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World Federation of Neurology

Seminars in Clinical Neurology

Multiple Sclerosis for the Practicing Neurologist

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Volume 5

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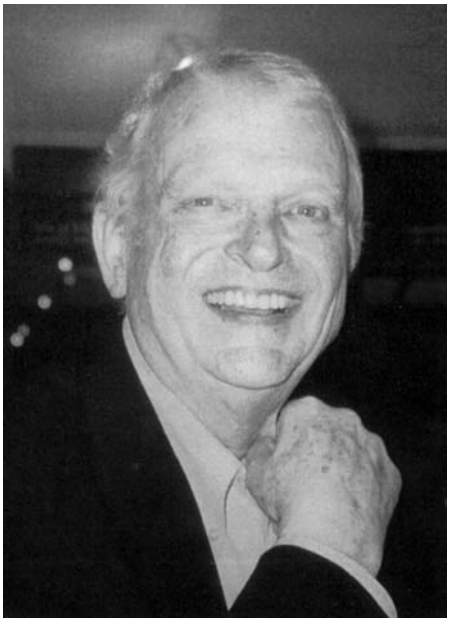
Dedication



This book is dedicated to Donald Winston Paty, MD, who was born in China in 1936 to a family of United States missionaries. In 1943 Don moved to the United States where he later completed his education in New York and Georgia. He received his medical diploma from Emory University in 1962, followed by an internship at Duke University, and a residency at Emory. During that time he took a civil service position in Borneo with the US Public Health Service where he provided medical care for the volunteers of the Peace Corps.

Dr. Paty then became involved in a research fellowship at the Demyelinating Diseases Research Unit in Newcastle-upon-Tyne, England, where he was introduced to neuroimmunology. He moved to London, Ontario in Canada where he became a faculty member of The University of Western Ontario in the Department of Neurosciences chaired by Dr. Barnett. He created the concept of the Multi-Disciplinary Research Multiple Sclerosis Clinics with their systematic follow-up. As a result, large datasets on multiple sclerosis (MS) were generated that have become the gold standard for MS epidemiological research around the world. Dr. Paty was very instrumental in the creation of the Canadian MS database.

In 1980 Dr. Paty moved to Vancouver and by applying sound neurological clinical principles he defined the potential contribution of magnetic resonance imaging (MRI) to the treatment of MS. In a series of sequential studies he described the course of lesions in the brain of MS patients. Focusing on T2 weighted images obtained at regular monthly intervals, he unraveled the dynamics of the demyelinating lesions with new lesions appearing, increasing in size, and shrinking, independently of each other but resulting in a disease burden that could be measured, quantified, and compared. The MRI findings were the "point d'orgue" which allowed for the approval of Interferon Beta-1b and subcutaneous Beta-1a in the treatment of relapsing-remitting MS. A fundamentally new approach was born that greatly influenced the treatment of MS in the following two decades and Don was highly involved in its development.

He received many prestigious awards including the first Dystel Prize and the Charcot Prize. In 2004, Don received the Canadian Meritorious Service Medal for the use of MRI in the diagnosis and treatment of MS. He played a key role in the development of the MS Society of Canada and contributed greatly to the scientific committee of the National MS Society. Don was a vital part of the two committees who have defined the diagnostic criteria for MS in the second half of the 20th century. His influence helped to create the concept of "Laboratory Supported MS," a designation he stressed should be used only for clinical trial and research purposes. The book, *Multiple Sclerosis* by Donald W. Paty and George C. Ebers, Oxford University Press, 1999, has become a milestone.

Despite his tremendous successes Don remained humble and approachable. He was the most supporting of mentors. He was extremely supportive of new ideas and studies that were brought to him with a level of enthusiasm that he would embrace. His support of young researchers in countries where MS study had not been traditional was particularly remarkable. His domination in the field culminated with the World meeting in Vancouver where every participating neurologist had the impression of being his private guest. Shortly after that meeting he became a citizen of the world and lectured in over 30 countries

Perhaps even more precious was Don's mission as an educator and a mentor. Don mentored a whole generation of MS teachers and investigators in London Ontario including: George Ebers, George Rice, John Noseworthy, Brian Weinshenker, and Tom Feasby. In Vancouver, many fellows came from around the world to further their training including: Adnan Al-Araji (Iraq), Alexis Boyko (Russia), Cavit Boz (Turkey), Philippe Cabre (French Western Indies), José Cabrera-Gomez (Cuba), Gilles Edan (France), Roger Hintzen and Raymond Hupperts (The Netherlands), Gaven McDonnell (Northern Ireland), Claude Vaney (Switzerland), and Ernest Willougyby (New Zealand).

But above all, Don was an attentive physician, devoted to his patients and they adored him.

Joel Oger, MD, FRCPC, FAAN

Preface

Over the last 15 years, interest in multiple sclerosis (MS) has increased probably more than for any other neurologic disorder. This arises from the simultaneous occurrence of magnetic resonance imaging (MRI) technology that has permitted clinicians to image the pathologic process and the development of therapeutical agents that have brought hope to patients. The neurologist is now better able to diagnose, follow, and treat these young patients compared to only accompanying the patient in the course of their disease a couple of decades ago. However, the progress in diagnosis and therapy has been overemphasized by some (with encouragement from the pharmaceutical industry), and many voices are beginning to call for more measured statements of success. It is unconscionable to ignore the hype that has recently accompanied these new discoveries in the diagnosis and treatment of MS.

Seminars from the World Federation of Neurology (WFN) focus on the needs of neurologists practicing in developing countries. At a time when MS is shown to be present all over the world and multiple reports suggest its increasing frequency in developing countries, it is essential that physicians in less-developed countries be wary of following the seductive attraction of new technologies being emphasized in the developed world.

This book places the emphasis on the clinical issues faced by neurologists practicing in developing countries when dealing with MS patients. We strongly feel that the diagnosis of MS is possible and acceptable without the use of high-cost confirming tests such as MRI. In parallel, treatment options not involving excessively costly disease-modifying drugs have been stressed. Although some of the immunosuppressants have not had a complete endorsement by evidence-based medicine, the association of high-dose steroids for relapses and long-term "soft" immunosuppressants such as azathioprine may very well be more effective than generally recognized and probably not much less effective than are disease-modifying drugs. They are certainly less costly, although a stable view of the cost–benefit comparison has not been reached at this time.

This book represents a high level of cooperation between many different people from different origins. It is an example of international cooperation across continents, countries, and religions.

Joel Oger, MD, FRCP, FAAN
Adnan Al-Araji, MB ChB, FRCP (Glasg.)

Editor's Preface

The mission of the World Federation of Neurology (WFN, wfneurology.org) is to develop international programs for the improvement of neurologic health, with an emphasis on developing countries. A major strategic aim is to develop and promote affordable and effective continuing neurologic education for neurologists and related health care providers. With this continuing education series, the WFN has launched a new effort in this direction, with this volume being the fifth course made available. The WFN Seminars in Neurology uses an instructional format that has proven to be successful in controlled trials of educational techniques. Modeled after the American Academy of Neurology's highly successful Continuum, we use proven pedagogical techniques to enhance the effectiveness of the course. These include case-oriented information, key points, multiple choice questions, annotated references, and abundant use of graphic material.

In addition, the course content has a special goal and direction. We live in an economic environment in which even the wealthiest nations have to restrict health care in one form or another. Especially hard pressed are countries where, of necessity, neurologic care is often reduced to the barest essentials or less. There is general agreement that much of this problem is a result of increasing technology. With this in mind, we have asked the faculty to present the instructional material and patient care guidelines with minimal use of expensive technology. Technology of unproven usefulness has not been recommended. However, at the same time, advice on patient care is given without compromising a goal of achieving the very best available care for the patient with neurologic disease. On occasion, details of certain investigative techniques are pulled out of the main text and presented separately for those interested. This approach should be of particular benefit to health care systems that are attempting to provide the best in neurologic care but with limited resources.

These courses are provided to participants by a distribution process unusual for continuing education material. The WFN membership consists of 86 individual national neurologic societies. Societies that have expressed an interest in the program and agree to meet certain specific reporting requirements are provided a limited number of courses without charge. Funding for the program is provided by unrestricted educational grants. Preference is given to neurologic societies with limited resources. Each society receiving material agrees to convene a discussion group of participants at a convenient location within a few months of receiving the material. This discussion group becomes an important component of the learning experience and has proved to be highly successful.

Our fifth course addresses the important area of multiple sclerosis. The Co-Chairs of this course, Professors Joel Oger and Adnan Al-Araji, have selected an outstanding faculty of experts. We very much welcome your comments and advice for future courses.

Theodore L. Munsat, M.D.
Professor of Neurology Emeritus
Tufts University School of Medicine
Boston, Massachusetts

Contents

CHAPTER 1

ETIOLOGY OF MULTIPLE SCLEROSIS

Jun-ichi Kira, MD, PhD

KEY POINTS

- MS is regarded as an autoimmune disease targeting CNS myelin.
- MS is heterogeneous with regards to its clinical course and preferential sites of involvement.

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Although the mechanisms involved in MS remain elusive, it is generally hypothesized to be an autoimmune disease that targets CNS myelin. MS is thought to be caused by a complex interaction between genetics and environment. To date, the strongest and most consistently associated factors have been shown to be class II major histocompatibility complex (MHC) genes, namely, human leukocyte antigen (HLA)-DRB1*1501-DQA1*0102-DQB1*0602 alleles, thus supporting the autoimmune hypothesis. In addition, to date, no single pathogen has consistently been found to be incriminated in MS. However, epidemiologic surveys demonstrated that upper respiratory infections were significantly associated with MS relapse. Therefore, various types of infectious pathogens might trigger an autoimmune response against CNS myelin in genetically susceptible individuals through molecular mimicry between infectious agents and CNS myelin components or through the liberation of self-proteins by tissue destruction, thus culminating in inflammatory demyelinating disease.

CLINICAL STUDIES INDICATE MS HETEROGENEITY

Most MS patients begin with relapsing-remitting MS (RR-MS), followed by a progressive course of MS (secondary progressive MS; SP-MS), although 10% to 20% of patients show progressive onset from the beginning without relapse (primary progressive MS; PP-MS). PP-MS affects older populations and predominantly males, and it has a poor prognosis. Magnetic resonance imaging (MRI) studies revealed that RR-MS and SP-MS showed a much higher frequency of gadolinium-enhanced lesions than PP-MS. Genetic studies also demonstrated that HLA association was distinct between RR-MS and PP-MS. Furthermore, interferon-β is only effective in RR-MS and SP-MS, not in PP-MS. These observations argue against MS being a single disease and support the notion that MS is etiologically heterogeneous.

In East Asians, MS severely and selectively affects the optic nerve and the spinal cord (opticospinal MS; OS-MS). This form of MS has a higher age of onset, a higher female to male ratio, frequent relapse, and results in severe disability when compared with conventional MS. It rarely involves a secondary progressive course. MS in Africans has similar features to that in East Asians. Using spinal cord MRI, longitudinally extensive spinal cord lesions extending over several vertebral segments were shown to be relatively common in OS-MS (about 50% of all patients), but are extremely rare in the MS found commonly in Caucasian populations. Cerebrospinal fluid (CSF) in OS-MS shows an absence of oligoclonal IgG bands and marked pleocytosis with occasional CSF neutrophilia. In agreement with these CSF findings, spinal cord lesions extending into the white and gray matters show severe tissue destruction, with heavy macrophage and neutrophil infiltrations in addition to many lymphocytes. These findings suggest that a distinct mechanism operates in this condition. Therefore, MS seems to be heterogeneous according to its clinical course and preferential sites of involvement; however, the mechanisms responsible for this distinction are still unknown.

KEY POINT

- MS pathology involves inflammatory demyelination, but distinct patterns of demyelination occur among clinical subtypes and individuals.

MS PATHOLOGY INDICATES HETEROGENEOUS MECHANISMS FOR DEMYELINATION

MS lesions are mainly located in the white matter of the CNS. The nature of these lesions is demyelination with relative sparing of axons. Remyelination is visible in acute-stage lesions, but is rare in chronic lesions, thus suggesting a temporal loss of the remyelinating capability of oligodendrocytes. However, a recent study using myelin basic protein (MBP) immunostaining indicated that demyelination in the cortical gray matter (cortical plaques) was also frequently encountered. This is usually rather difficult to visualize using ordinary hematoxylin and eosin staining. In all lesions, varying degrees of infiltration occur, both by macrophages immunoreactive for myelin proteins and by lymphocytes consisting predominantly of T cells. All these findings are compatible with the autoimmune hypothesis targeting CNS myelin.

Recent studies on biopsied and autopsied materials suggest the existence of a heterogeneous pathology of demyelination. Evidence includes (a) sharply demarcated demyelinating lesions with infiltration by perivenous inflammatory cells (T cells and macrophages), which was accompanied with abundant remyelination; (b) deposition of immunoglobulins (mainly IgG) and complement C9neo antigen along with disrupted myelin sheaths, in addition to inflammatory infiltrates; (c) predominant oligodendrocyte apoptosis, as shown by nuclear condensation and fragmentation, that was characterized by an early loss of myelin-associated glycoprotein (MAG); and (d) the nonapoptotic death of oligodendrocytes in the periplaque white matter adjacent to active inflammatory demyelination. These patterns may be observed in different patients or in one individual. Although the majority of MS lesions are characterized by inflammatory cell infiltrates, heterogeneous mechanisms are suggested to cause demyelination.

Another MS pathology recently has been described in newly forming lesions. Extensive oligodendroglial apoptosis and microglial activation with few or no lymphocytes or myelin phagocytes were observed. Viral infection, secretion of cytotoxic substances from microglia, or ischemic or hypoxic stress may be a trigger for oligodendroglial apoptosis, but the cause still remains to be clarified.

As mentioned, OS-MS shows extensive necrotic lesions preferentially in the spinal cord and optic nerves and is characterized by neutrophilic infiltration. These pathologic features are distinct from classical MS lesions but seem to be similar to those reported in relapsing NMO. Severe forms of OS-MS appear to be identical to relapsing NMO, yet the identity of both conditions is still a matter of debate. However, small foci of classical demyelinating lesions in the periventricular white matter of the brain are also found in OS-MS and relapsing NMO, which might suggest that both conditions represent one extreme type of MS.

NEURODEGENERATION IN MS

Disability largely depends on axonal loss in MS. Axon degeneration first occurs during acute demyelinating attacks and second during the chronic progressive phase. MRI and magnetic resonance spectroscopy (MRS) undertaken in MS patients during the early course of illness (less than 5 years) indicate that brain atrophy and loss of axonal integrity occur in the early course of the disease. According to results of clinical trials of immunomodulatory drugs, reduction of relapse and new lesion formation are associated with a decrease of disease progression and brain atrophy in RR-MS. On the contrary, in SP-MS, neither disease progression nor brain atrophy is suppressed by the drugs, yet new lesions on brain MRI are reduced, thus suggesting the existence of irreversible axonal damaging processes at this stage.

Pathologic studies reveal that large amounts of axonal loss occur in acute MS lesions, with infiltration of T cells and macrophages, suggesting a close relation of axonal loss at this stage with inflammation. Axonal transection is seen in the distal accumulation of proteins, such as amyloid precursor proteins, transported by axonal flow, at the site of axonal damage, and a correlation between the numbers of $CD8^+$ T cells and the extent of axonal damage also was found. Therefore, acute axonal transaction

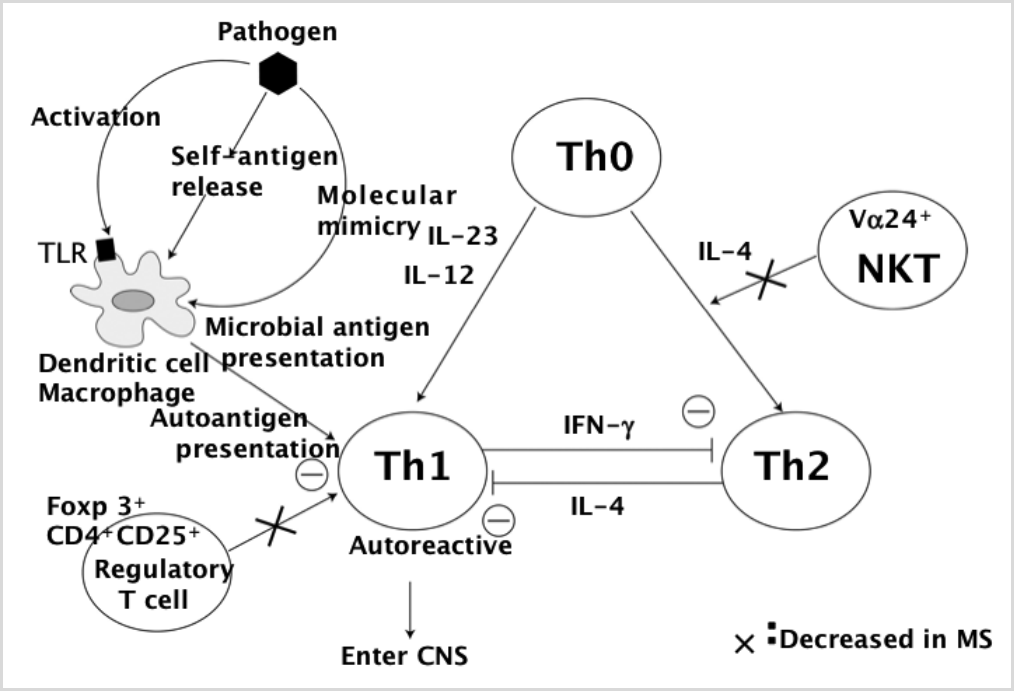


FIGURE 1.1 **Hypothetical mechanism of the inductive phase of multiple sclerosis. TLR, toll-like receptor, which recognizes components of pathogens; NKT, natural killer T cells; CNS, central nervous system; x, possible loss in MS.**

can be induced by those $CD8^+$ T cells recognizing neural antigens in the context of the MHC class I molecules expressed on demyelinated axons. The neurotoxic products of activated macrophage and microglial cells, such as nitric oxides and free radicals, also may contribute to axonal damage.

In chronic plaques, a considerable reduction of axon density (about 60%) has been reported. Moreover, axonal loss also is present in the normal-appearing white matter.

Secondary axonal loss occurs as a result of previous attacks in the absence of efficient repair capability. Persistent low-grade inflammation also contributes to axonal loss. Naked axons are especially vulnerable to various neurotoxic substrates and may degenerate in the absence of oligodendroglia-derived trophic signals. In cortical plaques, where microglial activation predominates while inflammatory cell infiltrates are generally sparse, neuronal apoptosis has been observed.

EPIDEMIOLOGY SUGGESTING BOTH ENVIRONMENTAL AND GENETIC FACTORS IN MS

The prevalence of MS differs widely worldwide. In Caucasians, MS occurs in about 40 to 100 persons in 100,000, whereas in most East Asians and South Asians it is less than 10 in 100,000, and among Africans it is even fewer. Such big differences seem to suggest that different genetic backgrounds among races strongly affect MS susceptibility.

In temperate zones, a south-to-north gradient of MS prevalence has been shown repeatedly. This tendency is seen in high-prevalence areas such as the United States, Europe, and Australia, as well as in low-prevalence areas such as Japan. Environmental factors related to latitude, shortage of sunlight, low temperatures, or even certain infectious pathogens more frequent in northern areas are suspected. For example, less ultraviolet light during the winter in northern areas causes lower vitamin D_3 production. Vitamin D possesses an

KEY POINTS

- The prevalence of MS markedly differs worldwide and among races; it is common in Caucasians and rare in Asians and Africans. Both environmental and genetic factors are suggested for MS risks.
- The association of MS susceptibility with the class II major histocompatibility complex, HLA DRB1*1501 allele, is consistently present in classic (conventional) MS among races.

KEY POINTS

- Infection possibly induces myelin-autoreactive T cells in individuals with MS susceptibility when such cells enter the CNS, encounter target antigens, and induce inflammation.
- Two types of immunologic tolerance occur: central and peripheral. *Central tolerance* is achieved by clonal deletion of autoreactive T cells in the thymus, whereas active suppression of autoreactive T cells by regulatory T cells is one mechanism of *peripheral tolerance*.

immunoregulatory function and suppresses the development of experimental autoimmune encephalomyelitis in laboratory animals. Thus, the lower production of vitamin D might partly explain the south-to-north gradient of MS risk. However, no factor has ever been shown to have a stronger association with MS occurrence than latitude itself. Interestingly, attenuation of the north-to-south gradient effect during the past few decades was reported by several recent studies. Therefore, the north-to-south gradient of MS risk supports the involvement of environmental factors, but this could change with modernization. In Japan, the ratio of conventional MS to OS-MS sharply increased in individuals born after the 1960s, when Japan's westernization started. This further supports the notion that environmental factors enhancing MS risks might be modified by modernization; that is, factors associated with modernization might increase MS risk in low-prevalence areas.

According to studies on immigrants, those who immigrated to high-prevalence areas from low-prevalence areas at an age of 15 or older showed a similar risk as that found in their area of origin, whereas those who immigrated at a younger age showed a lower risk than that in their area of origin. Therefore, this suggests that environmental factor(s) act during childhood to enhance MS susceptibility. A migration study in the United States indicated that these factors did not act right after birth, because MS death rates among migrants who were born in northern areas and then migrated south were not significantly different from migrants born in the south and who migrated north; if these factors acted right after birth, the MS death rate should be higher in the former.

The temporal clustering of MS during certain periods and the geographical clustering of MS in certain areas have also been reported. If these clusterings are true, environmental factors are most likely transmissible agents, yet it remains undetermined whether they merely increase MS susceptibility or directly cause the disease.

Studies in Canada revealed that MS risk was 300 times higher in twins, and the concordance rate of MS in monozygotic twins is significantly higher than in dizygotic twins (about 30% versus 5%), indicating the importance of genetic background. However, this also suggests that genetic factors are not decisive, because 70% of monozygotic twins are discordant. Moreover, the observation that age-adjusted MS risk is significantly higher in full siblings than half-siblings strongly suggests that familial occurrences of MS are attributable to genes, not to family microenvironment. Because maternal half-siblings and paternal half-siblings show no significant changes in age-adjusted MS risks, maternal genomics (such as mitochondria and genomic imprinting) and environmental factors (such as intrauterine and perinatal factors and breast feeding) are not contributory. In addition, age-adjusted MS risk did not differ significantly between half-siblings raised together or apart, thus suggesting that environmental factors exert their effects on a large population scale, rather than on a familial microenvironmental level.

ASSOCIATION OF HLA WITH MS

Numerous linkage and association studies to identify MS genes have been performed. These have revealed that no single gene induced MS, but rather that MS was a polygene disease. Thus, various genes play cumulative small roles in MS susceptibility. To date, only the association of MS susceptibility with the HLA DRB1*1501-DQA1*0102-DQB1*0602 haplotype has been consistently shown, mainly in Caucasians. African Americans, who have an HLA haplotype distinct from Caucasians, show selective association between MS susceptibility and the HLA DRB1*1501 allele but not the DQB1*0602 allele, thus underscoring the critical role of the DRB1*1501 allele in MS. In Asians, a significant association between DR2 (DRB*1501) and MS has also been found in Palestine, Jordan, and Turkey. Even in Japan, conventional MS has repeatedly been shown to be associated with this allele, whereas OS-MS is associated with the DPB1*0501 allele. Thus, at least in the main form of MS, DR2 (DRB1*1501 allele) confers MS susceptibility among races, supporting the autoimmune hypothesis. Polymorphisms of other genes, especially those modulating the magnitude of immune responses such as

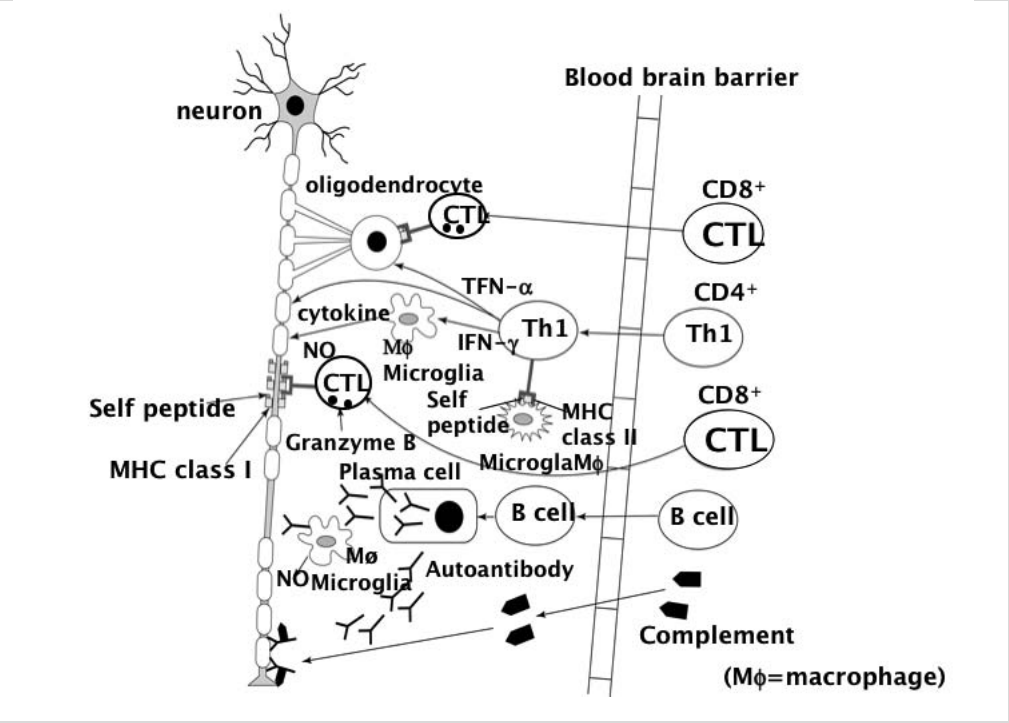


FIGURE 1.2 **Hypothetical mechanism of the effector arm of multiple sclerosis. CTL, cytotoxic T cell; BBB, blood–brain barrier.**

cytotoxic T-lymphocyte antigen-4 (CTLA-4), nitric oxide synthase (NOS2A), and IL-4 receptor are also associated with certain races, but require confirmation for other races. Genes other than HLA appear to have minor or distinct effects among races with different genetic backgrounds.

CURRENT HYPOTHESIS OF MS

Autoimmune Hypothesis The nature of MS lesion pathology involves inflammatory demyelination with relative sparing of axons. This supports the hypothesis that MS is an autoimmune disease targeting CNS myelin. Even in severe destructive lesions in the spinal cord of OS-MS, Schwann cells remyelinate the remaining axons, suggesting that CNS—not peripheral nervous system (PNS)—myelin is the target of the autoimmune attack. Myelin protein–autoreactive T-cell lines and clones have been established from peripheral blood lymphocytes taken from MS patients and from healthy subjects. Autoreactive T cells from MS patients were shown to react not only with various myelin proteins but also with various epitopes on one myelin protein molecule. Such epitope spreading was seen only in MS patients, whereas in healthy individuals autoreactive T cells reacted only with one myelin protein or with limited epitopes. Myelin-autoreactive T cells from MS patients mainly produce Th1 cytokines and, by analogy of EAE myelin-autoreactive Th1 cells, are possibly responsible for the initiation of CNS inflammation.

Myelin-autoreactive T cells are not clonally eliminated from the T-cell repertoire even in healthy individuals, but these cells are usually quiescent, possibly through suppression by immunoregulatory cells such as Foxp 3–expressing $CD4^+CD25^+$ regulatory T cells and $V\alpha24^+$ natural killer (NK) T cells. Disruption of immune regulation by an ill-defined trigger might result in the activation of myelin-autoreactive T cells in peripheral blood, after which activated T cells can enter the CNS. If these cells encounter target antigens within the CNS, they are retained in the

KEY POINTS

- The CD25 molecule is the IL-2 receptor α-chain. CD25+CD4+ T cells comprise 5% to 10 % of all T cells and represent naturally occurring regulatory T cells. The Foxp 3 gene encodes *surfin*, a transcription factor that, when mutated, causes immune dysregulation, polyendocrinopathy, enteropathy, and X-linked syndrome (IPEX). It is a master control gene for the development of natural CD25+CD4+ T cells.
- Loss of regulatory cell function also is suggested in MS.
- Antimyelin antibody and CD8+ cytotoxic T cells might also participate in tissue destruction in MS.

KEY POINTS

- No single pathogen has ever been consistently identified in MS, but temporal oligoclonal expansion of B cells, as well as $CD8^+$ cytotoxic T cells, suggest the involvement of certain infectious pathogens.
- Axonal and oligodendroglial losses are profound in some forms of MS with little inflammation, which might suggest the existence of degenerative components.
- An autoimmune mechanism for MS is the most likely cause; however, the responsible antigen remains to be clarified.

CNS and can locally expand and perpetuate CNS inflammation.

The immunostaining of T-cell subsets in MS lesions unexpectedly demonstrated that infiltrating T cells were predominantly $CD8^+$ T cells, especially in the CNS parenchyma, whereas $CD4^+$ T cells constituted a minority. This finding argued against the Th1 model for MS and suggests a role of $CD8^+$ T cells in MS tissue damage. However, relatively small numbers of myelin-autoreactive Th1 cells might initiate intrathecal inflammation, and $CD8^+$ T cells might play a role in the effector arm of the disease. $CD8^+$ T cells in MS lesions contain granzyme B, a substance found in cytotoxic granules, and these are considered to represent a large proportion of cytotoxic T cells. Because MHC class I molecules can be induced in constituent cells of the CNS, $CD8^+$ T cells might target CNS cells expressing MHC class I molecules. Demyelinated axons express MHC class I molecules, and therefore can be a target of $CD8^+$ cytotoxic T cells.

The presence of oligoclonal IgG in the CSF and intrathecal clonal expansion of B cells, as shown with overusage of certain heavy-chain variable region genes, suggest that the humoral immune response focuses on limited antigens. However, it is still unknown whether this antibody response is the cause or result of CNS inflammation.

Infectious Hypothesis It has been suggested that a number of pathogens are associated with MS, including recently reported *Chlamydia pneumoniae*, but nothing has been widely proven. Although oligoclonal expansion of B cells and $CD8^+$ T cells in the CNS supports the infectious hypothesis, it is currently thought that nonspecific infections, rather than certain specific infections, trigger the autoimmune process against CNS antigens that causes MS.

Degenerative Hypothesis Neuronal loss has been shown to occur early in MS, and a specific MRI technique revealed that brain atrophy was visible even in the early course of the disease in some brain areas. In PP-MS, axonal and oligodendroglial losses are profound, remyelination rarely occurs, yet inflammation is scarce. Moreover, IFN-β clearly suppresses relapse and inflammation in RR-MS and SP-MS, as seen on sequential MRI; however, its protective effects on disability progression and brain atrophy is modest. These observations suggest the importance of degenerative components in MS.

SUMMARY

Increasing evidence indicates that MS is not a single disease, but is etiologically heterogeneous. An autoimmune mechanism with cellular and humoral components is suspected, but the responsible antigen(s) remains unknown. In addition, the mechanism producing the progressive phase still remains to be elucidated. Several drugs modify the longstanding course of the disease, however, their therapeutic effects are far from satisfactory, especially on accumulation of irreversible disability and progressive axonal loss. Further studies hopefully will provide better therapeutic measures for MS in the future.

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CHAPTER 2

CLINICAL FEATURES OF MULTIPLE SCLEROSIS

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CLINICAL COURSE OF MULTIPLE SCLEROSIS

It may be observed that no two cases of any disease are alike, but this is particularly so for multiple sclerosis (MS). Huge heterogeneity occurs in the clinical course and great variety in the clinical presentation at onset and with the passage of time, reflecting the number of sites for which demyelinating plaques have a predilection—optic nerves, periventricular white matter, cerebellar peduncles, brainstem, and spinal cord.

Most symptoms are nonspecific for MS and have important differential diagnoses, which will be covered in detail elsewhere. Some symptoms are considered minor and transient, in that they are often initially ignored by the patient themselves or explained innocently away by those clinicians to whom they present. Hence the delay between onset of the first relevant symptoms and actual investigation and diagnosis is often considerable.

The modal time for onset of MS symptoms is during the third and fourth decades of life, with an average age of onset of 30 years (Figure 2.1). Cases have, however, been occasionally described in children as young as 1 or 2 years, and MS may sometimes present in patients older than 60 years. Females predominate by a ratio of 2 to 3:1 over males, but among those with a later age of presentation and in those with a primary progressive course the distribution between the sexes is more even.

Several broad clinical phenotypes of MS are recognized. Initially, approximately 85% of patients follow what is known as a relapsing-remitting course (RR-MS) characterized by *relapses*—"bouts" or "attacks"—followed by recovery (complete or partial) and periods of clinical stability known as *remission*. A relapse is defined as a focal disturbance of neurologic function affecting a white-matter tract and lasting for more than 24 hours. Although somewhat arbitrary, it is accepted that no more than one relapse can occur every 30 days. The remaining patients, approximately 15%, do not have clear relapses but experience a gradual decline over time, described as a primary progressive course (PP-MS).

Typically, patients initially in the relapsing-remitting group eventually enter a stage of the disease known as the secondary progressive phase (SP-MS). At this stage, patients have fewer relapses but recovery is more incomplete as the capacity for remyelination declines and axonal loss progresses, thus resulting in the accumulation of disability. Progression also may occur between, and in the absence of, relapses. Although the transition to the secondary progressive phase is difficult to determine in the individual patient, it is estimated that at 15 to 20 years from disease onset, 50% of initially relapsing-remitting patients will have entered the secondary progressive phase. The typical spectrum of disability and impairment in a population of MS patients is shown in Figure 2.2. The Kurtzke scale on which this is based is discussed in detail in Chapter 9.

More optimistically, some patients may never enter such a secondary progressive phase or at least may not accumulate significant disability until decades have passed since onset. This, the mildest form of MS that is clinically apparent, has been labelled *benign MS*. This concept is widely quoted by neurologists when helping patients to come to terms with their diagnosis.

Definitions of the benign category are varied and hence the proportion of patients

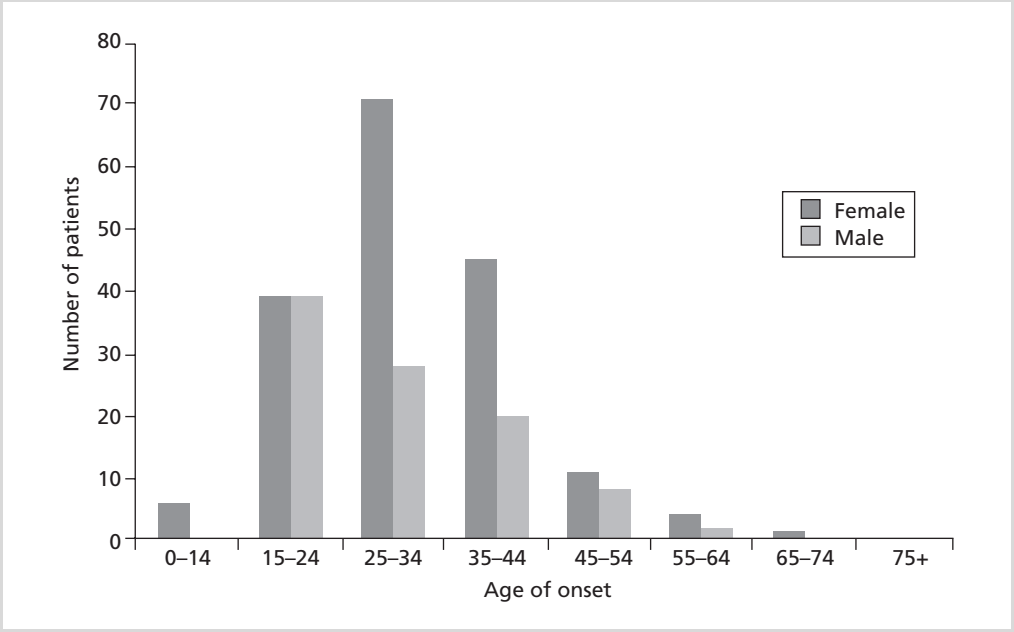

FIGURE 2.1 **Age of onset of MS by gender.**

said to fit within this group is estimated widely at between 5% and 40%. Some studies have indicated that some patients who apparently had benign disease eventually become significantly disabled at a further 10 years of follow-up; it may prove that a relatively low Kurtzke score (≤2.0), 10 to 15 years from onset will prove a more robust and meaningful definition of benign disease.

Conversely, regarding prognosis, it is generally agreed that the onset of a progressive course carries a poor prognosis. However, the value of this observation is limited, because transition from a relapsing-remitting to a progressive phase can only be determined after progression has already occurred, thus it is not a predictive or prognostic criterion.

In a detailed veterans' study it was claimed that the disability status 5 years from diagnosis is predictive of the subsequent course. Less than 8% of those with mild disability at 5 years (Kurtzke Disability Status Scale [DSS] score < 3) were severely disabled (DSS 6–10) 10 years after diagnosis, and only 11% were severely disabled at 15 years.

Regarding relapse rate, McAlpine suggested that a low relapse rate is associated with benign disease. Confavreux found that the mean duration between the first and second relapse was much longer in benign cases. An association also has been demonstrated between short first remission (less than 1 year) and an increased risk of progressive disease. Significant differences also have been shown in the survival curves of disability between patients with a high or low number of attacks in the first 2 years after onset of MS and also between patients with a short or long inter-attack interval.

The prognostic significance in MS of age of onset, gender, and nature of the initial symptoms have been examined. Again, until relatively recently, some controversy had surrounded all these factors. Although several investigators indicated that females had a relatively favorable course, some found no gender influence, and one group actually found that males had a more favorable course. Most investigators have found a worse prognosis in patients who are older (generally > 40) at onset. Few have shown significant differences in patients younger than 40, although one group did demonstrate a negative corre-

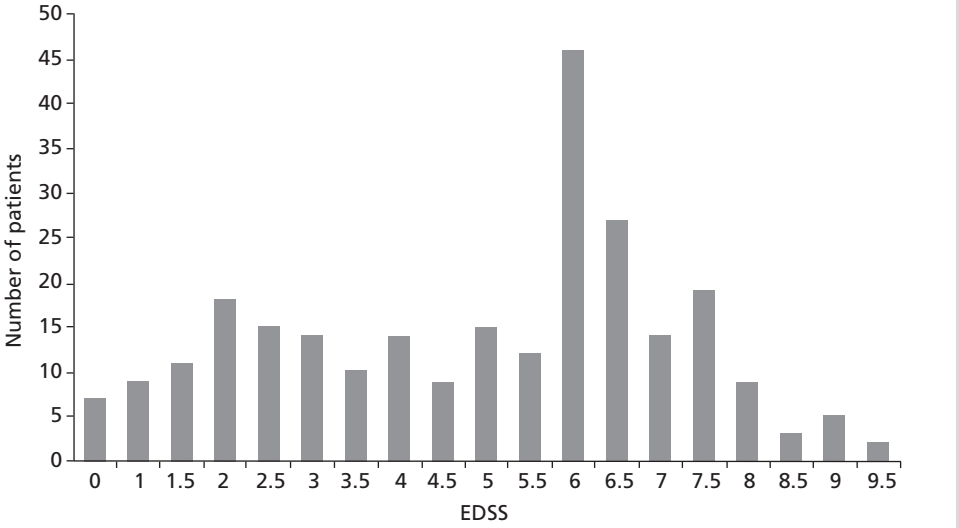

FIGURE 2.2 **Distribution of Kurtzke EDSS scores in a population-based MS sample.**

lation coefficient between age of onset and the percentage of patients in each age group under 40 with a benign illness. Several groups have found optic neuritis to be a favorable initial symptom. By comparison, motor or cerebellar symptoms at onset have been deemed unfavorable.

