Response to our first issue of Multiple Sclerosis Monitor and Commentary was excellent. The consensus was that we fulfilled our goal of placing recently published articles about the pathogenesis and care of multiple sclerosis (MS) into context. This, the second issue, has the same intent. By matching experts with topics in which they have experience, we have an opportunity to go beyond the restraints of published manuscripts to consider what relevance, if any, new information may have to our understanding of MS and its care.

In this issue, the topics addressed are as intriguing as in our inaugural issue. These include whether systemic infections increase the risk of MS relapses, whether cholinesterase inhibitors may have a role in preventing cognitive loss in MS, and what role high-dose cyclophosphamide may have in the control of moderate to severe MS. Of less immediate importance to clinical management but no less intriguing, the phenomenon of remyelination in MS and the correlation between plaque load and axonal loss are examined.

Keeping current with the medical literature is an increasingly daunting task. We hope this publication can facilitate the process by not only summarizing recent information but providing expert commentary on its relevance and importance. Comments are welcome. We have added two new ways to communicate with us. First, please feel free to e-mail us at msmonitor@delmedgroup.com. We would like to hear your comments on some of the articles we addressed as well as your thoughts on the publication. Or, on page 11, please take a moment to fill out the issue evaluation form and fax it back to us at 201-612-8282. We look forward to hearing from you and sharing your comments with readers in the next issue.

Robert P. Lisak, MD
Wayne State University School of Medicine
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The risk of relapses in multiple sclerosis during systemic infections. Commentary by Aaron Miller, MD

High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis. Commentary by Hillel Panitch, MD

Cognition and fatigue in multiple sclerosis: potential effects of medications with central nervous system activity. Commentary by Luanne Metz, MD, FRCPC

How to successfully apply animal studies in experimental allergic encephalomyelitis to research on multiple sclerosis. Commentary by Robert Lisak, MD

Suicidal ideation in multiple sclerosis. Commentary by Randolph B. Schiffer, MD

Effects of donepezil on memory and cognition in multiple sclerosis. Commentary by Steven Schwid, MD

Remyelination is extensive in a subset of multiple sclerosis patients. Commentary by Robert Zivadinov, MD, PhD

The contribution of demyelination to axonal loss in multiple sclerosis. Commentary by Robert Zivadinov, MD, PhD
The risk of relapses in multiple sclerosis during systemic infections.

First Author and Institution:
Jorge Correale. Raul Carrea Institute for Neurological Research

Citation:
Neurology. 2006;67:652-659

Objective:
Assess risk of multiple sclerosis (MS) relapses, magnetic resonance imaging (MRI) activity, and T-cell responses to systemic infection.

Type of Evaluation or Study:
Prospective, uncontrolled clinical assessments with laboratory analyses and imaging.

Result:
Systemic infections were significantly related to MS relapse and increased MRI activity.

Conclusion:
These results emphasize the role of an activated immune system in driving MS and may provide guidance about which immune mediators drive disease.

As MS is widely believed to be an autoimmune disease, it is reasonable to speculate that any stimulation of inflammatory mediators might have a negative impact on the course of MS or the risk of relapse. In this study, 60 patients with MS were prospectively monitored for change in disease status in relation to systemic infections. Over an average follow-up of 20 months, 53 patients had 127 infections for an average of 1.2 infections per year. A variety of signs of increased MS activity were observed that correlated with these episodes of systemic infection, including an increased number of clinical relapses, an increase in active lesions on MRI, and an increase in inflammatory mediators.

All of the patients recruited for this study had definite relapsing-remitting MS. Although almost all of the patients (87%) were receiving an immunomodulatory therapy, such as interferon or glatiramer acetate, none had been treated with a steroid or another immunosuppressant drug within the 3 months of entering the study. After baseline studies of clinical status and activity of inflammatory mediators were performed, patients were instructed to contact the study center immediately if they experienced symptoms of infection. A subgroup of 20 patients was evaluated with MRI both at baseline and at regular intervals relative to infection or MS relapse.

Of the 127 infections, the cause was documented in 73 (57%). Clinically, a marked spike in the number of clinical relapses that peaked 2 weeks after the onset of systemic infections was observed. By week 5, the number of relapses had fallen back to baseline. An increase in cells producing such cytokines as interleukin-12 (IL-12), tissue necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) also peaked at about 2 weeks after the onset of infection. While these cytokines were nonspecific, additional experiments suggested that autoreactive T cells could be stimulated by these increases in the presence of a cognate antigen. In the subgroup being followed with MRI, there was also an increase in gadolinium-enhancing lesions at week 2 of the at-risk period after infection.

