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

Without departing from our customary formula, our first issue in 2011 highlights an array of thought-provoking studies on both the clinical and the research sides of multiple sclerosis (MS). On the clinical side, we invite Dr. Joshua Adler, Chief of the Pain Management Center at the VA Hospital in Detroit, to comment on a study suggesting a substantial subjective effect from chronic pain on function in neurological diseases, including MS. On the research side, Dr. Walter Royal of the VA Multiple Sclerosis Center in Baltimore critiques a study of the immunomodulatory effects of vitamin D. He provides context about why vitamin D may frame the early-in-life interplay between sunlight and Epstein-Barr virus for MS risk. Dr. Alberto Ascherio of Harvard School of Public Health comments on another vitamin D study that supports the idea of the nutrient as a potential modulator of the clinical course of MS.

From a basic research perspective on MS, Dr. Paula Dore-Duffy, who is Chief of the Division of Neuroimmunology at my own institution, is not impressed with a study that implicates angiogenesis in the pathology of MS. She provides insight about the difficulty of determining whether any upregulated biologic process is part of the problem or part of the solution in a given disease.

A pilot study to prove that treadmill training improves function in patients with primary or secondary progressive MS is considered a step forward by Susan Bennett of the Department of Rehabilitation Science at the State University of New York at Buffalo. Very little clinical research has been done with exercise training in progressive MS, so a controlled trial is a welcome opportunity for some evidence-based support for modifying the impact of MS on a group of individuals with few therapeutic options.

Finally, we have a commentary from Dr. Daniel Wynn, a clinician in Northbrook, Illinois, who examines the significance of quality-of-life data generated by an international study of the disease-modifying therapy glatiramer acetate.

We encourage you to consult the original sources, but we hope that we can provide some broad insight into at least some of the recent topics in the MS literature. 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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Psychosocial factors and adjustment to chronic pain in persons with physical disabilities: A systematic review.

First Author and Institution:
Mark P. Jensen, PhD, University of Washington School of Medicine, Seattle, Washington.

Citation:
Archives of Physical and Medical Rehabilitation. 2011;92:146-160.

Objective:
Evaluate whether psychosocial factors affect the adjustment to chronic pain.

Type of Study:
Data extraction from previously published studies.

Result:
Psychosocial factors, such as coping mechanisms for pain and beliefs about the significance of pain, were found to be important predictors of pain levels and physical functioning.

Conclusion:
In neurological conditions, including multiple sclerosis (MS), psychosocial factors are important mediators of pain and may be important potential targets for better pain control.

In this evaluation, published studies evaluating pain control in adults with physical disabilities due to MS, spinal cord injury (SCI), cerebral palsy (CP), muscular dystrophy (MD), or acquired amputation (AA) were retrieved from the literature. Studies had to evaluate at least one psychosocial predictor, such as catastrophizing, coping responses, beliefs about pain, or social factors. Three reviewers tabulated the data.

Of the 29 studies that met the criteria to be included in this analysis, 14 involved studies of patients with SCI, nine evaluated patients with AA, three included patients with CP, two with MS, and one with MD. Of the 24 studies employing multivariate analyses, at least one psychosocial predictor was significantly associated with increased pain or reduced functioning. Often more than one psychosocial variable was a significant predictor. The results did not vary substantially among the neurological diagnoses. Psychosocial variables were also significantly associated with a global rating of quality of life.

The implication of this study is that psychosocial factors should be routinely targeted in comprehensive care schemes designed to improve patient functioning and quality of life.

Commentary:
Joshua E. Adler, MD, PhD
Chief, Pain Management Service
John D. Dingell Veterans Administration Medical Center
Wayne State University
Detroit, Michigan

The results from this study are consistent with the care that is already being offered in good comprehensive pain clinics. The importance of psychosocial factors on the experience of pain both in regard to quality of life and in regard to its effect on activities of daily living is already well recognized. This effort to conduct something of a meta-analysis of studies with a relatively disparate group of disorders was a little unusual, particularly when considering the differences in the types of pain associated with the conditions studied. While pain in MS is often directly related to the underlying disease, pain in MD is typically secondary to muscle weakness. Still, acute pain relief with medications such as opioids is not associated with long-term benefit in any of these conditions.