Probably the most authoritative data regarding these prognostic factors comes from Ontario, Canada. There, male sex, late onset, and being seen by a health care provider from onset of MS were all associated with an adverse outcome. Optic neuritis at onset was favorable, whereas slow onset of a motor deficit and cerebellar involvement was associated with a poor outcome. Progressive disease from onset (± relapses) was a negative factor prognostically. Although a large Danish cohort found no benefit for optic neuritis over brainstem or spinal onset in RR-MS, females and those with an early onset were more likely to have a benign course. In addition, a monoregional onset predicted a better prognosis compared with a polyregional onset.

Overall, therefore, data from natural history and other studies tend to indicate that the following factors are more likely to indicate a relatively favorable course:

- Female sex
- Early age at onset
- Monosymptomatic rather than polysymptomatic onset
- Sensory symptoms or optic neuritis at onset
- Full recovery from early relapses
- Low relapse frequency in the first 5 years

Conversely, males, those with a progressive course from onset, motor symptoms at onset, polysymptomatic onset, incomplete recovery from early attacks. and a high relapse rate in the first 5 years are factors that tend to predict a less favorable outcome. It must be remembered that observations such as these are derived from large cohorts of patients, reflecting patterns and trends. Patients with apparently favorable features may do worse than expected (and vice versa), making the direct translation to the individual patient consulting the clinician somewhat more difficult.

In the consensus document produced by Lublin and Reingold following an international survey, PP-MS was defined as disease progression from onset with occasional plateaus and temporary minor improvements, the essential element being a gradual, nearly continually worsening baseline with minor fluctuations but no distinct relapses.

Although estimates vary widely, it is reasonable to assume that PP-MS represents 10% to 20% of the MS population. Whereas a significant female predominance exists in RR-MS, in PP-MS, the ratio is generally more even and actually has been found to be reversed. Most studies also find that PP-MS has an older age at onset than does RR-MS, typically around 40 years, some 10 years later than those with relapsing-remitting disease. Overwhelmingly, the typical initial presentation in PP-MS is a progressive myelopathy, whereas visual loss at onset is uncommon. A comparison of the demographics and typical symptoms at onset in the two broad groups of RR-MS and PP-MS is shown in Table 2.1.

A further category of transitional progressive MS (TP-MS) is also sometimes described, in which patients follow a progressive course at some time remote from a single attack. The term is not widely used, probably only applies to a very small proportion of patients and, in clinical practice, such patients are likely to be difficult to distinguish from either secondary or primary progressive MS.

SYMPTOMS AND MANIFESTATIONS OF MS

Optic Neuritis Optic neuritis is one of the classical presentations of MS. Obviously, it is not pathognomonic of MS and an important differential diagnosis must be considered. One of the commonest presenting manifestations of MS, it is typically unilateral (95% of cases) and characteristically subacute in onset, evolving over several days to reach maximal severity. The typical visual field defect seen is a central scotoma, with particular deterioration in colour discrimination. Other field defects, including altitudinal field defects and monocular hemianopias may less commonly be demonstrated.

Patients may experience photophobia and pain around and behind the eye (90% of patients), particularly on eye movement when the inflamed nerve is being stretched. Scintillations and obscurations on eye movement (movement phosphenes) also may be described. Funduscopy may reveal a swollen disc with blurred margins (one-third of patients), erroneously leading to concerns about papilledema and raised intracranial pressure, whereas, following recovery, there may be residual pallor of the disc, particularly on its temporal aspect, indicating demyelinated nerve fibres. Such pallor usually develops after 4 to 6 weeks. During the acute phase an afferent pupillary defect is likely present (loss of the direct, and preservation of the consensual light reflex) on the affected side (Marcus-Gunn pupil), which usually resolves following recovery from the episode. Most recovery occurs within approximately 6 weeks, but further gradual recovery may continue for 12 months.

Uhthoff phenomenon is a pattern classically described in patients with current or previous episodes of optic neuritis (Case 3),

TABLE 2.1 **Comparison of gender ratio, age, and symptoms at onset in relapsing-remitting and primary progressive MS. (Data derived from a population-based prevalence study [RRMS], and clinical cohort [PPMS] in Northern Ireland).**

Clinical phenotype	RRMS (n = 245)	PPMS (n = 111)
Female/Male ratio	2.5:1	1.3:1
Age at onset (yrs)	30.4	39.5
Symptoms at onset (%)		
Motor	19.0	67.6
Sensory	37.1	18.0
Brainstem/cerebellar	27.4	10.8
Optic neuritis/visual loss	23.0	3.6
Sphincter	3.2	4.5

but it should probably not be regarded as specific to optic nerve demyelination. Typically, the patient complains of reduced vision, even transient blindness, with exercise or heat exposure that then resolves on rest or cooling. It is believed to occur due to the delayed conduction block of a partially demyelinated optic nerve. In practice, this mechanism is also likely to explain the so-called "hot bath sign" in which patients find it difficult to get out of a bath because of increased weakness caused by the rise in body temperature.

Another phenomenon seen in optic nerve demyelination is the *Pulfrich effect*, in which patients mistakenly perceive objects moving in a linear pathway as moving elliptically. This is produced by delayed conduction along one optic nerve compared with the other.

Sensory Symptoms Sensory disturbances probably represent the commonest symptoms at the onset of MS and affect the vast majority of patients (over 90%) at some stage in the clinical course. The patient experience of sensory disturbance will be variously described as tingling, burning, or numbness reflecting dysesthesia, paraesthesia, or sensory distortion. Evidently, the area of disturbance depends on the location of the lesion. Symptoms may be localized to a few digits or a single limb, and a hemisensory syndrome, a spinal cord level, or a dissociated sensory loss may be present. A characteristic presentation in MS is with the "useless hand" syndrome. In this, patients have selective impairment of upper extremity proprioceptive function with preserved crude touch, and motor and cerebellar functions. Although disabling if present, the useless hand syndrome usually resolves spontaneously. Pseudoathetosis may be demonstrated on clinical examination: With the eyes closed, the patient is unable to maintain the outstretched fingers and hand in a steady position.

Facial sensory changes in the form of a trigeminal sensory neuropathy may occur. Patients usually report numbness of two or all divisions of the trigeminal nerve, along with intraoral numbness.

Cerebellar Disturbance Cerebellar dysfunction in MS is unfortunately among the most challenging aspects of the disease to manage. Features of cerebellar disturbance include gait ataxia, truncal ataxia, dysarthria, nystagmus, intention tremor, and titubation. The last of these would not typically occur at initial presentation. The tremor can be intensely disabling and, although many pharmacologic agents are employed in its treatment, few if any are of any proven clinical value. In the most severe form. the patient may have a rubral tremor, where even the very thought of movement can provoke tremor at rest. This reflects involvement of the superior cerebellar peduncles or red nucleus. The patient may be reduced to sitting on one limb to suppress the movement. Thankfully, such disabling symptoms are usually a later manifestation of the disease.

The scanning speech typical of cerebellar involvement is also usually not demonstrated until late in the clinical course, with dysarthria estimated to affect only 3% to 5% of patients at onset.

Eye Movement Disturbance Nystagmus is the commonest disturbance of eye movement seen in MS. This can present in several forms. The most frequently seen is gaze-evoked, horizontal jerking nystagmus. The

CASE 1

A 30-year-old woman was referred from a medical team because of spasms affecting the left side of her face, left arm, and leg, intermittently for the past 5 days. She was in the fourteenth week of her second pregnancy. Two years earlier, and approximately 6 weeks postpartum she had an episode of visual blurring affecting the right eye, evolving over 24 hours and recovering gradually and completely over a period of 10 days. On examination now, she did indeed have spasms affecting the left arm and leg, lasting a few seconds and provoked by changes in posture and triggered by touch. No alteration of consciousness was present, and electroencephalogram (EEG) had been normal. MRI showed multiple periventricular and callosal lesions typical of demyelination. A diagnosis of tonic spasms was made and, in view of the stage of pregnancy, no treatment was offered. The spasms resolved spontaneously over the next week.

CASE 2

A previously well 23-year-old female patient presented with a history of tingling developing in both feet. Over the next 24 hours, both feet became numb and, over a further 48 hours, the symptoms evolved further such that she became numb from the chest downward. She was assessed clinically and found to have brisk reflexes in all four limbs, together with bilateral extensor plantar reflexes and a sensory level at approximately T2. No significant weakness was present, and cranial nerve examination was normal. MRI scanning of brain was normal, but MRI of cord revealed an area of high signal intensity in the upper dorsal cord that enhanced following gadolinium contrast injection. The patient was treated with a reducing course of oral steroids and a full recovery occurred over the next month.

fast phase of this nystagmus is usually in the direction of gaze. It is a nonlocalizing sign, potentially being due to lesions in the brainstem or cerebellum.

Other forms include pendular nystagmus, which is usually present in patients with a combination of visual and cerebellar deficits that impair fixation and the control of movement, respectively. Pendular movements may be seen in the primary position and are exaggerated by movement. At the most severe, patients may experience oscillopsia and be unable to read easily.

Less commonly seen forms of nystagmus in MS include convergence-induced nystagmus and periodic alternating nystagmus.

Ataxic nystagmus is seen in patients exhibiting the phenomenon of *internuclear ophthalmoplegia* (INO). Sometimes mistakenly referred to as being pathognomonic of MS, this reflects a lesion in the medial longitudinal fasciculus (MLF), a tract that connects the sixth nerve nucleus in the pons with the contralateral medial rectus subdivision of the third nerve nucleus in the mesencephalon. Consequently, the patient exhibits failure of full adduction in the ipsilateral eye together with irregular nystagmus in the contralateral abducting eye. Because the two MLF tracts lie quite adjacent to each other, bilateral INOs often are seen. Obviously, a spectrum of severity is present in INOs: Many are asymptomatic, and most are partial and only demonstrated by rapid saccadic eye movements.

Lesions adjacent to the MLF may also give rise to the "one and a half syndrome," in which complete paralysis of eye movement to one side is present, with failure of adduction to the contralateral side.

Other ocular palsies that may be seen include skew deviation, in which vertical divergence of the eyes occurs, usually in the presence of an INO and more rarely, Parinaud syndrome. Subtle disorders of eye movement include saccadic intrusions such as square wave jerks, and saccadic oscillations such as ocular flutter.

Brainstem Disturbance Involvement of the brainstem may be manifest in the facial sensory disturbances or eye movement disorders already discussed. Peripheral involvement of the facial nerve also may occur, leading to lower motor neurone facial weakness (Bell palsy). This is estimated to occur in 1% to 4% of patients at some stage in the clinical course. Full recovery is typical, but aberrant reinnervation and myokymia may occur. Facial myokymia, a rapidly flickering contraction of the facial muscles particularly around the eye, may occur in the absence of any previous facial palsy.

Vertigo occurs as the presenting symptom in approximately 16% of patients, and bouts of vertigo occur at some stage in over 50% of patients. It can be extremely disabling during an acute relapse with vomiting, collapse, and curtailing of ambulation. Some authors have found that initial presentation with vertigo is associated with a subsequently relatively benign course. However, because vertigo occurs commonly enough in the non-MS population, it may simply occur coincidentally in patients who later go on to develop real clinical manifestations of MS.

Decreased taste sensation is rarely described by patients, but there are occasional case reports in the literature of this occurring in the context of a relapse, and it has been described as a problem in approximately 1% of patients. Hearing problems are certainly more common and problematic, but complete permanent hearing loss is

extremely unusual, and involvement is most commonly unilateral.

Dysphagia may occur during an acute relapse at any stage in the clinical course, but it is most commonly identified as a problem in those well established in the progressive phase. Overall, it occurs in up to 45% of patients. Weight loss and poor nutritional status may result, with increased risk of aspiration and pneumonia. Some patients will require specific dietary consistencies and a small number will need assisted feeding via percutaneous gastrostomy.

Dysarthria of the pseudobulbar (spastic) type may occur with brainstem involvement. The vocal cords are spastic, resulting in high-pitched, low-volume speech with slurring of consonants.

Motor Symptoms Motor symptoms and disability arise from the involvement of several pathways, including the corticobulbar and corticospinal tracts, together with the cerebellar and sensory pathways. Existing deficits also may vary in response to mood, fatigue, temperature, and exercise.

The most common motor deficit results from limb weakness. This can follow various patterns initially, although ultimately patients may experience weakness in all four limbs, typically in a pyramidal distribution, with the extensors being relatively weaker in the arms and flexor groups being weaker in the legs. Initially, the most common pattern of weakness will be that involving both lower limbs, although involvement of a single leg or ipsilateral leg and arm also are seen. Involvement of both arms without lower limb weakness is extremely unusual and should suggest an alternative diagnosis.

The clinical examination may itself be relatively unimpressive in eliciting hard clinical signs. The patient may simply report a change in exercise ability or may report extreme tiredness on a hot day or alternatively after getting out of a hot bath or shower. In these circumstances, the examination may not demonstrate any significant weakness, despite impressive symptoms, because the routine neurologic examination does not test stamina. Other clinical findings may be elicited however, including brisk reflexes and extensor plantar responses. All such findings may also only be elicited by exercising the patient in the clinic.

Significant spasticity may not be commonly found at initial presentation, apart from in those patients following a primary progressive course, but it will eventually feature in 70% to 80% of patients. As with all the symptoms in MS, varying degrees occur, through the full range of the Ashworth or Modified Ashworth scale. Spasticity may vary in the context of a relapse, at times of stress, with concurrent infection, and even at different times of day in the same patient in the context of fatigue.

Many potential aggravating factors exist (Table 2.2). At worst, patients may develop contractures, particularly flexion contractures at the knees, which interfere with seating and transfers. Hip adductor spasticity causes particular problems with sphincter management, sexual function, perineal hygiene, and dressing. Spasms, which do not only occur in severely spastic limbs, may also interfere with transfers and other activities of daily living and, if painful, may cause sleep disturbance.

Both spasticity and spasms may be amenable to a variety of measures, pharmacologic and surgical, but treatment is not necessarily always desirable. Patients with weak floppy legs will find it difficult to stand

TABLE 2.2 **Factors that may influence spasticity.**

Unpredictable	Preventable
Renal stones	Change in temperature/humidity
Bowel impaction	Fatigue
Pneumonia	Posture
Progression of disease/relapse	Stress
Urinary tract infection	Restrictive clothing
Menstruation	Psychological factors
Deep vein thrombosis	Pressure sores
Wounds or infections	Ingrown nails

CASE 3

A 36-year-old schoolteacher was referred for consideration of disease-modifying therapy for MS. Onset of first symptoms was 10 years earlier, with subacute onset of visual loss in the right eye that had recovered spontaneously and without treatment. A diagnosis of optic neuritis had been made at that time. The disease was then clinically quiescent until 8 years later, when he noticed that on bending his neck, shock-like sensations would shoot down his back and into both legs. This had persisted for 3 months and resolved spontaneously. Twelve months ago, he had experienced visual loss in the left eye, and now, despite having his vision recovered, he was no longer able to go jogging or cycling, because after a short period of such exercise he would experience visual loss in both eyes that would settle promptly but only with a period of rest.

and walk, but spastic limbs may actually allow a degree of weight bearing because of the involuntary contraction of antigravity muscles. It is notable how many MS patients with very weak limbs "use" their spasticity to execute transfers.

Muscle wasting is not commonly seen in MS and, if noted at time of presentation or early in the clinical course, alternative diagnoses usually should be considered. However, relatively debilitated patients may be vulnerable to pressure palsies, and wasting of the hand and thigh muscles may be noted in those with advanced disease.

Sphincter Disturbance Disturbances of micturition are the presenting feature in approximately 5% of cases of MS, but problems with bladder function eventually affect the majority of patients to some extent. In view of the common etiology within the spinal cord, bowel and sexual function problems often co-exist; few male patients who have significant micturition problems do not have erectile dysfunction.

Patients with bladder problems will have a variety of symptoms including frequency, urgency, incontinence, hesitancy, retention, and nocturia. In detrusor muscle hyperreflexia, impaired bladder storage is present, caused by rises in intravesical pressure that are disproportionate to bladder volume; this gives rise to the sense of urgency and frequency experienced by the patient and may result in the inadvertent leakage of urine. In detrusor sphincter dyssynergia, opposing mechanisms occur simultaneously—those that precipitate bladder emptying and those that close the sphincter. Consequently, patients experience hesitancy and retention with a significant postvoiding bladder residual.

The estimated prevalence of bowel problems varies, but figures of 46% to 68% for bowel symptoms in general, and 43% for constipation in particular, have been documented. Constipation is clearly not unique to MS, but commonly is seen in disabling neurologic disorders. It results from a variety of factors, including spinal cord involvement with slowed passage of the stool through the bowel, increased water absorption, and desiccation. There are also present the negative effects of weakness of abdominal muscles, reduced activity, poor diet, drugs, and an understandable but counterproductive desire to limit fluid intake because of concurrent bladder problems. As with the bladder, frequency and urgency may occur, but the most distressing problem is that of faecal incontinence. This may occur as a result of lost rectal sensation, but may also be triggered by drugs or arise from a spurious diarrhoea with loose bowel bypassing an impacted stool.

The occurrence of sexual dysfunction correlates closely with bladder impairment. It is a major cause of distress, relationship strain, misunderstanding, and marital breakdown. Although not commonly a feature at presentation, again, apart from those with primary progressive disease, it is a significant issue even in the relatively able-bodied patient. Erectile dysfunction has been found to affect up to 91% of men, and between 56% and 72% of women with MS report sexual difficulties. The problems experienced do not simply reflect the autonomic disturbances that occur in MS but are multifactorial and may involve issues related to fatigue, loss of libido, low mood, spasticity, unpredictable loss of bladder control, and loss of normal sensation.

Fatigue Fatigue is considered the most disabling symptom by many patients with

CASE 4

A 35-year-old part-time carpet fitter was referred for consideration of disease-modifying therapy. At the age of 20 years, he had experienced a 10-week spell of poor balance. He had attended his general practitioner and the possibility of MS was mentioned. He was treated with a reducing course of oral steroids and made a full recovery. No hospital referral was made. He then remained well until 9 years later, when he developed weakness in both legs, together with unsteadiness of gait. On this occasion, he was investigated, and both MRI of brain and cerebrospinal fluid (CSF) analysis contributed to confirmation of the diagnosis of RR-MS. Subsequently, he has continued to have relapses, invariably having only partial recovery and not returning to the previous baseline level. In addition, even in the absence of clear relapses, he has felt himself slowing down, together with increasing fatigue and a gradual decline in both visual and cognitive functions. On examination, he has a Kurtzke Expanded Disability Status Score (EDSS) score of 5.5, with an ataxic spastic paraparesis, upper limb ataxia, and a left internuclear ophthalmoplegia (INO).

MS. Different forms of fatigue occur, and how much is due to the disease itself and how much is due to related factors (depression, lack of sleep due to nocturia or spasms) can be difficult to discern. Fatigue may be related to ordinary activity and respond to a period of rest. Fatigue also can be unpredictable, without any particular exercise stimulus. Typically, patients with MS are at their best in the mornings and require rest periods in the afternoon. Unfortunately, for some patients fatigue is constant and all pervasive, not responding to either sleep or rest. In some, it may simply reflect a period of relapse, and they subsequently recover; or it may be a transient phenomena in response to changes in climactic conditions such as undue, dehydrating heat.

Fatigue has been identified as a significant issue for 84% of patients with MS. Unfortunately, some of these patients may receive little sympathy from the less well informed if they have few outward signs of disability. Regrettably, in this author's experience, it is also sometimes the case that those who have fatigue as an early feature may not have their symptoms treated with the appropriate merit, leading to an undue delay in diagnosis (Case 6).

Cognitive Disturbance It is estimated that cognitive deficits occur in up to 60% of MS patients. Frank dementia has long been recognized as occurring in patients with advanced disease, but more recent evidence has shown that even in patients with apparently early mild MS, 50% have a degree of cognitive deficit, although this may not be noticed by the patient or indeed actually be disabling.

The overall correlation of cognitive performance with physical disability is poor, and clinicians will be familiar with the MS patient who is relatively ambulant but profoundly cognitively impaired, in contrast to the numerous patients who have been wheelchair-bound for several years but have only minor, if any, cognitive problems.

CASE 5

At the age of 39 years, a former pilot noticed that his walking distance was gradually in decline, and he was becoming more fatigued than normal. No history of previous remote episodes of neurologic disturbance was present, and there was no remission in his symptoms. After 12 months, he began requiring a cane to assist with walking. A diagnosis of MS was established following investigation, in particular there being typical lesions on MRI and bilateral delay in visual evoked responses. Over the next 3 years, he experienced gradual further decline in lower limb function with increasing weakness, spasticity, and spasms, required training in intermittent urinary self catheterization and treatment for erectile dysfunction. Although upper limb function was relatively preserved, 5 years from onset of first symptoms he was essentially wheelchair dependent.

CASE 6

A 34-year-old divorced woman with two children presented with a 3-month history of reduced mobility and was admitted via a casualty department to a general medical unit. The examination findings were those of a moderate spastic paraparesis. Further history from the patient revealed that, 6 years earlier, she had begun complaining of tiredness. She was seen by a number of hospital specialists and a diagnosis of chronic fatigue syndrome was made. Two years after the onset of these symptoms, she had a 2-week episode of lower limb weakness when she was effectively housebound. This recovered spontaneously. Subsequently, she complained of muscle aches and pains, and further assessment by a hospital specialist led to revision of the diagnosis to fibromyalgia. She experienced bladder problems, and she recalled a spell during which she would bend her neck and experience tingling in both hands. Her marriage broke up, and she had increasing difficulty coping with her young children.

Investigation on this current hospital admission included MR imaging of the brain and cord revealing multiple lesions consistent with demyelination, and CSF analysis that was acellular and positive for oligoclonal bands. Relaying the diagnosis to the patient was unusually met with some relief, because she thought that doctors did not believe her symptoms and that she could even be imagining them herself.

Although some researchers have identified a correlation between performance on psychometric testing and the severity of magnetic resonance imaging (MRI) lesions, others have failed to do so.

Mood disorders are also common in MS and include depression, euphoria (much less common than is generally perceived), and psychosis. Depression has lifetime prevalence in MS of approaching 50%. It is likely to be partly reactive to the consequences of the illness (impact on relationships, work, financial loss, problems with self-esteem, pain, and sleep disturbance to name but a few) and also due to some constitutional effect of the disease process. Suicide is an increased risk in MS and may account for as many as 15% of the fatalities.

An overt psychotic episode may be the initial presenting feature of MS, although rare, and in patients with frontal lobe involvement there may be a Klüver-Bucy state, with hyperphagia and loss of usual social and sexual inhibition.

Pain and Paroxysmal Symptoms It is disappointing how many patients are told that pain is not usually a feature of MS. Unfortunately, it will be a feature for almost every patient at some time during the course of the disease. Pain can be classified into two broad categories: paroxysmal pain and chronic pain.

Trigeminal neuralgia is the most common form of paroxysmal pain in MS, and its characteristics are well known. Other phenomena include *tonic spasms* (Case 1) and *Lhermitte phenomenon* (Case 3). Tonic spasms are brief, tonic contractions occurring in a hemiparetic distribution and lasting a few seconds to a couple of minutes. No loss of consciousness occurs, but the spasms are often painful and may occur up to 30 times a day. The pathophysiology of the spasms is unclear, but they may occur due to fluxes of ionized calcium at the site of a plaque.

Lhermitte symptom is sometimes erroneously referred to as a sign and results from plaque within the cervical cord. Characteristically, the patient describes electric-like shocks and tingling moving down the spine and into the arms and legs on forward flexion of the neck. Other neck movements may produce similar symptoms. The phenomenon occurs in approximately 2% to 3% of patients as the initial symptom, but it is not specific for MS, because it also occurs in compressive cervical myelopathy and subacute combined degeneration of the cord. All these paroxysmal pain syndromes may remit spontaneously, and those that do not often respond to small doses of carbamazepine.

Chronic pain is highly prevalent in those with well-established disease and is multifactorial. It may result from poor posture, spasticity, contractures, lumbar pain, or persistent dysesthesia.

Epilepsy is relatively prevalent in the overall population, and it would therefore not be surprising for MS patients to coincidentally have both conditions. However, MS itself does appear to increase the risk of seizures by two- to threefold and may be more prevalent in those with higher loads of cortical and subcortical plaques.

VARIANTS AND RELATED SYNDROMES

Dealing in appropriate depth with the potential variants of MS lies outside the scope of this chapter. However, some mention should be made of Marburg disease, Schilder disease, Balo concentric sclerosis, Devic disease, and acute disseminated encephalomyelitis (ADEM).

Marburg disease is an aggressive form of MS with a malignant course. It is multifocal, and some lesions may be associated with mass effect. It is often fatal within weeks to months of onset.

Schilder disease is a difficult concept, given that some of the initially described cases ultimately turned out to have diseases other than MS, and many were actually found to have adrenoleukodystrophy. Some cases, however, are likely to be related to MS. Usually beginning in childhood and following a progressive course, there occurs widespread, confluent or diffuse areas of demyelination involving the cerebrum, cerebellum, and brainstem, with axonal loss and often cavitation. The clinical features are similar to MS, but dementia and other cortical features are more prominent.

Balo concentric sclerosis is characterized by rings of myelin separated by rings of demyelination. Lesions may be seen in the cerebral hemispheres, cerebellum, brainstem, spinal cord, and optic chiasm. Typically affected patients are young and present with an acute monophasic illness. Deficits may be present in higher cortical function, and signs of raised intracranial pressure are common. Although frequently fatal, some patients survive, with eventual involvement of the initially uninvolved rings of myelin.

Devic syndrome or *neuromyelitis optica* is a syndrome of bilateral optic neuritis and transverse myelopathy, usually occurring in quick succession. Heterogeneity is common, with some patients following a relapsing-remitting course and some experiencing a monophasic illness. Some patients with the syndrome undoubtedly have a form of MS, whereas others may have one of a variety of autoimmune or granulomatous disorders, such as systemic lupus erythematosus (SLE) and sarcoidosis. The term Devic disease is probably best reserved for patients with no evidence of disease outside the optic nerves and spinal cord, and who have had other potentially responsible disorders excluded.

ADEM is most commonly seen in children and young adults, although it appears to spare very young children (< 2 years). It is related to recent infection or vaccination in the majority of cases, with the number of responsible agents being considerable, but measles, rubella, and varicella being among the most common precipitants. The clinical spectrum is very broad, from a subclinical course to fulminant, rapidly progressive disease with seizures and coma. Neurologic symptoms begin 1 to 3 weeks after the onset of infection, and symptoms peak within several days. Differentiation of ADEM from MS in adults can be very difficult, and we know that 35% of adult cases with a working diagnosis of ADEM have a second episode of neurologic disturbance compatible with MS within 12 months. MRI findings are often impressive, with extensive areas of demyelination; considerable overlap with MS occurs. Basal ganglia lesions are seen in ADEM but not MS, but are only helpful discriminators in the small proportion of patients who actually exhibit these. Similarly, clinical and MRI evidence of infratentorial lesions is certainly more common in ADEM, but these occur frequently enough in MS also. Fever, meningism, and loss of consciousness usually are seen only in ADEM, and aphasia is also more common. The blood–brain barrier is more often disturbed in ADEM, showing higher cell counts, but again overlap occurs, and oligoclonal bands, more common in MS, also may not be a useful distinguishing feature.

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CHAPTER 3

SPECIAL INVESTIGATIONS IN MULTIPLE SCLEROSIS

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The commonly used special investigations in multiple sclerosis (MS) are neuroimaging, cerebrospinal fluid (CSF) examination, and evoked potentials (EPs) (Box 3.1).

BOX 3.1
Special investigations aim at:

- Documenting the dissemination of lesions in space (EP, MRI)
- Documenting the dissemination of lesions in time (MRI)
- Confirming the presence of intrathecal inflammation (CSF)
- Excluding conditions that mimic MS (MRI or CT scan)

These tests are very helpful in establishing the diagnosis, but none provides a result that is pathognomonic of MS or can reliably distinguish between various pathologies. Not all suspected MS patients should have all these tests; the decision relies entirely on clinical judgment. In a neurology practice in which some or all of these tests are not available, an increased reliance should be placed on clinical judgment. When the results of all three tests are normal, this strongly suggests an alternative diagnosis.

NEUROIMAGING

Magnetic resonance imaging (MRI) has replaced computed tomography (CT) as the neuroimaging method of choice in MS work-up (Figures 3.1–3.7). MRI has sensitivity per-

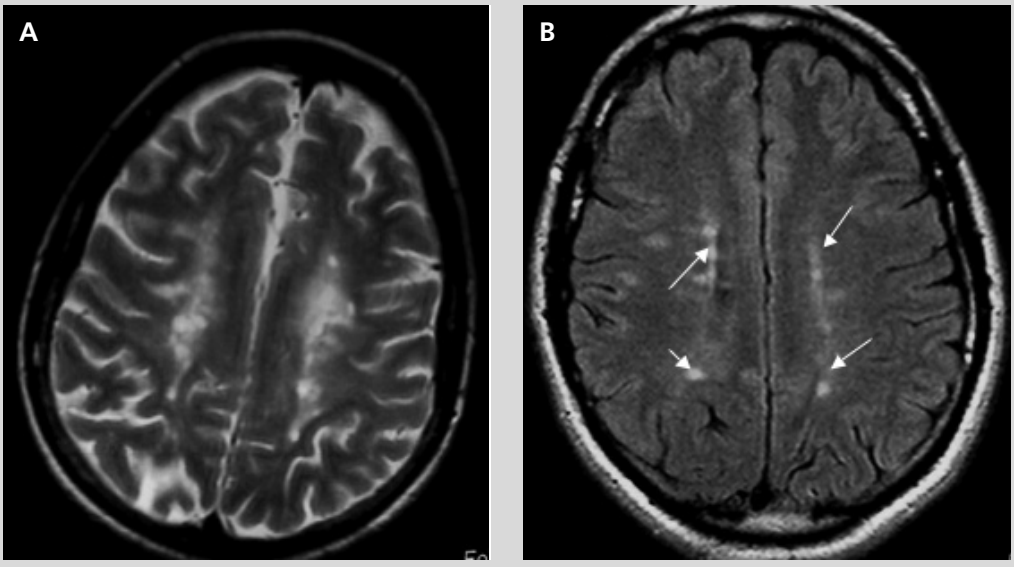

FIGURE 3.1 **Periventricular T2 high signal intensity areas with blurred margins perpendicular to the body of lateral ventricles. (A) Axial T2 weighted sequence and (B) axial flair sequence.**

KEY POINTS

- When a physician is not sure of the quality and reproducibility of any paraclinical analyses, extreme care must be taken in using the results as evidence for supporting a diagnosis of MS.
- About 4% of healthy control subjects of all ages can have periventricular changes that cannot be distinguished from MS.
- In patients after the age of 50, nonspecific brain MRI abnormalities, especially of the periventricular area, become increasingly common.

KEY POINTS

- Typical new MRI lesions enlarge slowly over 4 to 6 weeks and then decrease in size over the next 10 to 14 weeks.
- White-matter lesions on MRI in young adults with clinically isolated syndromes are, in almost all instances, due to MS.
- MRI is the best means to measure changes in disease activity.

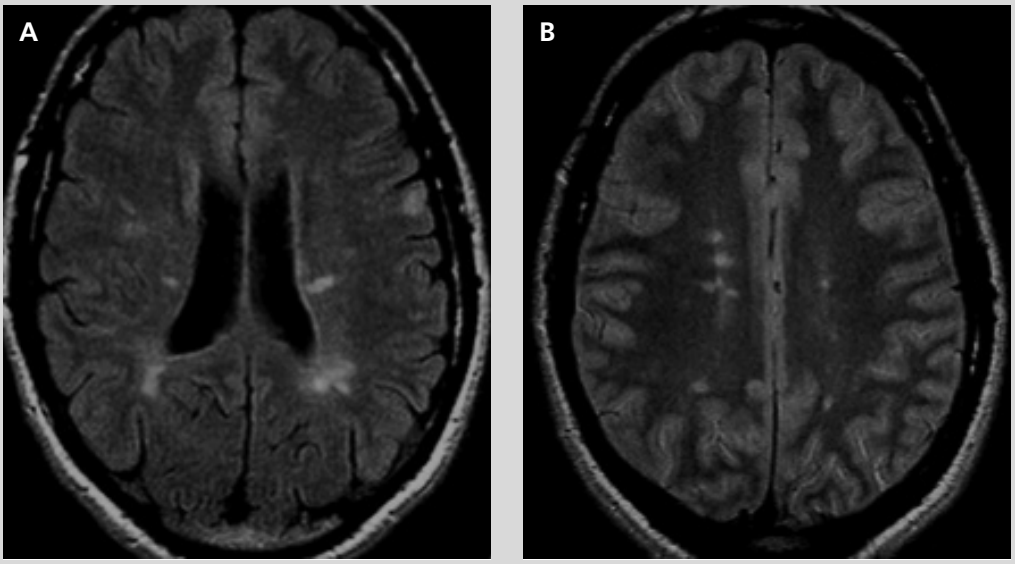

FIGURE 3.2 **Periventricular T2 high signal intensity areas with blurred margins perpendicular to the body of lateral ventricles. (A) Axial flair sequence and (B) axial proton density sequence.**

haps 10 times that of CT in detecting MS lesions. The diagnosis and the understanding of MS have been transformed since the introduction of the MRI in 1981. There remain limited uses for CT in MS evaluation (Box 3.2). There is no doubt that MRI is the most useful single test in the diagnosis of MS, but it must remain only a supportive factor in what is

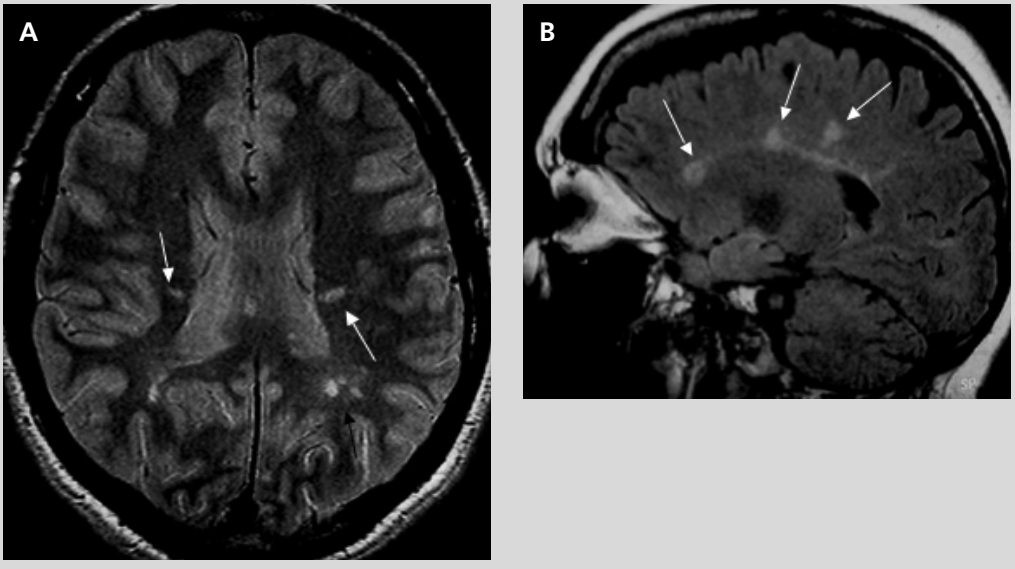

FIGURE 3.3 **T2 high signal areas perpendicular to the ventricles as arrowed on the (A) axial proton density sequence and (B) sagital flair sequence.**

BOX 3.2
CT of the brain might be useful when:

- MRI is not available.
- Patient has a contraindication to MRI (e.g., embedded metallic appliances, pacemaker).
- MRI can't be done due to phobia, morbid obesity, or other factors.

BOX 3.3
MR imaging has become established as the most important paraclinical tool for:

- Diagnosing,
- Understanding the natural evolution, and
- Monitoring the efficacy of experimental treatments in MS

ultimately a clinical diagnosis. However, its contribution, in the context of the entire clinical and laboratory picture, is often decisive. MR imaging also has greatly impacted our thinking about the disease process in MS.

MR images depend on the relative amount and physiochemical environment of water protons in each area of the brain and spinal cord (Boxes 3.3 and 3.4). Changes can be characteristic, but they are not specific for any pathologic process; however, the shape and distribution of the MRI abnormalities are often highly suggestive of the diagnosis.

BOX 3.4
MS lesions are very common in:

- Periventricular white matter (Dawson fingers)
- Centrum semiovale
- Corpus callosum
- White matter tracts (fornix, chiasm, optic nerves)

Common sites include:

- Pons
- Medulla
- Cerebellar white matter
- Spinal cord
- Optic nerve

Less common sites of MRI lesions include:

- Gray matter
- Basal ganglia
- Cortex

Gray matter lesions are relatively rare in MS but commonly seen by pathologists.

Clinically silent lesions are found throughout the brain, even in eloquent areas such as the optic nerve and spinal cord. New lesions on the other hand, accompany most new symptoms; thus explaining why MRI now is frequently used also for treatment monitoring.

The advent of MRI techniques to study patients over the last two decades has drawn attention to the potential importance of nor-

KEY POINT

- MRI is the most sensitive single predictor of clinically definite disease in follow-up.

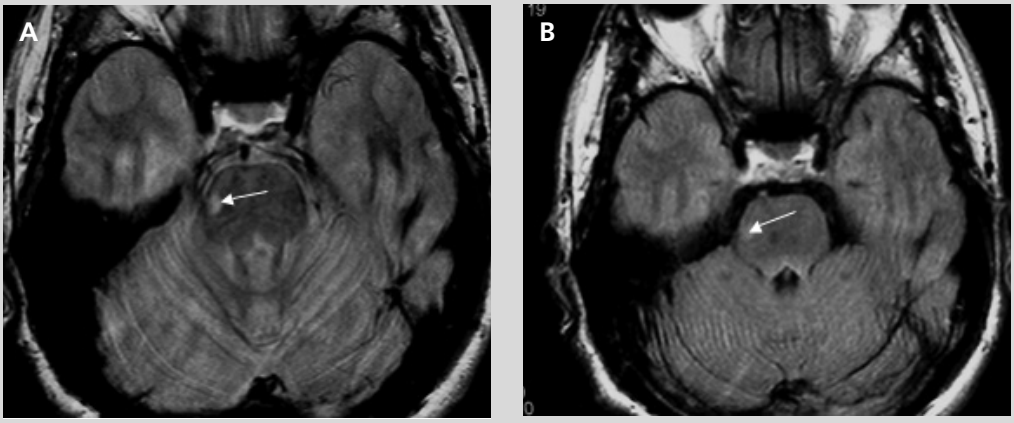

FIGURE 3.4 **T2 high signal area of demyelination in right lateral pons. (A) Axial proton density sequence and (B) axial flair sequence.**

KEY POINTS

- Characteristic MS abnormalities are best demonstrated by proton-density or T2-weighted MRI images.
- Abnormalities are seen in the periventricular region of 98% of CD-MS patients.

