The successful management of multiple sclerosis (MS) is built upon the psychological and social well-being of individuals. Unfortunately, MS often is characterized by such symptoms as chronic fatigue, persistent pain, clinical depression, and other affective characteristics that can have an adverse impact on psychological function.

“Over 80% of those with MS have some mood or affective symptoms. These can occur at any stage of the disease, frequently before any neurologic deficits are noted. What has been striking is that depression in those with MS is not only more common than in the general population, but also more common than in other chronic medical conditions,” said Lydia A. Chwastiak, MD, MPH, a board certified psychiatrist with the University of Washington Multiple Sclerosis Rehabilitation Research and Training Center in Seattle, at the recent Consortium of Multiple Sclerosis Centers (CMSC) conference held in Chicago. In persons with MS, the lifetime prevalence of major depression is approximately 54%.

The presence of comorbid depression is associated with increased disability, pain, and fatigue, as well as decreased quality of life. These symptoms often are interrelated. For example, persistent pain is found in approximately half of those with MS and may lead to avoidance of certain activities, resulting in deconditioning, further disability, and increased likelihood of depression. Likewise, depression may cause social withdrawal and avoidance of activity, leading to rapid deconditioning and heightened pain.

Poorer treatment compliance also has been found in depressed individuals. “One study looked at the impact of depression on multiple sclerosis and found that those who were depressed had decreased adherence to treatment with disease-modifying agents, and that if those people were treated for depression, the depression resolved and treatment adherence improved,” Dr. Chwastiak stated.

Perhaps most alarming is the fact that persons with MS are at greater risk for suicide. A large Danish study of over 5,000 individuals with MS found that the cumulative lifetime risk of suicide from onset of MS was 1.95%, with male gender and onset of the disease before the age of 30 years showing a higher association. Depression was present in over 50% of completed suicides.

While depression is very common in MS, certain factors increase its likelihood. “In our own study,” Dr. Chwastiak con-
tended, “we used the Center for Epidemiological Studies Depression Rating Scale (CES-D) and found that a CES-D of 16, which indicates significant depression, was met by 40% of our community-dwelling sample, while a score of 22, indicating a major depressive episode, was found in 31%. These higher scores were associated with an EDSS [Expanded Disability Status Scale] score of more than 6.5, lack of social support, and a recent diagnosis at a younger age.” Individuals who were within one year of diagnosis were much more likely to be severely depressed, according to Dr. Chwastiak, as were those with the highest EDSS scores, suggesting potential groups to monitor for depressive symptoms and possible treatment interventions.

**THE ROLE OF EXERCISE**

Exercise can play a key role in the management of MS, helping to maintain physical and emotional well-being. “People who exercise have a decreased risk of cardiovascular disease, diabetes, and cancer. Exercise also reduces anxiety and depression. Studies have found that exercise improves strength, conditioning, mobility, fatigue, mood, and social interaction in the MS population and, among health-promoting behaviors, it has the strongest link to quality of life,” said Kimberly D. Blake, PhD, at the CMSC conference. Dr. Blake is a postdoctoral fellow in the Rehabilitation Medicine Department of the University of Washington School of Medicine in Seattle.

Exercises that have proved beneficial to people with MS include stretching, strengthening, and aerobic conditioning. Minor adjustments in daily routine can also provide more opportunities for physical activity, and those with MS...
should consider making such modifications as taking the stairs rather than the elevator or parking farther from the store rather than taking the closest spot.

Many people with MS are interested in developing an exercise routine to manage their fatigue, which is one of the most serious problems afflicting those with the disease. However, according to Dr. Blake, they may need counseling. Her group is conducting a study on the value of brief counseling in improving the health and wellness of those with MS. “We are targeting particular areas, such as exercise, fatigue and stress management, communication, social support, and substance abuse,” she said. People who want help dealing with one of these areas are randomized into treatment, usual care, or wait-list groups. The treatment group receives a face-to-face motivational interview session and a feedback session with a social worker, followed up by five telephone counseling sessions over a three-month period to promote good health behaviors. Currently, 95 individuals have enrolled in the project.

A pilot study, which included eight people, showed good results, with 50% meeting or exceeding their original goals and 25% making moderate progress. “We think researchers should continue to examine ways to extend the benefits of health-promoting behaviors to more people with MS, and telephone counseling may be a viable means of doing so in some people,” Dr. Blake concluded.

**Work Is Therapeutic**

For many people, work is a defining aspect of their lives, providing not only income but a sense of self-worth and regular social interaction; all of these help maintain psychological health. Approximately 90% of those with MS have a work history, and 60% were working at the time of their diagnosis, according to Kathryn M. Yorkston, PhD, a language and speech pathologist who is Professor of Rehabilitation Medicine at the University of Washington School of Medicine in Seattle. However, “those figures drop off, with only 20% to 30% still working 10 to 15 years after diagnosis,” she noted at the CMSC meeting.

