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 *MS Monitor and Commentary*, the complexity of characterizing MS pathology is reflected in a paper reviewed by Dr. John Kamholz of Wayne State University. He evaluates a study that suggests defects in mitochondrial DNA may be a key to neurodegeneration in secondary-progressive MS. Dr. Kamholz is impressed with the concept and sees real potential in this direction of research. Likewise, Dr. Gary Cutter of the University of Alabama at Birmingham reviews a study from Sweden that looks at passive exposure to tobacco smoke as a potential risk factor for the development of MS. He can't argue with the focus of the paper, but finds the study has significant methodological limitations.

Revisions to the McDonald diagnostic criteria, which have more immediate clinical relevance, are discussed by Dr. Ruth Whitham of the Oregon Health & Science University. Dr. Whitham suggests that rather than altering current practice, these criteria align recommendations with what many clinicians are already doing.

Other commentaries in this issue include one by Dr. V. Wee Yong of the University of Calgary, in which he is asked to interpret a study that attempts to identify additional anti-inflammatory mechanisms for glatiramer acetate. He suggests this study supports efforts to look beyond the T cell in understanding disease-modifying therapy. Next, Dr. Massimo Filippi of the University Hospital San Raffaele in Milan is called upon to evaluate a study that associates specific MRI changes early in the disease with the subsequent risk of cognitive dysfunction. As someone who has done work in this area, he indicates that this is a promising direction of research but it has no immediate clinical application because all of the markers are being studied from a population-based perspective. Dr. Pat Coyle of the State University of New York at Stony Brook then weighs in on the subject of pregnancy in patients with MS. She welcomes new data suggesting pregnancy outcomes are good even in women on disease-modifying therapies.

We hope you find these studies and the commentaries to be thought provoking. If you have comments or suggestions, please feel free to reach me at msmonitor@delmedgroup.com.

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MS MONITOR AND COMMENTARY

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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.

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Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.

First Author and Institution:
Chris H. Polman, MD, PhD, Free University, Amsterdam, The Netherlands.

Citation:
Annals of Neurology. 2011;69:292-302.

Objective:
Explain recent revisions in the McDonald Criteria, a diagnostic tool for multiple sclerosis (MS).

Type of Study:
Consensus document.

Result:
New, more simplified diagnostic criteria for MS are expected to provide a level of accuracy at least as good as that of previous criteria with the potential for fewer magnetic resonance imaging (MRI) examinations.

Conclusion:
These revisions may promote more widespread and uniform use of the criteria and may allow earlier diagnosis of MS.

MS is diagnosed through a combination of clinical manifestations, MRI findings, and laboratory abnormalities. New information generated since the 2005 revision of the McDonald criteria has provided the impetus for modifications designed to facilitate diagnosis without foregoing the previous levels of sensitivity or specificity.

The single most important revision may involve a redefinition of the role of MRI. While the new criteria, like the previous, require dissemination of lesions in both space and time (DIS and DIT), an MRI that shows both enhancing and non-enhancing lesions in a single scan is now considered an acceptable demonstration of DIT. Previously, sequential scans were required. DIS criteria have also been simplified.

Commentary:
Ruth Whitham, MD
Professor of Neurology
Oregon Health & Science University
Portland, Oregon

The authors provide a convincing argument that these revisions will be simpler to use than the previous criteria while providing the same or an improved sensitivity and specificity. In particular, the new criteria for DIS will be easier for non-imaging specialists to apply, no longer necessitating a "pocket card" to reference cumbersome criteria. The revisions actually bring the McDonald criteria closer in line with typical clinical practice, and these criteria help validate a more flexible timing of MRI. Earlier diagnosis of MS may be possible because a diagnosis can be made based on a single scan, if enhancing and non-enhancing MS lesions are present on the same scan. However, I think some caution may be warranted in relying on a single scan for demonstration of DIT, depending on the severity of the first attack and the clinical urgency to begin disease-modifying therapy. There may be less urgent clinical circumstances where it is appropriate to perform a second scan rather than risk making a diagnosis prematurely. More flexible MRI timing and a reduced number of required MRIs are helpful from many perspectives, including reduced cost and improved patient satisfaction.