Overall, the study contributes to other evidence that systemic infections increase the risk of MS relapses. During the at-risk period in the weeks following a systemic infection, the relative risk of an acute exacerbation was increased by 3.2-fold relative to a period in which there was no episode of infection. The authors noted that there was no discernible difference in the risk of MS relapse for bacterial vs. viral infections. Although the authors cautioned that this study may be criticized because of its lack of blinding, they indicated that this is an attractive area of research to pursue pathways of MS disease and to identify new opportunities to prevent relapses. If further studies support these observations, it will be important to determine how nonspecific stimulation of the immune system activates autoreactive T cells. The authors expressed the opinion that increased cytokine activity alone is unlikely to drive autoimmune processes without simultaneous upregulation of an antigen that directs inflammatory activity to myelin or other targets.

Commentary:
Aaron Miller, MD
New York University
New York, New York

This study of the risk of relapses in MS during systemic infection is both similar and different from previous studies looking at the same issue. The study was conducted in a rigorously systematic fashion, with clinical data supplemented by prospective MRI data in a subset of patients and complementary immunological investigations. A blemish on the study design, acknowledged by the authors, was the unblinded nature of the investigators who determined the existence, severity, and duration of the relapses. This study confirmed the finding of others that viral infections (the vast majority causing upper respiratory syndromes) were associated with an increased risk of relapse. Unlike previous studies, however, these investigators also found a higher relapse rate following bacterial urinary tract infections. An explanation for this discrepancy is not readily apparent.

The demonstration of more gadolinium-enhanced lesions in the group with infection-associated relapses—not a consistent finding in prior studies—provides some reassurance about the validity of the clinical observations. In their immunological analysis, the authors speculate that the heightened relapse activity may relate principally to an increased myelin-specific T-cell sensitivity to cognate antigen induced by the infectious process through one of several hypothetical mechanisms. Further work will be required to confirm and extend this conclusion.
High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis.

**First Author and Institution:**
Douglas E. Gladstone. State University of New York at Stony Brook

**Citation:**
Archives of Neurology. 2006;63:1388-1390

**Objective:**
Evaluate effects of high-dose cyclophosphamide (HDC) in patients with refractory multiple sclerosis (MS).

**Type of Evaluation or Study:**
Open-label, prospective pilot study.

**Result:**
A variety of clinical improvements were accompanied by an improvement in quality-of-life (QoL) scales and a reduction in Expanded Disability Status Scale (EDSS) scores.

**Conclusion:**
HDC stabilizes MS and improves QoL in at least some patients with refractory disease. Further analyses are warranted.

Cyclophosphamide, a chemotherapeutic agent in widespread use for cancer, is toxic to T and B cells, a mechanism of action that has theoretical benefit for controlling MS. In this study, HDC was studied as a second-line therapy for patients who were not achieving adequate control of MS with conventional therapies. Patients were eligible for this study if they had refractory relapsing-remitting MS (RRMS) or secondary progressive MS (SPMS) defined as a score of 3.5 higher on the EDSS despite use of a minimum of two disease-modifying therapies.

Of the 13 patients initially recruited, of which seven had SPMS, 12 were evaluable. The median EDSS score was 6.5. Three weeks prior to initiating HDC, all remittive therapies were stopped with the exception of steroids. HDC was administered at a dose of 200 mg/kg adjusted to ideal body weight on each of 4 consecutive days. Antibacterial, antifungal, and antiviral prophylactic therapies were administered. Patients were monitored with magnetic resonance imaging (MRI), EDSS scoring, and QoL measures.

On MRI, all patients had abnormalities at baseline. Of the 11 patients who had MRI studies at a central location permitting detailed analyses, nine (82%) had 15 or more lesions. Over the course of follow-up, no patient showed sustained worsening on EDSS evaluation. On neurological examination, five of the 12 patients for whom there was an average of 15 months of follow-up demonstrated a sustained response as defined by a decrease of ≥1.0 in EDSS score. There were also benefits for specific neurologic complaints. In particular, bladder dysfunction, which was reported by all patients at baseline, improved in 75%.