Dr. Yorkston’s presentation focused on a qualitative study that she and her colleagues at the University of Washington’s Multiple Sclerosis Research and Training Center are conducting as part of a project to explore the resources that people with MS use to maintain their jobs. Thus far the investigators have interviewed 37 people with MS. “Participation in the workplace is highly valued by the people with MS that we interview,” Dr. Yorkston reported. She acknowledged that fatigue and cognitive demands can sap the limited reserves of those with MS (studies have found cognitive deficits in 30% of employed and 70% of unemployed persons with the disease). Although employment “comes at a price, it is worth it because work is therapeutic,” she noted. Individuals report that having a job helps stave off depression and takes the mind off pain.

Increased vigilance and awareness is one coping method used by those with MS to continue functioning at their jobs. Some persons report exerting greater effort to walk properly or to speak without slurring. “People adopt a variety of strategies to maintain employment. One woman who works in a corporate office goes in early in the morning but tries not to stay late. That way, she can manage the work on her own schedule, and the work gets done. Others ask for help from coworkers when they need it.”

Dr. Yorkston also stressed the important role that health care providers have in encouraging people to work. “Many of those who responded believe that they are encouraged to quit by their health care providers because providers have equated work and stress and think that exposure to stress exacerbates MS. However, many have a great desire to continue working and feel that with a combination of accommodation and the proper resources, they can do so.” Dr. Yorkston suggested that health care providers inquire about the cognition and employment issues of those with MS and refer individuals to rehabilitation counselors for consultations about possible accommodations in the workplace. “It is important to start the process of accommodation early, before a person gets to the point of crisis, when intervention is much more difficult.”

Because cumulative cognitive deficits in such areas as memory, multitasking, and problem solving may reduce a person’s ability to cope with a job that formerly was done with ease, counseling may be essential to maintaining employment. “There has to be a big cognitive shift on the person’s part, and it’s our responsibility to help them do that, to find the right match in the world of work that will accommodate the status needs and histories of these folks, but will also accommodate some of the cognitive difficulties they have,” said David C. Clemmons, PhD, another CMSC presenter, who is Associate Professor of Neurology at the University of Washington School of Medicine in Seattle.

Such efforts by people with MS and health care providers alike cost little in comparison with their payoffs in terms of better psychological health and quality of life. In turn, individuals who have a better quality of life may find it easier to adhere to medication regimens and may experience improved physical health.

**References**


Laurel Ranger is a freelance writer based in Randolph, NJ.

IMMUNOTHERAPEUTIC APPROACHES FOR THE TREATMENT OF MULTIPLE SCLEROSIS

By Laurel Ranger

Within the past decade, new agents have emerged for the treatment of multiple sclerosis (MS), and while a cure has yet to be found, considerable hope has been raised. In conjunction with this, developments in magnetic resonance imaging (MRI) and data from brain biopsies have provided evidence of the physiologic effects of these agents on brain lesions as well as a glimpse into the pathogenesis of MS. Advances in genetics may also aid in our understanding of this disease. As our knowledge increases, we may be able to target particular variants of MS and achieve improved therapeutic outcomes.

One of the more interesting findings of the MRI and biopsy research has been the pathogenic heterogeneity of the disease. “Although the focus of MS research has been on identifying a pathogenic mechanism that would allow us to devise a single optimal therapy to treat all individuals, those who treat persons with MS realize this disease is extremely heterogeneous—not just clinically, but radiographically, genetically, and pathologically,” said Claudia F. Lucchinetti, MD, speaking at the recent Consortium of Multiple Sclerosis Clinics (CMSC) conference, which was held in Chicago. Dr. Lucchinetti is Associate Professor of Neurology at the Mayo Medical School in Rochester, Minnesota.

Lesion Patterns

Dr. Lucchinetti’s research has led her to characterize lesion patterns based on four factors: the distribution of myelin protein loss, the geography of the plaques, the extent and pattern of oligodendrocyte destruction, and the evidence for immunoglobulin in complement activation, as determined by MRI and serial biopsy. In pattern one, there is myelin destruction in active lesions, numerous oligodendrocytes and repair in the lesions, variable T-cell presence, and prominent macrophage involvement. The second pattern is similar to the first, but also exhibits a noticeable deposition of complement C9 neoantigen within the active lesions. Lesions of patterns one and two typically surround blood vessels and have equal loss of myelin-associated glycoprotein (MAG) and myelin oligodendrocyte glycoprotein (MOG).