As the authors acknowledge, these criteria were validated primarily in Caucasians and adults. We need confirmation that the changes in criteria are also valid in other racial and ethnic groups as well as in children. The authors also emphasize the importance of excluding neuromyelitis optica in the differential diagnosis of MS, especially in Asian and Latin American populations, including testing for serum aquaporin-4 autoantibodies.

These new criteria appear to be an incremental improvement over the previous guidelines, but how clinicians will ultimately rate their usefulness to clinical practice is yet to be seen. M

Glatiramer acetate modulates TNF-α and IL-10 secretion in microglia and promotes their phagocytic activity.

First Author and Institution:
Refik Pul, MD, Hannover Medical School, Hannover, Germany.

Citation:
Journal of Neuroimmunology and Pharmacology. 2010;Epub ahead of print.

Objective:
Evaluate whether glatiramer acetate (GA) has direct effects on the microglia in the central nervous system (CNS).

Type of Study:
Experimental study with rodent microglia in tissue culture.

Result:
GA was found to directly modify activity of microglial cells.

Conclusion:
These results introduce the possibility that GA modifies progression of multiple sclerosis (MS) not only by activating T cells in the periphery, but by directly altering inflammation pathways in the CNS.

Disease-modifying therapies such as GA and the interferons provide protection against the progression of MS by reducing inflammatory activity. The major activity of GA appears to be an indirect effect stemming from its ability to shift T lymphocytes from pro-inflammatory type (Th1) to regulatory anti-inflammatory type (Th2) cells, which then migrate into the CNS to modify inflammatory activity. However, other effects, including direct CNS effects, are possible.

In this study, the goal was to evaluate the direct effect of GA on microglial cells, which can act as antigen-presenting cells in the CNS, thereby mediating the local inflammatory response. Rat microglia were cultured under standard conditions and then exposed to GA. Several variables of glial function were then evaluated during GA exposure, including the release of the cytokines interleukin-10 (IL-10) and tissue necrosis factor alpha (TNF-α) and the quantification of phagocytic activity.

Direct modulation by GA of microglial function was observed. In particular, secretion of IL-10, an anti-inflammatory cytokine, was increased, while secretion of TNF-α, a pro-inflammatory cytokine, was reduced. GA also promoted microglial phagocytic activity.

The results of this study, which is the first to associate GA with an ability to increase microglial phagocytic activity, are consistent with the hypothesis that this agent has T-cell-independent activities.

Commentary:
V. Wee Yong, PhD
Professor
Hotchkiss Brain Institute and the Departments of Oncology and Clinical Neurosciences
University of Calgary
Calgary, Canada

It is widely recognized that GA may provide protection against MS by anti-inflammatory activities other than the indirect alteration in T-helper cell activity. For instance, GA has been found to polarize antigen-presenting cells in the periphery towards an M2 anti-inflammatory/regulatory type. The findings of this study are interesting as they support the potential for a direct effect within the CNS, but there are a number of limitations in regard to their relevance to the clinical situation. First of all, the experiments were conducted in culture using tissue from an animal model. The greatest problem for speculating about the clinical relevance of these results is that we do not yet have good evidence that GA reaches the CNS in biologically active quantities, particularly at the levels used in these experiments. The authors of this study cited one experimental study that did support biologically active concentrations of GA in the CNS, by virtue of being brought there by systemic antigen presenting cells, but this study is controversial and not yet replicated. This is an important issue for drawing conclusions about direct CNS activity, because even if we see changes in microglial activity after GA administration, it would still be possible that these effects were secondary to systemic changes in immune activity that subsequently affected activity in the CNS. However, this study does suggest that GA has the potential for anti-inflammatory activity in the CNS if it is able to cross the blood:brain barrier in sufficient quantities.

These types of data are intriguing and support further research to look beyond T-cell activity to understand the mechanisms of GA. M

MRI predictors of cognitive outcome in early multiple sclerosis.

First Author and Institution:
Mathilde S.A. Deloire, PhD, University Victor Segalen, Bordeaux, France.

Citation:
Annals of Neurology. 2011;76:1161-1167.

Objective:
Identify magnetic resonance imaging (MRI) predictors of cognitive outcome in patients with multiple sclerosis (MS).