Major improvements were recorded in QoL scores. An increase in scores that was considered both statistically and clinically significant was observed in all patients, and these improvements were observed across a broad number of domains, including physical health, vitality, and social functioning. In addition, 88% of patients reported a reduction in symptoms of fatigue. A reduction in neurological symptoms and an improvement in QoL were observed whether or not patients had enhancing lesions at baseline.

Adverse events were limited to the acute treatment period and were consistent with those reported with use of this agent in cancer patients. This included neutropenia for a median of 9 days, which often required a platelet infusion. Almost half of patients had febrile neutropenia. Nausea, often requiring antiemetics, was also common. Transient serum chemistry abnormalities requiring administration of electrolytes were also observed in a substantial proportion of patients, but there was no long-term morbidity associated with treatment.

The results of this small study provide initial evidence that HDC may be an appropriate second-line therapy for MS patients refractory to disease-modifying drugs. The authors called for further studies to confirm the safety and efficacy of HDC in the management of refractory MS and to determine which patients are the most appropriate candidates.

**Commentary:**
Hillel Panitch, MD
University of Vermont
Burlington, Vermont

This paper describes a novel approach to intensive immunosuppression with ultra-high-dose cyclophosphamide given as a single 4-day infusion of 200 mg/kg, a dose far higher than any used in other comparable studies of MS therapy. It is one of a series of articles advocating this approach in autoimmune diseases, and reports results of a small uncontrolled study in 12 patients with worsening RRMS or SPMS who seemed to stabilize or improve after treatment.

There are several problems with the study that detract from its impact, including the mixed population, short duration of follow-up (6-24 months), and potential confounding by the use of multiple other therapies, including mitoxantrone, prior to HDC treatment. The outcome is difficult to interpret as four of the five patients who improved had RRMS, in which major reductions in EDSS scores often occur spontaneously as patients recover from relapses. There was apparently no significant effect on MRI activity, and the QoL assessments, although they seem to show trends toward improvement, are presented without statistical analysis. Finally, although the authors claim the therapy is relatively safe, six patients developed febrile neutropenia and all required transfusions and treatment with filgrastim. The technique appears to be safe only in comparison with hematopoietic stem cell transplantation, which involves a much more toxic conditioning and anti-rejection regimen.

Better evidence of safety and efficacy, in the form of a randomized controlled clinical trial, would be needed before this approach could be advocated for general use, even in severe refractory MS.
Cognition and fatigue in multiple sclerosis: potential effects of medications with central nervous system activity.

First Author and Institution:
Barry S. Oken. Portland Department of Veterans Affairs Medical Center

Citation:
Journal of Rehabilitation Research and Development. 2006;43:83-90

Objective:
Evaluate the effects of treatments for multiple sclerosis (MS) on cognitive activity.

Type of Evaluation or Study:
Retrospective analysis of MS medications active in the central nervous system (CNS).

Result:
When compared with MS patients not taking a medication active in the CNS, those who were taking medication had impairment on several measures of cognitive function, including processing speed.

Conclusion:
Although cautioning that a causal relationship has not been demonstrated, the authors recommend controlling for drug use when evaluating cognition and fatigue in MS patients.

M S has been linked with cognitive impairment in several previous studies. Although medications that are active in the CNS, particularly those that affect neurotransmitters implicated in cognitive processing, have been associated with cognitive impairment, there have been limited studies of the influence of CNS-active drugs on cognition in patients with MS. In this study, 70 MS patients who were participating in a prospective study of the effect of yoga and exercise on cognition were retrospectively analyzed for the influence of CNS-active drugs on cognition. The analysis was conducted by comparing cognitive function and symptoms of fatigue in 52 patients who were taking a drug with CNS activity, such as an antidepressant or an antiepileptic drug, with 18 patients who were not.

Of the patients taking CNS-active drugs, 29% were taking a selective serotonin reuptake inhibitor (SSRI) and 17% were taking another psychoactive drug, such as bupropion or trazadone. Other commonly used drugs were antiepileptic agents (17%), amantadine (17%), baclofen (16%), and anticholinergics (13%). In the course of the study, standardized tests were offered to all patients, whether or not they were taking CNS-active drugs. These measured a variety of cognitive functions, and included the Paced Auditory Serial Addition Test (PASAT) for attention, the Stanford Sleepiness Scale (SSS) for alertness and fatigue, and reaction time testing.