Lesions of pattern three are quite different. “Here we found that while the typical plaque showed myelin loss, when you looked around the blood vessels there were often rims of myelin that had been spared,” Dr. Lucchinetti noted. “The key finding was that there was a striking loss of MAG relative to MOG and other myelin proteins. We also found that oligodendrocytes were undergoing apoptosis, and there was no complement activation and only limited repair.” Lesions of pattern four are the rarest. These lesions have oligodendrocytes dying within what appears to be perfectly normal myelin; here again, there is minimal repair but no MAG loss or complement activation.

“In lesions of patterns one and two, the target seems to be myelin, as our autoimmune models would suggest, whereas in patterns three and four, it looks as if the oligodendrocyte may be the target, which is more reminiscent of viral, toxic, ischemic, or metabolic problems,” she said. Although the differences in lesion patterns have not yet shown a distinct association with the clinical forms of MS, as defined by relapsing-remitting (RRMS), secondary progressive (SPMS), progressive relapsing MS (PRMS), or primary progressive MS (PPMS), Dr. Lucchinetti is of the opinion that these variations may account for the heterogeneity of treatment seen with MS and may also suggest potential therapeutic targets.

For example, among those with pattern two lesions, the presence of complement C9 neoantigen suggested that a positive response to plasma exchange, or plasmapheresis, might occur. In fact, Dr. Lucchinetti and colleagues did find that preliminary results were encouraging in a small group of individuals. “We had 11 such people with active MS on biopsy who received plasma exchange for a fulminant attack. All of our responders had pattern two lesions or antibody-mediated injury pathology, whereas the person with pattern one lesions and all three of those with MAG loss (ie, pattern three lesions) were nonresponders.”

Dr. Lucchinetti further noted that although much research is needed, the loss of T1 lesions, as revealed by MRI, may be a marker for remyelination and, therefore, may help distinguish patterns one and two from three and four (in which lesions do not repair and remyelinate). An investigation into whether these lesion patterns remain distinct within individuals over time is currently under way.

continued on page 9
Meeting Highlights

The annual meeting of the Consortium of Multiple Sclerosis Centers (CMSC) took place this year in Chicago from June 5 to 9. The following sections review a variety of international presentations.

Pilot Study of Ask-the-Nurse Information Line

A presentation by Deena Lisak, RN, MA, Connie Nesbary, MA, LPP, LLP, and Rose Taylor detailed an Ask-the-Nurse pilot study. Initiated at the Michigan chapter of the National Multiple Sclerosis Society (NMSS-MI), which serves over 15,000 clients with MS, the purposes of the study were to assess the needs of clients of the NMSS-MI chapter, to use the data for program and material planning, to confirm the need for such a program, and to assess whether the program would be replicable in other NMSS chapters.

Phone calls were tracked for 10 months, from July 2001 through April 2002, and call issues were derived from clients and from questions asked at a large ambulatory MS clinic at the University of Calgary, a study of which was presented at the CMSC meeting in June 2001. Typically, when calling, individuals leave their name, phone number, and medical question on voice mail at a toll-free number. The NMSS volunteer nurse is available one day per week to return calls, and all contacts are recorded with the reason(s) for the call, diagnosis date, caller address, phone number, county, and response to client. For this study, each issue presented during the calls was recorded rather than the number of actual calls. Follow-up calls were made by the volunteer nurse as needed, but were not tracked. Percentages were used to compare issues addressed during the contacts.

During the 10-month period, the NMSS volunteer nurse handled a total of 433 calls. Eighteen percent of the callers asked about disease-modifying medications and 12% asked questions about other medications. The next highest percentage of inquiries dealt with neurologic and non-neurologic referrals, symptom management, and other MS issues; all of these were at 9%. The remaining issues addressed were psycho-social (6%), newly diagnosed cases and research (5% each), MRI (4%), chemotherapeutic agents, intravenous methylprednisolone, complementary and alternative medicine, and equipment (3% each), and calls from professionals (1%). Additional issues to consider recording are insurance, employment, and informational literature. Some issues, such as symptom management, may be broken down into specific symptoms addressed (such as fatigue, pain, vision problems, etc).

The average call was 30 minutes in duration, with some as long as 90 minutes, although time was not documented. Individuals seemed to need someone to listen to them, to discuss issues in detail, and to receive factual materials by mail. They also seemed to want objective information to relieve their concerns, and referrals were made as needed.

Based upon the number of calls (an average of 11 per week) and the variety of issues addressed, the authors concluded that there is a need among people with MS for this type of service and that this program could easily be replicated in other NMSS chapter offices. Further studies could be done on the differences and similarities among chapter programs, based upon calls made to individual MS clinics. The authors also suggested that MS clinics may want to consider replicating the Calgary study.