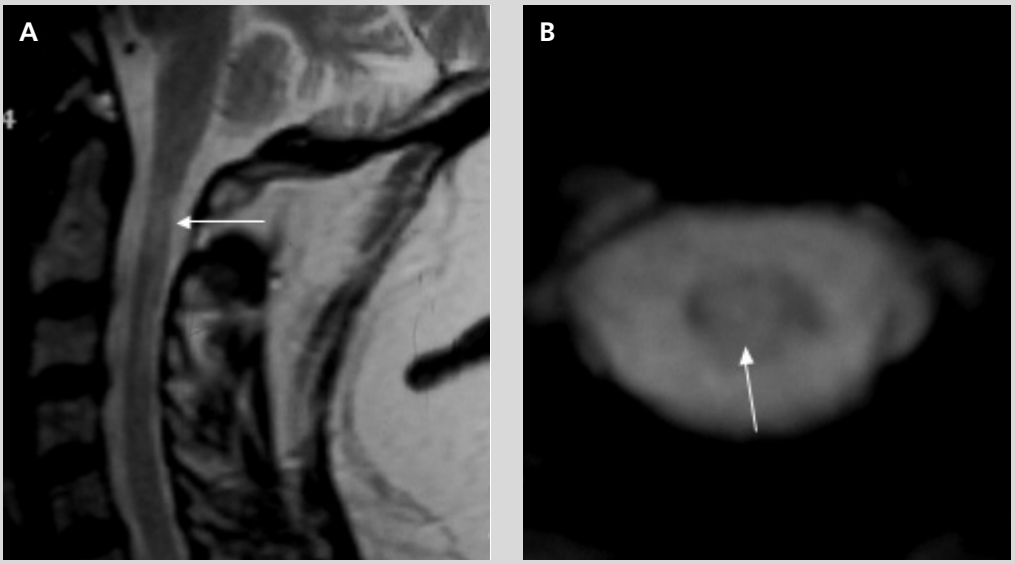

FIGURE 3.5 **Central T2 high signal areas in cervical cord. (A) Sagittal T2 weighted sequence and (B) axial T2 weighted sequence.**

mal-appearing white matter abnormalities (NAWM). Quantitative MRI abnormalities have been reported in NAWM in many studies, and more recent quantitative structural and functional MR studies have identified grey matter abnormalities.

Basic Magnetic Resonance Imaging Technique To generate MRI signals, the body is exposed to an external magnetic field that causes protons to align in an orientation parallel or antiparallel to the external magnet. A radiofrequency (RF) pulse transfers energy to the protons, which resonate with the pulse, causing some of the protons to alter their orientation. The RF pulse is discontinued and the protons relax, returning

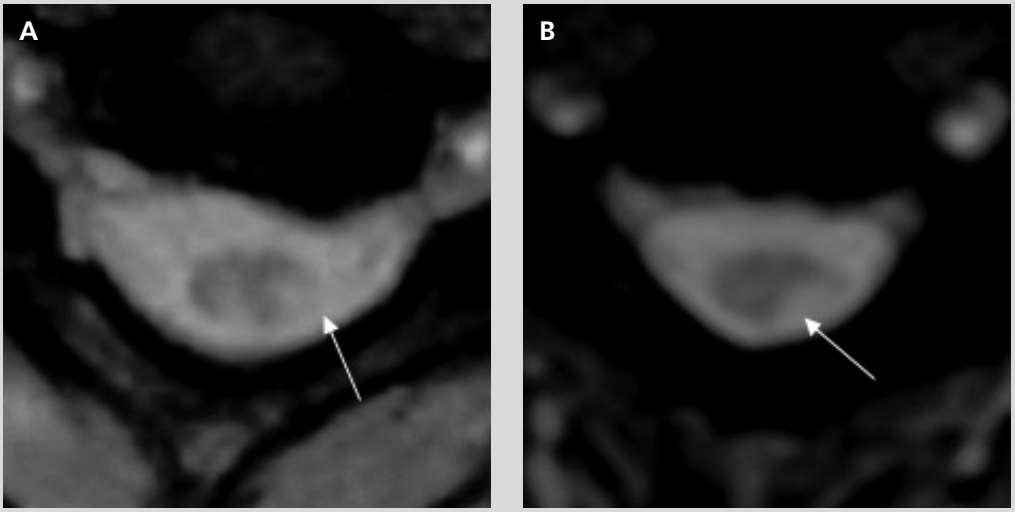

FIGURE 3.6 **Left posterio-lateral T2 high signal areas in cervical cord. (A) Axial gradient echo and (B) T2 weighted sequence.**

to their resting state. Measurements of this relaxation phase are used to create images. Two relaxation times, T1 (longitudinal) and T2 (transverse), are important when using conventional magnetic resonance technology for the imaging of MS lesions. Contrast is influenced by the selected weighting of these relaxation times. T1 weighting uses a short delay between pulses, whereas T2 weighting uses a longer delay; this accentuates the differences in T2 relaxation time. Those abnormalities seen with conventional MRI that are most often used to determine disease activity in patients with MS are hyperintense lesions visualized on T2-weighted images, hypointense lesions visualized on T1-weighted images, and gadolinium-enhanced (Gd^+) hyperintense lesions visualized on postcontrast images (Boxes 3.5, 3.6, and 3.7).

Contrast-Enhanced Magnetic Resonance Imaging Contrast-enhanced MRI visualizes lesions in more detail. Varieties of gadolinium-DTPA enhancements include uniform, focal homogenous, and ring enhancement (complete and incomplete):

- Enhancement shows the earliest detectable changes in the development of new lesions; it lasts for 2 to 8 weeks, rarely more than 2 months.
- Contrast-enhanced MRI can detect cortical lesions previously unrecognized by standard MRI because the blood supply to the cortex is four times that of the white matter.
- Simultaneous finding of both enhancing and nonenhancing lesions increases the likelihood that the lesion is due to MS and might be taken as evidence for lesions of different ages (dissemination in time).
- Following steroid treatment, a strong suppression of enhancing lesions occurs, which correlates with a decrease in myelin breakdown products as well as with clinical remission.
- β-Interferons suppress enhancement in a dose-dependent level; this effect is usually seen as early as the second month of starting therapy.

Magnetic Resonance Imaging and Disease Course In relapsing-remitting MS (RR-MS), brain abnormalities consist mainly of focal lesions on T2-weighted images.

BOX 3.5
Characteristic brain MRI features in MS:

- Asymmetrical
- Periventricular region more common than peripheral
- Brainstem surface more common than deep branch
- Lesions abut inner surface of corpus callosum
- Ovoid (right-angle) lesions
- Cerebellar peduncle and cerebellum
- T1-hypointense lesions
- Enhancing lesions (ring, rim, or solid)
- Mixed, enhancing and nonenhancing
- Generalized atrophy, but central atrophy more common than peripheral atrophy
- Minority of lesions show mass effect

BOX 3.6
Clinical guidelines for brain and spinal cord MRI in MS (MRI protocol for the diagnosis and follow-up of MS and CMSC [Traboulsee, Li and, Paty]):

Suspected MS:

- Baseline evaluation
  - Brain MRI recommended (with gadolinium)
  - Spinal cord MRI if presenting symptoms are at the level of the spinal cord and have not resolved, or if the brain MRI is nondiagnostic
- Follow-up evaluation:
  - Brain MRI recommended to demonstrate new disease activity

Established MS indications:

- Baseline evaluation
  - Brain MRI recommended (gadolinium optional)
- Follow-up of MS
  - Unexpected clinical worsening
  - Reassessment of disease burden before starting disease-modifying therapy.
  - Suspicion of a secondary diagnosis

KEY POINTS

- Persistent hypointense T1-weighted images correlate more closely with disability than do T2-weighted images; these are known as *black holes*.
- T2 hyperintensities can be due to edema, demyelination, or severe destructive changes.
- T1 is used to define anatomy, detect enhancing lesions, and define black holes.

KEY POINTS

- The frequent involvement of the corpus callosum is due to lesions spreading from the ventricular surface along the ependymal veins that project into the adjacent white matter.
- A negative brain MRI cannot independently exclude a diagnosis of MS; some patients with well-characterized MS have lesions only in the spinal cord.
- MRI is not a prerequisite for the diagnosis of MS in both the Poser and McDonald criteria.

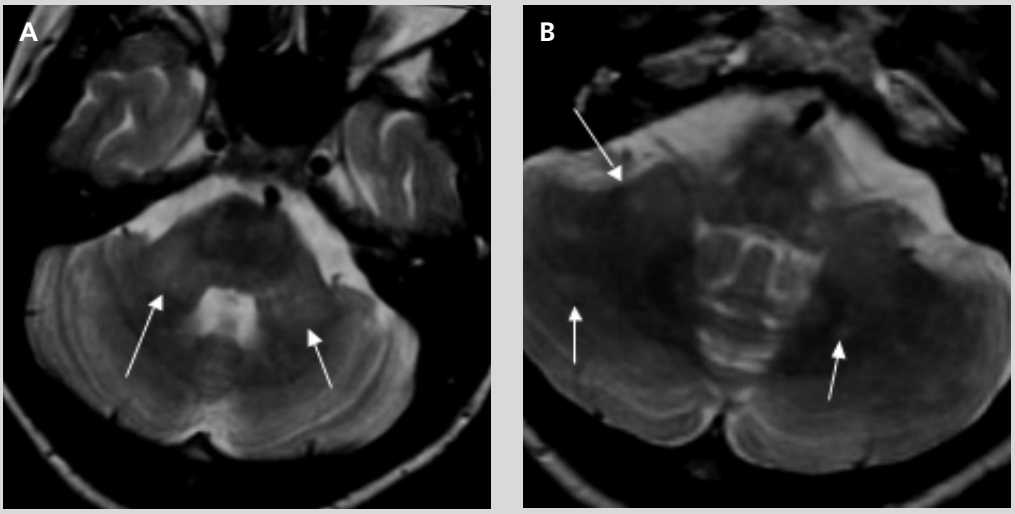

FIGURE 3.7 **Axial section with T2 high signal intensity areas in bilateral cerebellar penduncles and cerebellum.**

In secondary progressive MS (SP-MS), MRI reveals many more lesions, which tend to be larger, and a larger proportion of these lesions are hypointense on T1-weighted images; brain atrophy is more pronounced.

In primary progressive MS (PP-MS), MRI often shows few brain lesions, and brain atrophy is less pronounced when compared with SP-MS patients. Apart from differences in the amount of focal lesions, abnormalities in the normal-appearing white matter are more pronounced in SP-MS and PP-MS when compared to RR-MS (Boxes 3.8 and 3.9).

BOX 3.7
Conventional MRI

MRI Technique	Pros and Cons
T2-weighted MRI	Marker of inflammation High sensitivity in detecting new lesions Low correlation with pathological specificity Poor correlation with disability Difficult to distinguish between edema, gliosis, demyelination, and axonal loss
FLAIR	Eliminates the usual intense, confounding signal of normal CSF Improves conspicuity of subcortical and cortical lesions Less optimal for lesions in the posterior fossa and spinal cord
T1-weighted MRI	More pathologically specific of tissue destruction than T2-WI Time-consuming and hard to reproduce
Gd+ T1-weighted MRI	Marker of BBB integrity Identifies the early inflammatory phase of a lesion Measures inflammation and demyelination Permits differentiation of active and inactive lesions

BOX 3.8
Newer MRI techniques

MRI Technique	Pros and Cons
Magnetization-transfer MRI (MT-MRI)	More pathologically specific than conventional MRI Measure damage to myelin and axonal damage Reflects brain matrix disorganization and provide indirect measure of its integrity or destruction
Diffusion-weighted MRI	Quantifiable imaging method Useful in assessing cerebral white matter disorders Can indicate demyelination through loss of fiber orientation Can indicate irreversible axonal loss Technically challenging Sensitive to patient's motion
Magnetic Resonance Spectroscopy (MRS)	More pathologically specific Allows quantification of chemical pathology within lesions and NAWM Measure extent of axonal injury or loss in white matter
Functional MRI (fMRI)	Shows good spatial resolution Shows cortical and subcortical gray matter structures Can be used to map regions of brain activation during motor tasks Can define abnormal patterns of activation in disease
Brain and spinal cord atrophy	Marker of axonal loss Important in assessing PP-MS Good correlation with cognitive dysfunction (brain) and physical disability (spinal cord)

BOX 3.9
Spinal-cord imaging in MS:

- Asymptomatic spinal-cord lesions are very rare in disorders other than MS.
- Presence of asymptomatic spinal lesions may help confirm a diagnosis of MS when few or no brain lesions are present, especially in PP-MS.
- Contrast-enhancement of MS lesions is rarer in the spinal cord than in the brain and, when it is seen, it is commonly in conjunction with new clinical symptoms.
- Diffuse cord abnormalities are associated with spinal symptoms, high disability, and a primary progressive disease course.
- Prevalence of cord abnormalities in established MS is quite high (74%–85%) and depends on the imaging method used and the group of patients. In clinically isolated syndromes, the prevalence of spinal-cord lesions is lower, especially if no spinal-cord symptoms are present (30%–40%).

CEREBROSPINAL FLUID EXAMINATION

Examination of the CSF (Boxes 3.10 and 3.11) has had a role in MS diagnosis for more than eight decades. In areas where MRI is easily accessible, the role of CSF examination has declined. However, because many patients are overdiagnosed using only MRI, lumbar punctures (LPs) are still indicated. In places with more difficult MRI access, CSF examination is practiced frequently. Although facilities for proper oligoclonal band (OCB) testing are difficult to find in developing countries (where MRI is also difficult to obtain), the use of general

BOX 3.10
CSF examination usually includes:

- Cell count and differentials.
- Protein and sugar concentrations.
- Immunoglobulins testing (oligoclonal bands [OCBs] and/ or IgG index)

KEY POINTS

- Because CSF adds a different kind of information—about inflammation and immunologic disturbance—it may be useful in situations in which the clinical picture is unusual or the imaging criteria for the diagnosis are not fulfilled.
- The demonstration of OCBs in the CSF but not serum, or of additional bands in the CSF despite abnormalities in serum, provide clear evidence that an intrathecal immunologic process is taking place.
- The absence of OCBs should lead to a careful reassessment of the evidence for the diagnosis.
- A positive CSF is not necessarily needed for the diagnosis of PP-MS according to the revised McDonald criteria.
- OCBs are positive in more than 90% of clinically definite "western" MS; it is less often reported in MS patients from other parts of the world, especially in those from Japan and the Arabic peninsula, even when the tests are done in reputable laboratories.

KEY POINTS

- Once OCBs are present in MS, they persist; disappearance makes the diagnosis highly unlikely.
- The neurologist has an obligation to ensure that CSF analysis is being done in the most reproducible fashion, using state-of-the-art technology. Failure to do so might result in unreliable measurement and lead to incorrect diagnosis.
- CSF findings outside the expected range should alert the clinician to consider alternative diagnoses.

BOX 3.11
Recommendations for CSF analysis in MS:

- The single most informative analysis is a qualitative assessment of CSF for IgG, best performed using IEF together with some form of immunodetection (blotting or fixation).
- This qualitative analysis should be performed using unconcentrated CSF and must be compared directly with a serum sample run simultaneously in the same assay in an adjacent track.
- CSF reports of qualitative analysis should be made in terms of one of the five recognized staining patterns of oligoclonal banding.
- Interpretation should be made by an individual experienced in the technique used.
- Neurologists must consider the results of all other tests performed as part of the CSF panel (e.g., cell count; protein, glucose, and lactate levels; and others).
- In certain cases, an evaluation using light chains for immunodetection can help to resolve equivocal oligoclonal IgG patterns.
- Consideration should be given to repeating the lumbar puncture and CSF analysis if clinical suspicion is high but results of CSF are equivocal, negative, or show only a single band.
- Quantitative IgG analysis (IgG index) is an informative complementary test but is not considered a substitute for qualitative IgG assessment, which has the highest sensitivity and specificity.

CSF analysis might help in the diagnostic process, when used in addition to clinical expertise.

Abnormality on CSF analysis aims at providing evidence for the immune and inflammatory nature of lesion(s). This is especially helpful when imaging criteria fall short, when they lack specificity (as in the older patient), or when the clinical presentation is atypical. CSF analysis does not provide information about dissemination of lesions or events in time or space (Box 3.12).

Cell Count and Biochemistry The cell count should be performed no later than 2 hours after obtaining the CSF; otherwise, changes in cell shape may hamper the ability to offer a correct and full differential cell count. A red blood cell count that is too high (5×10^9/L to 7×10^9/L) probably indicates a traumatic tap, rendering other quantitative measurements possibly uninterpretable. Higher than normal (N) ($N < 5 \times 10^6$/L) WBC counts are found in one-third of MS cases, very high CSF WBC counts ($> 50 \times 10^6$/L) are unusual in MS, whereas modest pleocytosis of 5 to 20 cells $\times 10^6$/L is frequent. In MS, lymphocytes usually make up to 90% and polymorphonuclear cells < 5% of the total cell count.

Low CSF glucose levels (when compared with serum, the CSF/serum ratio is < 0.4) and very high total protein content (e.g., > 1 g/L) are more consistent with an infectious or neoplastic process. Lactate, where available, is a good substitute and has an advantage over paired CSF–plasma glucose measurements in that only a single CSF measurement is required. Total protein is normal in about two-thirds of patients, but modestly elevated (0.5 to 0.7g/L) in the remainder. It is said to reach 1 g/L in less than 1% of MS patients (always in advanced cases with enlarged ventricles).

Immunoglobulins G Testing Isoelectric focusing (IEF) on agarose gels followed by immunoblotting should be the gold standard for detecting the presence of OCBs. Other methods, such as polyacrylamide gel combined with IEF and silver staining of proteins, might have proved useful in the past, but they lack specificity for IgG (Box 3.13).

Rarely will quantitative IgG analysis (IgG index) findings be elevated in the absence of OCBs, whereas the converse is commonly true. Thus, when the clinical suspicion is

BOX 3.12
CSF testing is particularly helpful in:

- Older patients who might present with late-onset progressive syndrome or with late presentation after first developing symptoms in which brain MRI changes might be related to age
- Patients with progressive myelopathy and equivocal brain and cord imaging

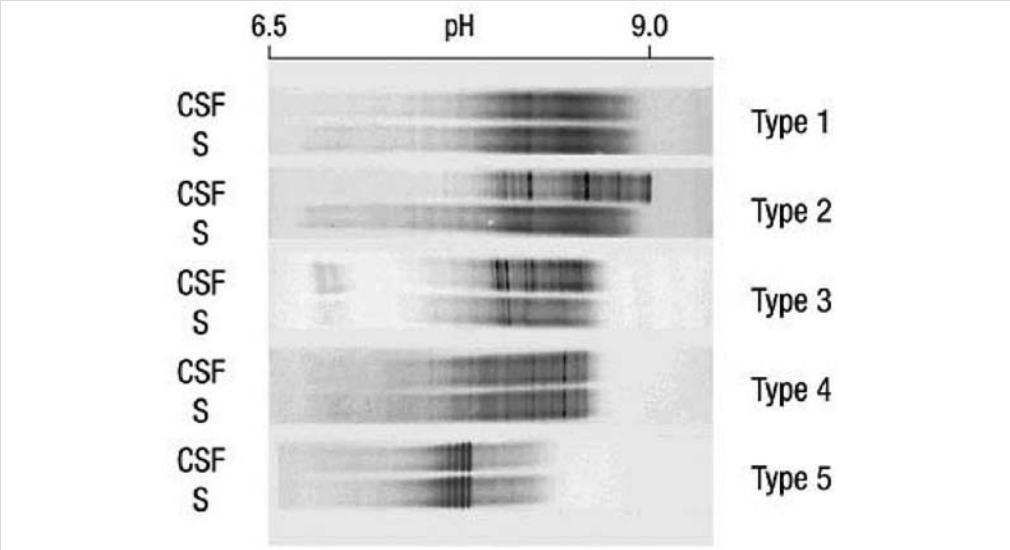

FIGURE 3.8 **Isoelectric focusing on agarose gels with immunoblotting. Note that all the OCBs present are due to IgG. There are five classic patterns: type 1, no bands in cerebrospinal fluid (CSF) and serum (S) sample; type 2, oligoclonal IgG bands in CSF, not in the S sample, indicative of intrathecal IgG synthesis; type 3, oligoclonal bands in CSF (like type 2) and additional identical oligoclonal bands in CSF and the S sample (like type 4), still indicative of intrathecal IgG synthesis; type 4, identical oligoclonal bands in CSF and the S sample illustrative of a systemic not intrathecal immune reaction, with a leaky or normal or abnormal blood–CSF barrier and oligoclonal bands passively transferred in the CSF; and type 5, monoclonal bands in CSF and the S sample; this is the pattern seen owing to the presence of a paraprotein (monoclonal IgG component). From Freedman MS, Thompson EJ, Deisenhammer F, et al., the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003;61(5):602–611, with permission.**

high and the test comes back negative for local synthesis of OCBs, this should be an alert to the clinician to reassess the case. More times than not, a negative test result is more likely to point to another disease than to be falsely negative (Figure 3.8).

BOX 3.13

Other possible causes of positive OCBs in CSF are:

- CIDP
- Collagen vascular disease
- Acute and chronic inflammations of the brain and meninges
- Paraneoplastic syndromes

EVOKED POTENTIALS

Evoked potentials (EPs) (Box 3.14) have been used in MS assessment for more than four decades. With the advent of MRI, the clinical diagnosis and monitoring of MS patients no longer requires routine EPs. Nonetheless, they may provide additional support, particularly in situations in which MRI abnormalities are few (e.g., in patients with primary progressive MS with progressive myelopathy) or when the MRI abnormalities have lesser specificity (e.g., in older individuals with risk factors for ischemic disease or in individuals with abnormal radiologic findings that do not satisfy the MRI specificity criteria for diagnosis) (Box 3.15).

The commonly used EPs in clinical practice are:

KEY POINTS

- The principal contributions of evoked potentials are in answering the questions: Is a clinically silent lesion present? Is the process of demyelination present?
- The role of EPs in the assessment of MS has largely been replaced by MRI.
- The identification of clinically unsuspected lesions is one major reason clinicians use EPs in suspected cases of MS.
- EP abnormalities are not always pathognomic of demyelination and, as with all laboratory investigations, must be analyzed in the context of the clinical findings and other test results.

KEY POINTS

- EPs can be useful to support the history of a previous relapse, optic neuritis (VEP), transverse myelitis (SSEP), or a brainstem relapse (BSAEP).
- VEP with substantial delay and a well-preserved waveform is characteristic of demyelination.
- Apart from VEP, the other EPs contribute little to the diagnostic process of MS.

BOX 3.14
Advantages of EPs:

- Objective
- Often more sensitive than detailed neurologic examination
- Can be recorded in patients who are anesthetized or comatose

Disadvantages of EPs:

- Rarely disease-specific and can be confounded by end-organ disease (for example, VEPs may be abnormal in ocular disease, SSEPs in patients with peripheral neuropathy, and BSAEPs in conductive and sensorineural deafness)
- Affected by age
- Require a degree of patient cooperation to obtain artifact-free recordings

BOX 3.15
The clinical utility of evoked potentials (EPs) is based on their ability to:

- Demonstrate abnormal sensory system conduction, when the history and/or neurologic examination is equivocal
- Reveal subclinical involvement of a sensory system ("silent" lesions), particularly when demyelination is suggested by symptoms and/or signs in another area of the central nervous system
- Help define the anatomic distribution and give some insight into the pathophysiology of a disease process

- Visual evoked potentials (VEPs)
- Somatosensory evoked potentials (SSEPs)
- Brainstem auditory evoked potentials (BSAEP)

Visual Evoked Potentials The standard technique of VEP stimulation (Figure 3.9) is to use a checkerboard pattern of black and white squares (pattern reversal stimulation) that occupy 32 degrees of the field. For special purposes, half-field and central-field stimuli are invaluable.

The normal pattern reversal–induced visual evoked potential is dominated by a large positive wave at approximately 100 ms. After optic neuritis, the classic findings are a delayed response (prolonged latency) and preservation of the waveform with almost normal amplitude. This delay persists in about 90% of adults, although the latency may decrease, sometimes reverting to normal. Occasionally, the latency from the affected eye remains within normal limits. In these circumstances, the observation of a pathologic latency difference between the eyes (different in different laboratories) may be diagnostically helpful.

A delay does not necessarily mean demyelination. Demyelination might have other causes, such as compression of the optic nerve. The cause of the demyelina-

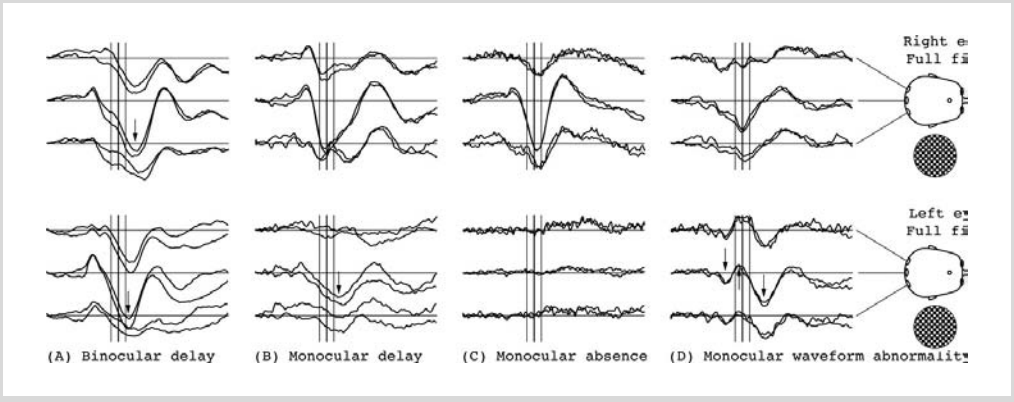

FIGURE 3.9 **Full-field monocular pattern reversal VEPs in four patients illustrating common forms of abnormality. From Walsh P, Kane N, Butler S. The clinical role of evoked potentials. *J Neurol Neurosurg Psychiatry* 2005;76:ii16–ii22, with permission.**

tion must be established from a consideration of the rest of the clinical and investigative picture.

Anything that impairs conduction in the retino-striate pathway is likely to give rise to abnormalities in the latency, amplitude, or waveform of the VEPs. The sensitivity of VEP to clinical disorders depends on the technique used to evoke them.

Abnormal VEP, typical of MS can be used to supplement information provided by a clinical examination to provide objective evidence of a second lesion, provided that the only clinically expressed lesion did not affect the visual pathway. Correct interpretation is essential (Box 3.16).

BOX 3.16

Other neurologic causes of abnormal VEP are:

- Familial ataxia (including Friedreich ataxia)
- Adrenoleukodystrophy
- Traumatic brain injury
- Toxic and nutritional causes, including B_{12} deficiency and alcohol–tobacco amblyopia
- Optic atrophies
- Compressive lesions affecting the visual pathway
- Sarcoidosis

Somatosensory Evoked Potentials SSEPs (Figure 3.10), elicited from the upper and lower limbs within 30 ms and 60 ms, respectively, of percutaneous electrical stimulation, are considered to be the result of action potentials and synaptic potentials from successive anatomic neural generators within the dorsal–lemniscus thalamic–cortical sensory system. After peripheral nerve stimulation, the resultant responses can be recorded from electrodes placed over the peripheral nerves. In the upper limbs, these compound nerve

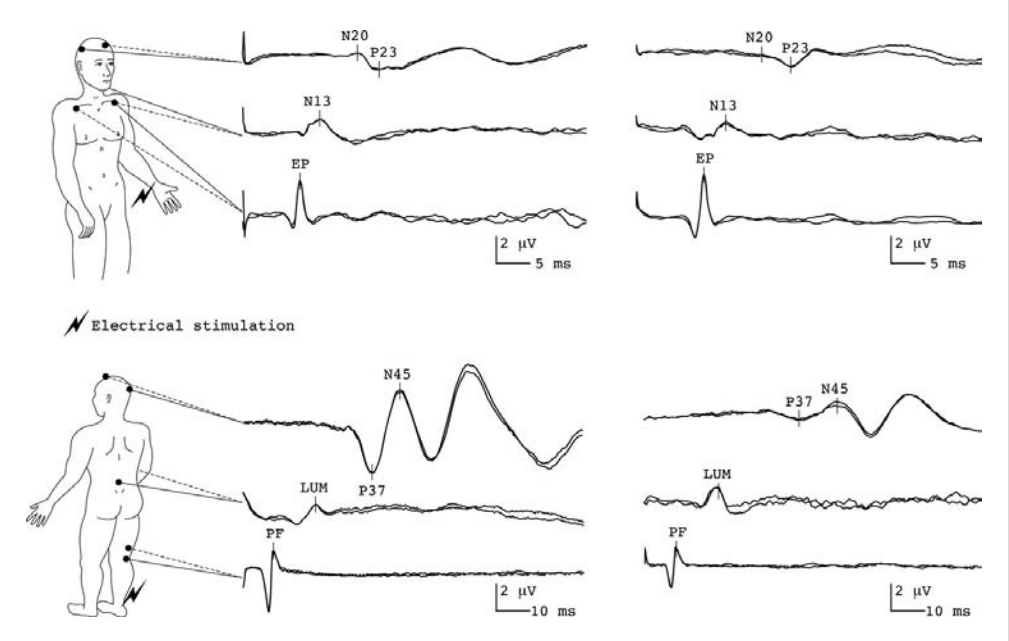

FIGURE 3.10 **Left side: Normal short latency somatosensory evoked potentials (SSEPSs) after stimulation of the median nerve (*top picture*) and posterior tibial nerve (*bottom picture*). Right side: Top picture shows normal median nerve SSEPSs, whereas the scalp potentials from the posterior tibial nerve (*bottom picture*) show a dispersed P37 potential with a prolonged latency. From Walsh P, Kane N, Butler S. The clinical role of evoked potentials. *J Neurol Neurosurg Psychiatry* 2005;76:ii16–ii22, with permission.**

action potentials are routinely recorded from the brachial plexus at Erbs point and in the lower limbs in the popliteal fossa after stimulation of the posterior tibial nerve at the ankle. The postsynaptic electrical activity from the complex synaptic arrangements within the spinal grey matter gives rise to a stationary potential that is recorded over the spinal segments of the nerve being stimulated. The upper-limb cervical potential is seen with a negativity over the neck posteriorly, at a latency of around 13 ms (and therefore called N13). The corresponding N22 reflects the activity coming from the spinal segments that receive the posterior tibial nerve. On the scalp, the cortical median N20 and tibial P37 responses are recorded from the contralateral hand area and the vertex, respectively, reflecting the cutaneous input to the primary somatosensory cortex.

When demyelination occurs within the central fibres of the dorsal column–medial lemniscal pathways, it leads to a delay or even an absence of the SSEPs. Such findings are said to be present in about 80% of patients with MS who do not have sensory symptoms or signs. An increase is noted in the diagnostic yield in those patients with sensory involvement, particularly from the SSEPs following stimulation of the lower limbs, which is probably due to the longer length of white matter that is being assessed. When the responses from the lower limbs are normal, the upper-limb responses will show additional abnormalities in less than 10% of the patients studied. It is, however, worth stimulating all four limbs, because the abnormalities may only affect one side in one-third of the patients studied.

SSEPs often also are abnormal in a variety of other conditions; therefore, they are sometimes used in theses diagnoses, including neurogenic thoracic outlet syndrome, myeloradiculopathies, Friedreich ataxia, hereditary spastic paraplegia, and leukodystrophies, together with infarctions and tumors of the spinal cord, brainstem, and thalamus.

Brainstem Auditory Evoked Potentials

In BSAEP (Figure 3.11), after auditory stimulation using clicks, a sequence of five peaks usually are recorded from an electrode placed over the vertex. These are referenced

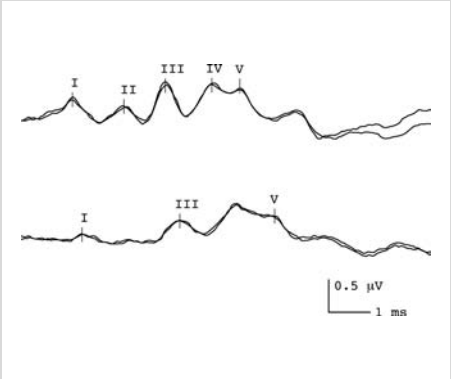

FIGURE 3.11 **Upper trace: Normal brainstem auditory evoked potentials (BSAEPs) following alternating click stimulation. Lower trace: Abnormal BSAEPs in a patient with an acoustic neuroma showing poorly formed waveforms with prolonged I–III interpeak latencies and subsequent I–V inter-peak latency. From Walsh P, Kane N, Butler S. The clinical role of evoked potentials. *J Neurol Neurosurg Psychiatry* 2005;76:ii16–ii22, with permission.**

to the ipsilateral mastoid. The compound action potential in the distal portion of the eighth nerve elicits wave I, whereas the proximal portion of the nerve, along with a contribution from the ipsilateral cochlear nucleus, generates wave II. Wave III is generated within the lower pons and probably represents multiple generators, because the signal passes from the ipsilateral cochlear nucleus to the ipsilateral superior olivary complex and, via the trapezoid body, to the superior olives contralaterally. The fibre tracts and nuclei responsible for the IV–V complex include the lateral lemniscus and contralateral inferior colliculus in the lower midbrain.

Interpretation of the BSAEPs usually involves measuring the absolute latency of the three most prominent vertex positive peaks—I, III, and V—along with an analysis of their relative interpeak latencies (IPLs), which may provide some anatomic localization of lesions. Conduction through the eighth nerve and the caudal brainstem is represented by the I–III IPL, whereas the III–V IPL probably represents transmission

through the rostral brainstem and midbrain.

The BSAEPs are more likely to be abnormal when demyelination affects the brainstem clinically, but they also can detect "silent" lesions in reportedly about 40% of patients who do not have symptoms or signs of brainstem involvement.

As with SSEPs, the electrophysiologic abnormalities are not pathognomonic of MS, but the BSAEPs are less sensitive and specific than are the SSEPs.

BSAEP abnormalities have been described in olivo-ponto-cerebellar-atrophy (OPCA), Friedreich ataxia, hereditary cerebellar ataxia, central pontine myelinolysis, hydrocephalus, subarachnoid hemorrhage, and the leukodystrophies, together with neurodegenerative and neuropathic disorders.

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CHAPTER 4

THE DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS IN MULTIPLE SCLEROSIS

Martin A. Lee, BM, BCh, MA, MRCP, DPhil and Jackie Palace, BM, DM, FRCP

KEY POINTS

- MS remains a clinical diagnosis.
- No better alternative diagnosis must exist.

Multiple sclerosis (MS) is a relatively common inflammatory condition of the central nervous system (CNS), with onset typically occurring during the third to fourth decade. The absence of a definitive test, wide variability in presentation, and the need for clinical trials has encouraged the development of clinical guidelines to help establish the diagnosis. These guidelines have been revised over time, most recently to incorporate modern imaging techniques and progressive forms of the disease, although the fundamental principle of requiring evidence of dissemination of lesions in time and space within the CNS in the absence of a better alternative diagnosis remains. This is particularly important in the era of magnetic resonance imaging (MRI), which may provide visually compelling but potentially misleading information if viewed in isolation from the clinical history. A large number of disorders may potentially mimic MS, and more extensive investigation is required in cases with atypical features. Here, the diagnostic criteria are reviewed together with conditions that may imitate MS.

DIAGNOSTIC CRITERIA FOR MS

Guidelines developed by an international panel (the McDonald criteria) on MS extend the previous Poser and Schumacher diagnostic criteria and have included a welcome simplification in the outcome of diagnostic evaluation at any one time into the categories MS, possible MS, and not MS. A diagnosis of MS continues to require objective evidence of dissemination of lesions typical of MS in both time and space. This places considerable importance on MRI in the diagnostic process fueled, in part, by its sensitivity to pathologic change and its widespread use in research and clinical trials. Few would argue, however, that the diagnosis of MS does not remain a primarily clinical one. Indeed, the diagnostic guidelines continue to allow a diagnosis of MS to be made on clinical criteria alone; that is, on a history of two attacks and objective evidence of at least two separate lesions occurring within the CNS for which no better explanation exists, with at least 30 days between attacks. It is acknowledged that in practice, however, scanning often is performed in this situation as a confirmatory measure.

The previous Poser criteria allowed historical information to be substituted for clinical evidence of one of the two lesions if the information was reliable, typical of MS, and not otherwise explainable. This option frequently was used in the clinical setting when a patient presented with a second episode typical of MS in the context of a history of a previous plausible episode and clinical signs of the most recent lesion. It was suggested that, where possible, corroboration of the previous episode always be sought from medical notes or family and the substitution made with caution. The current recommendations suggest that, with a history of two attacks but signs of only a single lesion, additional MRI evidence be required of dissemination in space. MRI is pre-eminent in defining the presence of multiple lesions and also aids in the exclusion of alternative diagnoses, particularly when signs are consistent with a single lesion. The criteria selected to define MRI brain abnormality in MS or dissemination in space (Box 4.1) attempt to balance sensitivity and specificity, although they are based on a relatively small data set and have not been unchallenged. Nevertheless, these criteria currently provide a benchmark and set the bar at five disseminated white matter lesions in the presence

KEY POINT

- In clinical practice, reliable historical data may be used as evidence of a second clinical lesion, especially when supplemented by paraclinical tests.

BOX 4.1
McDonald criteria for dissemination in space (one of the following):

Clinical evidence of two lesions

Or

Clinical evidence of a single lesion plus one of the following:

A: MRI—Three of the following:
A Gd-enhancing lesion or nine T2-hyperintense lesions
At least one infratentorial lesion
At least one juxtacortical lesion
At least three periventricular lesions

Or

B: Two or more lesions consistent with MS
Plus CSF oligoclonal bands

(*Note:* one spinal cord lesion can be substituted for one brain lesion but not a juxtacortical or periventricular lesion.)

of an infratentorial lesion or nine without an infratentorial lesion, in those cases where no gadolinium-enhanced lesion is present. In situations in which clinical evidence is inadequate and MRI is not available, the Poser criteria (Box 4.2) are likely to remain relevant, allowing a second lesion to be defined using other paraclinical tests (of which visual evoked potentials [VEPs] are the main alternative tool). If paraclinical evidence is not available to provide objective evidence, little may be lost by clinical follow-up to allow examination during a subsequent attack (Case 1).