The only cognitive tests to show significant differences involved measures of reaction time and fatigue, both of which showed deficits for those taking a CNS-active drug relative to those who were not. However, there were trends for greater impairment in patients taking CNS-active drugs on several other measures, such as working memory. Although the authors emphasized that causal relationships cannot be assumed from this data, stressing in particular that it is difficult to disentangle fatigue from depression or the CNS activity of the medications taken for depression, they did conclude that drugs with CNS activity may be a factor in cognitive impairment.

As a result of the observations in this retrospective analysis, the authors suggested that CNS-active drugs should be used as a covariate whenever assessing studies in which fatigue or cognition are measured outcomes. Although they noted that efforts to evaluate cognition in other diseases associated with CNS pathology, such as Alzheimer’s disease, often involve either weaning patients from all medications that might affect cognitive function or ensuring that patients remain on stable doses, they cautioned that this is far more difficult in advanced MS in which patients often depend on antidepressants to maintain a stable mood or on anticholinergics for bladder control. The potential for excluding patients on CNS-active medications to bias a study evaluating changes in cognition in patients with MS led the authors to recommend study designs that will control for the influence of these drugs.

Commentary:
Luanne Metz, MD, FRCPC
University of Calgary
Calgary, Alberta

Most practicing clinicians would likely hypothesize that many CNS-active drugs may affect cognition, so it is no surprise that this concept is now supported by research.Clinicians, however, will also recognize that fatigue and changes in cognition can also be a consequence of many of the symptoms that lead to the use of these drugs (pain, sleep disorders, and upper motor neuron syndromes in addition to depression). This study is therefore important as it demonstrates that patients using CNS-active drugs have, as a group, worse fatigue and cognitive function than those not using these drugs. It does not, however, determine if it is the drugs themselves, or the symptoms that lead to their use, that are responsible for this difference. Therefore, while use of CNS-active drugs should be considered a covariate in studies of fatigue and cognition, the symptoms for which they are being used should also be considered. Furthermore, in clinical practice, fatigue and cognition should be evaluated before and after initiation of these drugs because the impact of treatment on fatigue and cognition will likely vary between individuals.
How to successfully apply animal studies in experimental allergic encephalomyelitis to research on multiple sclerosis.

**First Author and Institution:**
Lawrence Steinman. Stanford University

**Citation:**
Annals of Neurology. 2006;60:12-21

**Objective:**
Editorial to establish potential for the experimental allergic encephalitis (EAE) model to provide guidance in treatment of multiple sclerosis (MS).

**Type of Evaluation or Study:**
Literature review with commentary.

**Result:**
Recent criticism has the potential to obscure the major contributions that the study of the EAE model has made to the clinical management of MS.

**Conclusion:**
Animal models rarely provide a perfect platform on which to study disease. While the EAE model has multiple limitations, it is likely to continue to provide insight about MS.

The EAE model for the study of MS has been in use for more than 70 years. Recently, this model has been criticized for failing to be of value for advancing the treatment of MS.

In emphasizing the importance of the EAE model, the authors of the current review noted that several medications now approved for treatment of MS were brought forward after successful testing in the EAE model. Two of the currently approved medications, glatiramer acetate and natalizumab, were developed on the basis of logical targets identified in studies based on the EAE model. Moreover, they contended that work with glatiramer acetate in MS in the EAE model has been critical in identifying mechanisms of action beyond those first targeted in experimental development.

Similarly, the authors credited the EAE model with demonstrating that α4 integrin is an appropriate target of an antibody, leading to development of natalizumab. Although the EAE model failed to provide any signal of progressive multifocal leukoencephalopathy (PML), which caused two deaths after the drug was approved and led to initial voluntary withdrawal of natalizumab, the α4 integrin target did provide insight about disease mechanisms, and natalizumab has since been re-released with new precautions to reduce risk of PML.

Although the authors conceded that there have been numerous drugs that have demonstrated substantial promise in the EAE model only to fail in clinical testing, they emphasized that the model remains an excellent focus of testing as long as investigators recognize that it is only the first step in drug development.