The importance of psychosocial influences on the experience of pain suggests that we cannot rely solely on analgesics. These are among data that underscore the need to look beyond medications for pain control. However, we also need to do well-controlled trials to show that treatments targeting psychosocial factors are effective. Rigorous studies are particularly important because of the large placebo effect associated with pain therapies. M

Health-related quality of life in relapsing remitting multiple sclerosis patients during treatment with glatiramer acetate: A prospective, observational, international, multi-centre study.

First Author and Institution:
Peter J. Jongen, MD, MS4 Research Institute, Nijmegen, The Netherlands.

Citation:
Health and Quality of Life Outcomes. 2010;8:133-139.

Objective:
Evaluate health-related quality of life (HR-QOL) over the first 12 months of glatiramer acetate (GA) therapy in people with multiple sclerosis (MS).

Type of Study:
Prospective, observational, multicenter study.

Result:
Significant improvements in overall HR-QOL scores were observed at both 6 and 12 months of follow-up after initiation of GA therapy, particularly in treatment-naïve subjects.

Conclusion:
An improvement in HR-QOL in patients with MS can be achieved soon after initiation of GA, and the relative improvement is sustained for at least 1 year.

Studies of disease-modifying therapies (DMTs) in MS have been largely focused on their ability to reduce relapses and slow disability. HR-QOL, although often measured, has rarely been a primary objective of analysis even though, from a patient's perspective, it may be the most important measure of a drug's efficacy.

In this investigator-led study, 197 patients with relapsing-remitting MS were prospectively evaluated for HR-QOL, fatigue, and depression for 12 months after initiating GA. Of these patients, 106 had not previously received an immunomodulating therapy, while the remaining subjects had received at least one previous therapy (typically interferon beta). Patients were measured at baseline, 6 months, and 12 months for HR-QOL using the Leeds MS QOL (LMS-QOL) scale, for fatigue using the Fatigue Impact Scale (FIS), and for depression the Beck Depression Inventory Short Form (BDI-SF).

At month 6, there was a statistically significant improvement in HR-QOL on the LMS-QOL scale ($P<0.001$) in treatment-naïve subjects. Specifically, >90% of the treatment-naive group was improved (41.1%) or unchanged (44.2%). In those who had been previously treated, the figures for improved and unchanged were 35.5% and 51.7%, respectively, leaving only 12.8% who scored worse than baseline on QOL ($P<0.001$). The HR-QOL improvements were sustained at 12 months. FIS scores were significantly improved at both 6 and 12 months in the total population, but BDI-SF scores did not change significantly.

The authors conclude that GA improves HR-QOL in approximately 40% of patients at both 6 and 12 months.

Commentary:
Daniel Wynn, MD
Director, Clinical Research
Consultants in Neurology Ltd.
Northbrook, Illinois

It is important to consider the effect of the DMTs on HR-QOL independent of disease-based measures of MS control. This is a well-performed study that demonstrates GA is well tolerated and improves patient well-being. These data are useful for clinicians looking to reassure their patients that treatment has a reasonable chance of improving HR-QOL and a low chance of making it worse.

We already have data from randomized trials that the major DMTs modify disease activity, but this study confirms that 90% of patients will have the same or better HR-QOL over the first year after starting GA. The proportions were somewhat lower in patients who switched to GA from another therapy, which is a common event in routine practice.

Having this data becomes more important as treatment options expand. At the same time that we need longer safety and efficacy data to provide the same level of confidence with newer agents as we have with the traditional disease-modifying drugs, we also will want to know the likelihood of actually improving HR-QOL. The 15 years of efficacy and safety data with GA and the interferons provides evidence that these treatments may not only be effective, but may also be associated with patient-perceived improvements in HR-QOL. M

Vitamin D has a direct immunomodulatory effect on CD8+ T cells of patients with early multiple sclerosis and healthy control subjects.

First Author and Institution:
Andreas P. Lysandropoulos, MD, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

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

Objective:
Determine if vitamin D has a direct effect on immune-cell function in patients with multiple sclerosis (MS) and healthy controls.

Type of Study:
Evaluation of in vitro cultures with cells derived from patients with MS and controls.

Result:
Cytokine expression from CD8+ T cells was altered in the presence of vitamin D.