Perhaps the greatest revision in the McDonald criteria is the use of MRI to potentially allow a diagnosis of MS in patients presenting with a first attack or clinically isolated syndrome (CIS). Here, a temporally dissociated second lesion is determined by demonstrating a new lesion unrelated to the original clinical episode. This sounds acceptable, but the devil here is in the detail because of the differing temporal dynamics of gadolinium enhancement and T2 lesions. The criteria require the demonstration of a new T2 lesion at least 1 month or more after the first clinical attack (recently revised down from 3 months). This requires a baseline scan at least 1 month after the initial clinical episode and a further follow-up scan showing a new T2 lesion not present on the baseline scan (Box 4.3). Alternatively, a single gadolinium-enhancing lesion at least 3 months after the clinical episode also confirms a new lesion; this potentially requires only a single scan. In addition, the MRI criteria for dissemination in space should also be met. Perhaps surprisingly, the concept of making a diagnosis of MS after a single attack using paraclinical tests is not a new one. The Poser criteria allowed a diagnosis of laboratory-supported definite MS to be made after a single attack, when objective clinical evidence existed in the presence of cerebrospinal fluid (CSF) oligoclonal bands, and paraclinical evidence of a new separate

BOX 4.2
Poser criteria for the diagnosis of clinically definite MS and laboratory-supported definite MS

	History clinical relapse	Clinical evidence of (number of lesions)	Para-clinical lesions	CSF OCBs[a]
Clinically definite MS	2[b]	2[c]		
	2[b]	1 and	1 or more	
Laboratory-supported definite MS	2[b]	1 or	1 or more	+
	1	2[d]		+
	1	1[d] and	1[d] or more	+

[a]Unmatched or less intense in serum
[b]Two clinical relapses involve lesions at different times and different sites.
[c]Can substitute clinical signs of one episode with strong typical historical information.
[d]Evidence of two different lesions separated in time (that is, both not present initially).

CASE 1

A 29-year-old female hairdresser presents complaining of painful visual loss in the left eye, developing over 24 hours. She described her vision as if looking through dirty glass. On direct questioning, she remembers an episode when her left hand and face became numb 3 years ago. The episode lasted only 4 days, and she saw no one about it. On examination, she has a left relative afferent defect, a normal-looking optic disc, and a central scotoma. The rest of the neurologic examination is unremarkable.

Discussion

- This patient has a history of two attacks and clinical signs of a single lesion. It is likely that her brain MRI scan will show discrete white matter lesions. This investigation is recommended (where available) under the current diagnostic criteria for confirming dissemination of lesions in space and a diagnosis of MS in this situation. It would also help to exclude an alternative diagnosis, such as a compressive lesion.
- If the MRI were positive, additional investigations are probably unnecessary in view of the typical history.
- The prognosis for visual recovery is good.
- A diagnosis of MS does not necessarily allow a more accurate prognosis to be given at this stage; the greatest predictor of disability is the onset of progressive disease.
- A follow-up appointment to document visual recovery, discuss the results of the scan, and provide further information should be made. If MS is diagnosed, the patients should be offered contact with an MS nurse.

lesion could be demonstrated at least 1 month downstream (such as a VEP change; see Box 4.2). The diagnosis of MS after a first attack may become increasingly important if early disease-modifying therapy is shown to delay or slow the progressive phase of the disease. At present, the therapeutic advantages of early diagnosis are debatable, and many clinicians may choose to await a second clinical episode.

Well-recognized qualitative as well as quantitative issues also exist in diagnosing MS, and defining an MS attack may not always be straightforward. Typically, symptoms evolve over a few days, persist for a few weeks, then improve, but a minimum requirement of 24 hours is generally accepted. Symptoms suggesting optic nerve, brainstem, or cord lesions are more specific than are transient distal sensory symptoms. The need for investigation following less specific symptoms, such as a single sensory episode, must be made on a case-by-case basis. Other MS symptoms such as Lhermitte and Uhthoff phenomena and stereotypic short-lived but multiple paroxysmal tonic spasms in an appropriately aged patient are likely to prompt investigation for MS. Fatigue is a common complaint in MS, but is nonspecific and rarely a presenting or isolated feature. When it does occur, depression commonly coexists. Distinguishing MS from depression-associated fatigue may be difficult. MS

BOX 4.3

Revised McDonald criteria for evidence of dissemination in time

History of at least two attacks

Or

History of a single attack plus one of the following:

A: A new T2 lesion on MRI scan demonstrated at least 1 month after the initial clinical event (requires two scans; a baseline scan 1 month after the first attack and a second follow-up scan)

Or

B: A new T1 gadolinium-enhancing lesion on MRI scan at least 3 months after the initial clinical event (requires a single scan only after 3 months)

KEY POINT

- Brain MRI is abnormal in 95% of patients with established MS.

fatigue is characteristically activity-induced, worse as the day goes on, exacerbates MS symptoms and signs, and is alleviated by a short period of rest. Features suggestive of lesions outside the white matter tracts, such as aphasia, seizures, and meningeal symptoms, may occur in MS but are unusual and should prompt a search for an alternative diagnoses.

It should be highlighted that the current McDonald diagnostic criteria are based on patients presenting with typical symptoms; these criteria define the minimum evidence required for a strict diagnosis of MS as used widely in research protocols and clinical trials. In clinical practice, their application often is relaxed, and a working diagnosis of MS may be acceptable when typical historical attacks occur in the absence of objective evidence (and where an alternative diagnosis is unlikely) and in the presence of typical but less stringent brain MRI abnormalities. Additional tests, such as VEPs and CSF analysis, are not always required by the diagnostic criteria but are often undertaken in older patients, in those with a progressive onset, or where MRI is nondiagnostic or not available. Asymmetrically delayed VEPs provide evidence of demyelinating lesion(s) within the optic nerve and help distinguish MS from ischemic white matter pathology in older patients. CSF oligoclonal bands do not provide evidence of lesion dissemination but confirm an inflammatory pathology and make alternative diagnoses less likely.

The character and location, as well as the number, of white matter lesions has importance in defining a positive brain MRI scan in MS, particularly if less stringent MRI criteria are being adopted. Typical lesion locations relatively specific for MS include the corpus callosum, floor of the fourth ventricle, and cerebellar peduncles, in addition to classically located periventricular white matter lesions (Figures 4.1 and 4.2). Lesions are usually greater than 6 mm in diameter, ovoid, and perpendicular to the ventricular wall, pointing toward the cortex. Studies suggest the brain MRI scan is abnormal in 90% to 95% of patients with clinically definite MS, although it is not generally this group of patients that causes diagnostic difficulties. A normal scan, or abnormal scan in a patient with atypical clinical features, should prompt the search for an alternative diagnosis or supplemental support for a diagnosis of MS. Spinal cord MRI may be of considerable diagnostic value in these groups, of whom a significant proportion with MS will have spinal cord lesions. Spinal cord lesions also help distinguish between inflammatory and age-related or ischemic pathology in cases where brain MRI abnormalities are nonspecific (Case 2). Negative oligoclonal bands in established MS does occur, but are an unusual finding and should prompt further evaluation. Where access to paraclinical testing is limited, the diagnosis requires clinical confirmation of dissemination both in time and space and increased vigilance in screening for alternative diagnoses.

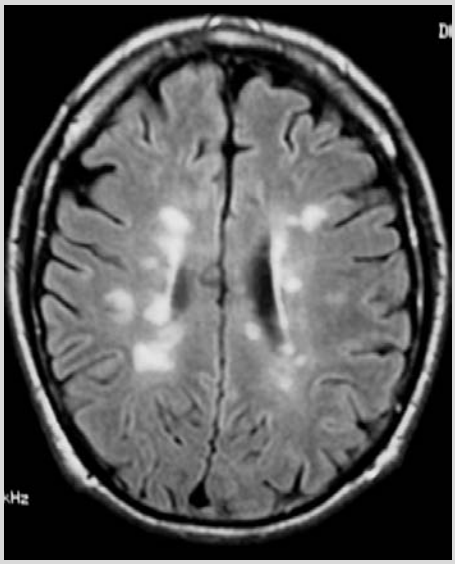

FIGURE 4.1 **Fluid-attenuated inversion-recovery (FLAIR) brain MRI showing typical periventricular white matter lesions in MS.**

POSSIBLE MS

A significant number of patients will fulfil some but not all of the diagnostic criteria and, in these patients, a definitive diagnosis cannot be made. A discussion with the patient about the prognosis may be informed by results of paraclinical tests,

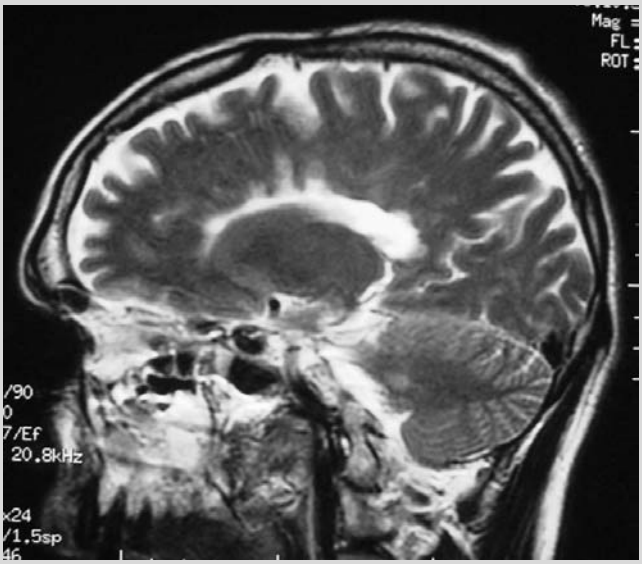

FIGURE 4.2 **Transverse callosal lesions in MS.**

CASE 2

A 65-year-old retired postman presents with a 2-year history of progressive gait disturbance, leg numbness, and urinary urgency. More recently, he has noticed some difficulty using his right hand. He is a smoker, has type II diabetes, and is taking an antihypertensive agent. On examination, power is relatively preserved, reflexes are exaggerated in his right arm and legs, and he has bilateral extensor plantar responses. His gait is spastic, and vibration sense is absent at the ankles. His brain MRI scan shows scattered supratentorial white matter lesions with a degree of atrophy. Spinal cord imaging shows an intrinsic cord lesion just above the C5/C6 level. A degree of cervical canal narrowing also is present at the C5/C6 level. Dynamic views do not demonstrate significant instability.

Discussion

- Distinguishing small-vessel ischemic lesions from inflammatory lesions on brain MRI can be difficult (Box 4.4). Inflammatory lesions are found transversely within the corpus callosum abutting the ependymal surface (see Figure 4.2) and are less likely to spare subcortical U-fibers. Ischemic lesions may show microhemorrhage on gradient echo sequences and involve deep nuclear gray matter, but a clear distinction may not be possible.
- Intrinsic spinal cord lesions (Figure 4.3) rarely occur with ischaemia and suggest an inflammatory pathology. Differentiating between spinal cord signal changes associated with mechanical cord impingement and that associated with MS is difficult where both may exist. The presence of CSF-specific oligoclonal bands and asymmetrically delayed VEPs suggests a diagnosis of MS.
- Marked bladder symptoms often occur early in intrinsic cord pathology such as MS but usually later in extrinsic compressive pathology.
- Repeat spinal cord imaging to exclude intrinsic cord tumour and demonstrate new discrete cord or brain lesions should be considered if the diagnosis remains in doubt.

KEY POINT

- Paraclinical tests may be used to provide evidence for the dissemination of a second lesion in time after a single attack.

BOX 4.4
Features distinguishing MS from age-related and vascular changes on brain MRI

MS	Ischemic/age-related change
Periventricular distribution	White and grey matter lesions including basal ganglia
Ovoid lesions long axis 90-degree to plane of lateral ventricles/point to cortex	
Subcortical lesions involve U-fibers	
Infratentorial lesions (brainstem/cerebellum)	
Corpus callosum lesions typical	Corpus callosum lesions rare
Spinal cord lesions common	Spinal cord lesions rare
Typical "open ring"-type gadolinium enhancement	Gadolinium enhancement rare
McDonald MRI criteria (Box 4.1)	

although some uncertainty is likely to remain. It is noteworthy that many patients pursue a definitive diagnosis in the belief that this will allow them to predict their future course. When they are made aware that a diagnosis of MS carries with it great variability regarding prognosis—and thus much uncertainty—patients are often less keen to pursue a diagnostic label. Clearly, the vigor with which the diagnosis is pursued may depend partly on the neurologist's view on the long-term advantages of disease-modifying drugs when initiated early on.

CLINICALLY ISOLATED SYNDROMES

The presence of an abnormal brain MRI at presentation in a CIS consistent with a first attack of MS increases the risk of conversion to MS over time. Studies suggest an approximate 80% risk of conversion to clinically definite MS at 10 years, although dropouts at follow-up make this a likely overestimate. Patients with a negative scan have an approximate 10% conversion risk at 10 years. In some cohorts, serum antibodies to myelin oligodendrocyte glycoprotein and myelin basic protein detected by Western blotting may be useful predictors of a short time to second relapse. The new diagnostic criteria allow an earlier diagnosis of MS to be made in patients with CIS by using follow-up MRI to define new lesion formation (see Box 4.3). The results of studies validating the accuracy of this additional diagnostic tool look promising, but longer-term follow-up is required. Their current primary use may be in identifying those with early MS for the purposes of clinical trials, although some argue that disease-modifying agents should be used in patients with CIS and high activity on MRI.

NEGATIVE TESTS

The brain MRI may be negative in 5% of patients with MS. This tends to occur early on in the course of relapsing-remitting disease or in primary-progressive patients in whom (it is thus assumed) spinal cord pathology predominates. Spinal cord imaging detects lesions in a significant proportion of these patients, and additional support for the diagnosis using oligoclonal bands and VEPs should be sought. The majority of patients with transient neurologic symptoms and negative investigations can be reassured that they don't have MS.

PROGRESSIVE DISEASE

The diagnosis of primary progressive MS requires an even greater emphasis on the exclusion of an alternative diagnosis because the clinical picture is less distinctive. The revised McDonald criteria provide specific provision for the diagnosis of MS in patients with progressive neurologic disease, but are understandably stringent. Dissemination in time and space is required by demonstrating

BOX 4.5
Current proposed criteria for the diagnosis of progressive MS:

Progression of disability over 1 year, *plus* two of the following:

- Positive brain MRI for dissemination in space (nine T2 lesions or four or more with positive VEPs)
- Two spinal cord lesions
- Positive oligoclonal bands

clinical progression over a year in the presence of spinal cord and brain MRI abnormalities (Box 4.5). CSF-specific oligoclonal banding is required if sufficient brain or spinal cord lesions are not present. VEPs may be substituted for up to five brain MRI lesions. However, these criteria are set as robust inclusion criteria for research protocols; in clinical practice some patients reasonably carry a working diagnosis of primary progressive MS after alternative causes are excluded, even when they don't totally fulfill all the criteria (Figure 4-4).

DIFFERENTIAL DIAGNOSIS IN MS

The diagnostic criteria have been developed to balance diagnostic precision with early diagnosis, and they are based on data primarily from patients with typical MS. Thus, these criteria must be applied with this in mind. Rates of MS misdiagnosis may run as high as 10%, even in dedicated MS clinics. Misdiagnosed patients risk both receiving inappropriate disease-modifying agents and missing out on effective therapy. Atypical clinical presentation and "red flag" features should prompt more extensive investigations for an alternative diagnosis, or at least careful follow-up until the picture becomes clear. The list of possible MS mimics is extensive and is classically categorized pathologically (see Table 4.1). In this chapter, we divide the differential diagnoses according to their clinical presentation, which may be practically more useful. In reality, the commonest differential dilemmas that arise include psychologically induced symptoms versus early relapsing-remitting MS, ischemic disease in the older patient, and other inflammatory

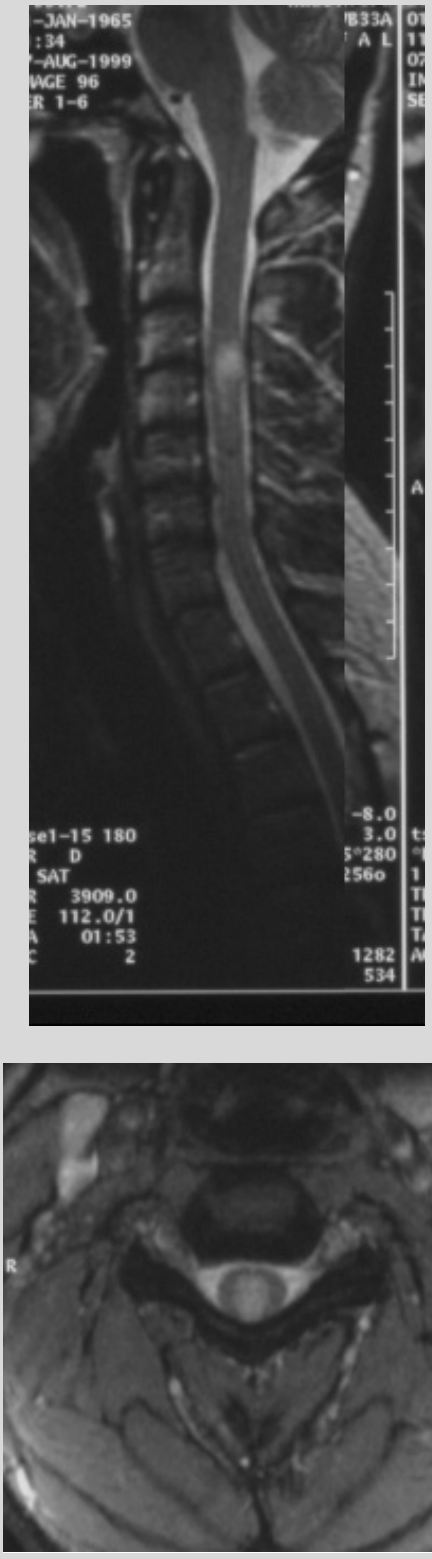

FIGURE 4.3 **Short cervical cord lesion in MS.**

KEY POINT

- "Red flag" features in MS:
  - Fever
  - Headache
  - Seizures
  - Meningism
  - Signs below the foramen magnum only
  - Absence of remission (especially in young)
  - Normal brain MRI
  - Absent oligoclonal bands
  - CSF pleocytosis > 10 lymphocytes
  - Raised ESR/systemic inflammatory markers

KEY POINT

- CSF-specific oligoclonal bands support an inflammatory etiology.

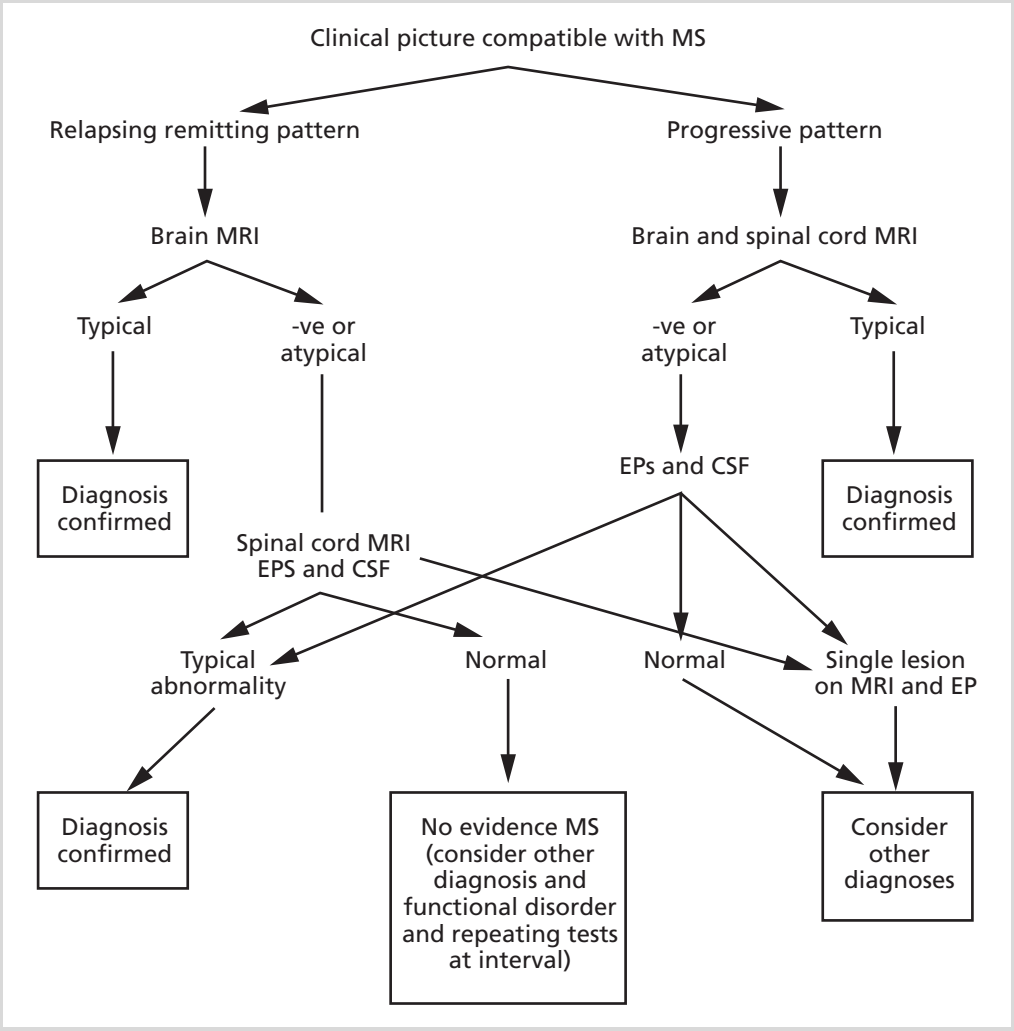

FIGURE 4.4 **MS diagnostic algorithm.**

cord conditions such as Sjögren syndrome, sarcoid disease, systemic lupus erythematosus (SLE), Devic's disease, and slow-growing intrinsic cord tumour.

Diseases with Multiple Lesions and a Relapsing Course

Cerebral Vasculitis Cerebral vasculitis may present with relapsing neurologic deficits including optic neuropathy and hemiparesis and can occur in isolation or associated with systemic disease. It is usually classified according to the size of the vessels involved. Associated neurologic features atypical for MS include headache, meningism, encephalopathy, seizures, and a rapidly progressive course. In addition, systemic enquiry may highlight weight loss, rash, arthropathy, and fever. Isolated or primary CNS vasculitis poses the greater diagnostic challenge, because systemic features and serologic markers usually are absent. The brain MRI may show supra- and infratentorial white matter lesions that resemble white matter plaques. A raised CSF protein level and lymphocytosis help to distinguish it from MS, but this is not a uniform finding. Angiographic abnormalities may help exclude MS, but usually only show changes with large- and medium-sized vessel vasculitis (i.e., those conditions usually

TABLE 4.1 Abbreviated Pathologically Categorized Differential Diagnosis of MS

MS variants
Balo disease
Schilder disease
Marburg disease
Overlap syndromes
Optic neuritis
Transverse myelitis
Other demyelinating disease
Devic's disease
Harding disease (Leber variant)
Acute/monophasic disseminated encephalomyelitis (ADEM)
Noninflammatory diseases such as PML, central pontine myelinolysis, and B_{12} deficiency (demyelinating)
Common leukodystrophies such as adrenoleukodystrophy (ALD)/metachromatic leukodystrophy (MLD) and Krabbe disease
Other inflammatory diseases
Vasculitis
Connective tissue disease (Sjögren syndrome, SLE)
Neurosarcoid
Whipple disease
Behçet disease
Infective disease (human T-cell lymphotropic virus 1 [HTLV1], tertiary Lyme disease)
Malignancy and genetic (HSP)
Vascular disease, including antiphospholipid syndrome

involving non-CNS sites as well). Additionally, the vascular changes often are not specific for vasculitis. Because primary CNS vasculitis is a small-vessel disorder, brain biopsy using meningeal sampling is the most definitive diagnostic test. This can also help exclude alternative infective, inflammatory, and neoplastic conditions. The risk of biopsy generally is believed to be less than that of inappropriate cyclophosphamide therapy. However, the noted investigations may fail to reach a diagnosis *in vivo*, and a definitive diagnosis of isolated CNS vasculitis may only become established at postmortem examination.

Systemic Lupus Erythematosus (SLE) CNS lupus is histologically neither a primary demyelinating disease nor a vasculitis, but a microvasculopathy. Clinically, it may mimic MS. This is less of a problem when CNS symptoms are accompanied by systemic features such as a photosensitive or malar rash, arthralgia, ulcers, proteinuria, and serologic markers such as dsDNA or anti-SM antibodies. The American College of Rheumatology diagnostic criteria claim good specificity (greater than 95%) in patients with at least three of ten non-neurologic features and an appropriate neurologic picture for SLE. Difficulty may occur in patients with an isolated relapsing CNS disease and positive lupus serologic markers, although this presentation is unusual in SLE (<5%). Unfortunately, typical MS investigations may

not be distinguishing: In SLE with CNS involvement, intrathecal oligoclonal bands are reported to occur in up to 45%, white matter lesions similar to those seen in MS also occur, and delayed VEPs are not uncommon. Features such as headache, seizures, encephalopathy, psychiatric symptoms (may be precipitated by corticosteroids), stroke-like episodes, or presentation in a black patient (Afro Caribbean-born) are more characteristic of SLE and unusual in MS. SLE patients also rarely present with optic neuritis or myelitis. The latter is often progressive, although onset may be acute or subacute. CSF abnormalities, such as an elevated protein and lymphocyte count and sometimes a reduced glucose level, may be found, but the CSF can be normal. Transverse myelitis in SLE often demonstrates spinal cord abnormalities that are continuous over several segments (so called *longitudinal myelitis*) unlike those in MS, which are short (usually less than two spinal cord segments). Response to treatment is variable and usually involves a combination of steroids, cyclophosphamide, and anticoagulation.

Antiphospholipid (APL) Syndrome This typically affects young women and can coexist as an entity in itself or with SLE, human immunodeficiency virus (HIV) infection, or lymphoproliferative disorders. Patients may present with arterial and venous thromboembolic CNS events causing focal CNS lesions that may resemble those seen in MS. A history of migraine, seizures, recurrent miscarriage, livedo reticularis, and peripheral venous thrombosis together with thrombocytopenia and a raised activated partial thromboplastin time (aPTT) all point to the diagnosis, which may be confirmed by checking for antiphospholipid antibodies. Transient APL antibodies may occur following acute infection and should be confirmed by repeat testing. Anticoagulation is usually advocated as treatment for this syndrome.

Sjögren Syndrome Sjögren syndrome may present with features similar to MS, including a fluctuating spinal cord and optic nerve syndrome (Case 3). The more usual neurologic manifestations of Sjögren syndrome are a sensory neuropathy including an isolated trigeminal mononeuropathy. Dry eyes and dry mouth are not uncommon general complaints and are often attributable to medication. However, sicca syndrome or the presence of another connective tissue disease may be relevant in patients with opticospinal MS. Further investigation for Sjögren syndrome requires speckled antinuclear, anti-Ro, anti-La antibodies, and a Schirmer test. Minor salivary gland biopsy is the most definitive test. CSF analysis, MRI, and VEP findings may not be distinct from those in MS, although CSF oligoclonal bands matched in the serum are more commonly reported, and the spinal cord lesions are usually long. The neurologic symptoms may respond to cyclophosphamide in addition to corticosteroids.

CASE 3

A 53-year-old woman developed subacute tetraplegia. Brain and spinal MRI was normal and CSF acellular. She made a partial recovery over 6 months after intravenous high-dose corticosteroids. Eighteen months later, she developed severe bilateral sequential optic neuritis and a left hemiplegia. Limb weakness partially improved, and her vision remained poor despite a further course of corticosteroids. Repeat MRI showed two infratentorial white matter lesions. MRI cervical cord showed an extensive cervical cord lesion extending over three levels. VEPs were delayed asymmetrically. She had unmatched CSF oligoclonal bands in addition to matched bands in the serum and CSF. She had a past history of two first-trimester miscarriages, an unprovoked ileofemoral deep vein thrombosis (DVT) for which she was on long-term warfarin, migraine, and one positive antiphospholipid antibody result. Her antineutrophil antibody (ANA) was raised without more specific lupus autoantibodies. Three months on, she presented with a right hemiplegia and a left optic neuritis, with no further recovery after 2 months. Partial improvement followed a course of plasma exchange. The patient subsequently developed keratoconjunctivitis sicca, xerostomia, and a photosensitive rash. Anti-Ro and anti-La antibodies and a Schirmer test were positive. A minor salivary gland biopsy

confirmed Sjögren syndrome, and she was started on a pulsed cyclophosphamide regime. Over the next 2 years, she had no further relapses and made a partial but slow recovery.

Discussion

- The initial differential included Devic's disease and antiphospholipid (APL) syndrome. CSF-specific oligoclonal bands, an acellular CSF, and brain MRI lesions are not typical in Devic's disease.
- Livedo reticularis, thrombocytopenia, and a repeat positive antiphospholipid antibody would have provided further support for a diagnosis of APL syndrome, but CSF oligoclonal bands would be unusual.
- Cervical cord lesions extending over more than one vertebral body length would not be expected in MS. Matched bands in the serum and CSF and poor clinical recovery after an attack are also against an optico-spinal presentation of MS.
- A number of other conditions may present with a Devic's-type clinical picture including Sjögren syndrome, sarcoidosis, Behçet disease, SLE, and ADEM. Review of the history, longitudinal follow-up, and additional tests should be considered in all cases with atypical features.

Behçet Disease (BD) The prevalence of BD is high in the Mediterranean basin and Japan, and it has been linked with the human leucocyte antigen B51 in these countries. Neurologic involvement occurs in approximately 5% of patients. Thrombophlebitic involvement can lead to cerebral venous thrombosis, but it is the parenchymal CNS involvement that can occasionally mimic MS. This is usually characterized by a relapsing brainstem syndrome and may be accompanied by sphincter disturbance and cognitive-behavioral changes. Optic neuritis and progressive transverse myelitis also is described. Diagnosis is made by highlighting a history of recurrent oral ulceration (greater than three episodes per year) in association with a combination of genital ulceration, skin lesions (typically papulopustular lesions, pseudofolliculitis, or erythema nodosum), pathergy, and uveitis (Figure 4.5). Relapses may be associated with fever, headache, and a raised erythrocyte sedimentation rate (ESR), all of which should prompt the search for a systemic disorder. MRI scanning usually shows characteristic brainstem and basal ganglia involvement, and the CSF is usually pleocystic with a slightly raised protein level. Oligoclonal bands are reported to be less common but can occur. A combination of immunosuppression usually is advocated, although a monophasic presentation is recognized.

Neurosarcoidosis The nervous system is affected in about 5% of patients with sarcoid disease and may rarely be the presenting and only feature. A steroid-responsive optic neuritis, brainstem disorder, or spinal cord disease may mimic MS. Cranial nerves, in particular the optic and facial nerves, commonly are affected. Sarcoid disease also may cause a meningitic–radicular syndrome, a brainstem–cerebellar syndrome, cognitive deterioration, and hypopituitarism. The diagnosis is suggested by associated meningeal, psychiatric, peripheral nerve, and muscle involvement and the presence of systemic disease. Cranial MRI may show multiple white matter lesions, but the presence of meningeal enhancement is helpful (when present) in distinguishing neurosarcoidosis from MS. The CSF often shows a significantly raised protein and cell count in active disease. CSF-specific oligoclonal bands are not usual. Data presented in abstract form (see references) from the National Hospital for Neurological Diseases found CSF-specific bands in only 5% of biopsy-proven cases. Serum and CSF angiotensin converting enzyme (ACE) levels do not routinely appear sensitive or specific. Subclinical hilar lymphadenopathy should be sought with a chest radiograph and, if possible, with high resolution computed tomography (CT). Abnormal respiratory function tests, particularly reduced transfer factor, are found in most cases of systemic sarcoidosis. ^{67}Gallium single-photon emission computed tomography (SPECT) scanning may show characteristic tracer uptake in salivary and lacrimal glands, chest and spleen; a positive Kveim test, if available, may provide addi-

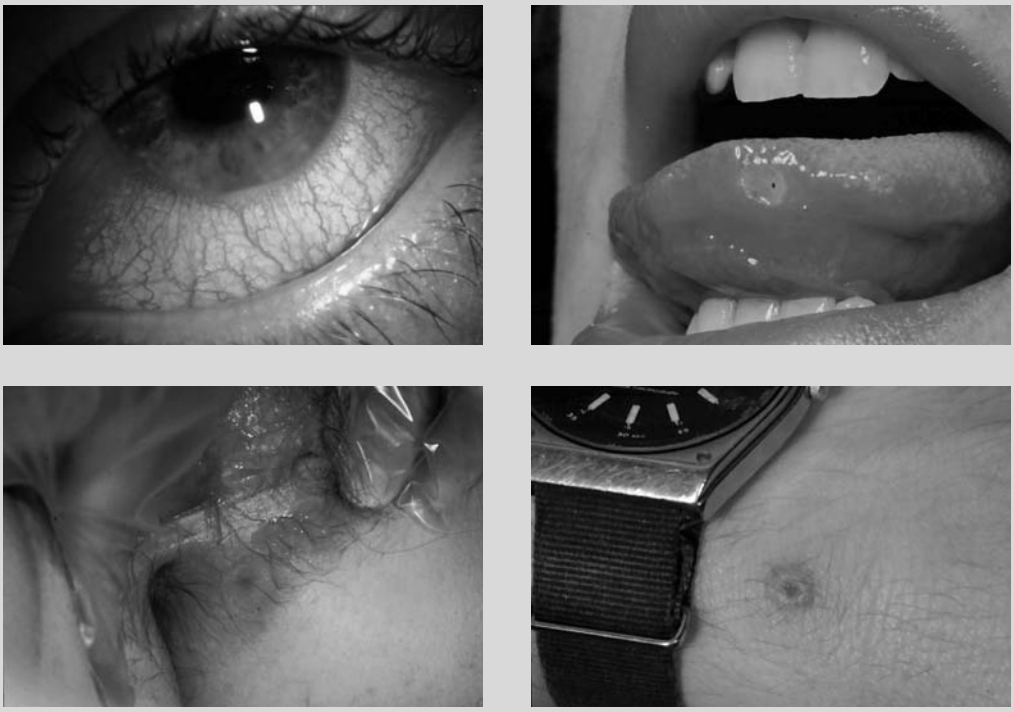

FIGURE 4.5 **Clinical features of Behçet disease. (A) Hypopyon iritis, with red eye and acute inflammatory cell sediment in the front chamber; (B) ulcer on tongue (C) multiple genital ulcers involving the labia; and (D) skin pathergy forming a pustule in response to trauma from watch strap.**

tional information. Ophthalmologic examination for evidence of uveitis can be useful. Definitive diagnosis, however, requires histologic confirmation of noncaseating epithelioid cell granulomas from neural tissue (usually a meningeal biopsy), with a probable diagnosis being made in cases of a clinical syndrome consistent with neurosarcoidosis and histologic evidence of systemic sarcoid disease (via pulmonary, lymph node, or conjunctival biopsy). Response to treatment can be disappointing. First-line therapy involves corticosteroids and methotrexate. More recently, radiotherapy and infliximab (anti-TNFα) also have been used in refractory cases.

Progressive Syndromes

MS Variants

MARBURG DISEASE. This is a rapidly progressive and often fatal form of MS, progressing over a short period of time, sometimes several months. It is not thought to be a separate disease entity.

BALO CONCENTRIC SCLEROSIS. This is a histologic MS variant, referring to a lesion characterized by concentric rings of demyelination and remyelination. A similar pattern is seen on T2-weighted and T1 contrast brain MRI scans and may be distinguished from a tumour or abscess by the usual "open-ring" appearance when enhanced with gadolinium. More typical MS lesions can be seen in association. A focal progressive neurologic syndrome is the typical clinical picture, although more benign clinical phenotypes are described.

SCHILDER DIFFUSE SCLEROSIS. Originally described in 1912, the number of cases reported in the literature for which an alternative diagnosis was excluded is very small. The condition usually presents in children with progressive visual loss, hemiparesis, and cortical features such as cognitive deficits, cortical blindness, and seizures. The condition generally is more aggressive than MS, and MRI shows one or two large white

matter lesions only within the centrum semiovale. Other conditions including subacute sclerosing panencephalitis (SSPE) and the leukodystrophies should be excluded. CSF findings are not specific. Electroencephalogram (EEG) shows generalized slowing in contrast to SSPE. Histologic examination shows widespread confluent demyelination, with more typical MS lesions frequently coexisting. Frozen section samples may be mistaken for astrocytoma, with the inflammatory histiocytic features of Schilder disease most easily demonstrated in paraffin-embedded material.

Progressive Spinal Cord Syndromes The progressive spinal cord syndromes are described in the section on transverse myelitis. Vitamin B_{12} deficiency and compressive lesions are treatable and potentially reversible causes of myelopathy and thus should be excluded. Hereditary spastic paraplegia does not always present with a dominant family history and pes cavus, and it should be considered when the spasticity is dominant and bladder symptoms mild. An absence of CSF-specific oligoclonal bands or MRI spinal cord lesions should prompt the search for an alternative diagnosis.

HIV INFECTION. The neurologic manifestations of HIV infection are protean. The only syndromes likely to cause confusion with MS include AIDS-related vacuolar myelopathy and AIDS-related dementia (although the latter tends to be more rapidly progressive than in MS). White matter lesions may occur on brain MRI. However, oligoclonal bands usually are absent. Testing for HIV antibodies should be considered where doubt exists.

HTLV-1. A progressive myelopathy due to HTLV-1 infection is seen in Afro Caribbeans and Japanese patients but is rare in Caucasians. Leg pain is common, and weakness is usually symmetrical. Brain white matter lesions do occur. Evoked potentials, if delayed, tend to be symmetrical, and CSF oligoclonal bands are matched in the serum. Antibodies to HTLV-1 are present in serum and CSF.

Infectious Disease

Lyme Disease Lyme disease occurs in the temperate, forested regions of Europe and Asia and in the northeastern and upper midwestern areas of the United States. A history of tick bite, characteristic rash (erythema chronicum migrans), and constitutional symptoms in association with a painful polyradiculopathy, facial palsy, or meningoencephalitis allow Lyme disease to be distinguished from MS in most cases. Optic neuritis has been described. More difficulty arises with so-called *tertiary Lyme disease*, in which a chronic progressive neurologic disorder may develop, such as a spastic paraparesis, in association with white matter lesions on brain MRI. The diagnosis is suggested by the appropriate early history and a marked CSF lymphocytosis. Confirmation is by detection of intrathecal antibody using immunoblot, and/or polymerase chain reaction (PCR) for the antigen, where available. A prolonged course of antibiotics is advised.

Neurosyphilis Now rare in developed countries except in association with HIV, this diagnosis is considered when headache and seizures are associated with the characteristic pupillary abnormalities. However, a meningovascular hemiparesis and oculomotor palsies also may be the presenting features. Optic neuritis also is described, but is usually bilateral and associated with disc swelling and enlarged blind spots. The CSF may be pleocystic. The diagnosis is highly unlikely in the presence of a negative serum *Treponema pallidum* hemaglutination (TPHA) assay. A positive CSF VDRL confirms neurologic involvement in the presence of a positive serum TPHA.