Type of Study:
Seven-year follow-up of patients with MS who underwent serial cognitive and MRI studies.

Result:
Change in cognitive score at 7 years was significantly associated with diffuse brain damage at baseline as well as central brain atrophy over an initial 2 years of follow-up.

Conclusion:
Data from this study indicate that a subset of patients with MS are at high risk of cognitive decline, and that there are MRI predictors of this risk at relatively early stages of the disease process.

A common complication of MS, cognitive decline can be an insidious process that impairs daily activities and quality of life.

In this study, 44 patients diagnosed with clinically definite MS were followed prospectively with sequential imaging studies as well as clinical evaluations and validated cognitive studies. The clinical and cognitive evaluations were conducted at 1, 2, 5, and 7 years of follow-up. The cognitive evaluations included the Brief Repeatable Battery (BRB). Cognitive decline was evaluated in relation to several measures of disease, including lesion load and the mean magnetization transfer ratio (MTR) of diseased to normal-appearing brain tissue.

While impairments in cognitive function were detected at baseline, further decline was observed over the 7-year follow-up. Over the same period, increased disease activity was observed with MRI as well as with such clinical measures as the Expanded Disability Status Scale (EDSS). At 7 years, memory loss was associated with diffuse brain damage as measured by MTR. Deterioration in information processing, another cognitive function, was associated with baseline global atrophy and diffuse brain damage. In addition, there was greater deterioration in information processing in those with the greatest central brain atrophy over the first 2 years of follow-up.

Based on these results, a correlation between specific brain lesions early in the course of MS can be made with subsequent risk of cognitive decline.

Commentary:
Massimo Filippi, MD
Director, Neuroimaging Unit
University Ospedale San Raffaele
Milan, Italy

This is not the first study designed to evaluate whether specific MS pathology is predictive of the risk of subsequent cognitive impairment, but it is one of the better studies conducted so far for several reasons. One is that it employed a long follow-up with a reasonably large sample. It also employed current technology, including MTR MRI, in the evaluation. The association made between specific types of MS pathology at baseline, such as diffuse brain lesions, and specific types of cognitive impairment, such as memory loss, was interesting and may be valuable for understanding how MS produces cognitive dysfunction. However, it is important to recognize that all of the studies so far, including this one, were designed to look at risk factors from a population-based perspective. We do not know whether these markers have any predictive value in individual patients. Such research is needed because early recognition of patients most at risk of cognitive decline would be very useful information not only for counseling patients, but for enabling the study of treatments that might preserve cognitive function in those at risk.

I am optimistic that sensitive markers for increased risk of early cognitive decline in patients with MS will eventually be found.

I am optimistic that sensitive markers for increased risk of early cognitive decline in patients with MS will eventually be found, but I think a detailed understanding of the relationship between the types of brain damage caused by MS and the likelihood of cognitive dysfunction is not very close. M

The Brazilian database on pregnancy in multiple sclerosis.

First Author and Institution:
Allesandro Finkelsztejn, MD, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil.

Citation:
Clinical Neurology and Neurosurgery. 2011;113:277-280.

Objective:
Evaluate outcomes in pregnant women with multiple sclerosis (MS).

Type of Study:
Retrospective analysis of medical records.

Result:
MS attack rates diminished markedly during pregnancy and rebounded during the post-partum period. The rates of obstetrical complications and birth defects were low.

Conclusion:
MS was not associated with a higher than expected rate of adverse outcomes even though a relatively high percentage of patients in this cohort were taking disease-modifying therapies (DMTs).

Several studies have now evaluated how MS affects the course and outcome of pregnancy. In general, these studies have found that pregnancy provides a protective effect against MS, and that the disease does not increase the risk for obstetrical complications. Some but not all studies have indicated an increased risk to the child, while the potential for complications from MS treatments used during pregnancy is unclear.

The goal of the current study was to collate outcomes data in Brazilian women who had MS during their pregnancy. The data were provided by treating neurologists who evaluated the medical records using consistent criteria. The 30 participating neurologists were from 21 cities in Brazil, which has the highest ethnic mixture in the world. The study included 128 women and 142 pregnancies. The average age at the time of pregnancy was 29.8 years, with a range of 16 years to 42 years.

