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, Dr. Mark Freedman of the University of Ottawa critiques a study addressing one of the most interesting puzzles in multiple sclerosis (MS): What is the key initiating event? The latest study was conducted in a pediatric population, and explores the chicken-and-egg problem of trying to isolate any single event as the key to rather than the result of the inflammatory process. Another, more immediately practical commentary from Dr. Tanuja Chitnis of Harvard Medical School is based on a study of criteria to diagnose MS in children. She praises the study for comparing the two most common magnetic resonance imaging (MRI) criteria side by side (McDonald and KIDMUS) but uses this platform to emphasize the need for better help in evaluating children with ambiguous MRI findings.

One of the most important roles for our commentators, who are specifically enlisted to evaluate studies in areas where they themselves are active researchers or which they have been following closely, is not just to critique the findings but to determine whether the study had a design capable of answering the question. Professor Nils Erik Gilhus of the University of Bergen, for example, notes that there are many good reasons to tell patients with MS not to smoke, but he explains exactly why a study showing greater MRI pathology in smokers versus non-smokers does not provide proof that smoking makes a difference in MS.

In this, our final issue for 2009, we hope that we have assembled our usual eclectic range of articles capable of reflecting the diversity of research in MS. The goal is a publication that adds perspective to common issues in MS, is easy to digest, and is engaging to read. For those who find a topic interesting, we always recommend consulting the original article in which the introduction and discussion sections in particular may provide valuable context. 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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Smoking is associated with increased lesion volumes and brain atrophy in multiple sclerosis.

First Author and Institution:
Robert Zivadinov, MD, PhD, State University of New York, Buffalo.

Citation:
Neurology. 2009;73:504-510.

Objective:
Compare magnetic resonance imaging (MRI) scans of smokers and non-smokers who have multiple sclerosis (MS).

Type of Study:
Prospective study with MRI.

Result:
Patients with a history of smoking had higher brain lesion volumes and more brain atrophy than patients with no history of smoking.

Conclusion:
The findings of this study are consistent with previous theories that the effects of smoking can be identified beyond the blood:brain barrier and may contribute to the progression of MS.

Several studies have associated smoking with an increased risk of MS, including studies showing a greater rate of conversion from a clinically isolated syndrome (CIS) to MS among smokers relative to non-smokers. However, few studies have examined the effect of smoking on MS with an objective tool.

In this study, the goal was to employ MRI to correlate smoking with MS pathology. Three hundred sixty-eight patients with MS were studied and any history of smoking was associated with highly significant increases in T1 (P=0.003), T2 (P=0.009) and gadolinium contrast-enhancing (P=0.043) lesion volumes. MRI also associated smoking with a decrease in parenchymal fraction (P=0.047) and increases in both lateral ventricle volume (P=0.009) and third ventricle width (P=0.024). Compared with non-smokers and consistent with the MRI findings, smokers had significantly increased Expanded Disability Status Scale (EDSS) scores (P=0.004).

Commentary:
Nils Erik Gilhus, MD
Professor of Neurology
Department of Clinical Medicine
University of Bergen
Bergen, Norway

The relationship between smoking and MS has been debated for some time. This is an interesting study that clearly supports an association, but it cannot be considered conclusive. Significant group differences were observed for both EDSS and MRI parameters between those who had smoked at least 6 months and those who had never smoked, but the effect of smoking seemed to be small and hardly suggested this as a major factor.

One reason to be cautious when interpreting these results is that no significant difference was observed between current smokers and ever-smokers. Thus, having stopped smoking did not appear to influence results. If smoking was an important factor, a correlation between the amount of smoking and MS severity on the basis of MRI would be expected. Also, it is particularly difficult to isolate smoking as a potential causative disease factor because it is associated with so many other types of variables, such as diet and alcohol intake, that might also be important risk factors.

Although this represents an important and relevant investigation, a study that demonstrated a difference in lesion and disease progression between patients with MS who quit or continued smoking would produce an even better demonstration of an effect. At the current time, we can safely advise patients to stop smoking for a variety of very strong health reasons, but this study does not give us a scientific basis for concluding that patients with MS who stop smoking will have a better outcome. M

Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe study): A randomised, double-blind, placebo-controlled trial.

