

Clinical Perspectives

Consortium of Multiple Sclerosis Centers

This special issue of *Clinical Perspectives* focuses on new research findings in some of the main areas experiencing advances in the science and medicine of MS pathogenesis and treatment – MRI in MS, cognitive impairment in MS, and pediatric MS. Selected symposia, scientific presentations from both the platform sessions and the Whitaker Research Track, as well as other talks are covered here that provide a solid glimpse – and worthwhile educational value – into some of the latest thinking and research achievements regarding this debilitating disease.

Opening Ceremonies— CMSC Presidential Address

A highlight of this year's annual meeting of the CMSC was the talk delivered by Eli Silber, MD (Department of Neurology, Kings College Hospital, London). Entitled "Epidemiology and Ethnic Patterns in MS," Dr. Silber reviewed some factors that may play important roles in the pathogenesis of MS.

MS EPIDEMIOLOGY – KEY TO THERAPEUTIC PROGRESS

"We should study the epidemiology of MS to improve our understanding of the genetic and environmental variables influencing the disease," said Dr. Silber. "By advancing our understanding of the epidemiology of MS, we will also improve our ability to identify the needs of people with MS, particularly in disadvantaged communities."

GENETICS AND RISK

For the general population, the risk of developing MS is approximately 0.02%, said Dr. Silber. If a child from a family without MS is adopted into a

Prevalence of MS—Some Racial Differences*

Very High	>100/100,000 eg, Northern Europeans, North American Caucasians
High	>50/100,000
Medium	>10/100,000
Low	<10/100,000 eg, mixed-race South Africans, Natives of the Carribean, African Americans†
Very Low	Occasional Reports eg, Africans, Orientals, Aborigines, Maoris, Eskimos, Native Americans

* Risk of developing MS for general population ~0.02%

† Editor's Note: The stated incidence among these groups may be too low, and is changing.

family that has members with MS, he or she will have the same risk of developing MS as the general population. However, this risk increases to approximately 2% to 3% if a person has a mother, father, sister, or brother with MS, and jumps to 30% if both parents have the disease. Moving from familial genetics of MS to racial differences, Dr. Silber told the group that "the incidence of developing MS for Africans, Orientals, Aborigines, Maoris, Eskimos, and Native Americans is extremely low....The incidence of developing MS for mixed race South Africans, natives of the Caribbean, and African Americans is somewhat higher. But Northern Europeans and North American Caucasians have the highest incidence of developing MS—greater than 100 in 100,000."

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In this Issue

ENVIRONMENTAL FACTORS ALSO IMPORTANT

How genetics and environment may influence the development of MS was next illustrated by Dr. Silber as he cited a study by Kahana, et al that compared the incidence of MS in Israelis of Sephardic descent to that of Sephardic immigrants to Israel. Results pointed to environmental factors since first-generation Israelis of Sephardic descent had a 1.4- to 1.8-fold greater prevalence of MS compared to that among Sephardic immigrants. “The latitude gradient might be an environmental factor in the development of MS,” commented Dr. Silber. “Amongst relatively homogenous populations there is a greater prevalence of MS farther from the equator.” In Australia and New Zealand, rates of MS are higher in the southern parts of both countries but in the United States, the prevalence is greatest in the North. This latter observation may be an ethnic effect, because Scandinavians settled in the northern United States. Do certain environments increase the risks of MS? Are others protective? Dr. Silber pondered these points as he further explored whether certain types of infections—experienced earlier or later in life—increase the prevalence of MS, and whether sunlight might act as an immune modulator.

“We need to take the information that we have and try to identify specific patient groups that are at risk for MS,” Dr. Silber concluded. “After we’ve identified those groups, we need to reach out to them and improve their understanding of MS. We also need to improve their access to health care, their access to social resources, and bridge language barriers.”

Symposia Coverage: Focus on Brain Tissue Measurements, MRI, Cognitive Function, and Quality of Life

CNS ATROPHY IN MS

Cerebral atrophy, a robust measure of axonal loss, is recognized in established MS, but less certain is whether atrophy is evident in early disease, and relates to lesion load and eventual clinical outcome. During the symposium, *Controversies in Brain Atrophy: When and Why*, Nancy Richert, MD, PhD (Staff Clinician, Neuroimmunology Branch, National Institute of

Neurological Disorders and Stroke, NIH, Bethesda) presented the “Natural History of Atrophy in MS.” Dr. Richert explored predictive factors for atrophy and whether its presence or absence on magnetic resonance imaging (MRI) can be used to reliably forecast disease progression and future disability.