**Commentary:**
Robert Lisak, MD
Wayne State University
Detroit, Michigan

EAE is the most widely employed animal model for MS research and has been for 70 years. It has been highly informative in increasing our understanding of immunopathogenesis of inflammatory diseases of the central nervous system including MS and acute disseminated encephalomyelitis (ADEM). Recently, the failure of treatments that are highly effective in preventing, inhibiting, and treating EAE to provide highly effective treatment for MS has sparked conversations and publications pointing out the failures and even calling into question the validity and usefulness of EAE as an experimental model for MS, a disease that has no counterpart in other species. For those involved in MS research for many years, we have seen ups and downs in the view of EAE as an “animal model of MS” before.

In this “Point of View” article, the authors briefly review the history of EAE and discuss two approved therapies for MS that were developed in the EAE model: copolymer 1 (glatiramer acetate) and monoclonal antibody directed at the-α4 peptide of the integrin VLA4 (natalizumab). In addition, mitoxantrone, also approved by the Food and Drug Administration, is effective in EAE, as are several other immunosuppressive agents that are employed in an “off label” fashion in a subset of patients with MS. Type I interferons, particularly IFN-β1, was not originally tested in MS because of a known therapeutic effect in EAE, but subsequent studies show type I interferons inhibit EAE and the original premises for the use of interferons in MS have yet to be shown to have anything to do with the effectiveness of these agents in MS. As the authors also point out, there are agents now being tested because of their effects in EAE, although the proof of effectiveness for many of these is still outstanding, pending the completion of ongoing and newly started therapies.

Steinman et al also take the opportunity to discuss how many of the concepts of the pathogenesis of MS come from or at least originated with findings in EAE. They also quite correctly point out that some of the problems and criticisms of the use of EAE as a model for MS research originate in asking too much of the EAE model or failing to use the different models/types of EAE to ask specific questions, assuming that all EAE should be perfect models of all stages of MS. There is no question that some agents that are effective in acute EAE and even in recurrent/chronic EAE have had limited effects in MS or even seem to exacerbate the disease. However one should remember that there is no currently approved therapy for MS that does not prevent, inhibit, and/or treat EAE.
Suicidal ideation in multiple sclerosis.

First Author and Institution: Aaron P. Turner, VA Puget Sound Health Care System

Citation: Archives of Physical Medicine and Rehabilitation. 2006;87:1073-1077

Objective: Identify risk factors for suicidal ideation in patients with multiple sclerosis (MS).

Type of Evaluation or Study: Mailed survey to MS patients.

Result: Depression and bowel disability were the only significant predictors of suicidal ideation.

Conclusion: Suicidal ideation is very common in patients with MS. Patients screened for depression, which is the most powerful predictor of suicidal ideation, should also be screened specifically for suicidal ideation.

Patients with MS have a rate of suicide that is more than seven times greater than that of an age-matched population, according to results of one analysis. Another risk assessment determined that suicide is the cause of death in approximately 15% of patients. Efforts to identify MS patients at high risk for suicidal ideation may be essential to initiating appropriate treatment and counseling before the act is pursued.

In this study, patients in the northeast region of the Veterans Affairs (VA) medical system who had received services for MS over a 5-year period were identified by computer. Surveys were sent to 1,090 eligible individuals. A second mailing was sent to nonresponders in an effort to increase response rates. The surveys included a 9-item evaluation of depression severity based on the Primary Care Evaluation of Mental Disorders (PCEMD) and questions on demographics, degree of disability, disease course, social support, and suicidal ideation.

Of the 1,090 patients contacted, 451 (43.7%) completed the survey and 445 provided sufficient information for statistical analyses. When demographics were compared in respondents and nonrespondents, there were no significant differences in age or gender. However, respondents were significantly more likely to be Caucasian and to be married than nonresponders. The mean age of the respondents was 55, and 60% reported a progressive component of MS. Only 14.5% reported employment outside of the home. Major depression was identified in 22.5%.

Asked specifically about the 2 weeks prior to completing the survey, 29.4% reported at least one episode of suicidal ideation. Persistent suicidal ideation was reported by 7.9%. On bivariate analysis, a variety of factors were associated with an increased risk of suicidal ideation, including a younger vs. older age, shorter vs. longer interval since the diagnosis, driving at least occasionally vs. not driving, and significant loss of bowel function vs. relatively preserved bowel function. However, on bivariate regression fully adjusted analysis, only impaired bowel function and depression remained significant. On adjusted multivariate regression analysis, only depression was significant, increasing the odds ratio of suicide ideation by 27% (OR 95% CI, 1.18-1.37; P<0.001).

