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

One of the most frustrating aspects of multiple sclerosis (MS) for both the patient and the clinician is disease unpredictability. Tools or methodologies that can predict the clinical course would have many advantages, including avoiding expensive, somewhat uncomfortable, and in some instances, potentially dangerous disease-modifying therapies (DMTs) in patients with a truly benign course of MS. Such tools might also allow trials to test whether more aggressive therapies will reduce or delay disease progression in cases where the disease is expected to rapidly advance. The promise of these advantages drives enormous amounts of worldwide research to generate new prognostic tools.

Several studies testing new predictive methods are included in this issue. For example, Dr. Elizabeth Fisher from the Cleveland Clinic evaluates a study that tried to use the rate of early brain atrophy to differentiate patients with typical MS from those with a benign course. Dr. Douglas Arnold of McGill University provides a critique of a study looking for magnetic resonance imaging (MRI) features that will predict disability after a first episode of optic neuritis. Neither is impressed by the studies they evaluate, but their perspective is illuminating.

Following our policy of evaluating both new directions in research and studies with immediate practical application, other articles evaluated by our invited experts include those examining the potential neuroprotective effects of current DMTs and the practical value of resistance training to slow functional deterioration caused by MS. As our experts are actively involved or have a strong interest in the topics that they are addressing, we hope our commentaries provide valuable perspective. The goal is to provide information in a form that is easy to digest. Comments and suggestions are welcome. 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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E. Mark Haacke has a research agreement with Siemens Medical Systems.

Michal Schwartz reports that he was an inventor for the use of glatiramer acetate in neurodegenerative diseases.

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Incidental MRI anomalies suggestive of multiple sclerosis. The radiographically isolated syndrome.

First Author and Institution:
Darin T. Okuda, MD, University of California, San Francisco.

Citation:
Neurology. 2009; 72:800-805.

Objective:
Evaluate clinical significance of incidental magnetic resonance imaging (MRI) anomalies that are suggestive of multiple sclerosis (MS).

Type of Study:
Prospective, cohort, natural history study.

Result:
Of subjects with incidental MRI anomalies but normal neurological examination, 25% converted to probable or definite MS, and 59% showed additional MRI activity over a median follow-up of 2.7 years.

Conclusion:
Individuals with incidental MRI abnormalities suggestive of MS are at reasonably high risk of developing more abnormalities or of having a first clinical attack of MS.

MRI examinations often find abnormalities such as unidentified bright objects in the central nervous system (CNS) that are difficult to interpret. The rate of conversion to MS is unknown.

Forty-one patients with MRI anomalies and a median age of 38.5 years were studied. The indication for the baseline MRI was migraine in about 1/3 of cases, with a broad range of complaints, such as low back pain, screening for aneurysms, panic attacks, and "spells" of uncertain etiology, listed as reasons for the remaining MRIs. The MRI abnormalities had to fulfill the McDonald MRI criteria for dissemination in space. Clinical examinations were performed at baseline in all patients; neurological exams were normal in all. Longitudinal clinical follow-up was available for 30 patients and longitudinal MRI data was available for 41 patients.

While radiological progression was identified in 59% of cases (24 of 41 patients), only 10 patients converted to CIS or MS. The median time to CIS or definite MS was 5.4 years. The presence of contrast-enhancing gadolinium lesions on the initial MRI predicted dissemination in time when repeat MRI was performed (hazard ratio of 3.4).

Commentary:

Fred Lublin, MD
Director, Corinne Dickson Goldsmith Center for MS
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Mount Sinai Medical School
New York, New York

This is an important and clinically relevant paper because it provides a basis for counseling patients who are referred with MRI anomalies. It is only the second study of which I am aware to address this issue. Although the number of patients followed is small and a longer median follow-up would be more reassuring regarding the relative risk of developing CIS or definite MS among patients with a MRI anomaly, the authors have taken a reasonable approach to characterizing the lesions and then prospectively evaluating the clinical course.