Conclusion:
This is the first evidence that vitamin D can confer anti-inflammatory effects on a T-cell population potentially important to MS control, and it promotes further study to explore clinical implications.

Numerous studies have implicated low levels of vitamin D as a risk factor for MS. However, there have been very few studies attempting to evaluate whether vitamin D has a direct effect on immune cells thought to participate in the development of MS, such as CD8+ cells.

In this study, CD8+ cells were cultured from peripheral blood mononuclear cells (PBMC) obtained from 10 patients with early MS (initial symptoms within 1 year) and 10 age- and sex-matched healthy controls. All had Epstein-Barr virus (EBV)-detectable CD8+ cells by enzyme-linked immunospot assay (ELISA). The cells were incubated with or without vitamin D ($1,25(OH)_2D_3$) for a week each time. Cytokine secretion in the supernatant was then measured.

The addition of $1,25(OH)_2D_3$ was associated with a diminished secretion of proinflammatory cytokines interferon gamma (IFN-γ) and tissue necrosis factor alpha (TNF-α) from CD8+ cells, and an increased secretion of anti-inflammatory cytokines interleukin-5 (IL-5) and transforming growth factor beta (TGF-β). The effects were similar in those with MS and the healthy controls. The immunomodulatory effects were similar even in CD4+ cell-depleted cultures.

These results encourage research to explore the role of vitamin D to prevent and possibly treat MS. The modifications in the immune response with vitamin D in patients with EBV-detectable CD8+ cells is consistent with other evidence that vitamin D modifies MS risk.

Commentary:
Walter Royal, MD
Research Associate Director
VA Multiple Sclerosis Center
Baltimore, Maryland

This is a very interesting and well-designed study that strengthens evidence suggesting that vitamin D can have important immunomodulatory effects in MS. EBV infection, especially during childhood, has been associated with an increased risk of developing MS. In the study, samples were analyzed from patients who had evidence of previous infection with the virus. The researchers examined vitamin D effects on the total T-cell population as well as specifically on CD8+ T cells, also called cytotoxic T cells, which have been shown to be present in large numbers on brains of patients with MS and to have a direct role in inducing demyelination and other damage in experimental models of the disease. They found that vitamin D could suppress the proinflammatory responses of CD8+ T cells in the patient samples that specifically target EBV. This effect, demonstrated in this in vitro model, suggests that vitamin D might have the same effects in vivo. This raises speculation that in healthy individuals who are infected with EBV, vitamin D might decrease the risk of future development of MS. While this is a possibility, this question can only be answered through additional research, including ultimately performing appropriately designed clinical trials.

The findings from this study are significant in their demonstration of possible effects of vitamin D on a well-documented risk factor for the future development of MS and in their implications for possible future directions for research in this area. M

Sun exposure, vitamin D and age at disease onset in relapsing multiple sclerosis.

First Author and Institution:
Tzu-Yun McDowell, MD, VA Medical Center, Baltimore, Maryland.

Citation:
Neuroepidemiology. 2011;36:39-45.

Objective:
Evaluate sun exposure, vitamin D intake, and timing of onset of multiple sclerosis (MS).

Type of Study:
Cross-sectional survey of MS registry population.

Result:
Low sun exposure from the ages of 6 to 15 years was associated with earlier onset of MS, while intake of cod liver oil in this same period of life was associated with a later MS onset.

Conclusion:
Previous epidemiologic studies have suggested low sun exposure and vitamin D intake in childhood increase the risk of MS; this study suggests they also affect the timing of MS onset.

Low sunlight and vitamin D exposure during childhood have been linked to an increased risk of MS, but few studies have attempted to evaluate the timing of these exposures relative to the timing of the onset of MS.

In this cross-sectional study, more than 4,000 participants in the Veterans Health Administration-Multiple Sclerosis Surveillance Registry were sent a questionnaire designed to elicit information about vitamin D intake and sun exposure during childhood. About 1/3 responded, and 948 were included in the analysis after several exclusions, such as for primary-progressive MS or foreign upbringing.

About half of the participants had lived in areas with low-to-medium solar radiation between the ages of 6 and 16 years. This group had a median symptom onset of MS that was 2.1 years earlier (P=0.02) than those living in areas with greater radiation during the same age range. In this period of childhood, regular intake of cod liver oil, the variable used to gauge vitamin D exposure, was associated with an onset of MS symptoms that was a median of 4.0 years later (P=0.02) relative to no regular intake of cod liver oil.