This study, which is among a minority of analyses to look at factors leading to suicidal ideation rather than completed suicide, confirmed that suicidal ideation is extremely common in patients with MS. Although the authors conceded that more research is needed to determine the factors associated with progression from suicidal ideation to completed suicide, they indicated that it is likely that most patients who complete suicide experience a period of suicidal ideation before the act. They maintained that efforts to screen patients for suicidal ideation may provide an important opportunity to intervene before ideation progresses.

Commentary: Randolph B. Schiffer, MD
Texas Tech Health Sciences Center
Lubbock, Texas
There is nothing which makes us feel more empty as health care providers than the death of one of our patients by suicide. Unfortunately, MS is one of the neurologic diseases in which suicide remains a continuous concern. Aaron Turner and his colleagues in Seattle have given us interesting new data concerning rates of suicidal ideation in a large cohort of MS patients within the VA health system.

The investigators performed a mail survey of suicidal ideation and depression severity of 1,032 MS patients who had received care in their VA Network between 1995 and 2000. They assessed suicidal ideation with the Patient Health Questionnaire (PHQ), a standardized instrument which has been used by other groups in MS populations. They assessed severity of depression using the US Preventive Services Task Force screening instrument. They received 445 responses. One hundred sixty-six of the subjects endorsed significant suicidal ideation on the PHQ, 35 of whom said that their suicidal ideation had been persistent during the past 2 weeks. Severity of depression was positively correlated with suicidal ideation.

We do not know for sure what the relationship is between suicidal ideation and suicidal action, and we do not know from this study that MS patients differ from people with other chronic diseases with regard to suicidal ideation. But the results are still impressive, and give pause to those who direct MS clinical programs. Should we be regularly screening for depression and suicidal ideation in these settings? Should we all be more aggressive in treating our MS patients with identified depressive syndromes? The data in the Turner publication argue that the answer to both of these questions is yes.
Effects of donepezil on memory and cognition in multiple sclerosis.

First Author and Institution:
Christopher Christodoulou, State University of New York at Stony Brook

Citation:
Journal of Neuroimmunology. 2006;245:127-136

Objective:
Determine if a medicine to preserve memory in Alzheimer's disease is effective for multiple sclerosis (MS).

Type of Evaluation or Study:
Single-center, double-blind, randomized, placebo-controlled trial.

Result:
Significantly more patients and physicians reported improved memory on donepezil.

Conclusion:
These results provide the basis for a large, multicenter trial to confirm the utility of donepezil in the treatment of memory impairments associated with MS.

Cognitive dysfunction has been reported in up to 60% of patients with MS. In this study, the goal was to evaluate an acetylcholinesterase inhibitor for improving cognitive function in MS patients. Acetylcholinesterase inhibitors have been associated with significant delay in diminishing cognitive function in patients with Alzheimer’s disease. The benefit of these agents is attributed to their ability to block acetylcholinesterase, thus increasing acetylcholine activity in the brain. Although the mechanism of cognitive loss is likely to be quite different in MS than in Alzheimer’s, it has been hypothesized that demyelination does interrupt cholinergic pathways. Several small and nonblinded studies have suggested that acetylcholinesterase inhibitors may provide benefit in MS patients.

In this study, donepezil, the first acetylcholinesterase inhibitor licensed for use in Alzheimer's disease, was administered to patients who met eligibility requirements that included a diagnosis of definite MS and at least mild verbal memory impairment as measured by the Rey Auditory Verbal Learning Test. All patients had a Mini-Mental Status Examination (MMSE) score of at least 26 at baseline. Other medications, such as disease-modifying agents, antidepressants, or anti-spasticity drugs, were permitted if patients had been on a stable dose for at least 1 month prior to entry and remained on that dose throughout the trial.

The 69 patients who were randomized in this 24-week trial received either 5 mg of donepezil for 4 weeks followed by 10 mg for 20 weeks or placebo. Patients were followed with monthly telephone contacts and clinic visits at weeks 4, 14, and 24. The primary outcome was change in Selective Reminding Test (SRT), but other cognitive tests were performed. Patients and physicians also assessed overall changes in cognitive function.