This study is a first step toward addressing an issue that has become more common as more MRIs are performed. These data do not specify how such patients should be managed, but they do provide a framework for defining MRI anomalies, considering the risk they pose for a demyelinating disease, and performing larger studies in which relative risk is evaluated in the context of specific anomalies. Overall, the data provide reassurance that the risk of a demyelinating disease is very low in the absence of enhancing lesions or other MRI findings consistent with MS. M

Quantitative in vivo magnetic resonance imaging of multiple sclerosis at 7 Tesla with sensitivity to iron.

First Author and Institution:
Kathryn E. Hammond, BS, University of California, San Francisco.

Citation:
Annals of Neurology. 2008;64:707-713.

Objective:
Quantify iron content in the basal ganglia of patients with multiple sclerosis (MS) and correlate with disability and disease duration.

Type of Evaluation:
Prospective magnetic resonance imaging (MRI) study in patients with MS and matched controls.

Result:
Patients with MS showed increased local fields of iron in the caudate, putamen, and globus pallidus that strongly correlated with disease duration.

Conclusion:
Local field shifts (LFSs) support a pathological role for iron content in MS and suggest that 7 Tesla (T) imaging may be a useful adjunct to clinical examination for monitoring disease severity.

Progress in the technology of MRI includes the 7T technique that permits improved resolution, including detection of subtle LFSs caused by magnetic compounds such as iron. There is a variety of evidence, particularly postmortem studies, suggesting that iron accumulates in several neurodegenerative diseases, including MS.

In this study, 19 patients with MS and 13 age- and gender-matched controls underwent 7T MRI with quantification of LFSs in specific areas of interest in the brain. The change in field shifts was then correlated with specific MS features, particularly disease duration.

Relative to controls, patients with MS had significantly greater LFSs in the caudate, putamen, and globus pallidus (P<0.01 for all). The degree of LFSs was strongly correlated with the duration of MS (P<0.001). The detection of a positive LFS also increased the total lesion count by more than 30%. The technique was particularly effective for imaging of veins that penetrated MS lesions.

Further studies are needed to determine whether LFS evaluations with 7T MRI can provide clinically useful information, such as better documentation of disease severity in the central nervous system independent of current clinical manifestations. These current data are promising.

Commentary:

E. Mark Haacke, PhD
Director, MR Research Facility
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Detroit, Michigan

The concept of employing phase shift MRI for iron quantification, which originated in 1997, has now been studied by numerous groups in neurodegenerative diseases.[1,2] Imaging MS with phase shifting began in our laboratory in the fall of 2005 (although a large body of work preceded our own[1-9]).

The current findings are consistent with previous histological studies and our own work at lower fields (1.5T, 3T, and 4T).

The presence of iron in MS raises at least two major questions that may help drive us toward a better understanding of the etiology of MS: 1) Does the finding of iron represent a chronic effect, representing tissue that is more severely damaged?; and 2) Does iron build up because of leaky vessels, damage to the vessel wall (iron in the form of hemosiderin), or from the breakdown of myelin (iron in the form of ferritin)?[10] In future studies, it will be important to follow patients longitudinally and investigate the presence of iron in acute fields (which suggest that iron is a valuable marker of the neurodegenerative process). M

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Glatiramer acetate positively influences spinal motorneuron survival and synaptic plasticity after ventral root avulsion.

First Author and Institution:
Juliana Milani Scorisa, MD, University of Campinas, Campinas, Brazil.

Citation:
Neuroscience Letters. 2009;451:34-39.

Objective:
Evaluate the effect of glatiramer acetate (GA) on synapse plasticity and glial reaction after ventral root avulsion (VRA).

Type of Study:
Experimental analyses in a mouse model.

Result:
GA treatment was neuroprotective after VRA and reduced glial reaction around motor neurons, which is consistent with increased stability of nerve terminals in the spinal cord.

Conclusion:
GA may preserve nerve circuits in the spinal cord in addition to its anti-inflammatory effects, an action that may play a role in therapeutic strategies to treat or prevent proximal lesions to the spinal cord.