The results of this study suggest that the timing of these environmental exposures influences the pathogenic course of disease at least in regard to onset.

Commentary:
Alberto Ascherio, MD
Professor of Epidemiology and Nutrition
Harvard School of Public Health
Boston, Massachusetts

This study uses the age at MS onset as the outcome of interest to specify the relationship of sun or vitamin D exposure during childhood to subsequent risk of MS. The hypothesis is interesting and potentially important, and the use of age at onset has the potential advantage of not requiring a control group. However, studies based on age at onset have their own pitfalls. As the youngest patients were less than 30 years old and the oldest were more than 70 years old, the study is comparing age at onset across birth cohorts that are several decades apart. Because age at onset is almost certainly correlated with birth cohort (young patients must have had a young age at onset), any factor that varies by birth cohort in the underlying population is a potential confounder. For example, the later age at onset among users of cod liver oil could reflect a decline in cod liver oil use in the population over time, rather than an effect of cod liver oil on age at MS onset. Adjusting the results by birth cohort could remove this potential confounding factor, but this was not apparently done in this study.

The hypothesis that higher vitamin D levels during adolescence or young adult life could contribute to reducing MS risk is gaining momentum, but only a large-scale, randomized trial can provide a definitive answer.

Overall, the hypothesis that higher vitamin D levels during adolescence or young adult life could contribute to reducing MS risk is gaining momentum, but only a large-scale, randomized trial can provide a definitive answer. However, more longitudinal studies are probably appropriate before attempting to start a trial that would have to involve hundreds of thousands of participants. M

Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: A pilot study.

First Author and Institution:
Lara A. Pilutti, BSc, BPHE, McMaster University, Hamilton, Canada.

Citation:
Archives of Physical and Medical Rehabilitation. 2011;92:31-36.

Objective:
Evaluate body-weight supported treadmill training (BWSTT) for improving function and quality of life (QOL) in progressive multiple sclerosis (MS).

Type of Study:
Prospective, pretest-posttest pilot study.

Result:
Significant improvements were observed on objective physical measures of training intensity and speed, which were accompanied by subjective improvements in physical and mental subscales assessing QOL.

Conclusion:
Preliminary evidence suggests that BWSTT improves QOL in patients with progressive MS, supporting the need for a larger, full-scale study.

The benefit of exercise for improving function in patients with MS has been well demonstrated in patients with relapsing-remitting (RRMS), but has been less well studied in other subtypes, such as primary-progressive MS (PPMS) and secondary-progressive MS (SPMS). Patients with PPMS typically have more rapid onset of disability and are more likely than patients with RRMS to have spastic paraparesis, making the benefits of exercise training less clear.

In this study, characterized as a pilot investigation, five patients with PPMS and one patient with SPMS were entered into a prospective study of BWSTT, which consists of a harness and overhead track to adjust the amount of body weight borne through the lower extremities. The BWSTT sessions were conducted three times per week for 30 minutes. Outcome measures, evaluated at baseline and again after 12 weeks of training, included Expanded Disability Status Scale (EDSS), MS Quality of Life-54 (MSQOL-54), Multiple Sclerosis Functional Composite (MSFC), and Modified Fatigue Impact Scale (MFIS).

All six patients improved walking speed on the treadmill (average improvement 34%; $P<0.001$) and the amount of weight bearing through the legs (42%; $P<0.001$). In addition, there was significant improvement on both the mental ($P=0.01$) and physical ($P=0.02$) subscales of the MSQOL-54. There were no significant changes in EDSS or MSFC scores and a nonsignificant reduction in MFIS scores.

This pilot study supports the benefit of exercise training in patients with progressive MS. The possibility that this type of exercise may improve daily function deserves further evaluation.

Commentary:

Susan Bennett, PT, DPT, EdD, NCS, MSCS
Clinical Associate Professor
Department of Rehabilitation Science
State University of New York
Buffalo, New York

This pilot study with a very small group of patients is important and well conducted. Patients with progressive MS have received very little attention in regard to physical rehabilitation, which may be particularly important because there are so few options for medical management. It is not surprising that there was no change in the EDSS score, which rarely changes with exercise, particularly over a period of only 12 weeks. It is also not surprising that there was improvement in quality of life, because we might expect to see some benefit just from the opportunity to interact and receive clinical encouragement.