TOWARDS NEW CONCEPTS IN BRAIN ATROPHY

Inflammation, with its cascade of responses, said Dr. Richert, characterizes early MS, ultimately leading to neurodegeneration – the predominant feature in later stages. Although gadolinium-enhancing lesions on MRIs indicate an inflammatory response – and higher risk for clinical relapse and later disability compared to MRIs without lesions – the correlation is weak and highly variable from patient to patient. However, future disability may be related to the presence of both gadolinium-enhancing lesions and T2 lesions that evolve into T1 hypointense lesions (T1 black holes) indicating demyelination with axonal loss. Cerebral atrophy progresses from the first phase in clinically isolated syndrome (CIS), and is observed in both gray and white matter. N-acetylaspartate (NAA), a specific neurochemical marker of neurons and axons, was measured longitudinally in association with spectroscopic imaging. Reduced levels of NAA were observed in normal-appearing white matter as well as in white matter lesions, indicating irreversible axonal loss as the disease progresses. According to Dr. Richert, these findings further demonstrate the global nature of MS and the need for researchers and clinicians alike to consider the insidious process of microscopic disease in normal-appearing white matter.

A ROLE FOR MRI IN ATROPHY IN CIS

Dr. Richert outlined subtle MRI signs of atrophy in CIS, including slight ventricular enlargement. Because, she cautioned, there is wide variability of treatment effects using different clinical outcomes, reproducible, objective measurement of volume for the brain and cervical cord can be a potentially valuable independent marker of the pathological process in MS. Atrophy appears to be confined to the supratentorial compartment during early MS, but becomes more pronounced in the whole brain and cervical spinal cord in secondary progressive MS (SPMS).

GRAY MATTER AND DMDs—A “HOT TOPIC”

Citing gray matter atrophy as one of today’s “hot topics,” Dr. Richert suggested it is an early sign in CIS. Indeed, significant loss in the gray matter fraction correlated with T2 lesion load in CIS patients who converted to symptomatic MS after 3 years. Given the potential importance of brain atrophy in the disease process, Dr. Richert emphasized that brain atrophy measurements be included in clinical trials, particularly those evaluating disease-modifying drugs.

Clinical Implications of Brain Atrophy

The timing and pathologic mechanisms involved in the development of brain atrophy in MS are not well understood, said Richard Rudick, MD (Director, Mellen Center for MS Treatment and Research, and Chairman, Division of Clinical Research, Cleveland Clinic Foundation, Cleveland) in his talk “Clinical Significance of Brain Atrophy in MS.” However, he went on, atrophy begins early, progressing 5- to 10-fold faster than normal during the course of disease.

MRI AND MS: ADDITIONAL MEASURES MAY BE HELPFUL

Measurements of brain volume are typically near normal at the time of presentation in patients with CIS, but ventricular enlargement becomes evident during the first year in patients who relapse. Rates of observed atrophy are similar in relapsing-remitting MS (RRMS) and SPMS. Echoing and reaffirming some of the views presented earlier, Dr. Rudick noted that although atrophy and the number of relapses do correlate, the link is weak and many MS patients with significant brain atrophy have few relapses. He cautioned that MRI results over time can vary widely depending on equipment (eg, new equipment or upgrades), sequencing of scans, positioning, patient factors (eg, head circumference), and other variables. These factors influence overall results and can make comparisons of follow-up MRIs problematic. According to Dr. Rudick, MRI techniques used to “normalize” the brain provide more accurate assessment of atrophy, but fail to completely solve the problem. Atrophy in the early stages of MS is largely subclinical but evidence of atrophy during the early stage of RRMS may predict severity of the underlying process and clinical outcomes years

later. Measurement of brain parenchymal fraction (BPF) is a sensitive technique that measures normalized brain volume. In an 8-year follow-up study of RRMS patients, BPF over the first 2 years correlated with both Expanded Disability Status Score (EDSS) and Multiple Sclerosis Functional Composite (MSFC) better than many clinical and other MRI changes. The early rate of atrophy was a strong predictor of the proportion of patients reaching an EDSS of 6 at 8 years.

Dr. Rudick believes therapy in MS patients will slow the rate of atrophy over subsequent years, and that therapy should be started early in the course of the disease.