First Author and Institution:
Giancarlo Comi, MD, Scientific Institute San Raffaele, Milan, Italy.

Citation:
Lancet. 2009;374:1503-1511.

Objective:
Assess ability of early administration of glatiramer acetate (GA) to delay the onset of clinically definite multiple sclerosis (CDMS).

Type of Study:
Multicenter, randomized, double-blind, placebo-controlled trial.

Result:
GA reduced the risk of progression to CDMS by 45% relative to placebo in patients with a clinically isolated syndrome (CIS).

Conclusion:
The study confirms that GA controls the pathological process initiated with a CIS and reduces the risk of a second neurologic attack, potentially reducing the rate of accumulated disability.

The identification of irreversible axonal damage at the first attack of MS provides a rationale for initiating disease-modifying agents during a CIS, the term for a neurological attack that has not yet produced lesions in the central nervous system (CNS) diagnostic of MS. GA, a disease-modifying therapy (DMT), is currently approved for the treatment of relapsing-remitting MS.

In this study, 481 patients at 80 sites in 16 countries with a CIS (unifocal manifestation with ≥2 T2-weighted brain lesions weighing ≥6mm on magnetic resonance imaging [MRI]) were randomized to 20 mg GA per day or placebo for up to 36 months. The primary endpoint was time to CDMS based on a second neurological attack. An interim analysis was conducted when 81% of patients had completed a 3-year exposure.

At the interim analysis, the risk of CDMS was reduced by 45%, producing a hazard ratio (HR) of 0.55 (95% CI 0.40-0.77; P=0.0005). The time for 25% of patients to convert to CDMS was almost doubled (722 days on GA versus 336 days on placebo). On MRI, new T2 lesions were reduced 58% (P<0.0001) by GA relative to placebo, as were cumulative T2 and gadolinium-enhancing lesions (P<0.0001 for both). Injection-site reactions were more common among patients receiving GA (56%) than placebo (24%). Patients on placebo had more serious adverse events than those on GA and there were no differences in laboratory findings between the two groups.

The consistency of the clinical benefit with the reduction in activity on MRI demonstrates that GA is an effective option for reducing the risk of CDMS in patients presenting with a CIS. The potential for early intervention to reduce long-term disability has yet to be demonstrated, but could be predicted based on this protection from progression.

Commentary:
Howard L. Zwibel, MD
Medical Director
Multiple Sclerosis Center
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This was a well-conducted study performed by leading clinical investigators in the field of MS. By meeting the clinical endpoints with this magnitude of effect, the study demonstrates that GA delays progression from CIS to CDMS. As was emphasized by the authors, the robust reduction in disease activity as measured by MRI—including a significant reduction in the number of new T2 lesions, the T2 lesion volume, and the number of gadolinium-enhancing lesions—reinforces the primary clinical endpoint.

The study demonstrates that clinicians should now feel comfortable using GA in patients with CIS to prevent progression to CDMS. The results also suggest that the range of activity with GA is comparable to that observed with the beta interferons. Of interest in this 3-year trial was that the incidence of lipoatrophy was only 3%. In fact, GA was well tolerated in this study, as it has been in past studies.

Although not all patients with CIS may opt to initiate a disease-modifying drug, we now have data from this trial to verify that early use of GA can be effective for delaying conversion to CDMS. M

Age-dependent B cell autoimmunity to a myelin surface antigen in pediatric multiple sclerosis.

First Author and Institution:
Katherine A. McLaughlin, MD, Dana-Farber Cancer Institute, Boston, Massachusetts.

Citation:
Journal of Immunology. 2009;183:4067-4076.

Objective:
Evaluate relative presence of myelin autoantibodies in pediatric multiple sclerosis (MS).

Type of Study:
Flow cytometric analysis of serum samples from patient cohorts.

Result:
Children under the age of 10 had a much higher prevalence of autoantibodies to myelin surface antigens (38.7% versus 14.7%) than older children.

Conclusion:
The different profile of autoantibodies in younger children relative to older children may provide insight about the disease processes of early-onset MS.

The setting of early onset of MS in children offers a unique opportunity to examine what might truly be the earliest immunologically relevant event in the disease pathogenesis. Antibodies directed against myelin proteins are purported to play a role in the disease, but whether they are responsible for inciting disease or develop in reaction to it is still unknown. Most myelin proteins are unexposed in their native state, but would be available to the immune system once damage occurs.