Traumatic lesions to the spinal cord can lead to permanent loss of function due to neuronal cell death. At present, there is no effective therapy directed at circumventing neuronal degeneration after such injuries. Although the effect of GA on motor neuron survival is unknown, this first-line disease modifying therapy for multiple sclerosis (MS) has demonstrated neuroprotection in a variety of settings, including clinical MS and animal models of MS such as experimental autoimmune encephalomyelitis (EAE).

In this study, avulsion of lumbar ventral roots was evaluated in an animal model prior to treatment with GA. Immunohistochemistry studies of spinal cord tissue obtained from the sacrificed animals were performed 14 days after treatment. Synaptic changes and glial activation was evaluated by immunolabeling relevant factors, such as synaptophysin, GFAP, and Iba-I. The area of glial reaction around the axotomized motoneurons was also measured.

Relative to placebo-treated mice, GA preserved synaptophysin labeling and significantly reduced the glial reaction in the area around the axotomized motoneurons. These effects are consistent with previous studies suggesting that GA, through preservation of neural structures and an anti-inflammatory effect, may elicit expression of neurotrophic factors such as BDNF and improve synaptic stability. These findings may lead to new treatment strategies for spinal cord lesions.

Commentary:

Michal Schwartz, PhD
The Maurice and Ilse Professorial Chair of Neuroimmunology
Weizmann Institute of Science
Rehovot, Israel

There is now a substantial amount of evidence from many centers, pioneered by our own, that GA exerts neuroprotective effects in the central nervous system (CNS). Although this neuroprotection is considered to be independent of its anti-inflammatory activities in MS when GA is given daily, the protection for other disease states has been found to be dependent on the regimen and route of administration. Research we performed has provided evidence that GA can work much like a vaccine in promoting neurotrophic factors to protect against neurodegenerative insults. However, the activities of GA in chronic administration appear to be highly dependent on the regimen and the disease, so that an acute regimen in one model/disease is not necessarily relevant to another.

There are many examples, such as the chronic motor neuron disease amyotrophic lateral sclerosis (ALS), in which the effort to develop a clinically relevant neuroprotective GA regimen has failed. Therefore, before translation to a chronic motor neuron disease, it is critical to select an appropriate model for investigation. While this study supports the potential of GA for neuroprotection, neither the model nor the regimen may be relevant to the goal of demonstrating protection in chronic motor neuron disease. The goal of determining how to employ the neuroprotective effects of GA to treat or prevent neurodegeneration is important, but there is a great deal of work in front of these investigators before speculation on the clinical relevance of the path they are pursuing can be meaningfully evaluated. M

Rate of brain atrophy in benign vs early multiple sclerosis.

First Author and Institution:
Susan A. Gauthier, DO, Brigham and Women's Hospital, Harvard Medical School, Boston.

Citation:
Arch Neurol. 2009;66:234-237.

Objective:
Compare brain atrophy rates over 2 years in patients with long-standing, clinically benign multiple sclerosis (MS) to those with early, typical MS.

Type of Study:
Prospective cohort study and retrospective database review.

Result:
Patients with benign MS had lower atrophy rates on the basis of brain parenchymal fraction than those with early, typical MS even after controlling for age, sex, and treatment.

Conclusion:
Low rates of brain atrophy may be a predictor of a benign course.

Currently, there is no method for identifying patients with a low risk of MS progression even though such a method would be highly useful for avoiding unnecessary therapies. Identification of a magnetic resonance imaging (MRI) predictor of benign MS might provide insight into the pathogenic basis for the differences seen in MS disease courses.

In this study, patients with benign MS, defined as an Extended Disability Status Scale (EDSS) score of ≤1.5 10 to 14 years from diagnosis or an EDSS score of ≤2.0 after more than 15 years, were drawn from a large database maintained on MS patients at the researchers' institution. Annualized atrophy rates were calculated from serial MRI measurements of brain parenchymal fraction over 2 years in these patients and in an age-matched cohort of patients within 5 years of a diagnosis of relapsing-remitting MS (RRMS). For comparison, atrophy on the T2-weighted and proton density images were annualized.