The authors acknowledge many of the limitations of their study, but I hope that they will better standardize their protocol if they pursue a larger study. It would be important to establish a specific protocol for incremental increases in walking speed or reductions in body weight support as patients respond to the training. In a larger trial, it will also be important to employ a control group that receives the same kind of clinical attention in order to demonstrate benefit from exercise not just from clinical interaction.

Like many centers, we already offer our patients with progressive MS an exercise protocol, and some have utilized the BWSTT, but it would be extremely valuable to have the data to support this approach. M

Angiogenesis is present in experimental autoimmune encephalomyelitis and pro-angiogenic factors are increased in multiple sclerosis lesions.

First Author and Institution:
Timothy J. Seabrook, MD, Novartis Institutes for Biomedical Research, Basel, Switzerland.

Citation:
Journal of Neuroinflammation. 2010;7:95-105.

Objective:
Evaluate whether angiogenesis is present during experimental autoimmune encephalomyelitis (EAE).

Type of Study:
Immunohistochemistry studies in an animal model of EAE.

Result:
Markers of angiogenesis and density of patent blood vessels were increased at the same time that meteorin, an inhibitor of angiogenesis, was decreased during relapse phases of EAE.

Conclusion:
Angiogenesis appears to be involved in the pathology of EAE, raising the possibility that these mechanisms may also be involved in the progression of multiple sclerosis (MS).

MS is an autoimmune disease characterized by perivascular leukocyte infiltration and demyelination thought to be induced by the inflammatory process. It is possible that the stress response to injury, which can include angiogenesis, contributes to the disease process.

In this study, angiogenesis was evaluated in the acute model of EAE in rats. Proangiogenic activity measurements included assays of vascular endothelial growth factor (VEGF) expression and blood vessel density.

During the relapse phase of EAE, VEGF expression was increased by inflammatory cells in the brains of the animals. Increased blood vessel density was also observed by several techniques including histology. A second set of experiments with tissue taken from patients with chronic MS demonstrated glial expression of VEGF and VEGFR2.

Taking these results together, the authors conclude that angiogenesis is increased in EAE and may participate in clinical MS. They further maintain that angiogenesis is most active in the relapse phase.

Commentary:
Paula Dore-Duffy, PhD
Chief, Division of Neuroimmunology
Wayne State University
Detroit, Michigan

The subject addressed by this investigation is potentially important. However, the role played by vascular homeostasis in disease activity is highly complex. In response to any stress signal, the blood:brain barrier (BBB) must undergo a number of adaptive processes that promote cell survival and repair, and maintain the balance of oxygen and glucose delivery to meet metabolic demand. These adaptive measures involve a series of cross-talk mechanisms between the cellular constituents, such as endothelial cells, pericytes, astrocytes, glial cells, and neurons. The strategies used to adapt to acute stress, such as hypoxia or stroke, are likely to be fundamentally different than those used to adapt to chronic stress, such as dementia, cancer, or MS. Restorative or deleterious effects depend on the state of the vessels at the time of the stress signal and the local microenvironment.

One must be very cautious in inferring that angiogenesis is contributing to the pathophysiology of any given condition.

One must be very cautious in inferring that angiogenesis is contributing to the pathophysiology of any given condition. An increase in VEGF in leukocytes is not necessarily deleterious or pathogenic. Leukocyte infiltration compromises the microvessel at the site of inflammatory lesions, inducing what has been termed "virtual hypoxia" (Khan O, et al. Brain. *2010;133:2845-2848). It is expected that the local vasculature would adapt and that VEGF would be produced. While adaptive angiogenesis may be induced, the authors have overinterpreted their data. For example, they identify meteorin, which was downregulated, as an inhibitor of angiogenesis, but meteorin inhibits angiogenesis by upregulation of thrombospondin, which is not the only endogenous inhibitor of angiogenesis. Meteorin has a more important role for cell differentiation.*

Although this study raises important questions, it is premature to imply that angiogenesis is required for disease progression in EAE or in MS. Caution must be imposed before considering modes of therapeutic intervention that alter vascular function. M

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