This is an impressive and ambitious study that represents an enormous amount of work both in respect to sample collection and the performance of sophisticated analyses.

These authors looked at a unique pediatric MS cohort for evidence of early immunoreactivity to myelin proteins, specifically myelin oligodendrocyte glycoprotein (MOG), since it is the only myelin antigen exposed in its native state. The finding of higher antibody titers directed to MOG in this very early disease cohort could implicate them as more likely to be disease "causing" rather than epiphenomena.

MOG autoantibodies were found in 4.3% of 254 sera samples from adults but 21.3% of 131 sera samples from children. Even more striking was the inverse correlation between MOG autoantibodies and age. While MOG autoantibodies were found in 14.7% of children aged 10 to 18 years, they were found in 38.7% of children younger than 10. Antibodies to two other surface antigens were common in adults but largely absent in children.

Commentary:
Mark S. Freedman, MD
Director, Multiple Sclerosis Research Unit
The Ottawa Hospital – General Campus
Professor of Neurology
University of Ottawa
Ottawa, Canada

This is an impressive and ambitious study that represents an enormous amount of work both in respect to sample collection and the performance of sophisticated analyses. The authors deserve credit for seeking appropriate controls and performing a broad range of evaluations that help to confirm that MOG antibodies are found more frequently in children than adults.

In effect, the study revisits a controversy that was greatly debated about a decade ago. What is the first event leading to demyelination in MS? This study, looking at very young children, provides support for formation of an antibody to MOG as this first step. However, it does not resolve the chicken-or-egg debate that surrounds this issue. Antibodies to MOG were found in only 21% of children, more commonly in the youngest of patients, but this leaves ~80% of MS unexplained. There are other potential issues which argue against MOG antibodies as the key initial event, such as the fact that MOG antibodies were found in high titers in sera but not in spinal fluid (although few cerebrospinal fluid samples were analyzed).

Although this study provides good circumstantial evidence that MOG antibodies are an important early event, more proof is needed. For example, it would be compelling to see Koch's postulates regarding a putative antigen addressed even in the experimental setting. Would disease resolve if antibodies are removed? Could these human antibodies induce disease de novo *in animals? Could tolerization to MOG prevent disease? And finally, are there cases of mothers with MOG antibodies measurable in serum that have babies suspected of early MS?* M

Magnetic resonance imaging at first episode in pediatric multiple sclerosis retrospective evaluation according to KIDMUS and lesion dissemination in space criteria.

First Author and Institution:
Asli Kurne, MD, Hacettepe University, Ankara, Turkey.

Citation:
Brain & Development. 2009; Epub ahead of print.

Objective:
Evaluate fulfillment of different magnetic resonance imaging (MRI) diagnostic criteria within 3 months of the first relapse for children with multiple sclerosis (MS).

Type of Study:
Retrospective review of MRIs at multiple institutions.

Result:
A small but substantial proportion of children with MS do not meet MRI diagnostic criteria at the time of the first relapse.

Conclusion:
Lack of prominent brain lesions rather than insensitive MRI criteria may be the obstacle to early diagnosis of MS in children with atypical features.

In children with MS, MRI findings are often atypical. The optimal set of criteria for establishing clinically definite MS remains controversial.

In this retrospective review in children and adolescents with clinically definite MS and at least 1 year of follow-up, the MRI findings within 3 months of the first relapse were re-evaluated using the McDonald and KIDMUS sets of criteria.

Of the 30 children evaluated, 25 (83.3%) fulfilled both the McDonald and KIDMUS criteria. The one child who met one set of criteria but not the other did not have lesions perpendicular to the corpus callosum (KIDMUS criterion). One patient negative for most MRI criteria demonstrated oligoclonal bands on cerebrospinal fluid (CSF) analysis. In the five patients who did not meet McDonald MRI criteria, two had brainstem symptoms, one had symptoms suggesting >1 neuroanatomic location for disease activity, and two had an optico-spinal pattern for symptoms. Expanded Disability Status Scale (EDSS) scores were similar among those who did and did not fulfill diagnostic criteria.