The results of this study are being used in program planning for the NMSS-Michigan chapter. An evaluation of the program, which may include a qualitative assessment of the reduction of anxiety, is under way.

Multiple Sclerosis Nursing in 2002: A Global Perspective
A Brief Assessment Tool for the Hospitalized Person With MS

According to Nancy Eckert, RN, BA, CSG, of the Multiple Sclerosis (MS) Centre of Lehigh Valley Hospital and Health Network in Allentown, Pennsylvania, it is imperative that the bedside nurse have readily available tools to assess the complex needs of the hospitalized person with MS. Toward that end, Ms. Eckert and her colleagues presented a nursing assessment for such individuals. Since those with MS who are hospitalized for surgical or medical procedures as well as for MS care have chronic health issues that require special consideration, obtaining a detailed profile that specifically addresses MS symptoms, symptom management, medications, treatments, and impact on activities of daily living is critical to understanding how these people are affected by the disease. These issues often are underserved by generic admission forms. Integration of this additional information facilitates the multidisciplinary planning that maintains the delicate balance that the individual with MS requires to stay as independent as possible.

The brief assessment tool allows nurses to extract information pertinent to the individual with MS and serves as a guide to help identify the special needs of this complex population. Access to an MS nurse clinician provides an opportunity to:

- Examine the needs of the person;
- Develop a specific tool to look at individual MS client needs;
- Formulate an interdisciplinary plan of care;
- Maximize and maintain a person’s independence;
- Identify and anticipate triggers that would provoke an MS exacerbation;
- Anticipate postsurgical needs via rehabilitation;
- Coordinate and access necessary services spanning the continuum of care; and
- Educate health care professionals regarding MS symptom management and the effects of a hospital stay.

Some of the clinically relevant findings that a nurse may identify using the assessment tool include: mobility issues; transfers and gait training; appropriate assistive devices; bowel and bladder management; awareness of temperature sensitivity and control of the hospital environment; associated individual needs related to interferon therapy versus postoperative febrile states; assistance with the activities of daily living; pain management; monitoring for exacerbation of MS symptoms; identification of strategies to prevent stress and fatigue; knowledge deficit of staff and allied health providers of MS symptoms, disease course, and management; the need for maintenance of MS symptom therapy without interruption; and the potential for miscommunication among members of the health care team (Figure).

The plan of care includes identifying gaps in the present admission assessment tool, developing a specific MS assessment tool, and acknowledging the need for a knowledge base that reflects evidence-based practice. Such a plan would provide a better understanding of individual needs, improve quality of care, and promote self-management and independence. In addition, it would maintain a person’s locus of control, minimize the length of time an individual is hospitalized, and would return a person to his or her optimal level of individual function.

Utilization of an assessment tool focused on the individual with MS allows that person to have an influence on the course of care while hospitalized and ensures continuity of care. Communication is facilitated by the MS nurse clinician, ensuring that all those involved in care have an adequate understanding of the person behind the disease. For these reasons and others, Ms. Eckert and colleagues concluded that the MS nurse clinician is a powerful resource for staff and physicians in planning and developing an effective plan of care.
Does Training MS Nurse Specialists Impact the Quality of Life of a Person With MS?

A poster presentation jointly sponsored by the Italian Multiple Sclerosis (MS) Society and the Cleveland Clinic Foundation examined the issue of whether MS nurse specialists affect the quality of life of an individual with MS. The study took place in Italy, where there are an estimated 50,000 people with MS, 20,000 to 25,000 of whom are followed in MS clinics. According to the researchers, nurses working in these clinics typically have no special knowledge or training in MS. The Italian MS Society conducted the study to assess whether the availability of a nurse with specific MS training meets the educational and ongoing care needs of those with MS and influences their quality of life. The study is part of a three-year initiative aimed at creating MS nurse specialists.

Ten nurses from MS clinics throughout the country participated in an intensive five-day training course organized by the Italian MS Society and completed an examination at the end of the course.

Following the training course, nurses recruited two groups of subjects. Group I consisted of the first 10 consecutive individuals who came to the MS clinic. They received a brochure introducing the option of meeting with an MS nurse, along with the nurse’s telephone number and appointment possibilities, a needs questionnaire, the Short-Form 36 Health Survey (SF-36), and a consent form. Group II consisted of the next 10 consecutive individuals; they received the same questionnaire and brochure as Group I. In addition, Group II also received a monthly phone call reminding each person that a nurse was available to discuss the topics listed in the brochure.

