specific associations influence MS risk. For example, primary-progressive MS may not be driven by the same up-regulation of inflammatory factors as relapsing-remitting MS. Without differentiating gene associations within these subtypes, it is possible that important loci will be masked.

Another problem with studies focused on genome-wide associations alone is that they overlook the role of epigenetics, which are likely to be important for mediating expression or lack of expression of implicated genes.

It is clear from studies so far that the genetics of MS are complex. Although the findings from this study are likely to be of limited value for clinical application, such as early diagnosis of MS, the effort to identify all loci that may participate in increasing the susceptibility for MS is an important step toward a more comprehensive understanding of this disease. M

UV radiation suppresses experimental autoimmune encephalomyelitis independent of vitamin D production.

First Author and Institution:
Bryan R. Becklund, MD, University of Wisconsin, Madison, Wisconsin.

Citation:
PNAS. 2010;107:6418-6423.

Objective:
Explore possibility that ultraviolet B (UVB) light lowers autoimmune risk independent of vitamin D.

Type of Study:
Controlled experiments in a mouse model of encephalomyelitis.

Result:
Continuous UVB light suppressed clinical signs of experimental autoimmune encephalomyelitis (EAE) with little effect on the 25(OH)D3 level, the commonly measured form of vitamin D.

Conclusion:
The association between UVB light exposure and reduced risk of multiple sclerosis (MS) has been attributed to increased vitamin D production, but this study suggests UV light has an independent, protective effect.

An increased prevalence of MS in higher latitudes where there is a relative reduced exposure to UVB light is among the evidence that UVB light exposure offers protection against this autoimmune disease. The prevailing hypothesis is that UVB spurs endogenous production of vitamin D, which is believed to have anti-inflammatory and/or neuroprotective effects.

To test whether UVB light offers independent protection against autoimmune diseases, a series of studies was conducted in the EAE model. When mice were exposed to UVB light, levels of serum 25(OH)D3 were measured to monitor vitamin D availability. Other downstream factors related to vitamin D metabolism, such as serum calcium levels, were also monitored. The effect of each variable was assessed with standardized EAE scoring.

Although continuous UVB light significantly suppressed clinical signs of EAE, it had a relatively modest effect on 25(OH)D3 levels. Indeed, these levels were not significantly different from levels observed in control mice by the end of the experiment, which lasted 30 days after immunization with MOG35-55. Dietary administration of 25(OH)D3 had no effect on EAE disease activity.

This study supports the hypothesis that UVB light offers protection against neurodegenerative autoimmune diseases by a mechanism independent of vitamin D metabolism. The increases in serum levels of vitamin D with UVB light exposure were not sufficient for a protective effect, and there was no protection from EAE observed with vitamin D supplementation independent of UVB light exposure.

Commentary:
V. Wee Yong, PhD
Professor, Department of Clinical Neurosciences
University of Calgary
Calgary, Canada

It is possible that UVB light has a protective effect independent of its ability to up-regulate vitamin D availability, and this an interesting focus of research. However, one must be cautious in extrapolating the current studies undertaken in a mouse model of encephalomyelitis (EAE) to MS in man. In particular, mice are nocturnal animals, so the effects of UVB light are quite likely to be different than they are in humans. In fact, while the authors found that UVB light exposure did not increase 25(OH)D3 levels, others have shown that UVB light exposure in humans to a degree where there is a pinkish hue to the skin raises serum 25(OH)D3 levels substantially. Perhaps, in mice, UVB light alters vitamin D status in a manner independent of 25(OH) D3 levels, but still dependent on the active form of vitamin D, 1,25(OH$_2$)D3. Thus, in mice, there may be a very different relationship between UVB light, the active form of vitamin D, and the effect on immune modulators.

The contention that UVB light ameliorates EAE independent of vitamin D would be stronger if the authors had also demonstrated that UVB light exposure was still protective in EAE mice selected for the absence of vitamin D receptors, to which active vitamin D must bind.

The authors have tackled an interesting issue but have not been able to dispel completely the long-standing hypothesis that UVB light primarily offers protection against MS by up-regulating vitamin D. M

Early high-dose intravenous methylprednisolone is effective in preserving retinal nerve fiber layer thickness in patients with neuromyelitis optica.

First Author and Institution:
Masahiko Nakamura, MD, Tohoku University Graduate School of Medicine, Sendai, Miyagi, Japan.

Citation:
Graefe's Archive for Clinical and Experimental Ophthalmology. 2010;Epub ahead of print.

Objective:
Compare patients with neuromyelitis optica (NMO) and multiple sclerosis (MS) with and without episodes of optic neuritis (ON).

Type of Study:
Retrospective evaluation of medical records.

Result:
Early intervention with high-dose intravenous methylprednisolone after onset of ON may be even more important in patients with NMO than MS because of greater and more rapid loss of optic nerve axons.

Conclusion:
In patients with ON, an early differential diagnosis between NMO and MS is important because the risks and management of nerve fiber damage differ in these groups.

NMO differs from MS in several ways, including in regard to histopathology. In this retrospective study, the clinical course was reviewed for 35 eyes in 18 patients with NMO and 28 eyes in 14 patients with MS in the context of change in retinal nerve fiber layer thickness (RNFLT) as measured with optical coherence tomography (OCT). At baseline, RFNLT was thinner in patients with NMO.