The attack rate during pregnancy fell from an average of 1.2 in the year prior to pregnancy to 0.2 during pregnancy. The rate was 0.7 during the 6 months after pregnancy. The rate of obstetrical complications was 4.9% and the rate of unfavorable neonatal outcomes was 1.4%. Although there was no control group, both figures were within normal values for Brazil.

At 69.7%, the exposure to MS medications during pregnancy was high. This included 48.6% taking an interferon and 14.1% taking glatiramer acetate. The average exposure was 8 weeks, often early in the course of pregnancy. There was no clear correlation between MS medications and adverse outcomes, such as low birth weights.

The pregnancy outcomes in women with MS in Brazil are similar to previous reports of the same kind, reinforcing evidence that uncomplicated pregnancies are common in women with MS.

Commentary:
Patricia K. Coyle, MD
Director
Stony Brook MS Comprehensive Care Center
Stony Brook, New York

This is an interesting study because it has collected data on a fairly large number of women being treated in a single country. There are all the limitations of a retrospective study, as the authors acknowledge, but it is always helpful to have more data. The good news is that the outcomes were good both in regard to the mother and the child. Normal neonatal measures, such as birth weight, were especially reassuring, because almost 70% of patients took a DMT at some point during their pregnancy. This is a relatively high rate, explained perhaps by a large number of pregnancies that were unplanned and occurred before treatment was stopped.

It is notable that 86% of the women breastfed their babies, even though many of these women were receiving steroids or intravenous immunoglobulins (IVIG), but one criticism is that the authors provide selective windows on the data. Of the many examples, we are not told clearly whether any women were taking DMTs during breastfeeding. Also, comparative data from pregnant Brazilian women without MS would have been helpful.

Overall, however, these results increase the data we have available to reassure patients with MS who are considering pregnancy. M

Exposure to environmental tobacco smoke is associated with increased risk for multiple sclerosis.

First Author and Institution:
Anna K. Hedström, MD, Karolinska Institute, Stockholm, Sweden.

Citation:
Multiple Sclerosis Journal. 2011;Epub ahead of print.

Objective:
Estimate risk of multiple sclerosis (MS) from passive smoking exposure.

Type of Study:
Population-based, case-control study using incident cases of people with MS in Sweden.

Result:
A significantly increased risk of MS correlated with ever exposure to smoking and the duration of exposure.

Conclusion:
A correlation between passive smoking and MS may warrant studies of other lung irritants, such as air pollution, which may point to a mechanism of MS development.

Numerous studies have associated active smoking with an increased risk of MS, but the literature regarding passive smoking and the risk of MS has been contradictory. In this population-based, case-control study in never-smokers, the incidence of MS was compared in those with and without daily exposure to cigarette smoke at home or work. Duration of passive smoking was also evaluated. The effect of passive smoking on risk of MS was also considered in the context of numerous confounding factors, including vitamin D status, ultraviolet radiation (UVR) exposure, and presence of antibodies for Epstein-Barr Virus (EPV). There were 695 cases drawn from neurology clinics around Sweden and 1,635 matched controls.

Those exposed to passive smoking had a 30% increased risk of MS (odds ratio 1.3, 95% CI 1.1–1.6) relative to those with no exposure to passive smoking; greater duration of exposure correlated with greater risk ;(P=0.003). There were only marginal changes in the odds ratio for MS among passive smokers after adjusting for confounding factors.

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

It is difficult to be overly critical of results that provide another reason why exposure to tobacco smoke is unhealthy, but there are a number of methodological problems to this analysis. The authors acknowledge many of these problems. One is that the response rates for the questionnaires were 98% for the cases, but only 73% for controls. In addition, while the study was designed to look at passive smoking in the context of other risk factors, such as seropositivity for EBV and vitamin D levels, blood samples were available for 93% of cases, but only about half of controls. A selection bias like this is important because cases, who may be interested in participating in an effort to find risk factors for their disease, necessarily have different motivation for recall of smoking exposure compared with controls. Even with the potential for recall biases that might be expected to increase the likelihood for an association, the increase in the odds ratio of MS in patients with a high duration of passive exposure to smoke was not enormous. This actually would be expected given the magnitude of the effects of passive smoking in other diseases and contexts.