Role of MRI in Optimizing Treatment

MRI findings can support clinical decisions as to when, or when not, to change therapy, and what to change therapy to, said Tony Traboulsee, MD (Clinical Assistant Professor, Neurology, University of BC, Vancouver). He presented data in his talk “Optimizing Treatment of Relapsing Remitting MS” during the symposium Defining Suboptimal Response to MS Treatment. Since MRI detects clinically silent disease, results will always poorly match clinical MS scales, he said, adding that although the use of MRI results can optimize therapy, particularly when new MRI activity signals active disease, testing is probably more important in early stages of MS.

MRI: CLUES TO SILENT DISEASE AND RELAPSE

Gadolinium-enhanced fresh lesions are often seen on MRI scans in early disease despite the absence of clinical symptoms. This is particularly meaningful for patients appearing to be in remission, since these lesions indicate active disease and higher risk of relapse within the next year compared to those without gadolinium-enhanced lesions.

In patients with CIS, there is moderate correlation between an increase in volume of MRI-visualized lesions in the first 5 years and the degree of long-term disability. Additionally, in RRMS, one can find MRI evidence of diffuse abnormalities in normal-appearing brain tissue, and global brain atrophy. However, Dr. Traboulsee cautioned about much individual variability in MRI findings in relation to clinical disease progression. Despite this call to pru-

dence, Dr. Traboulee did point out that one important clinical use of MRI findings is as an indicator of whether therapies are working.

Assessing Cognitive Function and QOL Parameters

Some degree of cognitive impairment occurs in about half of people with MS during the course of their disease, most commonly memory, information processing, and executive functions. Testing for early cognitive dysfunction and assessment of cognitive deficits and strengths allow health care professionals, patients, and caregivers to prepare coping strategies for activities of daily living and plans for the future. In the symposium Cognition and Affective Disorders in MS, Richard H.B. Benedict, PhD (Professor of Neurology and Psychiatry, SUNY Buffalo School of Medicine, and Jacobs Neurologic Institute, Buffalo) reviewed the predictability and reliability of MRI and traditional assessments of neuropsychological impairment in his presentation "Detecting Cognitive Disorders in MS." Correlations between neuropsychological tests and MRI indices indicate that brain atrophy may account for more variance for cognitive impairment than T2 lesion burden. Central atrophy was powerfully associated with neuropsychological morbidity, said Dr. Benedict.

SCREENING FOR COGNITIVE IMPAIRMENT

In clinical practice, screening for neuropsychological impairment with conventional methods is typically time-consuming, and it requires a neuropsychologist to interpret results. According to Dr. Benedict, a brief, 5-minute self-report procedure, the MS Neuropsychological Screening Questionnaire (MSNQ), can be used in the office or clinic as a tool for quick and inexpensive screening for cognitive impairment. The questionnaire uses a grading system of 0 (not at all) to 4 (very often and greatly interferes), covers a battery of 15 items, and has good sensitivity (0.83) and specificity (0.97). It can be administered by clerical staff and scored quickly by the clinician. If the MSNQ is positive, a minimal routine neuropsychological examination can be ordered, followed by a more comprehensive assessment as appropriate.

MS Neuropsychological Screening Questionnaire (MSNQ)

- 0** not at all
- 1** rarely and no problem
- 2** occasionally, seldom a problem
- 3** very often and disruptive
- 4** very often and greatly interferes with life

- easily distracted
- lose focus when listening
- slowed problem solving
- trouble describing programs recently watched
- forgetting appointments
- forgetting what is read
- instructions repeated
- reminded to do tasks
- forgetting errands
- difficulty answering questions
- difficulty tracking two things at once
- missing the point of conversations
- difficulty controlling impulses
- laugh/cry with little cause
- talk excessively

In administering various tests to detect cognitive disorder in MS, Dr. Benedict stressed that during repeat assessments, alternative forms of the tests should be used. When the same form is used repeatedly, the validity of results is compromised because of patient delayed recall and recognition.