Devic's Disease (Neuromyelitis Optica) Devic's disease is pathologically distinct from MS and appears to be a microvasculitis or vasculopathy, rather than a demyelinating disease. Clinically, it is characterized by acute episodes of optic neuritis (bilateral or rapidly sequential) and a subacute transverse myelitis, with no evidence of lesions outside the optic nerves or spinal cord. The brain MRI is normal, and spinal MRI usually shows elongated longitudinal spinal cords lesions (Figure 4.6) that are not typically seen in MS. CSF is usually negative for oligoclonal bands, and pleocytosis and an elevated protein level are not uncommon during an attack (Box 4.6). The optico-spinal form of MS commonly seen in Japan is probably the same disease. Recovery and prognosis is generally poor,

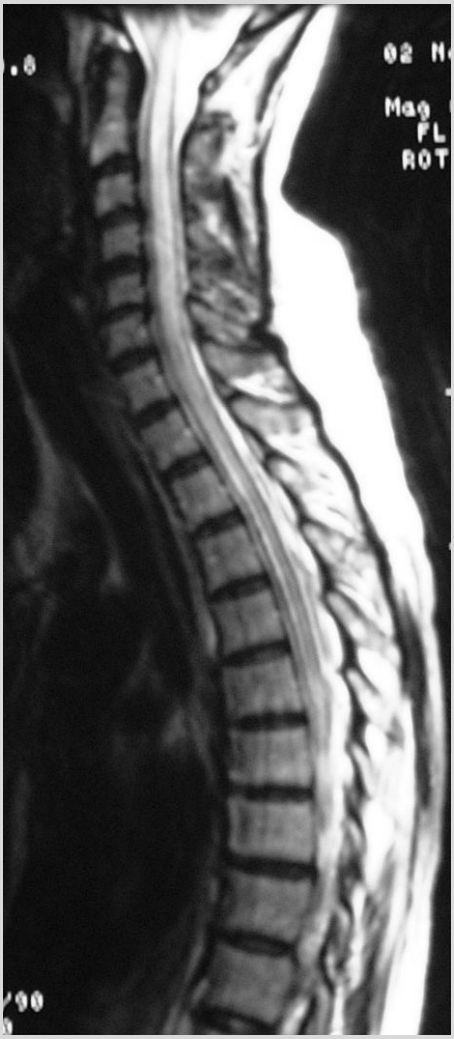

FIGURE 4.6 **Elongated spinal cord lesion in Devic's disease.**

although a response to immunomodulation and in particular plasma exchange has been reported. Confusion arises when this clinical phenotype is seen in MS and other CNS inflammatory disorders (such as Sjögren syndrome, sarcoidosis, Behçet disease, and SLE/antiphospholipid syndrome, and ADEM) (Case 3). In such cases, it may be referred to as Devic's syndrome. Thus, optico-spinal syndromes require a screen for these diagnoses and, where the optic nerve involvement is severe, the Leber mutation should be excluded. Reports of a specific neuromyelitis optica (NMO) IgG antibody that binds to a water channel protein aquaporin-4, in the brain may prove useful in identifying a group of patients who respond to plasma exchange.

Leukodystrophies Leukodystrophies include metabolic abnormalities of lysosomal (Krabbe disease and metachromatic leukodystrophy [MLD]) and peroxisomal (adrenoleukodystrophy [ALD]) function usually present in childhood but may present in young adulthood with features similar to those of progressive MS. Brain MRI typically shows extensive confluent white matter high signal, and enhancement may be seen with contrast.

Metachromatic Leukodystrophy Metachromatic leukodystrophy (MLD) is an autosomal recessive condition presenting with progressive psychiatric, cognitive, and pyramidal features. Peripheral nerve demyelination is frequently found. The MRI changes have a posterior predominance and subcortical pattern. Diagnosis is usually confirmed by white cell enzyme studies show-

BOX 4.6
Distinguishing features in MS and Devic's disease

Feature	Devic's disease	MS
Clinical involvement beyond the spinal cord and optic nerves	Rare	Common
Clinical recovery	Rare	Common
CSF pleocytosis	Common	Rare
CSF oligoclonal bands	Rare	Common
Elongated and swollen MRI spinal cord lesions (> two vertebral body lengths)	Common	Rare
Lesions on brain MRI	Rare	Common

ing low arylsulfatase A activity. Gene mutations have been identified.

Krabbe Disease Krabbe disease, also an autosomal recessive condition, usually presents with a spastic paraplegia, has MRI and nerve conduction findings similar to MLD, and is diagnosed by demonstrating a deficiency of white cell galactosylceramidase.

Adrenoleukodystrophy X-linked adrenoleukodystrophy of adult onset most commonly presents with the adrenomyeloneuronopathy (AMN) phenotype, characterized by a progressive spastic paraplegia in males. The usual cognitive and adrenal involvement may be a late or subclinical feature, and brain MRI may show only a few discrete lesions. Diagnosis is confirmed by demonstrating elevated plasma very-long-chain saturated fatty acids (VLCFAs). Twenty percent of female carriers may develop a spastic paraparesis, and 85% of these also will have raised VLCFAs. Gene analysis for mutations within the ABCD1 gene is also possible. Several treatments, including early bone marrow transplantation, have been tried with variable success. There remain a further group of biochemically uncharacterized leukodystrophies, including the sudanophilic leukodystrophies, that also may present in adulthood.

Features of the adult-onset leukodystrophies that should aid in their differentiation from MS include a clinical picture of a progressive cognitive and pyramidal syndromes, associated confluent white matter MRI changes with U-fibre sparing, negative oligoclonal bands with an elevated CSF protein level, and neurophysiologic evidence of a peripheral demyelinating neuropathy.

Other Leukoencephalopathies Patients with *cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL) have confluent high signal areas on T2-weighted images throughout the deep white matter that may superficially resemble those seen in MS. However, the history of migraine, recurrent stroke, and a dominant family history should distinguish this condition. The disorder is due to mutation in the Notch3 gene on chromosome 19.

Mitochondrial disorders may have atypical clinical features and distinguishing MRI abnormalities (subcortical and non–large-vessel distributed lesions), an increased lactate-to-pyruvate ratio in serum and CSF, and absent oligoclonal banding. Diagnosis may be aided by muscle biopsy and appropriate DNA testing.

Cerebrotendinous xanthomatosis is mentioned because it may present with a progressive spinocerebellar ataxia without characteristic tendon xanthomas. It is treatable. Diagnosis is made by measuring serum cholestanol. Treatment with oral chenodeoxycholic acid may reverse or halt progressive deterioration.

Hereditary Spinocerebellar Ataxias Symptoms are usually progressive, symmetric, and a family history often is present. Optic atrophy and sensory involvement may both occur but the latter is distal in distribution. Skeletal abnormalities and peripheral nerve involvement are useful distinguishing features from MS. Imaging may show atrophy, and CSF analysis is unremarkable. DNA testing may be diagnostic.

Malignancy With the advent of neural axis MRI, CNS malignancy masquerading as MS is rare but should not be forgotten. Relapsing and sometimes multifocal syndromes may occur with meningiomata, gliomata, lymphoma, and metastasis, sometimes needing biopsy in ambiguous cases.

Monophasic Syndromes

Optic Neuritis Optic neuritis presenting with subacute unilateral visual loss may occur as a clinically isolated syndrome or as a presenting manifestation of MS. Pain with eye movement is present in 70% of patients, and a relative afferent pupillary defect confirms an optic neuropathy. A papillitis with disc swelling, perivenous sheathing, or hemorrhages may be seen. More than 90% of patients begin to show improvement by 5 weeks and attain vision of 6/12 or better at one year. In children, optic neuritis is more frequently bilateral and follows viral infection. It usually has a good outcome and is rare in older age groups.

Certain clinical features should prompt a search for an alternative diagnosis. Pain that restricts eye movement or wakes the patient from sleep is unusual with inflammatory optic neuritis and suggests a posterior scleritis or granulomatous condition. Papillitis

KEY POINT

- Features suggesting an alternative diagnosis to inflammatory optic neuritis include:
  - Presence of optic atrophy at presentation
  - Severe disc edema
  - Bilateral visual loss
  - Loss of vision to no light perception
  - Painless sudden onset
  - Pain lasting > 2 weeks
  - No recovery after 1 month
  - Older age

associated with a macular star is not associated with a risk of developing MS. So-called "neuroretinitis" should prompt testing for *Borrelia*, *Bartonella*, and syphilis serology as well as considering sarcoid disease. The outcome in idiopathic neuroretinitis usually is favorable. Compressive optic neuropathies always should be considered where unsatisfactory visual recovery occurs or other atypical features are present, such as a progressive history of more than 2 weeks. Ischemic optic neuropathy is usually sudden in onset, painless, and occurs in an older age group. The visual field defect is usually altitudinal. Toxic optic neuropathies are bilateral and painless. *Leber hereditary optic neuropathy* typically occurs in young men, is sequentially bilateral, painless, and associated with peripapillary telangiectasia, a positive family history, and visual loss. An MS-like illness in women who have a Leber optic neuropathy mitochondrial DNA mutation is reported. Evoked potentials, MRI, and CSF examination can be indistinguishable from MS, and a family history is not always present. The pathologic basis of the extraoptic nerve involvement is unclear. Thus, severe and disproportionate optic nerve involvement in the context of other MS-like features can be seen as a rare presentation of Leber optic neuropathy as well as in Devic's disease.

If the initial features of optic neuritis are atypical, both neurologic and ophthalmologic assessment may be necessary. MRI is helpful in excluding a compressive cause and in demonstrating optic nerve sheath enhancement in those steroid-responsive optic neuropathies associated with sarcoid and chronic relapsing inflammatory optic neuropathy (CRION).

The 5-year optic neuritis treatment trial showed treatment with high-dose intravenous methylprednisolone accelerated visual recovery and reduced the probability of short-term conversion to MS but did not affect the final visual outcome. The risk of developing MS after isolated optic neuritis is approximately 40% at 10 years, with a much lower risk in children. A positive brain MRI scan at presentation (present in about 60%) almost doubles this risk.

Transverse Myelitis Some distinction is made between idiopathic transverse myelitis (ITM), myelitis due to secondary causes. and myelitis as a presentation of MS. MS-related transverse myelitis is more commonly partial, asymmetric, and sensory in character; associated with better recovery; and the MRI lesions are shorter in length. Idiopathic transverse myelitis tends to present as a more rapidly progressive complete spinal syndrome with paraplegia and sphincter disturbance. Spinal shock and meningeal symptoms may be associated; the thoracic cord is affected most commonly. A preceding history of viral infection or vaccination may be found in ITM, and (as with acute disseminated encephalomyelitis) the CSF may exhibit a mononuclear pleocytosis, raised protein levels, and absent oligoclonal bands. Imaging more commonly demonstrates a single elongated spinal cord lesion with destructive changes. Secondary causes should be sought, including viral infection with HIV, herpes zoster, and type II herpes simplex. Connective tissue diseases, HTLV-1, and dural arteriovenous malformations also should be considered after excluding compressive lesions in atypical MS cases, particularly where symptoms are progressive.

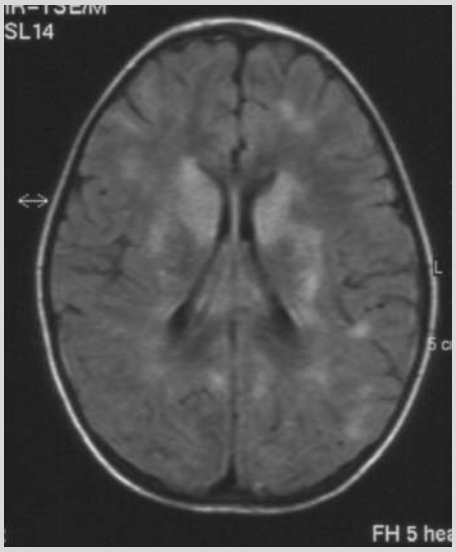

FIGURE 4.7 **Typical confluent grey and white matter lesions in ADEM.**

CASE 4

A 55-year-old woman developed a partial cervical transverse myelitis that responded modestly to intravenous (IV) methylprednisolone. Unfortunately, she relapsed shortly after and became tetraplegic. A strong family history of autoimmune disease was present, and the patient had a previous history of arthralgia. MRI showed multiple white matter lesions in her brain and extensive signal change with swelling in her spinal cord. VEPs were delayed from the right eye. CSF showed 10 lymphocytes, a mildly elevated protein level, and positive (unmatched) CSF oligoclonal bands. Anti-Ro antibodies were positive, and serum IgG elevated. She was provisionally diagnosed as ANA negative SLE and treated with cyclophosphamide followed by prednisolone and azathioprine. She made a near complete recovery after 6 months.

Five years later, she suffered a further episode of transverse myelitis affecting the thoracic level. A positive Schirmer test prompted a salivary gland biopsy that was normal. The patient was given IV methylprednisolone followed by a maintenance dose of prednisolone. Reduction in the daily dose of prednisolone below 15 mg was associated with further episodes of transverse myelitis. Unfortunately, the patient developed pancytopenia on azathioprine, and longstanding cardiac dysfunction and breast carcinoma prevented the use of other immunosuppressants.

Six months later, the patient was admitted drowsy, weak, and hypothermic. Some improvement occurred with high-dose prednisolone. Three years later, she was readmitted drowsy with seizures and died. Postmortem examination revealed typical features of ADEM with hemorrhagic changes, in addition to more typical MS plaques associated with severe axonal loss. No features were present to suggest SLE or Sjögren syndrome.

Discussion

- The initial presentation of a partial cervical cord syndrome with brain MRI lesions and unmatched CSF oligoclonal bands was not of those features typically seen in monophasic idiopathic transverse myelitis.
- An expanded cervical cord lesion, mild CSF pleocytosis, and history of arthralgia with positive anti-Ro antibodies raised the possibility of transverse myelitis in association with a connective tissue disease rather than typical MS.
- Her final two exacerbations were associated with encephalopathic features and seizures more typical of ADEM. This woman appears to have had an overlap of syndromes of recurrent ADEM (MDEM) and MS.

Acute Disseminated Encephalomyelitis ADEM occurs mostly in children and young adults in association with a prodrome of headache, malaise, fever, and a history of prior infection. There follows a rapidly progressive or simultaneous multifocal neurologic syndrome with headache, drowsiness, and meningeal signs, all of which would be unusual in MS. Bilateral optic neuritis, seizures, and coma point away from MS. The mortality rate is about 15%, and recovery may only be partial. A history of preceding viral illness, vaccination, or other immunologic challenge should be sought but is not always identified. CSF analysis shows a lymphocytic pleocytosis with raised protein levels. Oligoclonal bands are present less commonly than in MS. MRI does not reliably distinguish acutely between MS and ADEM, but lesions in the latter tend to be more widespread, confluent, less discrete, and may involve deep nuclear grey matter (Figure 4.7). Gadolinium enhancement in some but not all lesions, or new lesions on follow-up scanning (after 3 months), supports MS. Significant lesion resolution favours a diagnosis of ADEM. Relapses with ADEM (multiphasic disseminated encephalomyelitis; MDEM) tend to occur early (within a 6-month period), although a chronic form of relapsing MDEM is described.

ADEM presents a wide spectrum. The syndrome may present with a relatively short-lived and benign cerebellar syndrome seen following varicella zoster infection in children through

to the consequences of Hurst disease. Acute hemorrhagic encephalomyelitis or Hurst disease may lead rapidly to coma and death, and is associated with a greater neutrophil-predominant CSF pleocytosis with associated red cells. CNS infection must be excluded in these patients. Histology shows fibrinoid necrosis and petechial hemorrhage without overt demyelination. High-dose steroids are used as first-line therapy, often with a 6-week tapering course. Other immunomodulatory therapies including intravenous immunoglobulin and plasma exchange may be tried in refractory cases.

SUMMARY

The revised diagnostic criteria for MS continue to emphasise the importance of defining evidence of white matter lesion multiplicity in time and space, but with an increased emphasis on MRI scanning. However, no definitive diagnostic test exists, and other conditions may present with features and imaging that mimic MS. The diagnosis of MS should be made when no better diagnosis is possible. Patients with atypical features require more extensive investigation and clinical follow up.

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CHAPTER 5

SYMPTOMATIC MANAGEMENT OF MULTIPLE SCLEROSIS

Randall T. Schapiro, MD

KEY POINTS

- Five types of fatigue are found in MS: normal fatigue, neuromuscular fatigue, deconditioning fatigue, the fatigue of depression, and MS-related fatigue (lassitude).
- Medications used to treat fatigue include amantidine (MS-related fatigue), modafinil (MS-related fatigue), pemoline (MS-related fatigue), fluoxetine (MS-related fatigue and the fatigue of depression), and 4-aminopyridine (neuromuscular fatigue).

The complete management of multiple sclerosis (MS) involves slowing the disease process, treating the symptoms, and addressing the psychological issues of those afflicted with the disease. This chapter is devoted to the symptom management of MS. This becomes the predominant issue for most in the management of MS.

FATIGUE

The single most common and the single most disabling symptom of MS is fatigue. Because it is an invisible symptom, it can lead to reactive depression: To the outside world, the person "looks so good" that it is often misunderstood what they can actually do. Managing fatigue begins with looking for medical and situational issues that may be contributing to fatigue. This includes, but is not limited to, thyroid disease, infections, heart disease, temperature aberrations, mononucleosis, and other causes. After these have been remedied, fatigue may be divided into five distinct types.

Type 1 is called *normal fatigue*. It is the fatigue seen in all persons when energy has been expended beyond capability. If one works hard, fatigue is likely. It is treated with understanding and ovation for the hard work. People with MS are not fragile, and they will not break because they worked hard. If they want to work to the point of fatigue, so be it. Occupational therapists, teaching activities of daily living using energy conservation can be very helpful in managing this type of fatigue.

Type 2 is *neuromuscular fatigue* or *short-circuiting fatigue*. It occurs when a demyelinated (or otherwise injured) axon is asked to fire frequently until a conduction block occurs. This person walks fairly well for a block, then limps for a block, then is unable to move for the last block. This fatigue is treated with rest stops that allow the nerve to recoup some function. A graded exercise program may allow for increased endurance over time, but it must be slow in its application.

Type 3 is the *fatigue of deconditioning*. If one is "out of shape" and asks the body to perform, it fails. This is true in both normal persons and patients with MS. This fatigue responds to getting back into condition.

Type 4 is *fatigue associated with depression*. If one is not sleeping well, eating well, and is feeling depressed, fatigue results. This type of fatigue must be recognized to be treated appropriately with counseling and antidepressant medication.

Type 5 is *lassitude or MS-related fatigue*. The most common and the hardest to understand fatigue, this variety presents as tiredness to the point of needing an hour of sleep. It occurs spontaneously and disables significantly. It is unrelated to depression or disease severity. It is likely neurochemical in origin, because neurochemicals such as amantidine and modafinil are helpful in its management. The specific serotonin reuptake inhibitors (e.g., fluoxetine) also may be helpful, even in the absence of depression. The neurochemistry for this type of fatigue has never been specifically worked out, but positron emission tomography (PET) scanning shows metabolic differences between those with this type of fatigue and those without it.

An algorithm for fatigue begins with its recognition. Elimination of other inciting causes, such as depression, infection, metabolic disease, and the like, separates out the other causes of fatigue from those fatigues associated directly with MS. Only then can proper management take place.

KEY POINTS

- Spasticity is best managed by:
  - Removing noxious stimuli
  - Beginning stretching, range of motion exercise programs
  - Instituting antispasticity medication such as baclofen, tizanidine, gabapentin, clonazepam, or dantrolene
  - Through the use of invasive procedures such as botulinum toxin, intrathecal baclofen, or dorsal rhizotomy.
- Paroxysmal symptoms of MS include trigeminal neuralgia, paroxysmal spasms, Lhermitte sign, and spasmodic dysarthria.

SPASTICITY

Spasticity is a common finding in those with MS. It is defined as velocity-dependent stiffness about a joint. The muscle stiffens the faster it is moved. Spasticity is not inherently a bad symptom. Many patients use lower-limb spasticity to generate gait or transfers. Sometimes, however, it can become very bothersome and needs significant attention. Noxious stimuli anywhere in the body will exacerbate spasticity. Thus, the first attempt at treatment revolves around eliminating pain in the body. This may be from a urinary tract infection or from a sore. After pain is treated, an exercise program is instituted. This usually concentrates on the stretching and range of motion exercises, but aerobic exercises can be effective also. Physical therapists may be involved in the initiation of the process. The actual exercising should be as independent as possible so that the person can do it easily on a regular basis.

A variety of medications are helpful for spasticity. Baclofen is the most commonly used pharmacologic agent and may be dosed from 5 mg to 160 mg each day, depending on the severity of the spasticity and the tolerance of the medication. Side effects include trading weakness for spasticity.

Tizanidine from doses of 2 mg to 36 mg is also frequently used but causes sedation and dry mouth, which often limits its use. Benzodiazepines (diazepam and clonazepam) relieve spasticity but are quite sedating and may be habit-forming. They are best used for nocturnal spasms. A variety of newer antiepileptic treatments, including gabapentin and topiramate, may add additional help for those in whom the standard antispasticity regimens are not successful.

For those with intractable spasticity, a "high-tech" approach is necessary. Cutting tendons, ligaments, and the spinal cord is, for the most part, a thing of the past. Sometimes, the injection of botulinum toxin (Botox) can relieve the muscle stiffness, but often the dose is too high to be effective without causing side effects. Canniboids are thought by some to be of value in treating difficult spasticity, but they have never been found to be effective in a well-conceived study. The baclofen pump allows for the administration of baclofen intrathecally, where it is most effective, in microgram aliquots. This can relieve almost any spasticity if dosed appropriately.

PAROXYSMAL SYMPTOMS

MS can have a very peculiar set of symptoms that come and go quickly and sometimes fiercely. *Trigeminal neuralgia* can occur outside the setting of MS but, when it occurs in a young person, it often is associated with MS. This lancinating pain is treated with anticonvulsant medication and sometimes with surgery.

Other paroxysmal symptoms include spasms of an arm or sometimes leg. Sometimes, a spasm of speech can occur. Electrical sensations down the spine, *Lhermitte sign,* are included in these symptoms. All may be treated using anticonvulsants. These medications include carbamazepine, phenytoin, topiramate, gabapentin, and others. Misoprostol also has been reported to be of value.

PAIN

Pain is surprisingly common in MS. Over 50% of patients will have pain of some sort. Pain is divided into two broad categories: neuropathic and musculoskeletal. *Neuropathic pain* usually presents as burning in a nondermatomal pattern on the body. It can be severe and difficult to treat. Most often, pain is projected toward an area of the body where hypesthesia is present. Antiseizure treatments, similar to those used for paroxysmal symptoms, are utilized. Pain medications usually are of no help in this situation.

Musculoskeletal pain may be due to poor posture or poor body mechanics during gait, or secondary to ineffective muscular compensation for weak and incoordinated muscle control.

BLADDER DYSFUNCTION

Among the more common complaints heard from MS patients are frequency and urgency of urination. Hesitancy and incontinence rank right up there as well. Apparently, because the nerve tracts to the bladder traverse long distances and are very myelinated, bladder irritability is very common in MS. Bladder continence varies from patient to patient. Many MS bladders are small and do

not store urine well. These bladders have uncontrolled contractions and very low residual urine. Some bladders are almost the opposite. These bladders contain a large volume, do not empty well, and have a large residual urine. Separately, a dyssynergia of the bladder and the urinary sphincter may be present, in which the bladder wants to empty against a closed, spasming sphincter.

The treatment must fit the situation. Working up bladder problems begins with checking for infection. Obviously, infection can influence urinary function and must be treated with appropriate antibiotics. That being remedied, a residual urine (either by catheterization or by ultrasound) helps determine a large from a small bladder.

Small bladders often are treated easily with anticholinergic medications. Oxybutynin and tolterodine are among the most popular, but imipramine and propantheline bromide function in a similar manner. Dosing should be such to decrease the bladder spasms, allowing for increased bladder capacity, while not interfering with other cholinergic functions (e.g., sweating, salivation, or tearing).

Large bladders are more difficult to treat. Urecholine may help stimulate the bladder to empty but often is ineffective. Catheterization techniques may be necessary to allow for appropriate elimination. Self-catheterization may be taught using a clean technique as opposed to a sterile technique. This procedure takes fairly good hand and sensory function. Incoordination or intense numbness may make this technique impossible for some MS patients to master. Chronic Foley catheterization often leads to chronic infection, but may be a necessary evil if self-catheterization is impossible. Asking a family member to perform intermittent catheterization will almost certainly change the personal relationship of that family member to the person with MS, and this usually is not desirable.

Dyssynergic bladders may respond to α-blockade with medication (Hytrin, Cardura). Often, self-catheterization is necessary to accompany those treatments. The dyssynergic bladder is best diagnosed using urodynamics. Although many opt for urodynamics at the front end of the work-up, it is more practical to reserve these studies for situations in which the initial evaluations and treatments have not produced the desired results.

Just how much residual urine to accept is somewhat dependent on the situation. The normal residual is zero to 20 cc. Less than 100 cc is clearly acceptable. In MS, it is not unusual to see a residual of 200 cc to 400 cc without much discomfort. It all depends on individual symptoms. If high pressures exist in the bladder (dyssynergic type), it is potentially possible to push urine up the ureters toward the kidneys, although, surprisingly, upper tract disease is quite rare in MS. If chronic infections have been present, an ultrasound of the kidneys and ureters is appropriate; cystoscopy may be necessary to find bladder stones that result from chronic bladder infections.

Urinary production is increased in the supine position during the night. This can result in frequent urination, causing a significant increase in fatigue. The production of urine can be decreased by the administration of antidiuretic hormone (desmopressin) at night. This may allow for less nocturia, a better night's sleep, and less daytime fatigue.

BOWEL DYSFUNCTION

Control issues surrounding the bowel are less common than are those involving the bladder but nonetheless can occur. Constipation is the most common bowel problem. Some constipation occurs because of self-inflicted dehydration to control bladder frequency. Drinking an increased amount of water usually solves the problem.

Recognizing the gastrocolic reflex that aids in elimination following a meal is the next simple step. Scheduling the bowel movement about 30 minutes following eating may be helpful.

Stool softeners are commonly utilized, along with bulk-forming agents. If no result occurs at the appointed times or appropriate other times, a glycerine suppository may be inserted to lubricate with gentle stimulation. If that fails, a more stimulatory bisacodyl (Dulcolax) suppository is used. (This strategy is most successful if an associated bowel program is followed, beginning with dietary and fluid changes.) On the second day, a glycerine suppository is tried and, if that

KEY POINTS

- A bladder management ladder includes the following steps:
  - Check for infection
  - Check for residual urine
  - If residual is low, begin anticholinergic treatment
  - If residual is high, review hand coordination and strength with a view toward intermittent self-catheterization
  - Consider urodynamic evaluation if treatment fails or if considerable urgency and hesitancy is present along with an inability to self-catheterize.
- A successful bowel program includes:
  - Training to eliminate after a meal (using gastrocolic reflex)
  - Bulk-forming agents
  - Glycerine suppository
  - Stimulant suppository
  - Judicious use of enemas

KEY POINT

- Medications for erectile dysfunction include Caverject, the medicated urethral system for erection (MUSE), sildenafil citrate (Viagra), vardenafil (Levitra), and tadalafil (Cialis).

fails, on day three, the stimulant suppository is given. Gentle enemas are reserved for more desperate situations on following days. Stronger oral agents are available if the bulk formers or stool softeners are ineffective.

Irritable bowel with loose stools can be problematic. This is especially true if mobility issues accompany bowel control. Larger amounts of bulk-forming agents with less accompanying water may help firm the stool, thus giving the patient more control.

SEXUAL DYSFUNCTION

Sexuality means more than sexual function. It encompasses relationships and feelings which are important areas to explore for all patients with MS. Sexual function is a part of sexuality that often is neglected by physicians, but is very important to those with MS. Sexual dysfunction is a common problem for both sexes, but obviously is handled differently.

Erectile dysfunction management has changed dramatically in the past 15 years. A decade or so ago, the only clearly effective treatment was the implantation of a penile prosthesis. This is a very rigorous surgical procedure with a mechanical end result. The erection is firm and controlled by the patient without much psychological input. In the past decade and a half, the role of vasodilating agents injected into the penis became practical. Prostaglandin, when injected into the shaft of the penis, gives a good workable erection but is fraught with complications and can result in priapism. It also requires good hand coordination to do the injection. The use of vacuum-induced erections, caused by a tube being placed over the penis and a vacuum induced by pumping air out of the tube, never became popular among those with MS. Placement of the prostaglandin in the urethral opening became available—the medicated urethral system for erection (MUSE); this method can work for many patients, but it has been supplanted by the use of oral erection-stimulating pharmacologic agents. Sildenafil citrate (Viagra), vardenafil (Levitra), and tadalafil (Cialis) all are used by men with MS-induced erectile dysfunction, with mixed results. These agents clearly have changed the approach to erectile dysfunction and, for mild to moderate dysfunction, are very practical. If they do not work at appropriate dosing, the other described methods can be put into use.

In women with MS, the problem often is decreased lubrication or decreased sensation. Sometimes burning in the vaginal area is present. Lubrication can be managed by vaginal packets of water-soluble jelly that open on impact or the use of lubricants such as Astroglide or Replens. The sensory disturbances are harder to manage. Vibrators or stimulation using a manual technique that utilizes cold, such as a frozen bag of peas, may work through the numbness or burning. Care must be taken to be gentle and exploratory in terms of region of stimulation. The Eros device induces increased clitoral blood flow and stimulation. This U.S. Food and Drug Administration (FDA)-approved mechanical instrument was designed to be used in this situation.

Decreased libido is a very difficult area to manage; it can be contributed to by depression and/or the use of antidepressant medications. Experimenting with the complicating agents (e.g., SSRIs) may be necessary. Sexual counseling may be necessary.

DEPRESSION

Depression is a primary symptom of MS. Its severity is far more than one would expect from a simple behavioral explanation. Depression resulting from neurochemical imbalance is more frequent and more distressful than expected. An appropriate approach must involve antidepressant treatment using medication and counseling.

EXERCISE

The concept of exercise in neurologic disease appears intuitive. However, if exercise is applied in an inappropriate manner, it can lead to increasing fatigue and disability. For decades, exercise in MS was downplayed because of these issues. In the past 15 to 20 years, however, new information about appropriate exercise techniques surfaced, and this information can be applied to MS with some success.

In beginning an exercise program, it is important to understand the goal of exercise. Exercises given for endurance training are

different from those for strength building. Exercises given to remedy balance problems are different from those used to help spasticity. An exercise prescription begins by describing the type of exercise needed, based on the goal. Then, the duration, frequency, and intensity of training should to be specified.

In MS, exercise science and physiology have provided new understandings that confirm the ability to build muscle strength if a nerve supply exists to sustain the muscle. If no adequate nerve supply exists, a compensatory strategy is developed to maintain muscle and allow for as much function as possible.

COGNITION

Problems with memory, foresight, planning, and judgment are present in over 50% of those with MS. They are a major problem for 10%. These figures should not be surprising when it is realized that the major flow of information in the brain is via myelinated tracts. Dementia resulting from MS demyelination is of a subcortical variety. Much of the information taken in by the patient is stored, but cannot be retrieved easily. As the disease progresses, storage is also a problem. The newer pharmacologic treatments for Alzheimer disease have been of minimal help at best. Cognitive dysfunction in MS is best treated by following the principles of (a) decreasing medication that may contribute to the problem, (b) treating depression vigorously, and (c) keeping the brain stimulated by preventing withdrawal from society.

WEAKNESS

Weakness is common in MS but is not due to inherent problems within the muscle. Although progressive resistive exercises may induce neuromuscular fatigue and actually appear to increase weakness, it is important to guard against disuse. Thus, it is essential to recognize those muscles having enough nerve supply to gain strength through exercise and those with just enough nerve supply to maintain their strength with exercise. For those without muscles without a nerve supply, a compensatory mechanism must be designed. This may involve bracing or using different muscles for function.

The potassium blocker 4-aminopyridine (4-AP) has been proposed to induce more efficient nerve conduction in demyelinated nerves. It has the downside of being epileptogenic and thus must be used carefully. The goal of 4-AP treatment is to improve nerve conduction, thus enhancing strength and potentially increasing energy.

BALANCE, INCOORDINATION, TREMOR

Balance, incoordination, and tremor issues occur readily in MS because the involved systems are so delicate and finely tuned. Abnormalities of the eyes, ears, cerebellum, long tracts of the spinal cord, and the cerebrum can all cause a balance dysfunction. No good medications exist for treating problems in balance and incoordination. Thus, the approach is to develop compensatory strategies to get around the problem. Exercising with a Swiss ball can be helpful. Physical therapists can teach vestibular and other balance exercises that can allow for compensation. Sometimes treating associated spasticity helps. At a higher level, more sophisticated devices exist that allow computer tracking and training for balance.

Tremor often is associated with balance and coordination problems. Tremors in MS are usually those of intent, although sometimes resting tremors also are seen. These tremors are exaggerated during time of stress. Tremor management begins by decreasing stress and fatigue, possibly using medications such as clonazepam and buspirone. β-Blockers such as propranolol also can be helpful. A variety of pharmacologic agents are available, any one of may be useful. These include ondansetron, isoniazid, primidone, and glutethimide. The trick is to find the right medication for the right person.

In addition to medication, bracing across a joint provides a low-cost, low side-effect management strategy. Weighting the arm with a 5-pound weight may be helpful. Deep brain stimulation has been tried anecdotally with mixed reviews.

AMBULATION DIFFICULTIES

Decreased ambulation may be the result of many different factors that have been discussed already, including spasticity, ataxia, and weakness. Although these factors

KEY POINT

- The exercise prescription must include:
  - Type of exercise
  - Duration of exercise
  - Frequency of exercise
  - Intensity of exercise

should be treated as efficiently as possible, the use of assistive devices is important to emphasize in managing the symptom of dysfunctional gait. Certain principles are important. These include the philosophy of getting the proper tool and using it early. The answer to disability is mobility. It is extremely important to have a philosophy of mobility. The goal is to make it easy and efficient. Canes, crutches, walkers, and ankle-foot-orthoses (AFOs) may make the difference between a patient being appropriately mobile or not. These assistive devices must be fitted properly and accompanied with proper instruction.

If ambulation is not the practical means of mobility, then the proper fitting of a wheelchair is essential. This has become a science in itself, and it requires specialized education that allows the technician to take into consideration all of a patient's variables. Wheelchair design is beyond the scope of this chapter.

SIDE EFFECTS OF DISEASE-MODIFYING AGENTS

The use of disease-modifying agents has produced a whole set of symptoms that require management. Interferons often produce a febrile reaction on their initiation. Experience has taught that the use of antipyretics before and after the injection helps, as does beginning with less than therapeutic dosages. Increasing the dose slowly, as tolerance to the febrile side effect is developed, increases the likelihood of success.

For those that are injected subcutaneously, care must be taken to ensure that the needle is clean and devoid of medication as it traverses the skin. Medications should be injected at a depth that puts the treatment beneath the skin, not into it. Pain can be decreased by cooling the area and by rubbing with a cool substance (usually an ice pack) following the injection. It is essential to rotate the injection sites and to avoid injecting through sensitive areas. Creases (abdominal, ilial, gluteal) should be avoided.

Education and observation about blood-associated dyscrasias and liver abnormalities are necessary.

High-dose interferons appear to have a higher incidence of side effects than do low-dose interferon. Glatiramer acetate appears to have the least likelihood of side effects, but has a unique rare systemic reaction characterized by flushing and chest discomfort with some trouble breathing. It is best treated by rest for 20 to 30 minutes after administration along with calming reassurance.

SUMMARY

One of the most important suggestions for symptomatic therapy is to engage the patient in a constructive dialogue. After reviewing the bothersome symptoms, choose the most troublesome symptom, decide on an approach, and treat it. Once this particular symptom has improved, begin management of the second, and so on. Many symptoms feed others, and sometimes relieving one symptom relieves or reduces many others. Proper symptom management will improve the quality of life of those with MS.

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CHAPTER 6

CORTICOSTEROIDS IN THE TREATMENT OF MULTIPLE SCLEROSIS

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KEY POINTS

- Glucocorticosteroids (GCSs) and ACTH are powerful immunosuppressive and anti-inflammatory agents used in MS relapses.
- Improvement of immunologic abnormalities in serum and CSF on administration of GCSs provides laboratory support for the use of GCSs in MS relapse.
- The reduction of Gd-DTPA–enhancing lesions, on administration of high-dose GCSs, provides a basis for the use of GCSs in MS relapse.

Glucocorticosteroids (GCSs) and adrenocorticotropic hormone (ACTH) are potent immunosuppressive and anti-inflammatory drugs. Since their discovery about six decades ago, GCSs have been used for a variety of human autoimmune disorders including multiple sclerosis (MS). After a clinical relapse, most MS patients will improve to some extent without treatment. Some will be left with clinically detectable neurologic impairment and, after a few relapses, substantial disability may accumulate. The main use of GCS and ACTH in MS has been to treat clinically significant relapses in an attempt to hasten recovery. It is not known if corticosteroids affect the eventual course of MS. The optimal dosage, route of administration, and duration of treatment of corticosteroids remain controversial.

MOLECULAR BASIS FOR THE USE OF GCSs

Glucocorticosteroids act by binding to the intracellular glucocorticoid receptor (genomic effect) resulting in up-regulation or down-regulation of specific genes that encode proteins responsible for several cytokines and adhesion molecules. Table 6.1 lists the genomic effects of GCSs.

Recently, it has been realized that additional nongenomic pathways exist for steroid effects occurring at higher concentrations. These result from action on membrane-bound receptors (specific nongenomic effects) or via physicochemical interactions with cellular membranes (nonspecific nongenomic effects). GCSs also result in apoptosis of CD4+ T lymphocytes and decrease the concentration of interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). The nongenomic effects accelerate the termination of inflammation and may provide the molecular basis for the use of high-dose corticosteroids given during pulse therapy.

EFFECT OF CORTICOSTEROIDS ON IMMUNOLOGIC ABNORMALITIES

Elevations of IgG, myelin basic protein (MBP), antibodies to MBP, and oligoclonal bands are frequently found in the cerebrospinal fluid (CSF) of patients with MS. In the active phase of MS, an increase in the number of lymphocytes in the CSF may occur. The administration of intravenous methylprednisolone (IV MP), high-dose oral prednisolone, and ACTH have been shown to improve the abnormal CSF parameters. The effects on immune functions provide a basis for the use of GCSs in MS (Table 6.2).

ANTI-INFLAMMATORY AND ANTIEDEMIC EFFECTS OF CORTICOSTEROIDS

The effects discussed in the previous section demonstrate that corticosteroids are powerful anti-inflammatory agents. In addition, by restoring the altered blood–brain barrier (BBB), the corticosteroids reduce the edema at the level of MS lesions. Therefore, in MS relapse, when active inflammation and edema play a dominant role in the causation of symptoms, corticosteroids improve conduction and quickly relieve symptoms.

