

INTRODUCTION

Single-topic issue on multiple sclerosis

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The articles included in this single-topic issue of the *Journal of Rehabilitation Research and Development* cover a broad spectrum of issues related to multiple sclerosis (MS). The articles range from topics involving epidemiology, neurophysiology, genetics, neuroimaging, immunology, and therapy of MS. There is also a series of articles focused on certain common and disabling symptoms in MS. The diversity of these topics is an indication of the current complexity of this field.

MS is the most common disabling neurological disorder to attack young adults of European descent in developed nations. Because of improvements in supportive medical care, most of these individuals will live a normal life span but with increasing levels of disability. Besides the personal and social impact of this disease, MS represents an increasing health-related cost estimated to be up to \$10 billion per year to the U.S. economy alone. The fact that this disease is characterized by a multifocal attack on the central nervous system explains the remarkable variability seen in symptoms and disability in persons with MS. Consequently, the care of these patients is characterized by the use of multiple concurrent medications and therapeutic modalities. Multiple healthcare providers are generally involved in the care of each patient, including specialties such as neurology, primary care, physiatry, urology, physical therapy, occupational therapy, speech therapy, and psychology.

The first article by Vollmer et al. uses data from the largest comprehensive database currently available on MS patients to describe the disease characteristics and treatment patterns of veterans as they differ from nonveterans. The data highlight the advanced stage of disability that generally characterizes veterans with MS receiving care in the Veterans Health Administration (VHA). Consequently, the VHA incurs even higher levels of healthcare costs from this population of patients than other systems. Data from this and similar databases should be helpful in assisting healthcare systems such as the



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VHA to better recognize the needs of MS patients and the special challenges their system faces when caring for this population.

Although the investigator community in MS is truly international, there are marked variations in treatment practices of MS patients throughout the world. Pozzilli et al. describe variations in the prevalence and treatment patterns of MS patients in

Europe. Of particular note is the interest in the use of azathioprine and intravenous immunoglobulin (IVIG) in treating MS in Europe as compared to the United States. Not discussed by these authors, but also of interest, is the marked variation in use of disease-modifying agents for MS (DMAMS) in certain European countries. In particular, the United Kingdom has been a major contributor to the development of new therapies for MS, yet interferons and glatiramer acetate that are commonly used DMAMS in most of the developed nations are rarely used in the UK. This appears to be solely because the influence of the National Institute for Clinical Excellence (NICE) committee that controls access to government-approved therapies by patients cared for by the National Health Service. The issue has been the cost effectiveness of these immunomodulating therapies. The NICE committee has performed analyses that have been questionable to some, based on very limited data from phase III trials. Needless to say, these analyses have not been favorable to the therapies.

One area of remarkable scientific advances in the last decade has been immunology. A significant contributor to this has been immunological research on animal models of MS. More recently, new immunological and molecular biological techniques have been applied to the human condition of MS, in general confirming observations made in the animal model. The role of CD4+ TH-1 T-lymphocytes as a central promoter of the pathology characterizing MS has been supported by a great deal of research. However, significant differences between the pathogenesis of the animal model and the human disease are beginning to emerge. Prat and Martin discuss the immunology of MS and relate it to the mechanism of action of recently approved DMAMS. The key message from this paper should be that we are at the beginning of a remarkable expansion in approaches to the immunotherapy of autoimmune disease. MS, like diabetes and rheumatoid arthritis, is poised to benefit substantially from the revolution taking place in the field of immunology.

It is now recognized that MS is clearly a complex genetic disorder with the genotype of individuals interacting with unknown environmental factors to determine the risk of disease development. The exact nature of the genetic factors determining risk

in MS remains somewhat uncertain. A number of the genes, particularly those associated with regulation of the immune system, have been implicated in the pathogenesis of MS. Baranzini et al. provide an excellent review for the nonspecialist of this rapidly expanding field.

Fatigue, occurring in 90 percent of persons with MS, and pain, occurring in 60 percent of MS patients, represent two of the more difficult symptoms to effectively treat in MS patients. Schwid et al. and Kerns et al. discuss our current, albeit unsatisfactory, understanding of the biological basis of these two symptoms. These are two of the most disabling symptoms from which MS patients suffer, and it is remarkable that so little research is funded in these areas. However, as both sets of authors point out, there is reason for hope.