More Symposia of Interest

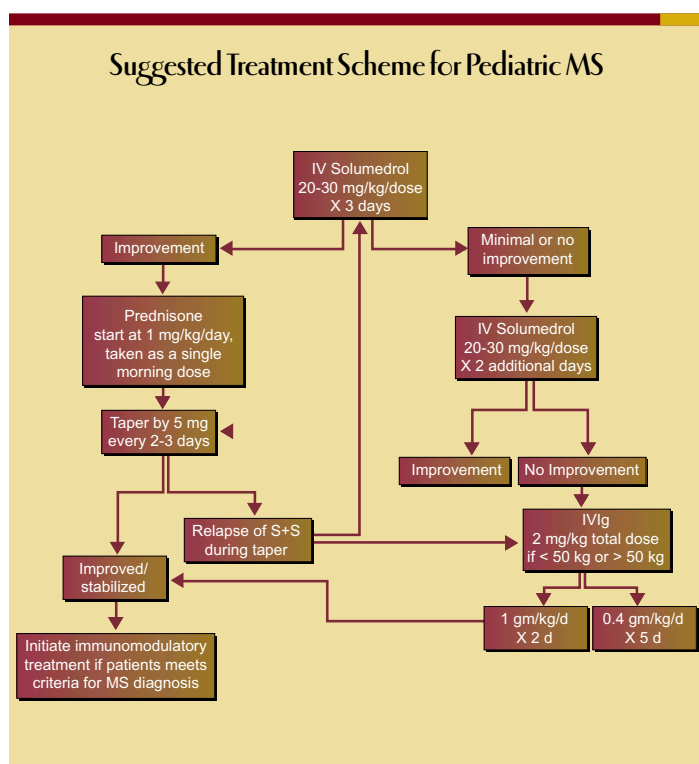
Treatment of Pediatric MS

Brenda Banwell, MD (Director of the Pediatric Multiple Sclerosis Clinic at Toronto's Hospital for Sick Children) started her presentation at the Pediatric Multiple Sclerosis Symposium by stating that physicians treating pediatric MS face a number of challenges that are not faced by physicians treating adult MS. Consensus guidelines exist for the diagnosis and treatment of adult MS, but

none have been developed for children and adolescents, and pediatric MS patients frequently don't meet the MRI criteria established for adult-onset MS, in particular, the McDonald MRI criteria. Moreover, childhood MS is often treated with the same pharmacological therapies as adult MS, but these have only been approved for adult populations and added risks for pediatric patients are less well known.

EXPERT SUGGESTIONS FOR TREATMENT

Pediatric MS treatments can be divided into 2 categories, according to Dr. Banwell: treatments used for acute episodes and medications designed to prevent or reduce relapses and progression. Acute episodes are those MS attacks that severely limit the patient's functioning and prevent attendance in school. For those patients, intravenous (IV) solumedrol, 20 to 30 milligrams per kilogram a day over 3 days, would be initiated by Dr. Banwell. IV therapy is followed by oral prednisone, initially at a dose of 1 milligram per kilogram a day, which is slowly tapered over 2 to 3 weeks. For a child who doesn't respond to 3 days of solumedrol, Dr. Banwell feels that the physician has 2 primary alternatives: either administer 2 additional days of solumedrol or administer IV immunoglobulin (IVIG).



MS-TARGETED IMMUNOMODULATORY THERAPIES

Designed to prevent or reduce MS relapses, the use of interferon-beta and glatiramer acetate are appropriate for use in children with confirmed MS, Dr. Banwell believes. The first step in treating children with such MS-targeted therapies is to establish baseline values for tests of function for the liver, kidney, and thyroid, and tests for electrolytes. Once established, Dr. Banwell would initiate immunomodulatory therapy at one-half of the patient's target dose (based on the child's weight) and gradually increase the dose, monitoring the child's liver function monthly for the first 6 months. (The target dose was calculated by dividing the child's weight (kg) by 50 and using the fraction obtained as the percent of the adult dose to be given, up to 100 percent.) If the child's AST levels become inordinately elevated, he or she should be given a significantly decreased dose; if the child's AST levels remain elevated, then therapy should be terminated. *(Editor's note: the investigation of adjunctive immune-based therapies, for example, targeted monoclonal antibody depletion of B cells, is being pursued for patients who fail interferon beta and glatiramer acetate-based therapy.)*

Dr. Banwell concluded with a brief discussion of cyclophosphamide, the efficacy of which in the treatment of MS is controversial. Large studies have suggested that it has a role for frequently relapsing, treatment-refractory patients. Dr. Banwell presented an overview of results of cyclophosphamide in 8 treatment-refractory pediatric patients with frequent MS relapses. Following cyclophosphamide treatment, 4 of the patients haven't experienced a single relapse, and 3 have experienced diminished relapses. Dr. Banwell cautioned, however, that cyclophosphamide should be considered only for select MS patients with very aggressive MS because of the severe side effects associated with cyclophosphamide that include an increased risk of future malignancies.

Dietary Supplements Relevant to MS

Because approximately 50% to 60% of MS patients use non-allopathic treatments, such as herbs and dietary supplements, physicians treating MS have a proliferating interest in

alternative treatments. Allen Bowling, MD, PhD (Medical Director of the Rocky Mountain MS Center in Englewood, Colorado) presented his talk during the Complementary and Alternative Medicine and MS symposium, and focused on herbs and dietary supplements that may be helpful – or deleterious – to MS patients.