EFFECT ON DIAGNOSTIC IMAGING

Contrast enhancement of MS lesions on computed tomography (CT) and magnetic resonance imaging (MRI) are evidence of disruption of the BBB and a marker of activity of the disease. It correlates with perivascular inflammation, a hallmark of actively demyelinating lesions. In relapsing-remitting MS (RR-MS) and secondary progressive MS (SP-MS), new asymptomatic cerebral MRI

KEY POINT

- GCSs should be used for exacerbations or relapses of functional significance. GCSs should not be used for minor symptom fluctuation.

TABLE 6.1 Molecular Basis for GCS Use in MS

- Down-regulate antigen presentation by monocytes
- Down-regulate adhesion molecules (E-selectin and ICAM-1) on vascular endothelium to prevent leukocyte migration in brain parenchyma
- Reduce breakdown of BBB by reducing activity of matrix metalloproteinases–proteolytic enzymes and thus reduce inflammation and vasogenic edema
- Suppress T-helper 1 (TH1) cell proliferation and functions
- Inhibit pro-inflammatory cytokines IL-2, IFN-γ, TNF-α, IL-1
- Induce gene expression of TGF-, anti-inflammatory cytokine.

lesions are associated with gadolinium (Gd)-DTPA enhancement for 2 to 6 weeks (similar to the course of clinical relapses). The Gd-DTPA-enhanced MRI now commonly is used to demonstrate the acute phase of inflammation and the breakdown of BBB in MS. Using this technique, several studies have demonstrated a substantial reduction of enhancement using high-dose IV MP.

USE OF CORTICOSTEROIDS IN CLINICAL PRACTICE

The beneficial results of high-dose pulse IV MP therapy in systemic conditions like lupus nephritis, glomerulonephritis, and acute transplant rejections prompted the use of high-dose IV MP in the acute relapse of MS. Using double-blind controlled studies, high-dose IV MP has been demonstrated to show significant improvement when compared to placebo in patients with MS relapse.

In clinical practice, the use of GCSs should be restricted to MS patients with exacerbations or relapses of functional significance such as visual deterioration, onset of paraparesis, ataxia, bladder dysfunction, and/or loss of manual dexterity. The use of steroids for symptom fluctuations without loss of function should be avoided (Case 1).

Table 6.3 gives the different corticosteroid preparations available with their estimated potency.

GCSs FOR MONOSYMPTOMATIC OPTIC NEURITIS

GCSs have been used for many years to treat monosymptomatic optic neuritis. A multicenter randomized, controlled trial of corticosteroids in the treatment of acute optic neuritis demonstrated that IV MP (1 gm per day for 3 days followed by oral prednisolone 1 mg/kg, tapered over 11 days) showed greater improvement of visual acuity, visual fields, and colour vision at 2 weeks when compared to oral prednisolone (1 mg/kg per day for 11 days) or placebo. Oral prednisolone alone was found to be ineffective and, surprisingly, increased the risk of new episodes of optic neuritis (Case 2).

Nearly 38% to 75% of patients experiencing monosymptomatic optic neuritis later develop clinically definite MS. This is more likely to happen in patients who have at least two periventricular lesions on MRI. In the optic neuritis treatment trial, the post-hoc analyses suggested that clinically definite MS (CDMS) was less likely to develop in IV MP recipients than in oral prednisolone

TABLE 6.2 How GCSs Improve Immunologic Parameters in MS

In CSF: reduction of IgG levels, MBP, antibodies to MBP, CSF lymphocytes

In serum: reduction of proinflammatory cytokines IL-1, IL-2, IFN-γ, TNF- α

CASE 1

Mr. AS, age 28 years, was diagnosed with clinically definite MS on the basis of multiple episodes affecting spinal cord, brainstem, and cerebellum. He had multiple lesions on MRI and oligoclonal bands in the CSF. He was left with diplopia and right finger-nose incoordination. He presented with a 2-day history of paresthesiae in both lower limbs extending up to the waist. The clinical status was unchanged, and no objective findings were related to new symptoms. Because the symptoms were not disabling, the patient was merely observed. The symptoms gradually receded over next 2 weeks.

Discussion

The new sensory symptoms are likely to be due to a fresh lesion in the spinal cord. For minor, nondisabling symptoms, one should not initiate high-dose steroids. These do not modify the disease and its long-term outcome. In addition, corticosteroids are not entirely free from side effects.

or placebo recipients after 2 years. The study, however, had limitations because of the small number of patients, and the study was not originally designed to detect differences of developing CDMS in different treatment groups.

TREATMENT OF ACUTE EXACERBATION OF MS

The Cochrane systematic review provides quantitative evidence favouring ACTH or methylprednisolone against placebo for treating acute exacerbations in patients with MS. In the various trials, benefit is seen in the form of quicker recovery and lowering of mean disability score at 1 week and 4 weeks. With respect to ACTH, it was postulated that adrenal steroids other than cortisol or possibly a direct effect of ACTH on neural tissue was responsible for a therapeutic effect. The subsequent endocrine work suggested that the cortisol response to ACTH is not consistently reproducible, may not be prompt, and endogenous steroid production may never reach the range generally recommended for autoimmune diseases. Besides, ACTH is hardly used to treat any systemic disease of presumed autoimmune etiology. The majority of neurologists use IV methylprednisolone for the treatment of a relapse of MS.

DOSE OF CORTICOSTEROIDS FOR USE IN A RELAPSE OF MS

No therapeutic benefit is seen when low doses of prednisolone (15 mg/day) or methylprednisolone (8 mg to 12 mg/day) are used. The benefits are seen when large doses of IV MP (1,000 mg/day or 15 mg/kg/day as infusion) are used for 3 to 5 days. Even in other systemic autoimmune disorders, the

TABLE 6.3 Corticosteroid Preparations

Estimated potency	Glucocorticoid	Mineralocorticoid
Short-acting (half-life < 12 hrs.)		
Hydrocortisone	1	1
Cortisone	0.8	0.8
Intermediate-acting (half-life 12 to 36 hrs.)		
Prednisone	4	0.25
Prednisolone	4	0.25
Methylprednisolone	5	< 0.01
Triamcinolone	5	< 0.01
Long-acting (half-life > 48 hrs.)		
Betamethasone	25	< 0.01
Dexamethasone	30–40	< 0.01

KEY POINTS

- IV MP (1,000 mg per day for 3 to 5 days) is recommended for use in acute optic neuritis. Oral prednisolone in conventional doses (1 mg /kg body weight per day) is not effective for acute optic neuritis.
- IV MP in the dose of 1,000 mg/day for 3 to 5 days is recommended for a relapse of MS. Oral MP (500 mg daily once a day for days followed by tapering dose over 11 days) can be used as an alternative.

CASE 2

Mrs. LN is a 26-year-old married woman with RR-MS. About 2 years ago, she had the first episode of spinal cord dysfunction resulting in mild paraparesis and hesitancy of micturition; she subsequently recovered. Six months ago, she had brainstem-cerebellar dysfunction resulting in diplopia, dysarthria, and gait ataxia. She received IV MP and improved.

She now presents with a 3-day history of visual impairment in the right eye with pain on moving the eyes. She could perceive a moving body in the right eye. Vision in the left eye was normal. She had minimal finger-nose-finger ataxia in the left upper limb, and both plantars were extensor. Brain MRI done in the past had shown multiple lesions consistent with MS.

She received IV MP 1 g daily for 5 days with rapid improvement in visual acuity. After 30 days, except for a small paracentral scotoma, the visual acuity in the right eye was near normal. To prevent further relapses, she has been recommended to start b-interferon therapy.

Discussion

For an acute episode causing significant functional disturbance (in this patient, severe visual impairment in the right eye), the use of high-dose MP is recommended. This patient showed rapid improvement on receiving IV MP. To prevent further relapses, β-interferon or glatiramer acetate should be advised.

benefit of corticosteroids is not seen with low doses, but only when high doses are administered. The molecular basis for the use of GCSs (especially nongenomic pathways) also supports the use of high-dose steroids to produce effective anti-inflammatory and immunosuppressive response. IV MP should be used soon after acute exacerbation or within 8 weeks of a relapse (Case 3).

TAPERING OF ORAL CORTICOSTEROIDS AFTER IV MP

Some, but not all, recommend a tapering course of oral corticosteroids following the bolus dose of IV MP. The question as to whether a short course of GCSs (3- to 5-day course of IV MP) should be abruptly terminated or if such a course should be followed by a tapering course of oral corticosteroids (over 11 days) has never been satisfactorily answered. Although abrupt withdrawal may suit some patients, the patients with acute MS relapse should be monitored carefully during corticosteroids withdrawal. Patients who regress clinically during corticosteroids withdrawal should be treated with corticosteroids in doses that effectively maintain clinical improvement during tapered withdrawal until a stable course can be sustained without corticosteroids.

CASE 3

Mrs. AM, age 30 years, was diagnosed with RR-MS. She had the first manifestation with optic neuritis at age 28 years, followed by diplopia after 6 months. She now presents with difficulty in walking, urgency of micturition, and sensory paraesthesia in both lower limbs. She needs support to walk and has brisk deep tendon jerks in lower limbs with bilateral extensor plantars. MRI studies reveal evidence of multiple lesions, with a new enhancing lesion in the lower cervical cord and another lesion in the paraventricular region.

She was given IV MP 1,000 mg daily for 5 days. A review after 2 weeks showed significant improvement. Although extensor plantars persisted, the paresthesiae had cleared up, and she was able to walk unaided. For prevention of future relapses, the disease modifying agents were recommended.

Discussion

For an acute relapse of functional significance (in this patient difficulty in walking, severe paresthesiae, and bladder urgency), IV MP (1,000 mg) as infusion is recommended for quick recovery.

IV MP VERSUS ORAL MP

In a double-blind, randomized, placebo-controlled study, oral high-dose MP (500 mg once a day for 5 days with a 10-day tapering period) was found to be beneficial for the treatment of acute relapse of MS. In two studies, oral methylprednisolone given in high doses was found to be as efficacious as the same dose administered by the IV route. The oral route was considered to be of advantage, because it could be given on an outpatient basis and therefore at reduced cost. Although IV MP generally is administered to hospitalized patients it can also be given on an outpatient basis. In clinical practice, the majority of neurologists use short-term high-dose IV MP in preference to oral MP for exacerbations of MS.

GCSs FOR REDUCING PROGRESSION OF DISABILITY

The role of GCSs as disease-modifying agents (for prevention of relapses and of disability progression) has not been studied adequately. In the few placebo-controlled clinical trials, no evidence suggests that GCSs delay the progression of disability in patients with MS. With the introduction of β-interferon and glatiramer acetate, it is doubtful if the intermittent use of GCSs with or without other immunosuppressive agents like azathioprine and cyclophosphamide would be tested as disease-modifying agent. Such studies may be relevant for the developing countries in view of cost considerations.

CORTICOSTEROIDS AND PRIMARY PROGRESSIVE MS

GCSs are not recommended for primary progressive MS (PP-MS). If given continuously, GCSs increase the risk of treatment side effects without producing significant benefit. A suitable form of therapy producing benefit, without causing treatment-related side effects, is not yet available. A combination therapy of high-dose intermittent pulse corticosteroids with another immunosuppressive agent may merit a carefully designed trial to study if it prevents progression and is well tolerated. Table 6.4 summarizes the indications of the use of GCSs.

TABLE 6.4 GCSs for MS: Indications and Controversies

Indications:

- High-dose MP for MS relapse
- Visual loss due to acute optic neuritis

Controversial:

- Intermittent use of IV MP as modifying agent for RR-MS
- Intermittent IV MP for SP-MS

Avoid:

- In PP-MS

COMPLICATIONS OF CORTICOSTEROID THERAPY

Tables 6.5 and 6.6 list the short- and long-term side effects of corticosteroids. In the reported series of short-term, high-dose corticosteroid treatment of MS patients, serious side effects are rare. These drugs should be used with caution in patients with preexisting similar problems. Psychic derangements range from euphoria, mood swings, personality changes, depression, and hypomania,

TABLE 6.5 Side Effects of the Short-term Use of Steroids

Minor:

- Transient facial flushing, metallic taste, insomnia, mild weight gain.

Significant::

- Infections (urinary tract), oral and vaginal candidiasis
- Elevation of blood sugar
- Rise of blood pressure
- Hyperacidity
- Ankle edema
- Acne
- Occasional arrhythmia
- Aggravation of seizure
- Euphoria, depression, hypomania, acute psychosis
- Acute chemical hepatitis marked by elevated liver enzymes

KEY POINTS

- GCSs are not recommended for PP-MS.
- Short-term, high-dose GCSs generally do not cause serious side effects. Frequent courses of GCS or long-term use can result in undesirable side effects.

TABLE 6.6 **Side Effects of Long-term Use of Steroids**

- Aggravation of diabetes
- Gastric or duodenal ulcer
- Reduction of immunity and liability to infections
- Gain in weight
- Moon facies
- Psychosis
- Insomnia
- Cataracts
- Osteoporosis
- Avascular necrosis of the hip joint

to frank psychosis. For steroid-induced or -aggravated depression, it is advisable to avoid tricyclic antidepressants. Antidepressants without anticholinergic activity, such as fluoxetine and trazodone, should be preferred. For manic depressive psychosis (MDP), lithium has been useful. More recently, valproic acid and divalproex also have been tried for MDP. Patients with preexisting MDP may benefit from the prophylactic use of lithium.

SUMMARY

A short course of IV MP is currently favoured for acute exacerbations of MS and an attack of optic neuritis. Serious side effects are relatively rare. No convincing evidence suggests that corticosteroids reduce the frequency of MS relapses or delay the progression of neurologic disability.

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CHAPTER 7

IMMUNOTHERAPY OF MULTIPLE SCLEROSIS: THEORETICAL BASIS AND PRACTICAL APPROACH

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KEY POINT

- MS is now seen as a disease mixing elements of both an immune disease and a degenerative disease.

Over the last 50 years, multiple sclerosis (MS) has been considered to be an autoimmune disease. Most authors supported a concept of accelerating immune stimulation, thus explaining why most relapsing-remitting patients become secondary progressive. However, MS is now seen as a disease mixing elements of both an immune disease and a degenerative disease; recent suggestions that the degenerative element could start very early have been appealing to many and are supported by pathologic studies showing axonal loss very early in the disease, even before the progressive phase. This author has found very appealing the most recent attempts to show how both phenomenon are linked.

This chapter covers the basics of immunology followed by the practical approach to immunotherapies in MS. We first review the basic immune mechanisms underlying the response to an antigen as the autoimmune theory holds that in MS, myelin proteins (or oligodendrocytes) are seen as foreign antigens by the immune system. We review experimental allergic encephalomyelitis (EAE), because many characterize it as "the animal model of MS" despite the fact that there exist many variations of this experimental disease that cannot qualify as a model of MS. We review the blood–brain barrier (BBB) and its disruption as the major biophysical obstacle that pathogenic immune system cells must traverse to reach their target. Finally, we describe the MS plaque in terms of immune content and what is known about the magnetic resonance imaging (MRI) correlations.

BASICS OF IMMUNOLOGY

The immune system is essentially made up of two arms: the innate and the educated immune system. The different cell types constituting the immune system and their deviation in MS include *effector cells*. These are B cells that secrete antibodies; *T-effector cells* (also known as T-helper cells); and killer (K) and natural killer (NK) cells, responsible for killing cancer cells and virus-infected cells. NK cells can kill directly, K cells are involved when an antibody has recognized an antigen bound to cells in what is called antibody-dependant cell cytotoxicity. In MS, ample evidence suggests that B cells are dysregulated. Such evidence comes from increased immunoglobulins in the cerebrospinal fluid (CSF), forming an oligoclonal pattern. This oligoclonal pattern is typical of chronic inflammatory conditions and probably secondary to clones of B cells that have established themselves inside the central nervous system (CNS) and are continuously stimulated by regulatory helper cells, the antigenic environment, or locally produced cytokines.

Regulatory cells are T-helper (Th) cells that help effector cells and T-regulatory cells that inhibit them. (The net effect of these two types of cells was called T suppression in the old literature.) These cells communicate through direct contact or through the secretion of cytokines.

Important for MS is the fact that there seems to be an imbalance in the function of T cells. Th cells can be conditioned to proceed towards a Th1 or a Th2 response. The Th1 response is characterized by the secretion of interferon-α (IFG-α) and interleukin-2 (IL-2), and the Th2 response is characterized by IL-4 and IL-10 cytokines. In MS, the fact that relapses are rare during pregnancy is suspected to be due to the fact, that during pregnancy and under the influence of

KEY POINTS

- The immune pathophysiology in MS could be summarized by the fact that myelin may be recognized as a foreign antigen.
- EAE, the animal model for MS, looks much more similar to acute disseminated encephalomyelitis (ADEM).

hormones secreted by the placenta, the immune response is shifted towards Th2, whereas it is thought that a Th1 shift is part of the immune abnormality of MS patients.

In Northern European countries where MS is frequent, during infancy, individuals must develop a Th1 immune response to viral infections such as measles, rubella, and other myxoviruses. This is in contrast with Africa, where individuals must develop a strong Th2 immune response to protect against parasites and GI tract infections. This contrast could be a contributory factor to the well-known north–south gradient observed in MS epidemiology.

In contrast to the educated immune system just described, the innate immune system is made up of complement factors, polymorphonuclear cells, NK cells, macrophages, and microglial cells. It is suspected that NK cells may have a regulatory role in autoimmune disorders and that microglia, which are derived from macrophages, play a role as effector cells. The innate immune system also may be involved in MS but has not been explored as extensively.

THE IMMUNE RESPONSE TO ANTIGENS

Every protein or peptide from the environment can be considered an antigen. If an individual's immune system does not recognize a substance as foreign antigen, the individual is said to be *tolerant*; if it does, he is said to be *responsive* or *sensitized*. The first step of the immune response consists of this recognition by macrophages and other antigen-presenting cells (APC), followed by *phagocytosis*. Phagocytosis is the digestion of peptides by enzymes in the endoplasmic reticulum and the presentation of these peptides back to the cell's surface through HLA class II (also called DR) antigen on APC and T-cell receptor on T cells together with accessory molecules. These accessory molecules, when present, amplify the immune response; when absent, they reduce it and limit its intensity. If the antigen is presented in the context of class II molecules and T-cell receptors, but without accessory molecules, the stimulated cells undergo *apoptosis* (cell death). However, if accessory molecules are present, the cells multiply and bring about a recall response (the genesis of *memory cells*). Subsequently, Th are activated and stimulate effector cells such as T cells, B cells, and NK cells.

The whole pathophysiology of MS may be summarized by the fact that myelin may be recognized as a foreign antigen. A certain number of concepts have been added to this: *antigen spreading* describes the fact that the immune response from a very specific *epitope* (a small part of the antigenic site) of one antigen tends, when the stimulus is repeated, to react against other antigens often seen together. That is, response is developed to myelin protein other than MBP, such as MOG. *Antigen mimicry* describes the fact that proteins that appear very different can have some peptides in common; when an immune response develops, this may generate a cross-reactive immune response.

EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS

When 6-week-old Lewis rats are injected subcutaneously with myelin basic protein (the most abundant constituent of CNS myelin), they invariably become paralyzed between 8 and 12 days. This monophasic illness often is fatal. At autopsy, the brain and spinal cord of these animals shows an abundant perivenous infiltrate of T lymphocytes. Since the initial description of this animal model, EAE has been a gold mine for immunologists and students as a model of the induction of the immune response. Unfortunately for neurologists, the rapid course of EAE, with its high death rate, no recurrence, and no demyelination cannot be recognized as mimicking MS. It looks much more similar to acute disseminated encephalomyelitis (ADEM), whether postviral, postvaccinal, or induced by the old type of antirabies vaccination. Investigators more interested in the etiology of MS have varied all parameters of the animal model, going back to the original experiments, which used daily IV injections in monkeys to generate (after months of injections) a model quite similar to MS: one producing demyelination and perivascular inflammation with relapses and remissions. Today, using younger animals and New World monkeys,

it is possible to reproducibly generate a chronic EAE model featuring recurrences, demyelination, and all characteristics of human MS. Unfortunately, this "chronic EAE" model is more expensive because new World monkeys are fragile and costly, and the experiment must last much longer. It has become a rule that any treatment of MS should be tested against the EAE animal model; however, many pharmaceutical companies have lost a tremendous amount of money by using the acute model, which responds to many treatments, but is not a reliable indicator of the potential response of human MS patients.

BLOOD–BRAIN BARRIER

The CNS is separated from the blood and serum by a continuous layer of cells that constitute the BBB. This barrier is made by endothelial cells inside the blood vessels; these cells are themselves united by *tight junctions* and rest on a basal membrane impermeable to cells and serum proteins. Inside the CNS compartment, the podocytes of astrocytes form the third element to be crossed. Different mechanisms assure the homeostasis of the CNS compartment inside the BBB. Some substances can freely cross the BBB, generally because they are lipid soluble. Other substances are transported by rate-limiting enzymatic mechanisms, such as electrolytes and sugar. Finally, proteins and cells are kept out of the BBB, but not without exception, as seen by the fact that proteins in CSF may reach a concentration of one-two-hundredth of their concentration in serum. Furthermore, cells are most probably scouting the CNS in non-negligible numbers and these cells transport information back to the immune system when they egress the CNS. The activation of lymphocytes, as well as the activation of endothelial cells, results in an increased number of moieties on the surface of endothelial cells and lymphocytes, which results in an influx of cells inside the BBB. This occurs when inflammation takes place, either through viral insult or through autoimmune insult. The process that leads to cells passing through the BBB can be transcellular or intercellular, but it involves these cells dissolving the basal membrane using metalloproteinases after a three-phase attachment involving rolling, slowing, and attaching.

Some attempts to inhibit the pathologic process in MS have involved the use of monoclonal antibodies against such molecules. Tysabri is a molecule that has shown great efficacy in inhibiting relapses in MS patients, but which, when used in combination with β-interferon or immunosuppressors, also has produced three cases of progressive multifocal leukoencephalopathy (PML), a slow viral infection of the CNS.

MS LESION DESCRIPTION

In MS, lesions of the CNS are called plaques. They affect essentially the white matter of both the brain and spinal cord. However, when *plaques* are juxtacortical, they often affect the contiguous gray matter. Plaques represent that area where the myelin has been destroyed and axons have been relatively spared. Plaques seem to evolve from demyelination, forming from infiltrating lymphocytes and macrophages laden with fat droplets to "sclerosis" due to a proliferation of astrocytes. When plaques are active, inflammatory cells (including lymphocytes and macrophages) are seen. This corresponds to the area where gadolinium enhancement can be seen on contrast-enhanced MRI. Later, when gliosis due to astrocytes proliferation is prominent, axon drop-out becomes a feature of the plaque. At this time, T2-weighted images reveal the presence of multiple lesions. Later, *black holes* appear, a feature of irreversible necrosis. Remyelination can occur in MS, but the myelin that is layered back is probably of a different quality and appears thinner on microscopic observation. This remyelination is thought to be the basis for the Uhthoff phenomenon, an increase in transmission block that occurs when the body temperature is raised—the basis for the "heat-sensitivity" of MS patients.

Plaques generally are present throughout the CNS in the white matter, but areas of predilection include the corpus callosum, the roof of the lateral ventricles (where they form Dawson fingers), and the angle of the ventricles, including the fourth ventricle. In the spinal cord, lesions occur most frequently in the posterior and lateral funiculi, most-

KEY POINT

- MS plaques seem to evolve from demyelination, causing infiltrating lymphocytes and macrophages laden with fat droplets to "sclerosis" due to a proliferation of astrocytes.

KEY POINT

- None of the immune therapies used in MS has been specifically designed for this indication, and their use in MS is more or less derived from their use in transplantation and cancer therapy.

ly at the cervical level. Demyelination in the brainstem can be a cause of death.

Immunologic studies of MS plaques have revealed that glial cells (both astrocytes and microglial cells) are activated and exhibit MHC type II antigens. Similarly, infiltrating lymphocytes show evidence of activation and the secretion of cytokines, mostly Th1 type (IL-2, IL-12). Effector mechanisms leading to myelin destruction involve NK cells and macrophages. It is not clear if the existence of the four distinct types of MS pathology suggested by Lassman and Luccinetti will endure the test of time, or if patients or their lesions can cycle through these apparently different aspects of MS pathology.

One of the most debated issues in MS research has been the question of the abnormality of the so-called normal appearing white matter (NAWM). Indeed, evidence has been generated, essentially by MRI studies, that between the "plaques of demyelination" the white matter is *not* normal. Some have put forward the hypothesis that a zonal or compartmentalized immune response exists in the CNS of MS patients: a zone of active inflammation around the blood vessels with cytokine attraction of lymphocytes, a zone of active demyelinations with sensitization against myelin at the periphery of active plaques, and a zone of bystander effect in the (not so normal) NAWM.

IS MS REALLY AN AUTOIMMUNE DISEASE?

The autoimmune disorders are a group of diseases in which antigen from the body itself is recognized as foreign and against which an immune response is mounted. When a specific immune response against a specific autoantigen is seen, it is extremely difficult to recognize if it is the primary cause of the disease or if it is merely a consequence of it. There are certainly diseases (generally due to an abnormal antibody response) in which the abnormal immune response (such as antibodies to the acetylcholine receptor in myasthenia gravis) is pathogenic and responsible for most of the clinical signs and symptoms. Other diseases in the same group include thyroid dysfunction (antithyroglobulin antibodies), anticardiolipin syndrome (anticardiolipin antibodies). In some other diseases, the relationship between autoimmunity and pathogenicity is less clear: Sjögren (SSA antibodies), lupus (anti-DNA), and rheumatoid arthritis (anti-IgG antibodies, also called rheumatoid factor). In MS, the relationship is even more tenuous and the evidence more limited. Evidence suggests that an autoimmune process is at work, such as the presence of oligoclonal bands in the CSF, but it is not clear if this is the primary event responsible for pathogenesis or a secondary event unrelated to the pathogenesis and merely an epiphenomenon. In any event, the treatment of MS has not yet yielded a substance that could be used to reduce the specific immune response in MS, and all the medications presently used are not antigen specific. The specific antigen in MS against which the immune response is originally mounted has remained elusive. It is possible that no one single antigen exists against which all MS patients react.

PRACTICAL APPROACH TO IMMUNE THERAPY IN MULTIPLE SCLEROSIS

Because of the absence of a known specific antigen that triggers an immune response in MS, antigen-specific therapies are unavailable. While these treatment avenues are being explored, however, specific immunotherapies have been developed on the basis of observed efficacy (Box 7.1). None of the immune therapies used in MS has been specifically designed for this indication, and their use is more or less derived from experience in transplantation and cancer therapy and applied on the basis of nonscientific evidence. Immunotherapies using corticosteroids focused at treating relapses are reviewed in Chapter 6. Here, we focus on immunosuppressors themselves and disease-modifying drugs, such as interferons and glatiramer acetate. Immunosuppressors are themselves subdivided into oral drugs such as azathioprine (Imurel/Imuran) and methotrexate, and into those used intravenously, such as mitoxantrone (Novantrone®) and cyclophosphamide. Disease-modifying agents include drugs such as interferon-β and glatiramer acetate (Copaxone®). We also will discuss the risks and benefits of natalizumab (Tysabri®).

BOX 7.1
Classification of medications available for use in MS:

Symptomatic medications for fatigue, bladder, spasticity, antidepressants, (see Chapter 5)

Immune therapies:

- Corticosteroids (see Chapter 6)
- Immunosuppressors
  - Azathioprine[a]
  - Methotrexate[a]
  - Cyclophosphamide[a]
  - Mitoxantrone[a]

Disease modifying drugs:

- Interferon-β[a]: β-1a IM weekly (Avonex® from Biogen-Idec), β-1b subcutaneously every other day (Betaseron® from Shering), and β-1a subcutaneously three times per week (Rebif® from Serono)
- Glatiramer acetate[a]
- Monoclonal antibody anti-VLA-4 (Tysabri®, Biogen-Idec/Elan)

For drugs presently being trialed go to www.nationalmssociety.org/pdf/research/clinicaltrials.pdf.

[a]Indicates drugs described in this chapter.

Finally, we review a number of medications that are being developed through clinical trials and research protocols and that aim at correcting immune abnormalities in MS.

For each drug discussed, we review the mechanism of action, dosage, and side effects and their practical management.

Azathioprine Azathioprine (Box 7.2) is an imidazole derivative of 6-mercaptopurine that has been widely used in transplantation and treatment of autoimmune diseases. It acts as an antifolate (so that measuring the increase in the mean corpuscular volume of RBC is a good means of evaluating compliance). Azathioprine has been used since the 1960s, most often in France, and this author has had a large experience with it. However, many early clinical reports have been published without generating convincing evidence. Three randomized double-blind placebo-controlled clinical trials (RDBPCT) developed in the 1990s finally showed some minor limited benefit (Ellison), or no benefit at all (British and Dutch trial). However, an excellent meta-analysis totaling 793 patients demonstrated that the drug has a positive effect overall (Yudkin, et al.). The probability of freedom from any relapse during 1, 2, and 3 years of treatment was significantly greater in the azathioprine-treated group (relative odds over 3 years 1.97; 95% CI 1.27, 3.04). After 2 years, there was a small difference in scores on the Expanded Disability Status Scale (EDSS) (–0.22; 95% confidence interval [CI] –0.43, 0.003) in favour of azathioprine treatment; this difference was sustained after 3 years.

The drug is administered orally at 2 to 3 mg/kg/day, with every other week follow-up of blood counts and alkaline phosphatases for the first 3 months. After this

BOX 7.2
Azathioprine sliding scale (J. Oger)

Instructions for the use of Azathioprine in MS:

- Have RBC, WBC, and platelets enumerated in blood every other week for 3 months and then monthly for 3 months, finally every third month.
- If WBC are over 3,500/mm^3, lymphocytes over 1,000/mm^3, and platelets over 200,000/mm^3, administer azathioprine (50 mg) four tablets a day (two b.i.d.) until the next blood count.
- If WBC are under 3,500 but over 3,000 or lymphocytes between 500 and 1,000 or platelets are under 200,000 but over 150,000, take azathioprine (50 mg) two tablets daily (one b.i.d.) until the next blood count.
- If WBC are under 3,000 or lymphocytes are below 500 or platelets are under 150,000 discontinue azathioprine until the next blood count is done.
- Once blood counts come back to acceptable levels, start again with 200 mg/day or with 100 mg/day, respectively
- Have alkaline phosphatase measured once a month. Discontinue azathioprine if levels show a tendency to progressively increase above twice the upper limit of normal.

period, quarterly checks appear sufficient for safety. For this drug to be of benefit, it is essential to obtain a reduction in the number of lymphocytes in blood, but to minimize the risk of side-effects one should pay very strict attention to follow-up blood work. If dosing is adapted to the results (see accompanying sliding-scale), bone marrow depression, which is a common occurrence at these high doses, can be avoided. Liver dysfunction is a concern, and the risk of micronodular cirrhosis is real but can be avoided by measuring the serum alkaline phosphatases (ALP). A progressive increase of ALP heralds cholestasis and cirrhosis; discontinuation of the drug is curative. An occasional patient can show an idiosyncratic reaction over the first doses with fever, skin rash, and hepatitis. This should lead to immediate cessation of the medication. Increased risk of leukemia and cancer has been reported but is limited (less than 1 in 800 patients/years). It is of note that, in most countries, regulatory authorities have not recognized the use of azathioprine in MS. Azathioprine is probably the least expensive of the immunosuppressors.

Azathioprine appears to be indicated to reduce the frequency of relapses, but it is more difficult to demonstrate its effect on disease course. This treatment should be done with very tight control of blood counts and ALP. It is clearly less expensive than the disease-modifying drugs interferon and glatiramer acetate.

Some use methotrexate instead of azathioprine, for the same indication but with less evidence. Methotrexate is used in MS at low doses, such as 7.5 to 15 mg once weekly; pulmonary fibrosis and liver dysfunction have been reported with its use.

Cyclophosphamide Cyclophosphamide (Box 7.3) is an alkylating agent related to the nitrogen mustards. It is a powerful immunosuppressant, cross-linking DNA in actively multiplying cells. Two studies have lead to nonconcordant conclusions (Hauser and Weiner versus Cooperative Canadian study); it is so difficult to make final conclusions that a Cochrane review stated that the treatment regimens and outcome measures were so different that no review was possible.

BOX 7.3
Use of cyclophosphamide boosters

The following recommendations have been made by the Northeast Cooperative MS treatment group for the long term use of cyclophosphamide boosters:

- Total WBC nadir 1,500 to 2,000/mm^3: 1-day booster dose of 800 mg/m^2/mo, accompanied by Solu-Medrol 1,000 mg IV
- Total WBC nadir < 1,500/mm^3: decrease dose by 100 to 200 mg/m^2
- Total WBC nadir > 2,200/mm^3: increase dose by 200 mg/m^2
- Total WBC count before cyclophosphamide dose should be > 4,000/mm^3:
- If 3,000 to 4,000, 75% of dose
- If 2,000 to 3,000, 50% of dose
- If < 2,000, booster not given and WBC count checked in 1 week

(Boosters should be given 1 day per month for 12 months, at which time effects of therapy should be re-evaluated. If therapy works, give booster every 6 weeks for another year, and then every 2 months for a third year; the authors do not advise administering cyclophosphamide for more than 3 consecutive years.)

The promoters of this treatment suggest that it improves the inflammatory component in rapidly evolving MS patients, using induction and reinduction regimens. Possible side effects include nausea, alopecia, infertility, bladder toxicity with hematuria, and possible bladder cancer as well as bone marrow depression and a risk of long-term increase in malignancy. Care should be taken to rule out infectious processes (mostly urinary tract infections [UTIs]) before administering cyclophosphamide.

Despite these negative reports, the regimen recommended by Weiner and the Northeast Cooperative MS treatment group was further refined by adding boosters every other month for 2 years after a 2- to 3-week IV induction treatment.

Cyclophosphamide is used for secondary progressive MS (albeit not approved), especially for patients with rapid progression. It is used in induction at 600 mg/m^2 daily for

5 days with IV Solu-Medrol. It has been suggested that this regimen be followed by monthly boosters, adjusting the dose to white blood cell (WBC) counts. Recommendations have been made by the Northeast Cooperative MS treatment group (Table 7.2).

Cyclophosphamide presently is used most commonly in France and the United States (in 6.9% and 5.5% of the patients, respectively, according to a Charcot report by Hommes and Weiner). There is some hope that using cyclophosphamide in combination with interferons or rituximab will be more effective

Mitoxantrone Mitoxantrone (Novantrone®) is a synthetic anthacenedione derivative used as an antineoplastic. In MS, mitoxantrone is used IV at 12 to 20 mg/m^2. It has been shown to alter the course of rapidly worsening RR-MS or SP-MS. It induces macrophage-mediated suppression of B cells, T-helper cells, and T-cytotoxic lymphocytes. In one trial (Edan), patients were treated with IV Solu-Medrol compared with IV Solu-Medrol 1,000 mg together with mitoxantrone 20 mg monthly for 6 months. The clinical part of the trial was not blinded, but the MRI evaluation part was double-blinded and showed a very significant reduction in gadolinium-enhancing lesions. In the MIMS trial (Hartung, et al.), patients received mitoxantrone in isolation at 12 mg/m^2 every 3 months for 2 years. Mitoxantrone was found to be significantly more effective than placebo in terms of clinical and MRI parameters. A Cochrane review and the TTA subcommittee of the American Academy of Neurology (AAN), following Goodin, et al., rated it as generating class III evidence. This rating was improved by evidence generated by Millefiorini, et al. and by Bastianello, et al., despite the fact that these trials included only a small number of patients: 51 (27 on mitoxantrone) and 25 (13 on mitoxantrone), respectively.

The TTA subcommittee report, despite its attempt to bring objectivity, has been unduly harsh on the evidence; we support the fact that mitoxantrone is beneficial for rapidly progressive relapsing MS and SP-MS, based on relapse rate disability and gadolinium-enhancement on MRI. It has been approved for use in rapidly progressive MS by the U.S. Food and Drug Administration (FDA). Although it is clear that interferons act essentially on the inflammatory component of MS and not on the secondary degenerative process, this has not been clearly shown for mitoxantrone.

The limitation in the use of this medication comes from its side effects, so much so that the AAN has not given it a level A recommendation. A lifetime dose limitation of 140 mg/m^2 is due to cardiotoxicity. Some 5% of treated patients complain of nausea, alopecia, UTI, amenorrhea, leucopenia, and elevated liver enzymes. Nausea, alopecia, leucopenia, and liver dysfunction respond well to cessation of the drug. A few patients, generally older, however, can remain amenorrheic. Five reports have been published of acute myeloblastic leukemia occurring between 3 months and 5 years after treatment. Although small in comparison to the total number of patients treated (now approaching 20,000) this is higher than spontaneous risk, and patients certainly need to be made aware of this deadly risk.

Cardiotoxicity is a complication common to long-term anthracoid therapy. It appears to be dose related and has been shown to appear above 140 mg/m^2. Patients should be monitored for left ventricular ejection fraction (LVEF) by ultrasound or multiple gated acquisition (MUGA) scan and, if the LVEF is $< 50\%$, the drug should be stopped. Data reported by Ghalie and Edan on 2,000 patients indicated no heart failure and, out of 12 patients whose LVEF dropped to $< 50\%$, only three did not recover.

Our routine is to give mitoxantrone 20 mg/m^2 together with IV Solu-Medrol if no infection or leucopenia is present and if LVEF is $> 50\%$. We repeat this monthly for 3 months and, if the LVEF remains $> 50\%$, we repeat this quarterly for 18 months. One then gets close to the dose limit, the greatest drawback to the use of this medication. We are eagerly awaiting results of trials in which mitoxantrone and interferons are used sequentially, because it is probable that mitoxantrone will reinforce the effect of interferons.

Mitoxantrone is an FDA-approved drug, and the use of mitoxantrone has spread,

more so in Europe (2.5% to 6.9% of patients) than in North America (0.5% to 1%). It is recommended for rapidly evolving MS patients "who have failed other drugs," being seen most likely as indicated after interferons have failed. Personally, this reviewer sees it as a possible alternative for use in high NAB-positive interferon-failure patients. We also recommend following the criteria used by Edan for its use, which included the presence of gadolinium-enhancing lesions.

Glatiramer Acetate (Copaxone®) Glatiramer acetate is a combination of four randomly associated amino acids. It is administered subcutaneously at a dose of 20 mg/day. It has received FDA approval. The mode of action of this medication is not clear, although it has been unilaterally claimed to extend to neuroprotection. This medication has been shown to reduce the frequency of relapses and slow disability in RR-MS. It has failed to demonstrate effectiveness in PP-MS. It reduces the accumulation of black holes on MRI and has a slower action on new T2-weighted lesions and gadolinium-enhancement than do the interferons. Its popularity is enhanced because it produces very few side effects, other than frequent lipodystrophy at injection sites and occasional reactions at time of injection with chest pain, chest constriction, alarming for the patient, but self-limited. The effect of glatiramer acetate on MRI parameters appears to be delayed by 6 months or so.