The authors conclude that the McDonald and KIDMUS criteria offer similar sensitivity, and CSF analysis may help in negative patients.

Commentary:
Tanuja Chitnis, MD
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Brigham and Women's Hospital
Assistant Professor of Neurology
Harvard Medical School
Boston, Massachusetts

Studies evaluating the fulfillment of the McDonald and KIDMUS criteria in children with MS are potentially useful. One novel aspect of this study was the side-by-side comparison of these two MRI criteria at the time of the first relapse, and the inclusion of CSF testing. However, there are some obstacles for evaluating the relevance of these data to other centers. One is that the MRI protocols were not standardized, which has the potential to affect the relative sensitivity of the two sets of criteria evaluated. While the average age at onset was 11.9 years, only six children in this series were under the age of 10, which is important because it has been noted in previous studies that younger children are more likely to have atypical MRI features. Although the authors conclude that the sensitivity of the two criteria are similar, a higher proportion met the McDonald criteria than the KIDMUS criteria (83% versus 64%, respectively). This study also did not formally assess the predictive value of the McDonald or KIDMUS criteria in children with an initial demyelinating event.

A more useful study would not only employ a standardized MRI protocol and include younger children, but also prospectively follow patients from the first demyelinating event and include data on clinical, genetic, and immunological variables.

The take-home message from this study is that the majority of adolescents with MS meet the McDonald and KIDMUS MRI criteria similarly at the time of the first attack, and that CSF testing may provide some additional information in ambiguous cases, but more diagnostic guidance is needed in difficult cases. M

Magnetization transfer ratio abnormalities reflect clinically relevant grey matter damage in multiple sclerosis.

First Author and Institution:
LK Fisniku, MD, Institute of Neurology, University College London, London, United Kingdom.

Citation:
Multiple Sclerosis. 2009;15:668-677.

Objective:
Evaluate correlation between grey matter (GM) changes and risk of long-term disability.

Type of Study:
Retrospective evaluation over 20 years.

Result:
On mean magnetization transfer ratio (MTR), GM peak height and GM fraction correlated with increased disability as assessed by the Expanded Disability Status Scale (EDSS) and MS Functional Composite (MSFC).

Conclusion:
GM changes are a more sensitive prognostic marker than white matter (WM) changes. More data are needed to determine how this information can be incorporated into clinical care.

Efforts to measure GM atrophy have been pursued because of the potential for changes in this area of the brain to track more closely with clinical disability than WM lesion load, which has not demonstrated a particularly strong correlation with disease progression.

In this study, 69 patients who have now been followed for a mean of 20 years (range 18 to 27 years) since presenting with a clinically isolated syndrome (CIS) were evaluated with MTR, which is sensitive for detecting tissue damage. MTR changes in the GM and normal-appearing WM (NAWM) were evaluated in the context of changes in the EDSS and MSFC scores and compared to MTR results in 19 healthy controls.

GM peak height on MTR, a measure of damage, correlated with changes in EDSS and MSFC scores and independently predicted disability. GM fraction also correlated with disability scores on the EDSS and MSFC. MTR values for NAWM mean and peak location provided significant distinctions between patients with MS and controls, CIS and relapsing-remitting MS (RRMS) as well as patients with secondary-progressive MS relative to RRMS, but were a less sensitive predictor of disability than MTR measures of GM.

The authors conclude that MTR abnormalities are found in both NAWM and GM but that GM abnormalities correlate better with clinical outcomes. These results suggest that MTR may provide more clinically relevant information for following patients long term than T2 lesion loads.

Commentary:

Omar Khan, MD
Professor of Neurology
Director, Multiple Sclerosis Center & Image Analysis Laboratory
Wayne State University School of Medicine
Detroit, Michigan

This is yet another remarkable study that is part of an almost 25-year-old ongoing effort by the Queens Square group led by David Miller. In this study, Fisniku et al studied MTR-based myelin tissue injury in the GM and WM after segmentation. They demonstrated the effect of GM injury on clinical disability, assessed via EDSS and MSFC scores, which accounted for almost 50% of the variance. At the same time, there was no correlation between NAWM MTR and EDSS score but a modest correlation with the MSFC score.

This is yet another remarkable study that is part of an almost 25-year-old ongoing effort by the Queens Square group led by David Miller.