The nurse completed a demographic form, and a contact record form for each person was kept for six

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>DEMOGRAPHIC &amp; DISEASE CHARACTERISTICS</th>
<th>GROUP I (n = 93)</th>
<th>GROUP II (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>Range</td>
<td>21–72</td>
<td>24–66</td>
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</tr>
<tr>
<td>SD</td>
<td>11</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>63 (68%)</td>
<td>60 (70%)</td>
</tr>
<tr>
<td>Male</td>
<td>30 (32%)</td>
<td>26 (30%)</td>
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<tr>
<td>Civil Status</td>
<td>Single</td>
<td>31 (33%)</td>
<td>34 (40%)</td>
</tr>
<tr>
<td>Married</td>
<td>54 (58%)</td>
<td>44 (51%)</td>
<td></td>
</tr>
<tr>
<td>Divorced/widowed</td>
<td>8 (9%)</td>
<td>8 (9%)</td>
<td></td>
</tr>
<tr>
<td>Employment Status</td>
<td>Employed</td>
<td>55 (59%)</td>
<td>42 (49%)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>38 (41%)</td>
<td>44 (51%)</td>
<td></td>
</tr>
<tr>
<td>Years Since Symptom Onset</td>
<td>Mean</td>
<td>10.10</td>
<td>9.86</td>
</tr>
<tr>
<td>Range</td>
<td>1–46</td>
<td>1–40</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>8.94</td>
<td>7.56</td>
<td></td>
</tr>
<tr>
<td>EDSS</td>
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<td>3.2</td>
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<tr>
<td>SD</td>
<td>1.8</td>
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<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>GROUP COMPARISON ON TIME 0 SF-36</th>
<th>GROUP I (n = 93)</th>
<th>GROUP II (n = 86)</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>Mean</td>
<td>.68</td>
<td>.60</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.44</td>
<td>.30</td>
<td>N/S</td>
<td></td>
</tr>
<tr>
<td>Physical Role</td>
<td>Mean</td>
<td>.46</td>
<td>.48</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.43</td>
<td>.41</td>
<td>N/S</td>
<td></td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>Mean</td>
<td>.62</td>
<td>.67</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.28</td>
<td>.28</td>
<td>N/S</td>
<td></td>
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<tr>
<td>General Health</td>
<td>Mean</td>
<td>.51</td>
<td>.50</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.22</td>
<td>.24</td>
<td>N/S</td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>Mean</td>
<td>.49</td>
<td>.49</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.22</td>
<td>.21</td>
<td>N/S</td>
<td></td>
</tr>
<tr>
<td>Social Functioning</td>
<td>Mean</td>
<td>.75</td>
<td>.63</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.77</td>
<td>.21</td>
<td>N/S</td>
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</tr>
<tr>
<td>Emotional Role</td>
<td>Mean</td>
<td>.70</td>
<td>.54</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.91</td>
<td>.41</td>
<td>N/S</td>
<td></td>
</tr>
<tr>
<td>Mental Health</td>
<td>Mean</td>
<td>.60</td>
<td>.61</td>
<td>N/S</td>
</tr>
<tr>
<td>SD</td>
<td>.22</td>
<td>.22</td>
<td>N/S</td>
<td></td>
</tr>
</tbody>
</table>
The needs questionnaire and SF-36 were repeated at six-month intervals. Nine out of 10 nurses passed the examination with a score of greater than 80%, which was the preestablished cutoff point. The same number of nurses also completed subject enrollment. A total of 179 individuals participated in the study. Table 1 shows the demographic and disease characteristics for both groups. There was no significant difference between groups on age, gender distribution, years since symptom onset, and the Expanded Disability Status Scale (EDSS). Although a higher percentage of subjects in Group I were employed and married, the difference was not significant.

Table 2 shows a comparison between groups on baseline SF-36. There was no significant difference on any subscale of the SF-36.

Table 3 compares SF-36 at Time 0 and Time 1 on 57 subjects from Group I who have completed two assessments by this report. A significant improvement was seen on the subscale emotional role ($P = .034$). There were no other significant differences.

This interim analysis indicates that individuals who participated in the MS nurse specialist program experienced an immediate benefit in their emotional well-being. Even with this positive outcome, the current data do not provide sufficient indication of the overall benefit of this program. Complete data will allow the researchers to understand the overall benefit of this training program for individuals with MS.

In addition to SF-36 results, the final analysis will indicate the extent to which people with MS believed their needs were met following the implementation of the nurse training program.

One limitation of this study is the use of the generic SF-36 to assess the benefit of this program to those with MS. Use of disease-specific measures may have provided better information, but these were thought to create a burden for the individuals in the project. Because this was a pilot study, the researchers thought it was important to maximize information obtained from the evaluation of the program, while minimizing responder burden.
UNDERSTANDING THE GENETIC COMPONENT

While the direct cause of MS may be environmental, genetics has long been known to play a key role in the development of this disease. With the decoding of the human genome, significant advances may be made in the near future in understanding the pathology of MS and in designing more effective therapies.