A total of 67 patients completed the study. In those randomized to donepezil, there was a 4.57 point increase in SRT score vs. a 0.68 increase in the group randomized to placebo. The mean difference of approximately 3.9 points was statistically significant (P=0.043). By self-report, 65.7% in the active treatment group vs. 32.4% on placebo (P=0.006) detected an improvement in cognitive function. By physician report, the proportions improving on active treatment and placebo, respectively, were 54.3% and 29.4% (P=0.036). There were no serious adverse events, but a higher proportion of patients on donepezil reported abnormal or unusual dreams (34.3% vs. 8.8%; P=0.01), and the increased rate of diarrhea on donepezil approached statistical significance (25.7% vs. 8.8%; P=0.064).

The results of this study substantiate earlier reports that acetylcholinesterase inhibitors may have a role in improving cognitive function in MS patients. However, the authors called for larger studies to further evaluate the benefit-to-risk ratio.

Commentary:

Steven Schwid, MD
University of Rochester
Rochester, New York

Until we have ways to repair nervous system damage in patients with MS, treatments for symptoms caused by demyelination and axonal damage will continue to be necessary. Although cognitive impairment may not be the most visible symptom, it is one of the most disabling. The cognitive effects of interferons and glatiramer acetate have been considered in clinical trials, but methodological limitations make these studies difficult to interpret. Presumably, even the most effective immunotherapy would only stabilize existing deficits. Rehabilitation may help patients with cognitive impairment function somewhat better, but more effective treatments are clearly needed. Based on a number of preliminary studies, cholinesterase inhibitors appear promising in this regard, even though a cholinergic deficit has not been demonstrated in MS as it has in Alzheimer’s disease.

In the largest and most rigorous study performed to date, Christodoulou et al studied patients with mild to moderate memory impairment and found that memory improved with donepezil compared with placebo. Although improvements were modest, they were apparent to both patients and physicians based on global impressions. Tests of attention and speed information processing did not show a treatment effect, but patients had minimal deficits in these domains, potentially limiting their sensitivity. Coupled with the well-characterized and generally benign side-effect profile of donepezil, these results are compelling enough to consider using it in cognitively impaired MS patients. However, several questions remain: Can these results be replicated in a multicenter study? Is donepezil only effective for memory impairment? Are there other clinical characteristics that can predict who will respond? Do anticholinergic and sedating medications affect patients’ responses? These issues are being addressed by an ongoing multicenter study.
Remyelination is extensive in a subset of multiple sclerosis patients.

The authors indicated that two important observations can be drawn from this study. The first is that remyelination in the form of shadow plaques is extensive and observed in a substantial proportion of patients. The second is that this remyelination is not restricted to early stages but is seen in all subtypes of MS, including primary progressive MS. While MS is clearly a progressive disease, these findings suggest that progression may not be linear but subject to some self-repair, a finding that may be important in better understanding the natural history of MS and in positioning therapy for maximum effect. In particular, it may be important to evaluate how current and future therapies affect repair mechanisms and can be directly targeted at enhancing this repair.

There are some limitations to this study. For example, the investigators cautioned that restricting the analysis to lesions of the forebrain precludes conclusions about remyelination in other areas of the brain or spinal cord. Also, although functional restoration of conduction has been shown by electrophysiology in some areas of remyelination, more information about CNS function controlled by tissue in shadow plaque areas is needed to fully understand the significance of this repair. Extensive study of this phenomenon is underway, according to the investigators.

Commentary:

Robert Zivadinov, MD, PhD
State University of New York at Buffalo
Buffalo, New York

Remyelination of the focal white matter plaques that characterize MS has been reliably reported for 25 years, but the frequency of this repair, particularly complete remyelination, has not been well documented. Demonstrating the extent of remyelination may be important to understanding the variability of clinical progression or the effects of therapies. In this very important study, the data demonstrated that one of the most important influences on the extent of remyelination was plaque location. Those lesions most likely to have substantial or complete remyelination were located in the deep white matter or were found subcortically. Regional magnetic resonance imaging (MRI) studies using techniques capable of monitoring remyelination-demyelination processes may contribute to a better understanding of this phenomenon. The authors of the study concluded that there is substantial variability in remyelination among patients, making it necessary to develop better tools to evaluate this type of healing in the context of therapeutic trials that include remyelination as an outcome. Several clinical trials using MRI techniques capable of monitoring remyelination-demyelination processes are currently underway. More studies are needed to determine the clinical significance of remyelination in terms of nerve conduction and functional recovery of the CNS. Development of surrogate imaging markers of remyelination is mandatory in order to translate these important observations into clinical practice.