Those exposed to passive smoking had a 30% increased risk of MS (odds ratio 1.3, 95% CI 1.1–1.6) relative to those with no exposure to passive smoking.

The design of the study was reasonable, although a sensitivity analysis to better control for missing data would have been appropriate. It should also be noted that the authors focused on duration of exposure rather than amount of exposure, as the latter is simply too unreliable to collect retrospectively. The authors do suggest that passive smoking is likely a trigger rather than a cause, with an implication that even avoiding passive smoking may not stop the disease, but rather delay its onset.

Overall, the study suggests that MS is another problem to throw in the pile of risks associated with exposure to tobacco smoke, but the paper has important limitations as to how environmental tobacco smoke is implicated. M

Mitochondrial DNA deletions and neurodegeneration in multiple sclerosis.

First Author and Institution:
Graham R. Campbell, MRes, Newcastle University, Newcastle upon Tyne, United Kingdom.

Citation:
*Annals of Neurology.*2011;69:481-492.

Objective:
Evaluate potential role of mitochondrial (mt) DNA deletions in multiple sclerosis (MS) pathology.

Type of Study:
Series of analyses performed on autopsy tissue samples.

Result:
Abnormalities in mitochondrial DNA, particularly deletions responsible for encoding respiratory chain complexes, are common in secondary-progressive MS (SPMS).

Conclusion:
Respiratory deficiency associated with mitochondrial DNA deletions may play a major role in the neurodegeneration associated with MS, identifying a potential therapeutic target.

Mt abnormalities have been implicated in the pathogenesis of several disorders of the central nervous system (CNS), including MS. Oxidative damage is widely regarded to play an important role in induced defects, as opposed to inherited defects, of mtDNA-related CNS diseases. Changes in respiratory chain activity, therefore, are a rational focus of efforts to evaluate the role of mtDNA abnormalities in MS.

In this study, mitochondrial respiratory chain activity was evaluated in the context of mtDNA abnormalities in neurons obtained from 13 individuals who died with SPMS. The neurons were evaluated with histochemistry, immunohistochemistry, laser dissection microscopy, and long-range and real-time polymerase chain reaction (PCR) analyses. The major goal was to demonstrate deficiency in respiratory chain reactivity in mtDNA from patients with MS compared with aged controls.

The greater density of respiratory-deficient neurons, defined as lacking complex IV and II activity, in SPMS tissue relative to control tissue was significant. Moreover, these neurons were found to have high levels of clonally expanded mtDNA deletions at a single cell level. The authors speculate that the extensive population of mtDNA deletions in MS gray matter may be caused by inflammation, and may make an important contribution to the neurodegeneration that characterizes MS.

Citing previous work performed by others, the authors suggest that the deletions noted in this study most likely arise during repair of damaged mtDNA. However, they attribute the respiratory deficiency to clonal expansion that occurs after the abnormalities develop.

Commentary:
John Kamholz, MD, PhD
Professor of Neurology
Center of Molecular Medicine and Genetics
Wayne State University
Detroit, Michigan

One of the major mysteries of the pathophysiology of MS is the mechanism of neuroaxonal injury, a major cause of patient disability. This paper is of great interest because it provides a plausible explanation for the underlying pathology of this process. The same group of authors has now published a number of papers in this area, and they are developing a good case for the potential importance of mitochondrial respiratory dysfunction as a part of the pathogenesis of neuroaxonal injury in MS.

This study suggests that as the inflammatory process progresses, mtDNA deletions accumulate within affected neurons, which then become respiratory-deficient, particularly during the progressive phase of the disease. Respiratory deficiency could then lead to axonal degeneration and/or neuronal death. This study is particularly interesting because it was performed in MS tissue rather than in an experimental model, such as experimental autoimmune encephalomyelitis (EAE), which has many limitations. This work will be even more interesting and may attract more investigators to the field if the authors can provide clearer mechanisms for the origin of the mtDNA defects, such as the production of reactive oxygen species.

In terms of clinical relevance, the critical issue is whether the mitochondrial respiratory defects can be prevented or reversed, and whether this will have an effect on the clinical course of the disease. In addition, these data could provide an important target for new therapies. Although this work is still at a relatively early stage, this is a promising area of research that will attract increasing attention in the future. M

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