“There is no question that within the next decade we are going to understand, at a molecular level, the inherited factors that predispose some people to MS,” said Stephen L. Hauser, MD, speaking at the CMSC conference on the role of genetics in the disease. “The stakes involved are enormous, as a thorough understanding of the genetic component of the disease may help us to design and target therapy precisely.” Dr. Hauser is Professor and Chairman of the Department of Neurology at the University of California, San Francisco.

It has long been known that a variant of the major histocompatibility complex (MHC) gene DR2 predisposes people to MS; the particular variant that does so is DRB1*1501.

“About half of those with MS in the US and Europe have this antigen, although 17% of those who do not have MS also carry the gene,” Dr. Hauser noted. Familial aggregation is quite common in MS, with siblings of those with MS carrying a 5% risk of developing the disease as well. Clearly, however, genes other than DR2 are implicated. The complexity of this issue is highlighted by the fact that the form taken by the disease often is dramatically diverse in different family members; further, in two thirds of identical twins, when MS develops in one, it does not develop in the other. “So, it is not likely that we are going to find clean genetic markers that predict a benign or a severe course,” he said. DR2 has been shown to modify the disease course, with those having two copies of the DRB1*1501 variant of DR2 typically having more severe disease than those with only one copy.

That 50% of those with MS are DR2-negative raises questions as to whether this, too, constitutes a distinct variant of the disease. “It leaves open the possibility that DR2-positive MS is a different kettle of fish from DR2-negative MS. I think it is tragic if we continue to ask clinical therapy questions without including in the analysis a response to DR2, especially in trials of drugs like glatiramer acetate (Copaxone®), which we think might be working via an interaction with DR2,” Dr. Hauser said.

TREATMENT IMPLICATIONS

“Our current therapies are working on the immunologic hypothesis of multiple sclerosis,” said Fred D. Lublin, MD, who is Professor of Neurology at Mount Sinai School of Medicine in New York City. Dr. Lublin also spoke at the CMSC conference. The interferon beta agents—interferon beta-1b (Betaseron®) and interferon beta-1a (Avonex®, Rebif®)—have many immunomodulatory properties, including the induction of immunosuppressive cytokines; inhibition of pro-inflammatory cytokines, such as IL-12 and interferon gamma; inhibition of antigen presentation within the central nervous system (CNS); and very potent effects on cellular migration into the CNS. Glatiramer acetate has several mechanisms of action as well, including the binding and possibly blockade of MHC molecules, antagonism of T-cell receptors, and a shift from Th1 helper cells to Th2 cells, which tend to be immunosuppressive.

All three interferon betas and glatiramer acetate have shown efficacy in the treatment of RRMS. Although modest results have been achieved in SPMS for interferon beta-1b in European trials, these results have not been replicated in US studies. While none of the currently available agents has shown any therapeutic benefit for PPMS, Dr. Lublin noted that a large trial with glatiramer acetate is under way in individuals with PPMS and should provide some very interesting data.

Combination therapy may prove more effective yet. Dr. Lublin observed that although there is some overlap between the interferon beta agents and glatiramer acetate, there are some unique differences in their mechanisms that may lead to an additive or synergistic advantage in combination. His group is currently combining interferon beta-1a once weekly with glatiramer acetate daily. “We are doing this as a safety trial, but it shows that you do not get an increasing number of gadolinium-enhancing lesions when you add glatiramer acetate to the regimen of those already on interferon beta-1a; this means the agents are not interfering with one another.”

Finally, knowing which treatments might be most effective in a particular variant of MS and whether a course is likely to be benign or aggressive, DR2-negative or DR2-positive, and complement C9 neoantigen-associated or not, would put a powerful weapon in the hands of clinicians. Evidence clearly suggests that early treatment lessens the chance of developing changes on MRI scans and lowers the risk of further attacks. Being able to target therapy precisely very early in the disease course is likely to be even more effective. The need for this kind of information is pressing, as data from placebo-controlled trials with interferon betas and glatiramer acetate indicate that while individuals rolled over from control groups onto active medication catch up in terms of relapse rates after several years of therapy, they do not do so in terms of disability. “There is an advantage to being on an active drug early on,” Dr. Lublin noted. “Also, we have the potential to hit people really hard. So we want to be able to predict for an individual early in the course of the disease whether we need to treat aggressively or not.”

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Two new consensus reports on use of magnetic resonance imaging (MRI) in people with multiple sclerosis (MS) have been released in recent months. Both reports conclude that MRI is highly valuable in the initial evaluation and diagnosis of MS. However, they also note that more data are needed before strong recommendations can be made on the use of MRI in follow-up evaluations or to guide treatment choices.