The basis for symptom generation in MS remains somewhat obscure. For some time, it has been apparent that demyelinated segments of axons have the capability to generate and redistribute sodium and potassium channels such that at least partial capability for signal transduction is restored. Dr. Stephen Waxman has elegantly elucidated the molecular biology of this phenomenon. In addition to discussing the issues of sodium channels in demyelinated axons, Dr. Waxman also addresses a recently reacknowledged fact. MS is not a disease of myelin; rather it is a disease of myelinated central nervous system axons. There is strong evidence that the major contributor to fixed disability in MS is axonal death with secondary neuronal death as a consequence of Wallerian degeneration. The cause of this axonal injury is not understood. This article discusses the current thinking on this extremely important topic.

Magnetic resonance imaging of the brain has been a remarkably powerful tool in the study of MS. It is widely accepted as the gold standard for surrogate measures of disease activity for clinical trials and natural history studies. It is the single most powerful prognostic tool available in the management of MS patients. In addition, it can separate the impact of the inflammatory process on the myelin compartment from that on the axonal compartment. In fact, because of the MRI studies, we now appreciate that axonal injury is the primary determinant of long-term disability in MS. The power of MRI to provide qualitative and quantitative information on

MS in vivo is discussed by Drs. Rovaris and Filippi. Drs. Ingle, Thompson, and Miller then discuss the peculiarities of primary progressive MS from an MRI perspective.

Tullman et al. present a comprehensive review of the current status of DMAMS. These agents are able to decrease relapse rate by up to 30 percent in patients with typical relapsing MS. They are also able to slow progression in these patients, although the magnitude of this is somewhat uncertain. As discussed, there is marked variation between individuals in their response to these agents. The basis for this is unclear. In addition, even when patients do apparently gain benefit from these therapies, it is often inadequate to prevent them from progressing in terms of disability. And finally, interferons seem to have very little, if any, benefit when patients with relapsing MS enter the secondary progressive phase of the disease or if they have primary progressive MS. Nevertheless, the future is bright because more effective therapies are possible. Indeed, in addition to novel therapeutic approaches, combination therapies are emerging as a potentially useful way to improve efficacy while minimizing toxicity.

Not discussed but relevant to this issue is the increasing complexity of clinical trials in MS. New study designs and improved outcome measures will be needed to maintain the current momentum of the immunological therapy trials in MS. Otherwise, progress in this area is in danger of becoming stalled by clinical trials that require more patients or money than are available.

For persons with advanced disability because of MS, as well as for patients who suffer from other demyelinating diseases, no area is more hopeful than the area of neural repair. Kocsis et al. summarize the current state of the art in cell replacement

therapies for remyelinating central nervous system axons. In fact, based on their work as well as the work of others, a first human trial has been undertaken to repair demyelinated axons in MS patients by the transplantation of autologous Schwann cells. Although the goals of this project are modest, the future is bright for similar efforts in other disease models. There are many different cell lines, including various types of "stem" cells, that are relevant to repair in MS and other disorders involving myelin injury, such as spinal cord injury, ALD, MLD, Pelizaeus Merzbacher's disease, etc. Indeed, once thought impossible, neural repair is now one of the more promising and exciting fields in neuroscience.

Until neural repair becomes a reality, assistive technology will be the predominant strategy available to clinicians for addressing functional limitations imposed by MS-related disability. Drs. Blake and Bodine provide an in-depth review of available assistive technologies relevant to the needs of MS patients. More importantly, they point out a critical need for research in this area, both to identify novel approaches to using technology to enhance function and, more urgently, to document the import and utility of current technologies. This latter issue is key if we are to defend coverage of these technologies by third party payers for our patients.

In sum, the articles in this special focus issue of the *Journal of Rehabilitation Research and Development* demonstrate the remarkable breadth of issues facing clinicians, investigators, and patients dealing with MS. But the "take home" message of this issue is that the tides have turned; progress is being made at an ever-increasing rate. MS as a medical success story is a real possibility in the not-so-distant future.

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