First Author and Institution:
Peter Patrikios, Center for Brain Research, Medical University of Vienna

Citation:
Brain. 2006;129(Pt 12):3165-3172

Objective:
Evaluate the incidence and distribution of remyelinated lesions in autopsies of multiple sclerosis (MS) patients.

Type of Evaluation or Study:
Multicenter, prospective collaboration employing systematic and standardized measures.

Result:
In 20% of autopsies, remyelination was extensive, most often in long-duration disease.

Conclusion:
Substantial remyelination occurs in both relapsing-remitting and progressive MS. This potential for variable remyelination should be considered in clinical studies that are testing strategies in which central nervous system (CNS) repair is an outcome measure.
The contribution of demyelination to axonal loss in multiple sclerosis.

**First Author and Institution:**
Gabriele C. DeLuca, University of Oxford

**Citation:**
Brain. 2006;129(Pt 6):1507-1516

**Objective:**
Evaluate the relationship between plaque load and axonal loss in patients with multiple sclerosis (MS).

**Type of Evaluation or Study:**
Autopsy analysis of tissue from the cerebrum, brainstem, and spinal cord of MS patients.

**Result:**
Correlations between plaque load and axonal loss were weak or absent.

**Conclusion:**
The lack of correlation between plaque load and axonal loss raises the possibility that demyelination is not always the key determinant of axonal loss in patients with MS. This lack of correlation may provide new insight on clinical variability of MS.

In this study, post-mortem material was gathered from the cerebrum, brainstem, and spinal cord of 55 individuals who had a diagnosis of MS prior to death. The age range of the patients at the time of death was 25 to 83 years. The major objective of the study was to place plaque as a total of white matter area into relationship with axonal density and total axon number. Both plaque load and axonal loss were quantified through software image analysis using standardized techniques. Evaluations of plaque load and axonal loss in the cerebrum and the spinal cord were also undertaken in a subset of the total population.

When compared with control specimens taken from individuals without a diagnosis of MS, there was a significant reduction in axonal number and density. Plaque load was more variable, although average measures were similar for men and women. Total plaque load did not correlate with brain weight or with duration of disease. When the relationship between axonal loss and plaque load was evaluated, there was a weak or no correlation. This was true even in the subset of specimens in which the cerebral hemispheres and spinal cord were evaluated. In a stepwise regression, correlations between total spinal cord plaque load, axonal density, and total axon number remained unimpressive or negative.

The major conclusion drawn from this study is that inflammation leading to increased plaque burden, demyelination, and axonal loss is at best an incomplete characterization of MS. The evidence from this study and from several previously published observations that correlations between plaque load and axonal damage are poor has been joined by new evidence that there is substantial loss of axons in areas in which no demyelination is observed. These observations have importance for new approaches to prognostication and in judging the effect of treatments, for which plaque burden may not be a good indicator.

Although the authors cautioned that there are several limitations to this study, including the innate biases of autopsy examinations undertaken with a specific hypothesis, they noted that this is one of the largest pathological cohort studies performed to sample for plaque load and axonal loss using sophisticated techniques. Although it must be considered that a cohort of MS cases selected at autopsy is likely to have more aggressive disease and/or increased disability than the average, the authors indicated that the best conclusion from these results is that the pathogenesis of MS encompasses both neurodegenerative and wallerian mechanisms of axonal loss. These concomitant pathophysiologic processes are compatible with the clinical variability of MS and deserve further evaluation in understanding MS etiology.

**Commentary:**
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The classic conception of the pathogenesis of MS is that autoimmune injury to myelin sheaths, or demyelination, accounts for most or all of the clinical manifestations. However, there are limited data correlating demyelination, axonal loss, plaque load, and disease history. The significance of this study is that it attempts to evaluate the contributions of different types of disease activity in the central nervous system (CNS) of patients with MS. This may have importance for gauging the effects of therapy. However, a potential limit in interpretation of these findings is related to the fact that the extent of demyelination in the corticospinal and sensory tracts did not correlate with the length of disease history.

The findings of this study are consistent with a series of recent evaluations that have demonstrated substantial loss of axons in areas not clearly affected by demyelination. These findings challenge the plaque-centered view of axonal damage. They support the possibility that neurodegeneration may take place independent of inflammatory demyelination related to plaque formation. It is notable that the authors suggested that the findings do not rule out the potential for several pathogenic processes to be involved, with some being more prominent than others in individual patients.
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