The annualized atrophy rate was significantly greater in the 40 patients with early RRMS when compared with the 39 patients with benign MS (-0.46 vs. -0.16; P=0.02). The difference remained significant in a multivariate analysis that controlled for age, gender, and treatment. When comparing only those patients from each group that had not been treated, the atrophy rate was still lower in the benign MS group, although the difference was no longer statistically significant, possibly due to small numbers.

A relatively low rate of atrophy appears to be a feature of benign MS 10 or more years after diagnosis, particularly when compared to early stages of RRMS, but the authors, cautioning that rates of atrophy may not be linear, indicate that further work is needed to determine the prognostic value of early atrophy measurements.

Commentary:

Elizabeth Fisher, PhD
Department of Biomedical Engineering
Lerner Research Institute
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Cleveland, Ohio

The results of this study are interesting, particularly because the mean rate of brain atrophy was lower in the patients with benign MS as compared to the patients with a more typical disease course, despite the fact that the groups did not differ in their baseline T2-hyperintense lesion load. The authors suggest that this finding may imply that relatively less irreversible tissue destruction and neurodegeneration occur in benign MS. It would be interesting to investigate this hypothesis further with a comparison of changes in the normal-appearing white matter and gray matter.

This finding may imply that relatively less irreversible tissue destruction and neurodegeneration occur in benign MS.

For the purpose of determining the prognostic value of the atrophy rate, the study had some limitations. In the benign group, atrophy rates were not determined at the time of first presentation, prior to the minimum of 10 years needed to make a clinical diagnosis of benign MS. This is the period of greatest interest for clinicians trying to identify those patients who are likely to have benign disease. It might have been more informative to determine atrophy rates early after diagnosis of benign disease and then compare these to the early atrophy rates in RRMS patients. M

Effects of resistance training in multiple sclerosis.

First Author and Institution:
F. de Souza-Teixeira, MD, University of Léon, Léon, Spain.

Citation:
Int J Sports Med. 2009; 30:245-250.

Objective:
Evaluate ability of moderate resistance training to increase muscle strength for the ultimate goal of preventing functional deterioration in multiple sclerosis (MS).

Type of Evaluation:
Uncontrolled, prospective study conducted over 8 weeks.

Result:
A variety of measurements of muscle function, including isometric strength, endurance, and maximal power, were increased significantly.

Conclusion:
The muscle improvements over a relatively short training period support additional studies to determine whether this approach can slow functional deterioration in MS.

Muscle weakness and impaired function are a major source of the disability that characterizes MS. Muscle training to halt this source of disability progression is particularly attractive because of the absence of treatment options to reverse the underlying disease. Previous studies have suggested that aerobic exercise may have health benefits in patients with MS, but the goal of this study was to evaluate strength training as a method to contain disease-related disability.

In this study, 13 patients with MS were recruited to participate in a study divided into two 8-week periods. The first was a control period. The second consisted of a twice-weekly strength-training program. The intensity of the training was designed to produce 40% to 70% of maximal voluntary contractions. Strength testing and clinical function testing conducted after the control and treatment periods were compared. Hypertrophy was evaluated with magnetic resonance imaging (MRI).

When compared with baseline, there were no changes in any measure after the control period. In contrast, the 8 weeks of strength training was associated with a 16% (P<0.01) improvement in isometric strength, an 84% (P<0.001) improvement in muscle endurance, and a 51% (P<0.001) improvement in maximal power. MRI revealed significant improvements in hypertrophy (P<0.05) in the quadriceps, while functionality as measured with the Up and Go Test also improved significantly (P<0.001). There were no injuries associated with the training.

The improvement in quadriceps hypertrophy with muscle training was called a novel finding by the Spanish investigators. They suggested that this finding is consistent with other evidence that even a short muscle resistance-training program can produce objective benefits, including improved functionality. Longer and larger studies are needed to confirm that these benefits translate into an improved quality of life.