RNFLT and best-corrected visual acuity were significantly correlated in both groups. Relapse rate was an important predictor of RNFLT loss only in the NMO group. The authors credited the early use of high-dose methylprednisolone to a reduction in relapses and a preservation of RNFLT in the NMO group.

The association of early treatment with preservation of RNFLT and visual acuity in NMO led the authors to urge early diagnosis and treatment in patients with ON who are positive for anti-AQP4 antibodies, which are diagnostic for NMO. Relative to NMO, MS inflammation appears to pose less risk for RNFLT loss.

Commentary:
Elliot Frohman, MD, PhD
Professor of Neurology and Ophthalmology
University of Texas Southwestern Medical Center
Dallas, Texas

Beyond the inherent problems of a retrospective study with a relatively small number of patients, some important parts of the methodology of this study were not explained. For example, it is not clear if these patients were drawn from a systematic chart review or selected by some other set of criteria.

The paper's results are consistent with previous studies, including one by our group, which correlates visual outcome following ON with RNFLT, but there are problems in this cross-sectional study with the conclusion that RFNLT is thinner in patients with NMO than MS, given that we have no information concerning the temporal relationship between the onset of visual symptoms in relation to the first OCT measurement. Although it is probably correct that early use of high-dose steroids improves outcome in patients with NMO, the authors used high-contrast visual acuity testing, which is less effectively correlated with RNFLT than low-contrast letter acuity or contrast sensitivity testing.

Although they recommend the AQP4 antibody as a diagnostic test, there are several problems with this approach. First, the results of the test may not be available within the 1 to 2 days they identify as being important to an improved outcome. In addition, an AQP4 antibody test only has a sensitivity of 50% to 75%. As such, a negative test would not preclude the NMO diagnosis or a benefit from steroid treatment whether the etiology is NMO or MS. In the ON Treatment Trial, those treated with high-dose steroids recovered faster, but also showed a benefit on preservation of low-contrast sensitivity at 6 months, the risk period during which the greatest degree of axonal loss is thought to occur after ON. M

Poor recovery after the first two attacks of multiple sclerosis is associated with poor outcome five years later.

First Author and Institution:
Thomas F. Scott, MD, Drexel University College of Medicine, Pittsburgh, Pennsylvania.

Citation:
Journal of the Neurological Sciences. 2010;292:52-56.

Objective:
Identify factors that predict progression in multiple sclerosis (MS)

Type of Study:
Retrospective analysis of single-center MS population.

Result:
On regression analysis, poor recovery from the first two attacks of MS was the best single predictor of progression 5 years after diagnosis, including a greater likelihood of experiencing disability.

Conclusion:
This study joins others in suggesting that greater early disease activity predicts greater progression even in an era in which most patients are started early on disease-modifying therapy (DMT).

MS is a heterogeneous disease with a largely unpredictable course, preventing clinicians from determining relative risk for progression over any given period of time. This lack of predictability complicates management decisions, including whether to offer aggressive therapy early in the disease course. Better prognostic markers are needed.

In this study, five risk factors were evaluated for their ability to predict progression in a series of patients followed over a period of more than 16 years. These risk factors were age greater than 40 at the time of the first attack; more than two attacks within the first 2 years of onset; an Expanded Disability Status Scale (EDSS) score >1.5 sustained for at least 6 months after the second attack or disease-defining follow-up magnetic resonance imaging (MRI) showing lesion evolution; male gender; and motor symptoms at onset.

When a regression analysis after an average follow-up of 94 months was performed on 207 patients, poor recovery after the first two attacks had the strongest individual predictive value for progression, when defined as either EDSS ≥3.0 or EDSS ≥6.0. Poor recovery after the second attack was associated with a 2.9-fold (P<0.001) increased relative risk of progression. In addition, the authors found that >2 risk factors increased the relative risk of progression 2.1-fold (P<0.001) relative to fewer risk factors.

This study supports the premise that patients with MS who recover more slowly after two attacks are more likely to experience progression over extended follow-up. Although the same observation has been made previously, most of the patients in this series had initiated DMTs soon after their diagnosis. The authors suggest more aggressive treatments may be appropriate for patients with MS with poor recovery after initial attacks.

Commentary:

Fred Lublin, MD
Director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis
Mount Sinai School of Medicine
New York, New York

For the clinician, the problem with the prognostic factors identified so far in MS is that they are somewhat predictive for a population of patients but they have very modest predictive value for the individual patient. This study used sound methodology to provide further confirmation that poor recovery from early attacks of MS predicts an increased risk of progression after 5 years. The fact that poor recovery from MS attacks in the early course predicts greater disability over time is a logical expectation, but it is useful to have these confirmatory data, which will be helpful for clinicians planning care.

One of the questions not answered by this study is whether the risk of progression posed by poor recovery early in the disease course is modified by treatment. If the importance of poor recovery after the first two attacks of MS is confirmed as a useful prognostic marker in a larger population of patients with MS, several additional questions will be raised, such as whether these patients should be managed differently. Certainly, much more work of this kind is needed. M

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