The polyunsaturated fatty acids, omega-3 and omega-6, may have a potential benefit to MS patients, said Dr. Bowling, because they may suppress immune function. The supplements containing omega-3 and omega-6 that he recommended are cod liver oil, sunflower oil, flaxseed oil, and evening primrose. However, he emphatically discouraged using those omega-3- and omega-6 -containing supplements with possible toxicities: borage seed oil, black currant seed oil, and spirulina.

NOTES OF CAUTION AND ADVICE

Dr. Bowling issued a warning about antioxidants, echinacea, alfalfa, astragalus, cat's claw, and ginseng. Because they may be involved in the stimulation and activation of T-cells and macrophages, they could potentially counteract the effects of immunomodulating drugs. Herbal supplements that he thought might be of benefit for MS patients are cranberry for urinary tract infection, St. John's wort for

depression, valerian for insomnia, ginkgo biloba for cognitive improvement, and kava-kava for anxiety.

Whitaker Research Track: Immunology Insights

Stress, Cytokines, and MS

Mathew Sorenson, PhD, a research fellow at the VA Hospital in Hines, Illinois, presented "Perceived Stress is Associated with the Production of IL-6 and IL-10 in MS Patients." MS patients frequently report that heightened states of stress have the potential to exacerbate their disease, so Dr. Sorenson and his colleagues sought to determine if perceived stress activates pro-inflammatory cytokines in peripheral blood mononuclear cells, resulting in increased MS symptomatology. In 42 MS outpatients and 36 controls, stress was measured by the Perceived Stress Scale, negative moods indexed by the Profile of Mood States, disease symptoms gauged by the Multiple Sclerosis Symptom Checklist, and pro-inflammatory and non-inflammatory cytokines measured by ELISA. Results showed that IL-6 and IL-10 correlated with psychological stress, mood disturbance, and disease symptomatology in MS patients. Hypothesizing that elevated

Workshop News

Automated Screening for Cognitive Impairment

Computerized evaluation measurements of cognitive dysfunction in MS patients will be easy to use, standardized, and provide immediate availability of results and the potential for built-in decision algorithms to evaluate changing scores. A workshop on "Screening for Cognitive Impairment in the Neurologist's Office," provided new information on the development of automated testing, which is both cost effective and time efficient, and screens various cognitive domains, including attention, learning and memory, and information processing speed.

Jeffrey Wilken, PhD, and Cynthia Sullivan, PhD (VA Medical Center, Washington and University of Maryland at College Park), and Robert Kane, PhD (VA-Baltimore and University of Maryland at Baltimore Medical Center) discussed several aspects of the computerized ANAM neuropsychological battery, which has reduced multiple tests into short repeatable test groupings. Some of its practical advantages include use with standard PC, simple interface, multiple test forms, and the potential for multilingual testing. Most computerized batteries for cognitive testing are proprietary. However, as automated testing procedures become more readily available, they will likely include computerized interpretation of scores, and test availability via the internet to accommodate patients.

levels of these cytokines were produced to counterbalance potential immune activation by stress, Dr. Sorenson and his colleagues also found that MS patients exhibiting a high level of stress had a significant increase in their production of TNF-alpha compared to low-stress MS patients.

Oligodendrocytes Utilize CXC Chemokine Receptors in MS

Kakuri Omari, PhD, research associate with Dr. Cedric Raine at the Albert Einstein College of Medicine in New York City, and a 2004 Whitaker Award honoree, presented “A Role for CXC Chemokines in the Oligodendrocyte Response in MS.” Oligodendrocytes have the capacity to remyelinate MS lesions early on, but, as the lesion ages, they gradually lose this capacity. Because animal studies have shown CXC chemokines, Cys-X-Cys motif-containing proteins secreted by astrocytes, to play a role in oligodendrocyte proliferation and positioning, the question as to whether or not CXC chemokines are involved in the repair response in human MS was investigated. The researchers analyzed CNS tissue from MS patients and from non-MS patients, and found that reactive astrocytes strongly expressed the CXC chemokines IL-8, Gro-alpha and IP-10 at the edge of active MS lesions; these chemokines were absent in controls. Moreover, Dr. Omari found that IL-1-beta strongly induced the production of IL-8 and Gro-alpha, and that interferon-gamma strongly induced IP-10 expression.