Interferon-β The β-interferons are a series of three injectable, commercially available drugs. These medications clearly reduce relapse rate and reduce the speed at which clinically isolated syndromes (CIS) are followed by a second relapse that leads to the diagnosis of clinically definite MS. They probably slow down (albeit only very partially) the rate at which disability accumulates. Their effect on MRI is dramatic, reducing new gadolinium-enhancing lesions and the accumulation of T2 lesions. Some of the interferons (IFNs) are used subcutaneously (IFN β-1a and β-1b), others are used intramuscularly (IFN-1a), either every other day or once weekly, at doses that are rather arbitrary. It is not clear if these parameters are important, but they have been imposed rigidly by companies and reinforced by regulatory agencies. A tendency exists among the MS population (as well as some neurologists) to roughly qualify the IFNs as being equal in their effects; this myth should be dispelled: A head-to-head trial comparing IFN β-1a 30 mcg IM once weekly (Avonex) to IFN β-1a 44 mcg subcutaneous three times per week (Rebif®) for 1 year showed a clear benefit of the high-dose subcutaneous medication (EVIDENCE trial). Similarly (albeit in a less rigourous design), comparing two interferons indicated that β-1b (subcutaneous) was superior to β-1a (intramuscular) on the short term. Further DBRCT are ongoing, studying the drugs' effects either head-to-head (IFN β1-b versus glatiramer acetate) or as a dose comparison of IFN β1-b.

These three medications all have some side effects in common, including postinjection flu-like symptoms, teratogenicity during pregnancy (class D recommendation), increased liver enzymes, and lymphopenia. These can be addressed by appropriate measures or follow-up blood work.

Each drug, however, differs in its injection-site reaction. IFN β-1a 30 mcg IM once weekly (Avonex®) has a clear advantage at this level. The more contentious issue is that of immunogenicity. This issue is contentious not in terms of the frequency of antibodies: It is agreed that neutralizing antibodies are lowest in Avonex®-treated patients (5%), intermediate in Rebif® (15%), and highest in Betaferon® (25%). However, these antibodies tend to disappear with continuous use in Betaferon®-treated patients. It is also not contentious that once high levels of neutralizing antibodies appear, the bioavailability is totally lost. However, the clinical effect is less clear, probably because the effect itself of these drugs is less clear cut. Nevertheless, patients have been shown to fare less well during years 3 and 4 of treatment if they are neutralizing antibody positive than if they are negative. The loss of benefit to Betaseron®-treated patients is established but less clear cut. The reduced benefit of the "high-dose" IFN in antibody-positive patients should be balanced against the higher benefit related to the higher dose (or frequency or route of administration), well demonstrated for year 1 of treatment and which we suspect is maintained further in

patients who do not develop antibodies. Most regulatory bodies have found it difficult to come to terms with the NAB issue, probably because drug companies have not put all their energy into sorting out this problem.

IMMUNOMODULATORY VERSUS IMMUNOSUPPRESSIVE DRUGS

In affluent Western countries, it is generally recommended to start treatment with disease-modifying drugs and to resort to cyclophosphamide or mitoxantrone if the disease appears to be extremely aggressive or if the interferons appear not to provide their expected benefit on relapses or if adverse events preclude continuous use (Box 7.4). It is generally left to the clinical acumen of MS specialists to distinguish between "expected" response to treatment and "treatment failure." When it is impossible to obtain such medications, a case could be made to start by using "soft" immunosuppressors such as azathioprine, cyclosporine, or methotrexate. This can be justified, because evidence exists that azathioprine is active, although no studies have demonstrated its efficacy on MRI findings and no head-to-head trials have been held. The probable benefit of the associations, either by concurrent or successive treatment, between disease-modifying agents and immunosuppressors is reserved to those individuals who can afford it. Early evidence has suggested that adding azathioprine on disease-modifying agent failure reduces the number of gadolinium-enhancing lesions. The educated

BOX 7.4

Complication common to all the β-interferons and how to reduce them:

Unwarranted expectations: education

- Expectations are often so high that patients believe that the drug is not providing the benefit expected by them. It is essential to spend sufficient time to bring these expectation to the levels demonstrated by trials.

Flu-like symptoms: progressive dosing and use of acetaminophen

- Flu-like symptoms with fever, rigor, and muscle ache generally arise early in treatment over a period of 3 to 6 months and last 3 to 9 hours. Generally, they subside as tachyphylaxis sets in. It is suggested to start the high-dose interferons (Rebif® and Betaseron®) with progressive dosing (e.g., Rebif at half of 22 µg injection for 2 weeks, then 22 mcg for the subsequent 2 weeks, increasing to 44 µg after a further 2 weeks). It is also suggested to use acetaminophen 800 mg 1 hour before the injection and 3 to 4 hours after each injection. When this is not sufficient, use of nonsteroidal anti-inflammatory drugs can be recommended. Some use small amounts of oral corticosteroids. Injections given at bedtime help keep the flu-like symptoms from occurring during the day and keep the patient active. Finally, when these cannot be tolerated, using a less-frequent injection protocol (once weekly) can also be useful, but then one has to settle for a lower-dose interferon (Avonex®).

Injection-site reactions in subcutaneous interferon: rotate injection sites

- Patients receiving subcutaneous interferons (Betaseron® and Rebif®) must be taught how to rotate injection sites, use an Autoinjector, and eventually use ice cubes to prevent injection sites reactions. Using these simples measures, ulcerations that took months to heal are not seen anymore. Still, each injection is followed by an erythematous indurated area that lasts for a few days to a few weeks. IM interferon (Avonex®) does not generate such a side-effect; however, some patients find that the length of needle needed for intramuscular injection can prevent them from self-injecting.

Depression-suicidal risk: treat depression first

- This is a complication that most patients with MS have to face. We do not think that suicidal risk is increased by treatment with interferons. However, because it often takes some time to start medications, we use this time to start patients on antidepressive medications if they exhibit clinical depression.

use of mitoxantrone (or cyclophosphamide) could also be imagined as an adjunct to azathioprine.

UPCOMING MEDICATIONS

Natalizumab (Tysabri®, Biogen-Idec) is a monoclonal antibody against VLA-4 that has shown more effectiveness in reducing relapse rate than have the interferons. The effect on MRI lesions is similar. The medication received FDA approval in November 2004; however, it was withdrawn from the market in February 2005 after the discovery that three patients had developed multifocal leukoencephalopathy. All had received the drug in association with immunosuppressors or interferon β-1a intramuscularly. In June 2006, the FDA approved its use under a strict surveilance program.

SUMMARY

The pathophysiology of MS has not yet been sorted out. Immunologic abnormalities have been found, and each of those findings has led to a hypothesis in pursuit of the development of specific therapies. Unfortunately, none of these avenues has generated a breakthrough. It is only through careful experimental trials that the effect of some medications have been evidenced. All of those which have reached marketing are based on trying to "modulate the immune system," although many of them do not have a good theoretical basis for their activity in MS. A number of them, however, are now available on the market and can influence the course of MS. They all work essentially on the inflammatory phase of the disease and are of limited usefulness to prevent progression. Their effect is limited, however and this evidence has fueled an intense competition for new medications in MS. These include biologicals (with their own problems), oral immunosuppressors (with their risks), and specific immune intervention either using basic protein derivative or modified antigens. No doubt, these strategies will eventually provide physicians and patients with new tools; however, none of the tools presently being developed seems to address the degenerative aspect of MS pathogenesis. We can only hope that this gap will soon be filled.

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CHAPTER 8

REHABILITATION IN MULTIPLE SCLEROSIS

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Multiple sclerosis (MS) is one of the most common causes of neurologic disability in young adults. In the relapsing-remitting form (RR-MS), the natural course of MS is classically characterized by relapses (in 58% to 66% of patients). With time, these relapses cause impairment and, within 10 years of onset, one half of the patients are affected by the progressive form; secondary progressive MS (SP-MS). Once the patient is on a progressive course, neither recovery nor spontaneous remission occurs, although some patients may have long periods of stability. MS also may begin with a progressive form (in 18% to 34% of patients) called primary-progressive MS (PP-MS). On average, 8 years from onset of MS, the patient will experience limitations in walking; by 20 years, the patient needs support to walk; and 30 years after diagnosis, the patient can only walk a few steps. Other functional systems and processes such as the visual system, the brainstem, cerebellum, cognition, bladder, bowel, sexual function, and sensory system also are affected progressively and cause significant disabilities in patients. These facts justify neurologic rehabilitation in MS as a process to help patients to reach and maintain their maximum physical, psychological, social, and vocational abilities and achieve an acceptable quality of life. To reach and maintain optimal function is essential in this progressive disease, and neurologic rehabilitation should be considered during all phases of the disease.

EVALUATION DURING THE NEUROREHABILITATION PROCESS

Patients affected by MS require an expert interdisciplinary rehabilitation team qualified in primary, secondary, and tertiary levels of care. This team should include a neurologist, occupational therapist, physical therapists, psychiatrist, family doctor, physiotherapist, nurse, psychologist, neuropsychologist, social worker, speech-language therapist, urologist, and internist.

The interdisciplinary team, in its different levels of attention, should focus on limiting the impairment, disability, and handicap that a person and his family might have as a result of MS. It is important to evaluate these parameters during the neurologic rehabilitation process. *Impairment* is considered as loss or abnormality of a psychological, physiologic, or anatomic structure or function (anatomic structural level); *disability* is the absence or restriction of a function as a sequelae of a specific impairment of the ability to perform a normal activity (functional level); and *handicap* is the unfavorable situation of an individual as a result of a specific impairment or disability that limits or restrains their performance (socioeconomic-cultural level).

The evaluation in MS rehabilitation focuses on those dysfunctions produced by impairment, disability, and handicap that affect the quality of life. It is important that all scales and instruments used in neurologic rehabilitation be evaluated according to their scientific qualities such as sensibility, validity, and clinical utility criteria.

Table 8.1 shows some of the scales used to evaluate the process of neurologic rehabilitation. Each process in rehabilitation should be assessed at least once using a scale. The value of scales is not absolute; each has its virtues and defects, but all provide valuable information. All evaluations should be performed or supervised by trained staff. The neurologist should diagnose the patient's clinical course of MS and reevaluate the patient once the neurologic

KEY POINTS

- Neurologic rehabilitation in MS is a process that helps an individual to achieve and maintain the top physical, psychological, and social-vocational capacities and a consistent quality of life.
- Patients affected by MS require an expert interdisciplinary rehabilitation team qualified in primary, secondary, and tertiary levels of care. This team should include a neurologist, occupational therapist, psychiatrist, family doctor, physiotherapist, nurse, psychologist, neuropsychologist, social worker, speech-language therapist, urologist, and internist.
- *Impairment* is a loss or abnormality of a psychologic, physiological, or anatomic structure or function. *Disability* is a loss or restriction of the capacity to perform an activity in terms of a frame considered as normal. *Handicap* is the unfavorable situation of an individual as a result of a determined impairment and disability that restricts or impedes the fulfillment of a role normal to the individual.

TABLE 8.1 **Neurorehabilitation Evaluation in Multiple Sclerosis**

1. Clinical history:	Questioning and physical examination
2. Scales:	
Impairment:	Expanded Disability Status Scale (EDSS)
	Multiple Sclerosis Impact Scale (MSIS)
	Scripps Neurologic Rating Scale (SNRS)
Disability:	Multiple Sclerosis Functional Composite
	(PASAT-3, Ambulatory Index, Nine-Hole-Peg test)
	Short and Graphic Ability Score (SAGAS)
	(Nine-Hole-Peg test, 10-Meters Walk test)
Handicap:	Environmental Status Scale
Quality of Life:	Multiple Sclerosis Quality of Life-54 (MSQOL-54)
	Multiple Sclerosis Quality of Life Inventory (MSQLI)
	Leeds Quality of Life Measure
	Short Form Health Survey Questionnaire (SF-36)
Cognition:	Minimal Assessment of Cognitive Function in MS
3. Others methods:	
Images:	Photos, videos, magnetic resonance images (MRI)
Biomechanical:	Muscular strength (Manual muscular tests)
	Range of motion (Goniometry)
	Muscular activity (Electromyography)
	Aerobic capacity/VO_2 max

rehabilitation program is ended. The use of clinical scales is detailed in Chapter 9.

NEUROLOGIC REHABILITATION AND THE CLINICAL COURSE OF MULTIPLE SCLEROSIS

This chapter evaluates the practical application of neuro-rehabilitation in clinical forms of MS. The data presented are based on results from controlled clinical trials that have evaluated the efficacy of interventions using rehabilitation. The use of this data assists the neurologist in determining the best interventions to use during routine medical practice and helps to achieve overall better outcomes for patients.

NEUROLOGIC REHABILITATION IN RR-MS

The clinical presentation of RR-MS includes minor and moderate levels of disability independent of subtypes. Two subtypes are described: RR-MS 1a, in which a complete recovery occurs after the relapse, and RR-MS 1b, in which a step-wise accumulation of disability occurs with each new relapse. In the progressive clinical course of PP-MS and SP-MS, relapses are present, but tend to decrease in frequency. Each relapse after the onset of RR-MS has a permanent negative effect in the degree of disability: 42% deteriorate by half a point and 28% deteriorate by 1 point on the Kurtzke Expanded Disability Status Scale (EDSS), which is run for 64 days after the acute episode. Traditionally, it has been recommended that people with MS should avoid neurologic rehabilitation during the acute period of relapse because of the fear of causing another relapse. However, recent clinical trials confirm the value of physical therapy programs during the acute phase of the relapse and in patients with RR-MS who had accumulated moderate to severe disability with incomplete recovery after relapse. Furthermore,

intervention using neurologic rehabilitation, especially an intensive program, might have positive effects even 6 months after the relapse. Case 1 follows a patient with RR-MS type 1b treated in our clinic.

Although no progression occurs between relapses in the clinical presentation of RR-MS, the increase in relapse frequency might produce sequelae with different grades of impairment and disability.

Three clinical trials have found that rehabilitation programs might improve the patient's condition between relapse in terms of physical condition, strength, reduction in motor fatigue, and quality of life. According to these results, intensive physiotherapy and rehabilitation programs in RR-MS are effective in the treatment of relapses, not only in the acute phase but also in its aftermath. Additionally, this treatment is also useful between relapses during the mild to moderate form of this clinical course.

KEY POINT

- Physiotherapy and intensive neurologic rehabilitation in RR-MS is effective in treating relapses during the acute phase and its sequelae. They are effective in mild to moderate types of this clinical course during the period between relapses.

NEUROLOGIC REHABILITATION IN PROGRESSIVE MS

The primary goal of rehabilitation in progressive MS is to limit impairment in functional areas despite the progression of the disease. In this section, we evaluate the following aspects of rehabilitation in a patient with progressive MS:

- Physical rehabilitation on the primary and secondary symptoms
- Occupational therapy and speech-language therapy
- Neurologic rehabilitation in impairment, disability, handicap, and quality of life

Physical Rehabilitation on Primary and Secondary Symptoms The primary, secondary, and tertiary symptoms in progressive MS are the result of alterations in impairment, disability, and handicap (Table 8.2). In this section, we analyze exclusively the primary and secondary symptoms. Primary symptoms include spasticity, balance impairment, motor weakness, and tremor.

Spasticity Spasticity is one of the most frequent symptoms seen in MS, especially in the progressive course. Its physiopathology is not well known, but the final common path seems to be due to α-motor neuron hyperactivity. This hyperactivity is triggered by an interruption of the descendent corticospinal, reticulospinal, and vestibular fascicles that control the α-motor neurons in the spinal cord through mono and polysynaptic pathways. Spasticity is the final result of a

CASE 1

Severe relapse without recovering in RR-MS 1b. The patient is a 27-year-old woman with a 7-year history of RR-MS and five previous relapses. She has been treated with intramuscular interferon-β1a weekly since the last relapse, but 4 months later, despite the treatment, she had an acute relapse with right hemiparesis and decreased visual acuity in her right eye. She received treatment with intravenous methylprednisolone 1 g/day for 5 days without improvement. She walked most of the time with a cane as unilateral support, had moderate to intense fatigue, and evidences an intense depression. She had difficulties with memory and thought process speed that affected her learning process at university. She also experienced urinary incontinence. Results of the neurologic exam showed the strength in the right side of her body at 3/5 and in the left lower extremity 4/5. Spasticity was severe in lower extremities. Bilateral hyperreflexia and Babinski sign was present. Mild bilateral upper extremity dysmetria was present, and right supranuclear facial paresis and temporal pallor of the left optic disc was noted. Her SNRS scale score was 67. EDSS: 6.0; Kurtzke Functional System Scale: Pyramidal: 4; Cerebellar: 2; Brainstem: 1; Bladder and Bowel: 1; Visual: 1; Sensory: 0; Cerebral/Mental: 2. The Nine-Hole-Peg Test showed delay in the execution of the test on the right upper extremity compared with the left upper extremity. Her ambulation index was 4. The magnetic resonance imaging (MRI) of brain showed an increase in the number of hyperintense lesions in juxtacortical, periventricular areas and corpus callosum, compared with the MRI taken 3 months before.

(continued on next page)

KEY POINT

- When spasticity is a problem, stretching exercises are effective when used in combination with antispasticity medication and complemented by the used of videos. Most people with progressive MS need therapy associated with exercises and medication for spasticity.

Discussion

- Therapeutic considerations include an intensive neurologic rehabilitation program.
- The immunomodulators drugs should be assessed. Interferon-β-1a weekly could be switched to interferon-β-1a three times a week or interferon-β-1b every other day, and the possible side effects decreased with anti-inflammatory prophylaxis therapy.
- Symptomatic therapy should be undertaken, using fatigue intervention and antispasticity medication orally according to the evolution of fatigue and spasticity.
- A neuropsychologic assessment is recommended to evaluate depression and cognitive impairment and then, according to the results, the possibility of psychotherapy sessions.
- Physical rehabilitation is recommended to normalize postural control, inhibit or reduce the patient's compensatory strategies (using her arms to help when sitting down or standing up), facilitate normal components of movement patterns , readapt balance and gait, and start a training program. Swimming pool sessions were deemed useful to improve cardiovascular fitness as well as muscle strength and tone, especially in right side of the body. It is important to progressively increase her physical capacity for the task.
- Occupational therapy was recommended to improve strength, coordination, precision, and rhythm when performing activities using the right upper extremity. An educational program involving energy conservation techniques and aerobic exercises designed to reduce fatigue was also developed.
- Physics medicine was consulted to develop sessions using magnetic fields for low-amplitude and frequency pulse therapy.
- A home exercise program was established.

After an 8-week intervention program, the patient's final evaluation showed that impairment improved by 14 points on the SNRS scale. Her EDSS scale was 3.5. Kurtzke Functional Systems Scale: Pyramidal: 3; Cerebellar: 1; Brainstem: 0; Bladder and Bowel: 0; Visual: 1; Sensory: 0; Cerebral/Mental: 0. The Nine-Hole-Peg test showed a significant improvement in the time taken for right upper extremity execution of the test compared with the initial measure. Her ambulation index was 2. An improvement occurred in the Environmental Status Scale to measure handicap, as well as in the MSQOL-54 for quality of life, especially in the cognitive and motor functions.

prolonged disinhibition of the stretch reflex components, but the exact mechanism is not known. γ-Aminobutyric acid (GABA) is the principal neurotransmitter involved in the presynaptic inhibition system. Because demyelination and axon damage might occur in all the central nervous system (CNS) in MS, spasticity may be the result of spinal or supraspinal lesions. In MS, spasticity initially affects the lower limbs, in particular the extensor muscles. Later, with disease progression, the flexor muscles are affected as well. Spasticity can decrease energy, inhibit motor control, and interfere with self-care, sexual function, and work.

Four types of exercises are used to treat spasticity in rehabilitation treatment: passive movement of the extremities using different ranges of amplitude, aerobic exercises, relaxation exercises, and stretching. Bobath's method also has been used, based on the principle of the balance between reciprocal innervation and activity and the postural tone needed to achieve an optimum equilibrium in the regulation and coordination of the movements.

The results of clinical trials to evaluate the effectiveness of exercise programs for spasticity in the progression course of MS have shown that stretching exercises are only effective if they are combined with antispasticity medication and complemented by the use of videos. Further clinical trials are needed to confirm that other methods of physiotherapy improve spasticity, using standardized measures of the efficacy of the different methods. Studies done in a center specializing in the treatment of spasticity in MS patients and using a multidisciplinary team have shown that approximately 82% of the

TABLE 8.2 Primary, Secondary. and Tertiary Symptoms in Progressive MS

Primary symptoms: Consequence of impairment

- Spasticity
- Weakness
- Tremor
- Unbalance
- Numbness
- Visual
- Cognitive
- Bladder and bowel
- Pain

Secondary symptoms: Consequence of disability

- Contractures
- Infections of urinary system
- Weakness
- Osteoporosis
- Decubitus ulcers

Tertiary symptoms: Consequence of handicap

- Social
- Professional
- Marital
- Psychological problems of chronic diseases

progressive MS patients needed a combination of exercise and medication.

Exercise on a stationary bicycle, aquatic fitness programs, and swimming—and especially the last two—have been suggested to be useful during hot weather because it is well known that two-thirds of patients with MS are sensitive to extreme temperatures, more so to heat than to cold. Initial studies showed improvement in spasticity when the temperature was decreased, but recently an opposite effect was confirmed: a significant increment in spasticity after a cold bath at 24°C. Finally, spasticity is not always viewed negatively in MS because when lower limb weakness is predominant, spasticity may compensate for the weakness and allow the patient to reach a good functional level.

In summary, evidence suggests that the treatment of spasticity in progressive MS is best served through a combination of stretching exercises complemented with videos and antispasticity medication.

Balance and Coordination Impairment Balance and coordination impairments in MS are the result of lesions to the connection between the cerebellum and brainstem. Because cerebellar functions depend also on proprioceptive mechanisms, it is not surprising to find gait abnormalities also caused by lesions of the posterior tracts. During the neurologic exam, the presence of significant damage in proprioception that improves when the eyes are open implies posterior tract damage, more so if no other cerebellar signs are present such as nystagmus, limb tremor, or dysarthria. Because ataxia does not respond to medication, many clinical trials have evaluated exercise programs for possible benefits. Many exercise programs can be designed to improve stabilization, equilibrium, coordination, and relaxation. Programs have been developed to increase proximal muscle function to help in limb stabilization and change-of-position techniques; these programs include biofeedback techniques, patterning, Frenkel exercises, and even therapy using animals, such as equestrian therapy.

Many clinical trials have evaluated the efficacy of exercise intervention programs to treat equilibrium and ataxia in progressive MS. Balance improvement was observed in those patients who received external and home physiotherapy using specific techniques for facilitation and functional improvement; in those using a specific balance program with lessons and exercises; in those using a general rehabilitation program; and in those using other techniques such as aerobic and aquatic exercises. In conclusion, using exercise interventions for equilibrium and balance improvement in people with progressive MS have revealed favorable results.

Muscle Weakness Muscle weakness is an important problem in patients with progressive MS. Most studies of strengthening programs, especially for the lower limbs, demonstrated an improvement in strength and lessened fatigue. Positive effects also were encountered using programs of aquat-

KEY POINT

- Interventions using exercises programs for equilibrium and balance in people with a chronic progressive course of MS have shown effectiveness.

KEY POINTS

- Exercise treatment has a positive effect on those functions related with muscle strengthening in progressive MS.
- Except for the use of splints and weighted wrist bracelets that might decrease tremor intensity, no neurorehabilitation programs are effective in improving tremor.
- The global impact of occupational therapy in MS has been confirmed in fatigue by educational courses in energy conservation, in upper extremity coordination, and strengthening exercise programs.

ic exercises; these effects were related to favorable changes in muscular strength, fatigue, work, mobility (such as changing basic corporal posture), walking, in-home and community ambulation, and equilibrium time. In summary, we can conclude that exercise has a positive effect in functions related to muscle strength in patients with progressive MS.

Tremor Tremor is one of the most difficult symptoms to treat in progressive MS. It is present in 58% of cases, affecting the upper extremities (58%), lower extremities (10%), head (9%) and trunk (7%). Tremor is severe in 15% of patients, and it is correlated with some degree of dysarthria, dysmetria, and dysdiadochokinesia. In patients in whom tremor is dominant in upper extremities, one-third have distal postural tremor, one-third have intention tremor, and 16% have postural and proximal kinetic tremor. Except for the use of splints and weighted wrist bracelets that can decrease the intensity of the tremor, but might worsen the weakness, no proof of effectiveness exists for neurologic rehabilitation. Some progress has been observed using stereotactic surgery and medication, but tremor still can be considered the most difficult symptom in persons with progressive MS.

Neurologic Rehabilitation of Secondary Symptoms in Progressive MS Secondary symptoms are produced as sequelae of primary symptoms. These symptoms include fibrous contractures, urinary infections, inhalation pneumonia, muscle weakness, osteoporosis. and decubitus ulcers. About 15% of patients with MS develop decubitus ulcers at some time during the disease, especially those with a greater degree of disability. Risk factors for decubitus ulcers in MS are weakness and spasticity of the lower extremities, which appear in people who remain in bed for long periods. The risks are even greater when sensory loss, cognitive impairment, bladder and bowel incontinence, malnutrition, and/or hypoalbuminemia are present. Ulcers can be prevented through exercise and mobilization, with frequent position changes for the MS patient in a wheelchair or bed. Studies of bone density in mature women with MS (average age of 50 years) have shown that one-third of these patients have osteopenia and almost one-fifth have osteoporosis. Although no studies exist on the impact of exercise programs in osteoporosis prevention, maintaining a regular exercise program is recommended, not only for bedridden patients but also for ambulatory patients with MS. (The symptomatic treatment of bladder, bowel, and sexual impairments are discussed in Chapter 5.)

Occupational Therapy in Progressive Multiple Sclerosis Occupational therapy is a support treatment that optimizes functional capacities. Its goal is to allow patients to participate in self-care, work, and recreational activities as needed. Generally speaking, patients with MS are sent to occupational therapy for symptoms such as fatigue and upper limb impairment (weakness, motor coordination impairment, sensory loss, and spasticity) that produce limitations in the development of social and daily life activities. The occupational therapist (OT) educates patients in energy conservation techniques, time management, efficient body mechanics, and task improvement both with and without aids. According to the result of an analysis of many clinical trials with high methodologic quality, evidence suggests that educational courses on energy conservation had a very positive impact on fatigue and in some aspects of the quality of life, preserving this improvement from 6 weeks up to 1 year. On the other hand, information-only courses have not shown efficacy.

In other measurements related to occupational therapy in patients with chronic MS, moderate improvement was found in the coordination of upper limbs after an exercise program. However, new studies are necessary to prove the efficacy in other aspects of occupational therapy in MS.

Speech-Language Therapy Although changes in phonation, oral articulation, swallowing. and respiration that are present in patients with MS are better evaluated and treated by a specialist in speech-language therapy, it is important for the neurologist to recognize the relevance of this impairment, which is more frequent in progressive MS. Impairments of word articulation and language use are termed *dysarthria* and *aphasia*, respectively. Dysarthria is impairment in

oral articulation that includes a group of alterations due to muscle control disturbance secondary to nervous system lesions. The frequency of dysarthria in MS in different studies is on the order of 23% to 51%, and it is classified as either spastic, ataxic, and mixed. Generally, patients with MS exhibit speech changes such as hypernasality, vocal harshness, inadequate tone level, and impaired amplitude control. The articulation is deficient, and increases in the breathing rate, air emission, and distress are noted. About 35% of patients have decreased vital capacity and 42% have inadequate ventilation. Rehabilitation interventions in the basic motor processes of speech include establishing strategies for dealing with problems in articulation, phonation, resonance, prosody, and respiration, with specific objective of improving the overall ability of the patient with MS.

In dysarthria, rehabilitation intervention has been observed to improve articulation precision, vocal sharpness, speech naturalness, resonance, duration of maintaining phonation, and quality of life. The efficacy of such rehabilitation treatment depends on the interaction between the patient and the speech-language specialist as well as the degree of impairment, activity, and participation.

Aphasia in MS occurs less frequently than does dysarthria, and it can be acute or chronic. Chronic aphasia, more common in progressive MS, seen in approximately 0.7% to 1% of patients, compared with acute aphasia, which is seen in about 0.81% of cases is more common in RR-MS. Aphasia was the initial symptom in 36% of the cases presenting with acute aphasia, and it has a good prognosis for improvement—on the order of 64% to 72.7%.

Swallowing disorders are characterized by the presence of dysphagia produced by impairment in the swallowing center localized on the brainstem. Dysphagia is present in 3% to 41% of patients with MS, and a significant correlation exists between dysphagia and severe brainstem damage (OR = 3.24; 95% CI 1.44–7.3) and the severity of the disease (OR = 2.99; CI 1.36–6.59). In the progressive phase, dysphagia may have severe consequences in MS patients including saliva and food inhalation with the possibility of developing malnutrition, aspiration pneumonia, and dehydration.

The objective of treatment for swallowing dysfunction in patients with MS is to maintain or improve the nutritional state of the patient. Areas for intervention include changes to the environment in which the patient feeds himself, food texture, attitude during the feeding process, changes in the neuromuscular process, and changes in the feeding methods developed as compensatory techniques. The effectiveness of these interventions has been evaluated in a study, the objective of which was to assess the swallowing function in 143 patients with progressive MS on whom an endoscopy was performed. It was found that 49 (34.3%) had this abnormality. The compensatory rehabilitation techniques were sufficient to eliminate dysphagia in 46 (93.8%) of the cases, thus decreasing the potential risk of inhalation and malnutrition. In respect to the risk of inhalation, videofluoroscopy studies showed at least 10% of patients with dysphagia exhibit signs of inhalation. This result showed the need of a complete assessment of the swallowing function in patients with MS who have dysphagia, especially those with brainstem damage and in those patients with progressive MS with severe disability. Although the risk of inhalation is approximately 10%, the compensatory rehabilitation techniques are effective, allow better nutrition for the patient, and avoid respiratory complications.

Respiratory insufficiency usually is described as the final stage in MS, with a lethality of 8%. However, in the majority of cases, poor and inadequate attention is given to the progressive aspect of the restrictive nature of the respiratory component of MS. Generally, therapeutics starts late, when the restrictive respiratory failure worsens in association with an obstructive component. Therefore, an early professional assessment and continuous treatment are needed, starting with an adequate classification of the respiratory failure and the use of noninvasive respiratory techniques. The application of noninvasive respiratory techniques on these patients is important to avoid or worsen respiratory failure. Clinical trials have confirmed the efficacy of a training program

KEY POINTS

- Dysarthria is present in 23% to 51% of patients with MS. Two clinical trials have indicated some efficacy of the neurologic rehabilitation program. Aphasia is a less common speech disorder.
- It is necessary to evaluate the swallowing function in all patients with progressive MS with brainstem lesions and severe disability. Compensatory rehabilitation techniques are effective in eliminating dysphagia to a high degree, thus allowing better nutrition and avoiding respiratory complications.

KEY POINTS

- Respiratory restrictive dysfunction is present early in people with MS. As the disease progresses, an obstructive component might appear. A rehabilitation program for inspiratory muscles in persons with advanced progressive MS is recommended.
- Even though neurorehabilitation does not improve impairment in a progressive course of MS, it has a positive impact in disability, handicap, and quality of life. The neurorehabilitation impact in quality of life is determined by disability and handicap more than by the functional deficit and progression. The neurorehabilitation process should be permanent during illness evolution, and it is the only treatment that might guarantee a good quality of life.

for improving the strength of inspiratory muscles, respiratory capacity, fatigue, and patient subjective perception in patients with advanced progressive MS. In summary, a rehabilitation program for inspiratory muscles in persons with advanced progressive MS has a beneficial effect on the strength of the muscles that participate in inspiration and it is recommended in the process of neurorehabilitation.

NEUROLOGIC REHABILITATION IN IMPAIRMENT, DISABILITY, HANDICAP, AND QUALITY OF LIFE IN PROGRESSIVE MS

Neurorehabilitation does not stop either disease progression or neurologic impairment in MS, but it does improve disability, personal activities, and participation in social activities. As a result, an improvement in handicap and in quality of life is realized.

The quality of life is determined more by disability and handicap than by functional deficit and progression of the disease.

A randomized, controlled, clinical trial conducted in persons with progressive MS showed the efficacy of an individualized 6-week exercising program to improve disability, as compared to controls. Nevertheless, no change was noted in impairment in any of the groups.

Other clinical trials that compared an exercise program treatment against controls in patients with progressive MS found a significant improvement in general health parameters related to quality of life, even after 9 weeks.

In another clinical trial, a group of MS patients participated in a rehabilitation program as inpatients. They were randomly divided in two groups: one receiving aerobic exercises and the other one receiving no exercises. Compared to the initial score, the group with exercises had a significant improvement in the aerobic threshold, an improvement in the quality of life according to SF-36 score, and an increment in the activity level.

Few studies have evaluated the follow-up of progressive MS patients after applying a rehabilitation program in the hospital; this was carried out in persons with progressive MS, in which 92% were followed and evaluated periodically for 12 months. Although the degree of impairment deteriorated by 1.2 points in EDSS over the course of the 12 months, an improvement in disability and handicap remained for 6 months, in the emotional state for 7 months, and in the physical component of quality of life as measured by the SF-36. This result indicated the need for progressive MS patients to maintain a continuous rehabilitation program in specialized centers and also in the community.

SUMMARY

Neurologic rehabilitation is a valuable component of MS treatment. This treatment might have a positive effect in patients with RR-MS who can be benefic during and after the acute phase, and between relapses. Even though the neurologic rehabilitation in progressive MS does not improve impairment, which continues to progress, it has a positive impact on many symptoms, disability, handicap, and many aspects of quality of life. The neurologic rehabilitation process should be continuous throughout the evolution of the disease, performed both at specialized centers and especially in the community.

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CHAPTER 9

MULTIPLE SCLEROSIS SCALES

Robert M. Herndon, MD

KEY POINTS

- The diagnosis of MS remains clinical. No single test or gold standard exist for the diagnosis, which requires clinical judgment.
- The Barthel Index is a rapid, efficient approach to assessing need for assistance.
- The Modified Ashworth Scale attempts to assess spasticity, which is a complex phenomenon and all of its features cannot be captured on any existing scale.

An understanding of the commonly used scales and measurements in multiple sclerosis (MS) is an important aspect of epidemiology, because employability and the amount and cost of the care needed for MS patients varies with the overall condition of the patient. Correct diagnosis is also important (as discussed in Chapter 1). In the absence of clear diagnostic criteria, it is easy to include other diseases and conditions in the initial diagnosis of MS, thus leading to severe problems in assessing disease frequency and severity. In MS, under-ascertainment in underdeveloped countries can lead to a severe underestimate of MS whereas, in the absence of magnetic resonance imaging (MRI), the misdiagnosis of diseases such as spinocerebellar atrophies as MS can lead to overdiagnosis.

Once the diagnosis is established, disease-specific rating scales and staging procedures are important in efforts to assess disability and the disability-related costs of specific diseases. This is important in many neurologic diseases, because it relates to employability and cost of care. For example, Bourdette and colleagues demonstrated that the cost of care of individuals with MS rose dramatically when their Kurtzke expanded disability rating scale score (EDSS) reached 6.5 or higher. Other scales are used to assess symptoms and the effects of treatment. In this chapter, we present a number of the scales that are used in the evaluation of MS patients, some of which are more widely used in neurologic disease and others that are specific to the assessment of MS (Table 9.1).

TABLE 9.1 MS Scales

Scale	Purpose	Advantages/Disadvantages
Barthel Index	Estimate independence and need for assistance	An effective 10 item scale, very efficient
Modified Ashworth scale	Estimate spasticity; may be used to monitor antispasticity medicines	Fair reliability
Kurtzke Expanded Disability Status Scale	Estimate disease progression	Widely used and understood, basically the gold standard but has, at best, fair inter-rater reliability
Multiple sclerosis functional composite	Follow disease progression in clinical trials	More reliable and accurate than EDSS but doesn't cover full range of disease, useful mainly in ambulatory patients
Hauser ambulation index	Assess mobility	A 10-point mobility scale (0–9), easily used but restricted to mobility issues
Disease steps	Assess disease stage	Similar to the Hauser, it is basically a mobility index. It is suitable self-report

GENERAL NEUROLOGIC SCALES USED IN MS

A few neurologic scales are used over a broad range of neurologic illnesses. Two of these that are frequently used in MS are the Barthel Index and the Ashworth spasticity scale.

Barthel Index The Barthel Index, originally published in 1965 by Mahoney and Barthel, has been modified repeatedly and comes in numerous versions with different scoring systems. It is a simple and straightforward 10-item scale used to assess functional independence and caregiver burden following a neurologic insult. It is intended to be a measure of what the patient does in terms of self-care on a daily basis, not what

1. Feeding	10 = independent, able to apply any necessary aids, feeds self in a reasonable time
	5 = Needs some help
	0 = Unable to feed self in a reasonable time
2. Bathing	5 = Independent, without assistance
	0 = requires assistance
3. Personal	5 = Washes face, combs hair, brushes teeth, shaves, etc.
grooming	0 = Requires assistance
4. Dressing	10 = Independent, ties shoes, fastens fasteners, applies braces
	5 = Needs help but does at least half of tasks in reasonable time
	0 = Requires major assistance
5. Bowel control	10 = No accidents, able to use enema or suppository if needed
	5 = Occasional accidents or needs help with enema or suppository
	0 = Frequent incontinence or major assistance
6. Bladder control	10 = No accidents, able to manage catheter bag, etc., if needed
	5 = Occasional accidents or needs help with device
	0 = Incontinent
7. Toilet transfers	10 = Independent with toilet or bedpan, handles clothes, wipes self, cleans bedpan if used.
	5 = Needs help
8. Chair/bed	15 = Independent, including locks of wheelchair and lifting footrests.
transfers	10 = Minimum assistance or supervision.
	5 = Able to sit, but needs maximum assistance to transfer.
	0 = Inferior performance.
9. Ambulation	15 = Independent for 50 yards. May use assistive devices, except for rolling walker.
	10 = With help for 50 yards.
	5 = Independent with wheelchair for 50 yards, only if unable to walk.
	0 = Inferior performance.
10. Stair climbing	10 = Independent. May use assistive devices.
	5 = Needs help or supervision.
	0 = Inferior performance.

From Mahoney FI, Barthel DW. Functional evaluation: the Barthel Index. *MD State Med J* 1965;14:61–65, with permission.

FIGURE 9.1 **The Barthel Index.**

the patient can do. It can be performed by any health care professional, and the scores are determined by either asking the patient or caregiver what the patient does on a daily basis (Figure 9.1).

Advantages and Disadvantages The Barthel Index is easy to use, reproducible, and familiar. Its disadvantages include that the scale has been modified repeatedly with numerous versions and scoring systems, which can lead to confusion regarding the results.