Although MRI has emerged as the most important tool for diagnosing MS as well as for monitoring disease progression and treatment outcome, the White Matter Study Group (WMSG) of the International Society for Magnetic Resonance in Medicine decided that an international consensus on determining the role of MRI in MS was needed. In response, the organization has released a consensus report based on workshops held during the first international meeting of the WMSG.

The group unanimously agreed that all people suspected of having MS should undergo MRI of the brain as soon as possible, in order to gather evidence for the diagnosis of MS and to exclude other potential causes of symptoms resembling those of MS. The following acquisition protocol was recommended:

- Baseline MRI satisfies the criteria of Barkhof et al (Brain. 1997;120:2059-2069) for the diagnosis of MS;
- First follow-up MRI obtained at least three months after baseline shows at least one active lesion; and
- Second follow-up MRI obtained at least three months after the first follow-up shows at least one additional active lesion.

The group considered MRI to be the best method to evaluate changes in disease activity and found that T2 lesions and T1-enhanced lesions “provided important information regarding two aspects of disease activity: whether the water content of a lesion rendered it visible and whether the blood-brain barrier was sufficiently abnormal that it could be detected following intravenous administration of paramagnetic contrast.” Unfortunately, these two parameters lack specificity and cannot detect activity in a lesion beyond a given threshold. Potential methodologies that offer improved sensitivity and specificity include magnetization transfer imaging, diffusion-weighted imaging, MR spectroscopy, and cellular MRI.

Furthermore, in terms of using MRI to assess treatment effects, “there was a general feeling that it made sense to consider MR findings in initial therapeutic decisions in those with early MS.” The imaging evidence that best supports the initiation of treatment is the presence of contrast-enhancing lesions. Another important consideration is the burden of disease on T2-weighted images. However, no specific number of lesions has been identified as a threshold for treatment initiation. The group had mixed opinions about using MRI to guide treatment choice or to alter management of affected individuals.

The second consensus report was prepared by the Consortium of MS Centers, which convened an expert consensus meeting in November 2001 to develop a standardized clinical MRI protocol and to decide whether routine follow-up MRI is warranted after MS has been diagnosed. Participants included MS neurologists and neuroradiologists from the United States, Canada, and Europe. The guidelines resulting from this meeting are available online (www.mscare.org) and will be updated regularly as new information becomes available.

The group concluded that a standardized MRI protocol “is essential for gathering meaningful follow-up information.” Brain MRI should be used in the initial evaluation and diagnosis of suspected MS cases and as part of the baseline evaluation in people with definite MS. Spinal MRI should be used in people whose presenting symptoms are at the level of the spinal cord and in people with ambiguous brain MRI results.

The MRI images should be obtained on a 1 Tesla or higher machine and the slice thickness should be 3 mm or less without gaps. The scan orientation for brain MRI should be on the subcallosal line using three planes and a localizer if available.

For brain MRI in a person being evaluated for MS,
the acquisition sequence should be:
1. Localization in three planes.
2. Sagittal FLAIR.
3. Proton-density and T2-weighted axial FSE.
4. Axial FLAIR.
5. High-contrast, T1-weighted 3D sequence (optional).
6. Gadolinium 0.1 mmol/kg over 30 seconds.
7. Postcontrast axial T1-weighted SE with a five minute delay.

Baseline evaluations and follow-up of people diagnosed with MS should follow the same pattern. However, only steps 1, 3, and 4 are required in this case; the other steps are optional.

For spinal MRI conducted following a brain MRI, an additional bolus of gadolinium is probably not required. The acquisition sequence should be:
1. Localization in three planes.
2. Postcontrast sagittal T1-weighted SE.
3. Postcontrast axial T1-weighted SE
   (through suspicious lesions).
4. Proton-density and T2-weighted sagittal FSE.
5. Axial T2-weighted FSE (through suspicious lesions).
6. High-contrast, T1-weighted 3D sequence (optional).

For spinal MRI not preceded by a brain MRI, the sequence should be:
1. Localization in three planes.
2. Sagittal proton-density and T2-weighted FSE.
3. High-contrast, T1-weighted 3D sequence (optional).
4. Sagittal T1-weighted.
5. Gadolinium 0.1 to 0.3 mmol/kg over 30 seconds
   (if required).
6. Postcontrast sagittal T1-weighted SE (if required).
7. Postcontrast axial T1-weighted SE
   (through suspicious lesions).
8. Axial T2-weighted FSE (through suspicious lesions).