This study supports previous observations published by the same group showing that GM volume and not WM volume correlates with secondary progression in MS (Fisniku et al, Ann Neurol. *2008), which was also confirmed in a longitudinal study by Fisher et al (*Ann Neurol. *2008). My colleagues and I have also demonstrated a strong association between GM volume and EDSS, as well as elevated cerebrospinal fluid (CSF) IgG index, suggesting a possible role of B-cell mediated humoral effect leading to GM injury (Khan et al,* Neurology. *2009). Further long-term studies are needed to provide insight into the longitudinal evolution of GM injury and atrophy in MS and to determine if there is a differential immune system effect in the WM and GM compartments in the CNS. This may consequently lead to better therapeutic strategies in MS with the primary goal of reducing long-term disability.* M

Multisequence-imaging protocols to detect cortical lesions of patients with multiple sclerosis: Observations from a post-mortem 3 Tesla imaging study.

First Author and Institution:
Francesca Bagnato, MD, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland.

Citation:
Journal of the Neurological Sciences. 2009;282:80-85.

Objective:
Compare multisequence-imaging protocols for detection of neocortical lesions in patients with multiple sclerosis (MS).

Type of Study:
Autopsy study.

Result:
The tested imaging sequences tended to provide complementary information about the presence of neocortical lesions, and the combination of different imaging sequences increased sensitivity.

Conclusion:
Conventional imaging techniques can be optimized to improve sensitivity for detection of neocortical lesions, although histopathological studies are needed to validate clinical relevance.

There is significant interest in developing effective methods of quantifying neocortical lesions in patients with MS because of their potential to provide prognostic information. These lesions are relatively small and provide poor contrast for visualization against normal gray matter. Despite improvements in the resolution of magnetic resonance imaging (MRI) and expansion of MRI protocols, progress in this area has been modest.

In this autopsy study conducted with tissue samples from a single patient who had advanced MS and severe cognitive impairment at the time of his death at age 70, four coronal slices were evaluated with several MRI protocols with results compared to slices obtained from cadavers without MS at the time of death. The protocols included enhancing lesion appearance by optimizing inversion time of T1-based magnetization-prepared rapid acquisition gradient-echo (MPRAGE) images from quantitative T1 measurement maps, and proton-density weighted (PDW) and dual echo T2-weighted (T2W) imaging at 3 Tesla.

No neocortical lesions were observed for non-MS tissue, but 40 lesions were detected with the imaging techniques in the MS patient. Of these, only eight (20%) could be identified with all methods of visualization. Alone, MPRAGE uniquely identified 10% of lesions, PDW found 7.5%, and T2W identified 12.5%.

The authors correctly point out that the study has several limitations, including the fact that tissue was evaluated in a single individual. Most importantly, they acknowledge that the lack of direct comparison of the detected lesions in regard to the pathology and presentation of MS prevents speculation about the relevance to the clinical setting.

Commentary:
Daniel Pelletier, MD
Associate Professor of Neurology
Andy and Debbie Rachleff Distinguished Professor
University of California, San Francisco
San Francisco, California

This study addresses an important topic but sheds little new information. There is certainly a great deal of interest in developing methods to detect neocortical lesions, which are strongly suspected of being important to progression of MS, particularly cognitive decline. In this study, the authors attempted to fine-tune currently available MRI techniques and drew the conclusion that T1- and T2-weighted imaging methodology provide complementary information, which is already well known. The authors did not attempt to place this in the context of histopathology, so we do not know whether the neocortical lesions detected represented all, most, some, or just a few of the lesions present. This makes the sensitivity of the different techniques difficult to compare. It also complicates efforts to use these findings to guide in vivo studies, where it will be important to correlate relative neocortical lesion activity with clinical disease.

Consistent with past studies, the conventional MRI employed in this study appears to have limited application for detection of neocortical lesions, but there are other techniques that do appear promising, such as use of novel contrast mechanisms for white and gray matter lesions, namely phase, susceptibility-weighted (SWI), or double-inversion recovery (DIR) imaging. It is likely that advances in neocortical lesion detection are coming, but it will then be critical to confirm that identifying these lesions has clinical utility. M

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MULTIPLE SCLEROSIS MONITOR and Commentary

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