Commentary:

Jay Meythaler, MD, JD
Chairman, Department of Medicine and Rehabilitation
Wayne State University
Detroit, Michigan

The underlying concept of this study is attractive, but the endpoint of interest is functional outcome rather than muscle strength. Although not much can be demanded of a small study undertaken over a short period of time, the conclusion is too strong for the data presented. While the authors called the approach promising, the reported increase in functionality did not correlate with the increase in muscle power. This is an important point, because isolated measures of motor performance do not necessarily translate into functional improvements. There was also no mention in this study of spasticity, which is an important confounder.

One reason to be cautious about assuming increases in muscle strength in MS will be beneficial is recent evidence from an animal model that associated exercise with a detrimental effect on function if it was conducted during an acute phase of a relapse. In this setting, possibly due to the ability of exercise to exacerbate inflammation, a delay in the initiation of exercise may produce a better long-term outcome. In evaluating strength training it may also be important to look closely at baseline disability because of different potentials for benefit or harm at specific points in the disease's progression. M

Early MRI in optic neuritis: The risk for disability.

First Author and Institution:
Josephine K. Swanton, MD, National Hospital for Neurology and Neurosurgery, London, UK.

Citation:
Neurology. 2009;72:542-550.

Objective:
Evaluate magnetic resonance imaging (MRI) findings as a predictor of disability in individuals presenting with optic neuritis (ON).

Type of Evaluation or Study:
Prospective, 5-year follow-up of individuals with ON.

Result:
In the overall study population, the presence and location of lesions seen on MRI at baseline (within 3 months of the onset of ON) and new T2 lesions at follow-up predicted disability. In 48% of patients who converted to clinically definite multiple sclerosis (MS), only spinal cord lesions predicted disability.

Conclusion:
Lesion number and location are predictive of disability in patients with ON. Only spinal cord lesions are predictive of disability in those who go on to develop clinically definite MS.

In this study, 143 patients with ON were recruited for a prospective study to evaluate the prognostic value of MRI features. At baseline, MRI measures included lesion number and location as well as activity within 3 months after onset of ON.

In the 106 patients who were available for evaluation at the end of 6 years of follow-up, ordinal logistic regression was employed to assess the association between early MRI findings and subsequent disability. Significant disability was defined as an Expanded Disability Status Scale (EDSS) score ≥2.5.

At the end of follow-up, 48% of patients had converted to clinically definite MS and 52% were still classified as having CIS. Lesion location (spinal cord and infratentorial lesions) and activity (gadolinium-enhancing lesions seen within 3 months of the onset of ON and new T2 lesions seen after 3 months) were early, independent MRI predictors of disability after 6 years in the whole study population. Lesion load at baseline was more useful for predicting conversion to MS than the risk of disability overall.

The authors suggest that further longitudinal investigations in CIS cohorts are needed to better characterize the evolution of MRI measures and the clinical course.

Commentary:

Douglas L. Arnold, MD
Montreal Neurological Institute
McGill University
Montreal, Canada

The main points of this study are not much of a departure from what is already known. One of the main conclusions is that individuals with ON with more gadolinium-enhancing lesions are more likely to have disability after several years of follow-up. This is basically a trivial restatement of what has already been well-established about the course of the demyelinating process.

The potentially more interesting finding is that the presence of spinal cord lesions predicts disability. The location of lesions as a possible predictor of clinical course has not been well studied in the past. Here, the investigators found that even small spinal cord lesions predict increased risk of disability. However, this finding probably does not have any immediate clinical relevance, because MRI of the spinal cord is not part of routine clinical practice. Moreover, most patients who had a lesion in the spinal cord also had lesions in the brain.

For what the investigators were attempting to evaluate, the methodology was reasonable, but this study is probably much more relevant to researchers trying to understand the importance of lesion location than it is for clinicians interested in better methods of prognostication. M

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