The guidelines do not recommend routine follow-up MRI, but the procedure is indicated in people with unexpected clinical worsening, for reassessment of T2 burden of disease for initiation of treatment, or if the health care provider suspects a secondary diagnosis.


NEW THERAPEUTIC TARGETS BASED ON BETTER UNDERSTANDING OF MS PATHOGENESIS

Recent technologies have allowed for a deeper understanding of the pathogenesis of MS. Large-scale analysis of gene transcripts and large-scale monitoring of the immune response with protein chips have identified possible new targets for therapy, according to the authors of a recent review article.

One such new target area includes matrix metalloproteases (MMPs), a family of enzymes involved in the “degradation of the extracellular matrix and the proteolysis of myelin components in MS,” the researchers reported. An intense effort to develop MMP inhibitors is currently under way.

Another approach is to inhibit the pathologic immune response against the myelin sheath. For example, treatment with altered peptide analogues of myelin basic protein modifies various immunologic markers and, more importantly, decreases the size of new white matter lesions. In one trial, 17 of 21 people who had active scans at baseline showed reduced volume of enhancement on MRI following four months of treatment with an altered peptide ligand (APL). However, in another trial involving the same APL at a higher dose, some people developed disease exacerbations and allergic reactions. Based on these two studies, the authors suggested that “optimization of dosage and timing of administration may allow further trials of this promising approach—an approach that involves shifting the balance of cytokines from autoimmune to suppressive.”

Large-scale analysis of transcripts in MS brain plaques has shown that osteopontin (OPN) transcripts were often detected in brain specimens from people with MS but not in specimens from healthy controls. In a murine model of MS, disease severity was reduced in OPN-deficient mice compared with OPN-positive animals. Further analysis suggested that “OPN may play a critical role in the modulation of Th1 immune responses in MS and [animal models of MS],” the authors noted. They added that “OPN is clearly situated at a number of checkpoints that would allow diverse activities in the course of autoimmune-mediated demyelination.”

Furthermore, data suggest that use of neuroprotective agents that block subtypes of glutamate receptors may be useful for treatment of the chronic degenerative phase of MS. During inflammation in both MS and animal models of MS, excessive amounts of glutamate are released by lymphocytes, brain microglia, and macrophages. This glutamate then activates AMPA receptors. Studies have demonstrated that blockade of AMPA receptors with antagonists ameliorates MS in animal models, even in clinical relapses when treatment is initiated after the onset of paralysis.

CONTINUING EDUCATION CONFERENCE CALENDAR

September 18–21, 2002
Seventh Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS)/18th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). Location: Baltimore, Maryland. Contact: ACTRIMS-ECTRIMS 2002, c/o National Multiple Sclerosis Society, 733 Third Avenue, Sixth Floor, New York, NY 10017; (212) 476-0465; fax: (212) 661-9735; e-mail: ae2002@nmss.org; Web site: www.actrimsectrims2002.nmss.org.

October 9–12, 2002
Second Congress of the Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS). Location: Monterrey, Mexico. Contact: Merced Velazquez, MD, by e-mail: mchvelazquez@infosel.net.mx or Victor M. Rivera, MD, at 6560 Fannin, Suite 1224, Houston, TX 77030; (713) 798-7707; fax: (713) 798-6273; e-mail: vrivera@bcm.tmc.edu.

October 13–16, 2002
127th Annual Meeting of the American Neurological Association. Location: New York City. Contact: Lori Anderson, ANA, 5841 Cedar Lake Rd, Suite 204, Minneapolis, MN 55416; (952) 545-6284; fax: (952) 545-6073; e-mail: lorijanderson@msn.com; Web site: www.aneuroa.org.

October 26–29, 2002
Sixth Congress of the European Federation of Neurological Societies. Location: Vienna, Austria. Contact: EFNS Head Office, University Campus, Alser Strasse 4, A-1090, Vienna, Austria. 011-43-1-889-05-03; fax: 011-43-1-889-05-03-13; e-mail: head office@efns.org; Web site: www.efns.org/efns2002.

November 2–7, 2002
32nd Annual Meeting of the Society for Neuroscience. Location: Orlando, Florida. Contact: Society for Neuroscience, 11 Dupont Circle, NW, Suite 500, Washington, DC 20036; (202) 462-6688; fax: (202) 462-9740; e-mail: info@sfn.org; Web site: www.sfn.org/AM2002splash.cfm.

November 28–30, 2002

April 5–8, 2003
35th Annual Meeting of the American Association of Neuroscience Nurses (AANN). Location: Atlanta. Contact: AANN, 4700 West Lake Avenue, Glenview, IL 60025; (888) 557-2266 (US only), (847) 375-4733; fax: (847) 375-6333; Web site: www.aann.org.

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