The researchers also found that the receptors targeted by IL-8, Gro-alpha, and IP-10—CXCR1, CXCR2, and CXCR3, respectively—were expressed on human oligodendrocytes in culture and in brain tissue. In particular, CXCR2 was expressed at high levels at the edge of active MS lesions where oligodendrocyte proliferation was prominent. Therefore, it appears that chemokine cross-talk between astrocytes and oligodendrocytes may play a role in oligodendrocyte recruitment and remyelination at the edge of MS lesions in humans.

Toll-Like Receptors and Chronic Immune Diseases

Drs. Michael Racke, MD (Texas Southwestern Medical School), Chair of the Whitaker Research Track, and Timothy Vartanian, MD, PhD (Harvard Medical School) collaborated to present data from their laboratories on the pivotal role of innate immunity in chronic diseases that involve immune responses. Pathogen-associated molecular patterns (PAMPs) have been shown to be needed for induction of experimental autoimmune encephalomyelitis (EAE) by inoculation of myelin antigens. PAMPs bind to toll-like receptors (TLRs) on the surface of innate immune cells. In the central nervous system these can be resident microglia or macrophages, delta-gamma T cells, or NK cells that have entered from the blood. There are multiple TLRs with variable responses depending upon the PAMPs they bind and the immune environment. For example, TLR-9 binding to the cell wall constituents of tuberculous bacilli can induce a type-1 response in adaptive immune cells. Microglia may also directly damage neurons once their TLRs are activated by release of nitric oxide and TNF-alpha. When TLRs are not activated by PAMPs, they may be involved in the regulation of axonal growth.

Scientific Platform Talk: More on MRI—Estimating Gray and White Matter Atrophy

The effects of MRI pulse sequences and segmentation algorithms may influence measurements of atrophy in gray matter and white matter. In this scientific platform presentation, Robert Zivadinov, MD, PhD (Department of Neurology, The Jacobs Neurological Institute, University of Buffalo, State University of New York), said segmentation of gray matter and white matter fractional volumes are usually evaluated by automated segmentation algorithms, but results vary according to the type of pulse sequence and algorithm used.

Comparisons of brain MRI segmentation (3D SPGR T1-weighted images, 2D-T1-weighted images, fluid attenuated inversion recover

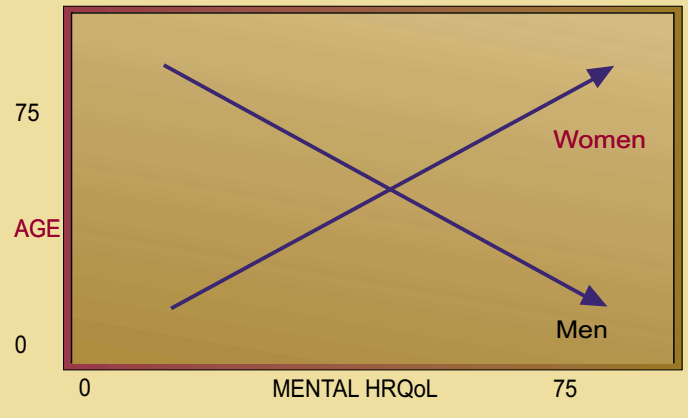
image, T2-weighted images) using three different segmentation algorithms (SPM2, SIENAX, Hybrid SIENAX) showed 3D SPGR T1-weighted images provide the most optimal pulse sequence for measuring atrophy in gray and white matter.

Scientific Platform Talk: More on Functioning—Impact of Comorbidities, Gender on QOL

Karen V.L. Turpin, MR, BScN, MSc (Department of Public Health Sciences, MS Patient Care and Research Clinic, University of Alberta) discussed “Deterioration in the Health-related Quality of Life (HRQoL) of Persons with RRMS.” In this scientific platform presentation, she outlined possible warning signs and factors in identifying high-risk patients who may be candidates for targeted and timely interventions.

Noting that HRQoL decreases substantially in the early stages of MS, Turpin reported the comorbid conditions most commonly reported by surveyed patients were headaches, muscle, bone or joint problems, kidney, bladder or urinary problems, and mental or emotional problems. Factors associated with poorer physical HRQoL were female gender, increasing age, unemploy-

Mental HRQoL and Gender—Age Interaction: Deterioration in Men and Improvement in Women



ment, comorbid conditions (muscle, bone, joint problems, breathing problems), increasing severity of fatigue and disability, and increasing frequency of relapses. Notably, mental HRQoL scores showed an interaction between gender and age: as MS patients aged, scores deteriorated in men, but improved in women.

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