Modified Ashworth Spasticity Scale The Ashworth scale for spasticity was originally published by Ashworth (1964) and subsequently modified from a five-point to a six-point scale (Bohannon and Smith, 1987). It is a subjective scale and has somewhat limited inter-rater reliability. It is usually performed by a physician or physical therapist. Typically, multiple muscles will be rated in each extremity (Figure 9.2).

Advantages and Disadvantages This is a relatively simple spasticity scale with fair inter-observer reliability. The meaning of the various levels is well understood. There is no more satisfactory scale available at the present time. It is suitable for gauging response to medications used for spasticity. The disadvantages of the Ashworth scale are primarily due to spasticity being a complex phenomenon, affected not only by the setting of the muscle spindles but by tissue viscosity or resistance and other factors including temperature. Precise means of assessment have proved elusive.

SCALES SPECIFICALLY DESIGNED FOR MS

The most widely used scale in MS is the Kurtzke Expanded Disability Status Scale (EDSS) (Figure 9.3). It was initially published as the disability status scale in 1955 (Kurtzke 1955) and subsequently expanded (Kurtzke 1983). It has become the de-facto gold standard in MS. Another scale, the MS Functional Composite, developed under the auspices of the U.S. National Multiple Sclerosis Society, has both advantages and disadvantages relative to the EDSS. One other scale, Disease Steps, which can function as a self-report scale, is being used, particularly where surveys are concerned.

Special Considerations At levels 4 to 6.5 with the EDSS, you have to actually walk the patient to get a valid score because patient estimates of how far they can walk are unreliable. Interpretation of steps is fairly complex and, for purposes of clinical trials, expanded definitions and scoring rules are necessary. In one recent trial, a 15-page explanation of how to score the Kurtzke was used.

Advantages and Disadvantages The scale has wide acceptance and is the de facto standard for MS trials. It is widely understood, so that most neurologists who work with MS patients have a general idea of how disabled someone with a particular score is. It covers the full range of the disease from asymptomatic to death from MS.

The Kurtzke scale has a number of important disadvantages. For the purpose of clinical trials, it is poorly responsive to change. Beyond the level of 5.5, an optic neuritis

O =	No increase in muscle tone
1 =	Slight increase in muscle tone manifest by catch and release or by minimal resistance at the end of the range of motion
1+ =	Slight increase in muscle tone manifest by a catch followed by minimal resistance through the remainder of (less than half) of the range of motion
2 =	More marked increase in muscle tone through most of the range of motion but affected part(s) easily moved
3 =	Considerable increase in muscle tone, passive movement difficult
4 =	Affected part(s) rigid in flexion or extension

From Bohannon RW, Smith MB. Interrater reliability of a modified Ashworth scale of muscle spasticity. *Phys Ther* 1987;67:206–207, with permission.

FIGURE 9.2 **Modified Ashworth Spasticity Scale.**

KEY POINT

- The Kurtzke EDSS is the most widely used scale in MS practice and clinical trials.

0.0 = Normal neurological exam (all grade 0 in FS*).

1.0 = No disability, minimal signs in one FS* (i.e., grade 1).

1.5 = No disability, minimal signs in more than one FS (more than 1 grade 1).

2.0 = Minimal disability in one FS (one FS grade 2, others 0 or 1).

2.5 = Minimal disability in two FS (two FS grade 2, others 0 or 1).

3.0 = Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.

3.5 = Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS grade 2; or two grade 3 (others 0 or 1) or 5 grade 2 (others 0 or 1).

4.0 = Fully ambulatory without aid, self sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps and the patient should be able to walk > 500 meters without assist or rest.

4.5 = Fully ambulatory without aid, up and about much of the day, may otherwise require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others or 1) or combinations of lesser grades exceeding limits of previous steps and walks > 300 meters without assist or rest.

5.0 = Ambulatory without aid for at least 50 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provision). (Usual FS equivalents are one grade 5 alone, others 0 or l; combinations of lesser grades.) Patient walks > 200 meters without aid or rest.

5.5 = Ambulatory without aid for at least 50 meters; disability severe enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or l; or combinations of lesser grades.) Enough to preclude full daily activities. (Usual FS equivalents are one grade 5 alone, others 0 or l; or combinations of lesser grades.) Patient walks > 100 meters without aid or rest.

6.0 = Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk at least 100 meters. (Usual FS equivalents are combinations with more than one FS grade 3.)

6.5 = Constant bilateral assistance (canes, crutches, braces) required to walk at least 20 meters. (Usual FS equivalents are combinations with more than one FS grade 3.)

7.0 = Unable to walk at least 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone.)

7.5 = Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in wheelchair a full day. (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone.)

8.0 = Essentially restricted to chair or perambulated in wheelchair, but out of bed most of day; retains many self care functions; generally has effective use of arms. (Usual FS equivalents are combinations, generally grade 4+ in several systems.)

8.5 = Essentially restricted to bed most of day; has some effective use of arm(s) ; retains some self care functions. (Usual FS equivalents are combinations generally 4 in several systems.)

9.0 = Helpless bed patient; can communicate and eat. (Usual FS equivalents are combinations, mostly grade 4+.)

9.5 = Totally helpless bed patient; unable to communicate effectively or eat or swallow. (Usual FS equivalents are combinations almost all grade 4+.)

10.0 = Death due to MS.

FIGURE 9.3 **Kurtzke Extended Disability Status Scale (EDSS).**

Functional Scale Definitions for the EDSS (Kurtzke)

FS-l Pyramidal Functions

0. Normal
1. Abnormal signs without weakness
2. Mild weakness (4+)
3. Moderate paraparesis or hemiparesis (strength 4/5 or 4–/5) ; or severe monoparesis—grade > 3/5
4. Severe paraparesis or hemiparesis; moderate quadriparesis; or monoplegia; there still may be movement somewhere; there may be severe weakness in three limbs—grades 3 or 2
5. Paraplegia, hemiplegia, or marked quadriparesis; there is no movement in the limbs. For example, both lower extremities or there is movement or severe weakness in four but not three limbs
6. Quadriplegia; no movement in four limbs
7. Untestable
8. Unknown

FS2 Cerebellar functions. Use finger-to-nose test, heel-to-shin test, rapid alternating movements, and gait. You are testing cerebellar function of trunk and limbs, not weakness.

If one or more limbs can't be tested for cerebellar dysfunction (e.g., paraplegia or hemiplegia), but the remaining limbs can be tested, score only the remaining limbs.

0. Normal. No evidence of cerebellar dysfunction. This may be used if one or more limbs are incoordinated due to weakness, apraxia, or sensory loss but not due to cerebellar dysfunction.
1. Abnormal signs without disability. Slight abnormality on formal testing but does not interfere with ADL.
2. Mild ataxia. Limb or gait ataxia in any or all limbs adequate to noticeably interfere with function when the targeted function is stressed, including stressed gait hopping, toes, heels. Physical or mechanical adaptation of the targeted activity is not necessary.
3. Moderate ataxia. Use this if there is moderate ataxia in any or all limbs, in gait or stressed gait. This is also used if there is severe ataxia of one limb. A moderate ataxia requires some physical or mechanical adjustment for the targeted activity to be completed (e.g., the patient must hold the wall to hop or be steadied by the examiner).
4. Severe ataxia in more than two limbs for routine activities and/or routine gait, but still functional albeit with difficulty (e.g., may still be able to walk with aids and feed self). Use also if only remaining testable limb(s) is severely ataxic.
5. Unable to perform coordinated limb or routine gait movements due to ataxia. Use also if only remaining testable limb(s) is unable to perform coordinated movement due to ataxia.
6. Untestable.
7. Unknown. Used after any number (0–5) to indicate that weakness (grade 3 or more on pyramidal) interfered with testing of any extremity.

FS3 Brainstem functions

0. Normal
1. Signs only (unsustained nystagmus, detectable impairment of saccadic pursuit or ocular dysmetria)
2. Sustained conjugate nystagmus, or incomplete INO, or other mild disability
3. Dysconjugate nystagmus (INO) or severe extraocular weakness, or moderate disability of other cranial nerves
4. Severe dysarthria or other severe disability of other cranial nerves
5. Inability to swallow or speak

FIGURE 9.3 **Kurtzke Extended Disability Status Scale (EDSS).**

6. Untestable

7. Unknown

FS4 Sensory Function

0. Normal

1. Detectable vibration or figurewriting decrease only in one or two limbs

2. Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory decrease alone in three or four limbs

3. Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or more limbs; mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three of four limbs

4. Marked decrease in touch or pain or loss of nociception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs

5. Loss (essentially) of sensation in once or two limbs, or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head

6. Sensation essentially lost below the head

7. Untestable

8. Unknown

FS4 Bowel and Bladder Function: Ask about both bladder and bowel; score the worst, as follows:

Bladder

0. Normal bladder function

1. Bladder symptoms but no incontinence

2. Incontinence < once per week

3. Incontinence > once per week but < daily

4. > Daily incontinence

5. Indwelling bladder catheter

6. Grade 5 bladder function plus grade 5 bowel function

7. Untestable

8. Unknown

Bowel

0. Normal bowel function

1. Mild constipation but no incontinence

2. Severe constipation but no incontinence

3. Rare (once per week) bowel incontinence

4. Frequent (> weekly but < daily) bowel incontinence

5. No bowel control

6. Grade 5 bladder function plus grade 5 bowel function

7. Untestable

8. Unknown

FS5 Visual Function (all visual acuity (VA) is best corrected)

0. Normal visual acuity better than 20/30 and no sign of optic nerve disease

1. Visual acuity (corrected) better than or equal to 20/30 with signs of optic nerve disease. For example, if there is an afferent pupil defect.

FIGURE 9.3 **Kurtzke Extended Disability Status Scale (EDSS).**

2. Worse eye with maximal visual acuity (corrected) of 20/40 or 20/50
3. Worse eye with maximal visual acuity (corrected) of 20/70; check both eyes
4. Worse eye with maximal visual acuity (corrected) of 20/100 or 20/200
5. Worse eye with maximal visual acuity (corrected) worse than 20/200 and maximal acuity of better eye of 20/60 or better
6. Grade 5 plus maximal visual acuity of better eye of 20/60 or worse
7. Untestable
8. Unknown.

FS6 Cerebral (or Mental) Function

0. Normal
1. Mood alteration only (does not affect DSS score)
2. Mild decrease in mentation
3. Moderate decrease in mentation
4. Marked decrease in mentation (chronic brain syndromemoderate)
5. Dementia or chronic brain syndrome; severe or incompetent
6. Untestable
7. Unknown

FS7 Other Functions (any other neurologic findings attributable to MS)

Spasticity

0. None
1. Mild (detectable only)
2. Moderate (minor interference with function)
3. Severe (major interference with function)
4. Untestable
5. Unknown

Other

0. None
1. Any other neurologic findings attributed to MS: Specify
2. Unknown

Definitions for motor and ataxia scales. Mild—A measurable abnormality in function that is noticeable to the patient and examiner but does not require any compensatory activity or assistive equipment to complete the tasks required. Moderate—As above, but some compensation whether physical or mechanical is necessary to complete activity required. Severe—Activity measured can be initiated but not consistently completed even with physical or mechanical adaptation.

Note: EDSS steps less than 4.5 refer to patients who are fully ambulatory, and the precise step is defined by the Functional System score(s). EDSS steps from 5 up are defined largely or entirely based on ambulation and mobility. Although functional system scores may still be done, they are provided as additional information and contribute to the EDSS only insofar as they affect mobility functions between EDSS 4.5 and 8.

*A Mental Function grade of 1 does not enter in FS scores for DSS steps.

From Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–1452, with permission.

FIGURE 9.3 **Kurtzke Extended Disability Status Scale (EDSS).**

KEY POINT

- The Multiple Sclerosis Functional Composite (MSFC) is much more precise and accurate than the EDSS, but lacks its range and is more complicated to use.

leaving the patient blind in one or both eyes would not affect the score. This has led to the unfortunate recommendation that only patients with a score less than 3.5 be included in clinical trials in MS, thus excluding most patients and severely complicating recruitment for trials. It is not an impairment or a disability scale but a mixture.

For example, a patient with severe MS who requires bilateral crutches for support when walking (EDSS 6.5) goes from mildly impaired vision to severe bilateral visual loss during an attack. Despite being much worse in terms of his ability to function, his EDSS is unaffected.

The distribution of patients on the scale in the hands of most investigators is bimodal, although Kurtzke insists that in his hands it is Gaussian. Additionally, the sensory and bowel and bladder scales are largely subjective, which makes them of limited suitability in clinical trials.

Over the last few years the inter-rater reliability of the Kurtzke scale has been recognized as an impediment to increasing its sensitivity. This has led Ludwig Kappos to standardize the way to apply it to patients. To attain this goal, he has created the "neurostatus," which is a new version of the EDSS in which each of the steps of each of the functional scales is defined and standardized. Furthermore, some of the scales become reduced in their span so as not to influence the EDSS in a disproportionate manner. This has been welcomed by industry and investigators alike, leading to the generalized use of this variant of the EDSS. An examination has been set up and neurologists now must pass a specific test to become "Neurostatus certified." Having passed this test over the previous 12 months, and having its validity extended yearly, is becoming a standard for neurologists wishing to participate in clinical trials. Please consult the website at www.neurostatus.net. Many of us regret that standardization of the administration of the EDSS has taken precedence over trying to improve this scale.

The Kurtzke scale is widely used and regarded as the gold standard. Its main current use should be for comparing current trials with previous trials that used the scale. Because of its poor inter-rater and intra-rater reliability, more quantitative scales, such as the MS Functional Composite Scale, are likely to be more useful in future clinical trials.

Multiple Sclerosis Functional Composite Scale The Multiple Sclerosis Functional Composite Scale (MSFC) test (Figure 9.4) is a combination of a timed 8-meter walk, Nine-Hole-Peg test done with each hand, and the paced auditory serial addition test, 3-second version. Test results are converted to Z scores, which allow the use of parametric statistics with this scale. The test was developed by a committee under the auspices of the National MS Society to improve test reliability and objectivity in MS clinical trials.

Timed 8-meter walk. The patient may use any walking aids needed and is timed over an 8-meter course twice; the times are averaged.

Nine-Hole-Peg test (9-HPT). This is a simple timed test of upper extremity function. The Nine-Hole-Peg test consists of a block with nine holes and nine pegs. The time it takes to insert all nine pegs, one at a time, and then remove them is measured, using each hand separately. It is done twice with each hand and the times averaged.

The 3-second paced auditory serial addition test (PASAT). The patient listens to a tape in which a single digit number is called out every 3 seconds. The task is to add the last two digits spoken. This involves stating the sum of the first two digits, dropping the sum, adding the second and third digits, and repeating this with the next spoken digit.

From Rudick R, Antel J, Confavreux C, Cutter G, et al. Recommendations from the National Multiple Sclerosis Society Clinical Outcomes Assessment Task Force. *Ann Neurol* 1997;42(3): 379–382, with permission.

FIGURE 9.4 **Multiple Sclerosis Functional Composite.**

Validation Test development was based on data from control patients in multiple clinical trials. The attempt was made to find simple, quantitative, and reliable measures that would allow smaller clinical trials. Further validation was accomplished through the IMPACT trial in secondary progressive MS, in which the EDSS failed to show a significant change but the MSFC showed a significant change in hand function and a borderline change in cognitive function (Cohen, et al., 2002). Although it has poor face validity, construct validity appears better than for the EDSS in the range between EDSS 4 and 9, where the EDSS is almost exclusively dependent on mobility because it includes a measure of upper extremity and cognition as well as a measure of lower extremity function. Neither cognitive function nor upper extremity function is captured at all well by the EDSS.

Administration The test is administered by a trained technician and requires a stopwatch, a tape player with a paced auditory serial addition test (PASAT) tape, recording sheets, and equipment for the Nine-Hole-Peg test. It takes about 15 to 25 minutes to administer the MSFC.

Advantages and Disadvantages This is a simple, extremely reliable (Kalkers, et al., 2004) measure of change in MS that is easily done by a trained technician. Its advantages include its efficiency, reliability, and reproducibility. It also simplifies the statistics that can be used to assess the data.

The disadvantage of the MSFC is that it requires equipment: a nine-hole-pegboard and pegs, stop watch, and PASAT tape and player with recording sheets. It does not yet include a measure of vision, though attempts are being made to update it with a visual measure. Although it covers the entire range of the disease, ambulation becomes uninformative when the patient can no longer walk 8 meters; thus, in clinical trials, it is generally used only in ambulatory patients. For example, a patient with moderately advanced MS is being followed using the MSFC. He develops a recurrent transverse myelopathy and loses the ability to walk more than a few feet. Since he can no longer walk 25 feet (8 meters), one of the three components of the MSFC has become uninformative as far as progression is concerned.

It requires initial patient training, particularly on the PASAT, to minimize learning effects. Finally, scoring is complicated because it requires averaging the baseline

KEY POINT

- The Hauser Ambulation Index is a simple, efficient mobility scale.

0. Asymptomatic; fully active
1. Walks normally, but reports fatigue that interferes with athletic or other demanding activities.
2. Abnormal gait or episodic imbalance; gait disorder is noticed by family and friends; able to walk 25 ft in 10 seconds or less.
3. Walks independently; able to walk 25 ft in 20 seconds or less
4. Requires unilateral support (cane or single crutch) to walk; walks 25 ft in 20 seconds or less.
5. Requires bilateral support (canes, crutches or walker) and walks 25 ft in 25 seconds or less; or requires unilateral support but needs more than 20 seconds to walk 25 ft.
6. Requires bilateral support and more than 20 seconds to walk 25 ft, may use wheelchair on occasion.
7. Walking limited to several steps with bilateral support; unable to walk 25 ft; may use wheelchair for most activities.
8. Restricted to wheelchair; able to transfer self independently.
9. Restricted to wheelchair; unable to transfer self independently.

From Hauser SL, Dawson DM, Lehrich JR, et al. Intensive immunosuppression in progressive multiple sclerosis: a randomized three-arm study of high dose intravenous cyclophosphamide, plasma exchange and ACTH. *N Engl J Med* 1983;308:173–180, with permission.

FIGURE 9.5 **Hauser Ambulation Index.**

KEY POINT

- The Disease Steps scale is a simple and efficient scale for staging disease that is suitable for self- report.

Methods: For Disease Steps, classification of a patient is determined by history and neurologic examination, as well as course of MS. The scale consists of the following:

0 = Normal: Functionally normal with no limitations on activity or lifestyle. Patients may have minor abnormality on examination, such as nystagmus or an extensor plantar. The course is relapsing-remitting with a return to baseline with or without treatment. These patients are not treated with any ongoing symptomatic therapy for MS.

1 = Mild disability: Mild symptoms or signs. These patients have mild but definite findings such as sensory abnormalities, mild bladder impairment, minor incoordination, weakness, or fatigue. There is no visible abnormality of gait. The pattern of disease is relapsing-remitting, but patients may not have a full return to baseline following attacks. These patients may use ongoing symptomatic therapy such as amantadine, baclofen, or oxybutynin.

2 = Moderate disability: The main feature is a visibly abnormal gait, but patients do not require ambulation aids. The pattern of disease is relapsing-remitting or progressive.

3 = Early cane: Intermittent use of cane (or other forms of unilateral support including splint, brace, or crutch). These patients use unilateral support primarily for longer distances, but are able to walk at least 25 feet without it. The pattern of disease is relapsing-remitting or progressive.

4 = Late cane: These patients are dependent on a cane or other forms of unilateral support and cannot walk 25 feet without such support (e.g., these patients may hang on to furniture inside their homes or touch the wall when walking in a clinic). Patients may use a scooter for greater distances (e.g., shopping malls). The pattern of disease is relapsing-remitting or progressive.

5 = Bilateral support: Patients require bilateral support to walk 25 feet (e.g., two canes or two crutches or a walker). They may use a scooter for greater distances. The pattern of disease is relapsing-remitting or progressive.

6 = Confined to wheelchair: Patients are essentially confined to a wheelchair or scooter. They may be able to take a few steps, but are unable to ambulate 25 feet, even with bilateral support. They may show further progression including worsening hand function or inability to transfer independently.

U = Unclassifiable: This category is used for patients who do not fit the above classification (e.g., significant cognitive or visual impairment, overwhelming fatigue, or significant bowel or bladder impairment in an otherwise minimally impaired patient).

From Hohol MJ, Orav, EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing disease steps and EDSS to evaluate disease progression. *Mult Scler* 1999;5(5):349–354.

FIGURE 9.6 **Disease Steps.**

values of the patients and determining the standard deviation in each patient cohort to arrive at the base Z score against which change is measured. Many patients find the PASAT unpleasant, and the refusal rate can be a significant problem.

Availability details, including a detailed manual on the use of the MSFC is available online from the National MS Society at http://www.nationalmssociety.org/. (*Note:* This is a good site for information on essentially all scales used in MS and is kept up to date.)

This is a highly reliable and efficient scale. It is much more sensitive and precise than the Kurtzke EDSS. It is more difficult to use, in that Z scores must be calculated and the clinical interpretation of the Z score is not intuitively obvious, as it is for the EDSS. The precision should allow the use of smaller numbers of patients in clinical trials relative to the EDSS. It is unlikely to find a place in office use, although the Nine-Hole-Peg test and timed gait components are used in the office setting in some clinics.

Hauser Ambulation Index The Hauser Ambulation Index (Hauser, et al., 1983) (Figure 9.5) is a straightforward historical and observational assessment of ambulation with a range from 0 (normal) to 9 (wheel-

TABLE 9.2 Other Scales Used to Assess MS

Scale	Purpose	Advantages/disadvantages
MS-QOL-54	Quality of Life; based on the Rand SF-36	Well-validated, allows comparison with other diseases
MS-QL[a]	Quality of life' more detailed than MS-QOL 54 with numerous subscales	Well-validated, long and very detailed; subscales can be used independently
MS impact scale (MSIS)[b]	A self-report scale on the impact of MS on daily activities	Has not been widely used but is extremely well designed and validated

[a]Subscales of the MS-QLI: All these are available on the U.S. National MS Society website. These have been individually validated and can be used independently: Modified Fatigue Impact Scale, Pain Effects Scale, Sexual Satisfaction Scale, Bladder Control Scale, Bowel Control Scale, Impact Of Visual Impairment Scale, Perceived Deficits Scale, Mental Health Inventory.

Modified Social support survey

[b]See Freeman JA, Langdon DW, Hobart JC, Thompson AJ. Health-related quality of life in people with multiple sclerosis undergoing inpatient rehabilitation. J Neurol Rehab 1996;10:185–194. A scoring manual is available from Dr. Jeremy Hobart, Consultant Neurologist, Peninsula Medical School, Dept. of Clinical Neurosciences, Derriford Hospital , Plymouth PL6 8DH, UK.

chair; unable to transfer independently). The test as a direct measure of mobility has face validity. Little further validation would appear necessary.

Assessment is generally done by a physician or nurse. At the lowest levels, it depends on a history from the patient or family members of interference with athletic activity or episodic imbalance. At levels from 3 to 9, it is basically an observational assessment of mobility.

The test is quite brief, involving observation of the patient walking and timing an 8-meter walk.

Advantages and Disadvantages The Hauser Index is extremely simple to use, with little opportunity for intra- or inter-observer variability. It is, however, inadequate as an overall measure of neurologic dysfunction in MS but can represent a useful component of an overall assessment. It is a simple and useful measure of independent mobility.

Disease Steps The Disease Steps scale (Figure 9.6) is an ordinal rating scale that provides a simple assessment of functional disability based primarily on mobility. It is simple and brief assessment.

Advantages and Disadvantages The Disease Steps is a simple scale with good inter-rater reliability, and it can be done quite rapidly. It is similar to the EDSS but with fewer steps. It does have a U-rating for unclassifiable patients. It can be done by anyone with minimal training.

Like the EDSS, however, it is primarily dependent on mobility and has no cognitive component.

SUMMARY

A number of other commonly used and efficient scales are used to evaluate MS (Table 9.2). Additional, more complex scales are available based on the Rand Corporation SF-36, such as the MS-QLI and the MSQOL-54, which can be found on the U.S. National MS Society web site. The MS-QLI has a variety of subscales including scales for fatigue, sexual dysfunction, bladder dysfunction, and other problem areas.

These scales are used to assess the impact of the disease and of therapies on the overall impact of the disease and treatments on quality of life. The MS-QLI subscales are useful for assessing changes in specific areas affected by the disease such as bowel and bladder control, sexual function, and cognitive effects.

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Herndon RM (editor). *Handbook of neurological rating scales*. New York: Demos Medical Publishing, 2005.

Rudick RA, Goodkin DE (editors). *Multiple sclerosis therapeutics*. London: Martin Dunitz, 1999.

United States National MS Society website. http://www.nationalmssociety.org. This is an extremely good source for scales used in MS. It contains information on the scales, their validation, and properties.

Wade DT. *Measurement in neurological rehabilitation*. New York: Oxford Medical Publications, 1992.

CHAPTER 10

CLINICAL TRIALS IN MULTIPLE SCLEROSIS: BASIC AND READING BETWEEN THE LINES

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KEY POINTS

- Good Clinical Practice (GCP) guidelines have been set to ensure that trials are conducted only where there is likely to be benefit from doing so, and that this benefit outweighs any potential risks from treatment.
- Evidence-based medicine (EBM) teaches physicians how to draw clinically meaningful conclusions from clinical trials and how to compare the results of different trials.

THE GOOD CLINICAL PRACTICE GUIDELINES

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Guidelines have been set to ensure that the trial is conducted only where there is likely to be benefit from doing so, and that this benefit outweighs any potential risks from treatment. There should also be sufficient pre-clinical information to be able to accurately predict the likely effects of the drug. The 13 principles also detail the requirements for the investigator, in terms of training and care of the patient, as well as the principle of informed consent; the confidentiality of patient information; the verification, analysis, and reporting of all data arising from the study; and the manufacture, handling, and storage of all investigational products. The most important GCP guidelines are shown in Table 10.1. The independent ethics committee should consist of a reasonable number of members who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. The investigators should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial. Prior to enrolling a patient, informed consent should be obtained, following a thorough and understandable description of the trial and the treatment, with its benefits and possible adverse reactions, and the use of placebo. Investigators should adhere to the ethical principles that have their origin in the Declaration of Helsinki. All serious adverse events should be reported immediately to the sponsor. A drug safety monitoring board (DSMB) must periodically evaluate safety reports in order to decide trial termination in case of accumulating adverse events. Accurate trial monitoring by specifically trained personnel assures that the rights and well-being of human subjects are protected; the reported trial data are accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with GCP. The sponsor should ensure that it is specified in the protocol or other written agreement that the investigators/institutions will permit trial-related monitoring, audits, ethics committee review, and regulatory inspections, providing direct access to source data and documents.

TABLE 10.1 **Good Clinical Practice (GCP) Guidelines From the International Conference on Harmonization (ICH) Working Group**

- Independent ethics committee
- Investigator's specific training
- Informed consent of trial subjects
- Safety reporting
- Premature termination of a trial
- Trial monitoring by trained personnel
- Direct access to source data/documents

HOW TO USE TRIAL RESULTS IN EVERYDAY CLINICAL PRACTICE

Evidence based medicine (EBM) teaches physicians how to draw clinically meaningful conclusions from trial data and how to compare the results of different trials. In most trials, in fact, the active drug is compared to

KEY POINT

- Well-designed and properly executed randomized clinical trials (RCT) provide the best evidence on the efficacy of health care interventions, and the CONSORT statement is published and updated almost every year to improve the quality of reporting of RCT.

placebo, and the results of different trials are not immediately comparable. EBM compares *disease event rate*. Disease event rate in the study population is compared to the expected disease event rate in the overall affected population, which is assumed to be similar to that of the group of patients treated with a placebo drug. Disease event rate is usually called the risk of the disease event and the *risk ratio* (RR) is how many times the risk of the disease event is greater (or smaller) in the actively treated group, in comparison with the *control* or *reference group*. If the risk of the disease in the treated group is equal to the expected risk (the risk in the placebo group), this means that the drug was not effective and the RR is 1. If the disease risk was reduced by the active drug, the RR will be below 1. To know if the reduction is significant, one looks at its *confidence interval*. If this range does not contain 1, this indicates that all risk ratios in this range have a less than 5% probability of being equal to 1; that is, they are significantly different from 1 at a probability level below 0.05. This is usually assumed as a satisfactory level of significance. EBM also calculates the risk reduction; that is, to what extent the active drug reduces the probability of the disease event compared to the placebo group (always representing expected disease event rate in the population). The most informative figure is the *absolute risk reduction* (ARR). Another informative figure is the *number of patients needed to treat* (NNT) to prevent the bad outcome, the disease event. NNT CI should not include 0 or a negative number, or, conversely be infinite. If the NNT is 0 or a negative number, this means that one need not treat patients to prevent the bad outcome. If it is infinite, this means that one would have to treat an infinite number of patients to prevent the bad outcome.

HOW TO ASSESS THE QUALITY OF CLINICAL TRIALS

Well-designed and properly executed randomized clinical trials (RCTs) provide the best evidence of the efficacy of health care interventions, but the quality of RCTs is not always equal. A group of scientists and editors from various fields of medicine developed the Consolidated Standards Of Reporting Trials (CONSORT) statement, which is published and updated almost every year, to improve the quality of reporting on RCTs. The objective of CONSORT is to facilitate the critical appraisal and interpretation of RCTs by providing guidance to authors about how to improve the reporting of their trials. The most important CONSORT items are shown in Table 10.2.

TABLE 10.2 Methodological Quality Criteria According to the Consolidated Standards of Reporting Trial Statement (CONSORT)

- Adequate central randomization
- Blind evaluation
- Prospective
- Multicenter
- Clear outcome definition
- Sample size calculation
- Interim analyses and stopping rules
- Adequate "Intention to treat"
- Good baseline similarity
- Protocol deviation reporting
- Side effect reporting
- Statistical significance of primary outcome results < 0.01
- Withdrawal criteria
- Adjustments for multiple analyses of secondary outcomes

Proper central randomization, with allocation concealment and blinding of investigators and patients to treatment assignment, is certainly the gold standard for RCTs, but the feasibility and the relative weight in the final estimate of treatment effect are often underestimated. *Allocation concealment* seeks to prevent selection bias, and it is always easily feasible. *Blinding* seeks to prevent observation bias, and it is not always easy, particularly when using drugs with very well-characterized side effects, like interferon-β, for example. Trials using inadequate randomization yield an evaluation of treatment effects exaggerated by 30% to 41% when compared with trials using adequate concealment of treatment allocation. By contrast, trials without double blinding yield an evaluation of

treatment effects exaggerated, on average, by only 17% compared with double-blinded trials. *Intention to treat* analysis is always stated, but not always eventually applied in the analysis of the results. All enrolled patients need to be included in the final analysis according to their original group assignment; drop-outs (that is, patients completely lost to follow-up, with no information at the end of the follow-up) are assumed to be bad outcomes; drug withdrawals (patients who discontinued treatment but remained in follow-up) are included in the analysis with the result of the final observation in spite of stopping treatment. Intention to treat avoids bias associated with nonrandom loss of participants (nonresponder patients, for example, more probably go out of the study). *P values* between 0.01 and 0.05 are only marginal significant and should be interpreted with caution.

DO MAJOR CLINICAL TRIALS IN MS FULFILL GCP AND CONSORT REQUIREMENTS?

Interferon-β In 1993, the IFNB-1b MS trial was published by the IFNB Multiple Sclerosis Study Group. It included 372 patients with EDSS scores of 0 to 5.5 and at least two relapses in the preceding 2 years. Patients were randomized to receive placebo or interferon-β-1b (50 or 250 μg subcutaneously every other day) for 2 years. Interferon-β-1b at a dose of 250 μg (8 million units), when compared to placebo, reduced the clinical relapse rate (–34%; $p < 0.0001$), the primary endpoint of the study. It also reduced the median number of T2-active lesions (–83%; $p < 0.009$) and the median volume of T2 disease burden (–17.3%; $p = 0.001$) on magnetic resonance imaging (MRI) scans.

Descriptions of the randomization procedures and sample size calculation are lacking (see Tables 10.1 and 10.2). Neither investigator's specific training nor trial monitoring by trained personnel are described. Risk ratios, absolute risk reductions, and NNTs were all statistically significant for the primary clinical endpoint (occurrence of relapses) and for MRI activity. They were not significant for the occurrence of disease progression, an outcome the study was not designed to test.

The MSCRG trial, published by Jacobs in 1996, included 301 patients with EDSS scores of 1.0 to 3.5 and at least two relapses in the preceding 3 years, randomized to receive placebo or interferon-β-1a (30 μg intramuscularly once weekly) for 2 years. This trial was stopped earlier than originally intended, and only 57% of patients (172/301) completed the full 2 years on study medication. Many results were then calculated using this subset of patients, and not on all enrolled patients according to an intention to treat analysis. After 2 years, interferon-β-1a, when compared with placebo, reduced the confirmed 1.0-point EDSS progression rate (–37%; $p = 0.02$), the primary endpoint of the trial. It also reduced the relapse rate (–18%; $p = 0.04$) and the median number of active (gadolinium enhancing) MRI lesions (–33%; $p = 0.05$). Median volume of T2 disease burden seen on MRI was also reduced, but this was not significant (–6.7%; $p = 0.36$). Descriptions of randomization procedures are lacking and not all the data were analyzed according to intention to treat (see Tables 10.1 and 10.2). No trial monitoring by trained personnel is described; the trial was prematurely stopped. Risk ratios, absolute risk reductions, and NNTs failed to reach statistical significance for all outcome measures (including the occurrence of disease progression, the primary endpoint of the trial).

The Prevention of Relapses and Disability by Interferon-β-1a Subcutaneously in Multiple Sclerosis (PRISMS) study, published in 1998, was a multicenter, controlled trial in which 560 patients with an EDSS score between 1.0 and 5.0 and at least two relapses in the preceding 2 years were randomized to 2-year treatment with placebo or interferon-β-1a (22 or 44 μg subcutaneously three times weekly). Interferon-β-1a at a dose of 44 μg, three times weekly reduced relapse rate (–32%; $p < 0.005$), the primary endpoint of the trial. It also reduced the confirmed 1.0-point EDSS progression rate (–30%; $p < 0.05$), the median number of T2 active lesions (–78%; $p < 0.0001$), and the median volume of T2 disease burden seen on MRI (–14.7%; $p < 0.0001$) when compared with placebo. In addition, although 22 μg interferon-β-1a three times weekly was more

KEY POINTS

- Interferon-β is the first drug that modified the course of RR-MS. It reduces relapse rate, MRI activity and, to a lesser extent, disease progression. Direct comparative trials indicated the need for frequent high-dose administration of interferon-β to optimize efficacy.
- Interferon-β-1b at a dose of 250 μg subcutaneously, every other day, reduces the clinical relapse rate; the median number of T2-active lesions; and the median volume of T2 disease burden on MRI scans. Risk ratios, absolute risk reductions, and NNTs were all statistically significant for occurrence of relapses and for MRI activity. They were not significant for the occurrence of disease progression.
- Interferon-β-1a at a dose of 30 μg, intramuscularly, once a week, reduces the confirmed 1.0-point EDSS progression rate, the relapse rate, and the median number of active (gadolinium-enhancing) MRI lesions. Risk ratios, absolute risk reductions, and NNTs failed, however, to reach statistical significance for all outcome measures.
- Interferon-β-1a at a dose of 44 μg, subcutaneously, three times weekly reduces relapse rate, the confirmed 1.0-point EDSS progression rate, the median number of T2-active lesions, and the median volume of T2 disease burden seen on MRI. Risk ratios, absolute risk reductions, and NNTs were all statistically significant both for clinical endpoints and for MRI activity.

KEY POINT

- Two major studies, INCOMIN and EVIDENCE, directly compared interferon β-1b (250 mcg, every-other-day) or interferon β-1a (44 mcg, three times weekly) to interferon β-1a, 30 mcg, once-a-week. They both support the hypothesis that the dose and dosing schedule have a major impact on the clinical efficacy of interferon β indicating the need for frequent high-dose administration of β interferon in order to optimize efficacy in patients with relapsing-remitting MS.

effective than placebo, a subgroup of patients with more severe disease (baseline EDSS score > 3.0) responded only to the higher dose. The trial was very well designed and reported (see Tables 10.1 and 10.2). Neither investigator's specific training nor trial monitoring by trained personnel are described. Risk ratios, absolute risk reductions, and NNTs were all statistically significant both for clinical endpoints and for MRI activity.

Randomized Comparative Trials of Different Interferon-β Treatment Protocols The evidence for Interferon Dose Effect: European – North American Comparative Efficacy (EVIDENCE) trial compared interferon-β-1a, 44 μg subcutaneously, three times weekly (n = 339) and interferon-β-1a, 30 μg intramuscularly once weekly (n = 338). This trial was a multicenter, prospective, randomized, assessor-blinded study. The initial phase of the study was 24 weeks, with patients having the option to remain on study medication for up to 48 weeks. At 24 weeks, interferon-β-1a given at 44 μg three times weekly had a significantly greater effect than at 30 μg once weekly on several relapse-related outcomes. Significantly more patients were relapse-free with the three-times weekly dosing schedule at 44 μg (74.9%) than with once weekly dosing at 30 μg (63.3%; p = 0.022). In addition, 44 μg of interferon-β-1a reduced the risk of suffering a first relapse by 30% and increased the number of patients free from new T2 lesions by 30%. At 48 weeks, clinical and MRI effects still favored the high-dose, three-times weekly interferon-β-1a, although the difference between the two groups became less pronounced. The study, although of short duration, was well-conducted, and the statistical analysis was performed well (see Tables 10.1 and 10.2). Risk ratios and absolute risk reductions with 44 μg three-times weekly interferon-β-1a compared to 30 μg once-weekly interferon-β-1a were all statistically significant.

The INCOMIN trial, published by Durelli and coworkers in 2002, directly compared the clinical and MRI efficacy of interferon-β-1b (250 μg every other day subcutaneously) to once-weekly interferon-β-1a (30 μg intramuscularly). INCOMIN was a controlled study in which 188 patients, with an EDSS score between 1.0 and 3.5 and at least two relapses in the preceding 2 years were randomized, with allocation concealment, to treatment with either drug for 2 years. Over the 2 years, every-other-day interferon-β-1b increased the proportion of patients without relapses (primary clinical endpoint) (+42%; p = 0.03); without new T2 lesions at MRI (primary MRI endpoint) (+112%; p < 0.0003); and without confirmed 1.0-score EDSS progression (+25%; p < 0.005); and slowed time to confirmed disability progression (p < 0.01) when compared to once-weekly interferon-β-1a. Blinded assessment was limited to the MRI analysis, which was performed on a subset of patients (80%) (see Tables 10.1 and 10.2). Ascertainment bias introduced by the open label clinical evaluation was probably marginal because clinical results were extremely consistent with MRI results.

Two major studies, INCOMIN and EVIDENCE, therefore, support the hypothesis that the dose and dosing schedule have a major impact on the clinical efficacy of β-interferon, indicating the need for frequent high-dose administration of β-interferon to optimize efficacy in patients with relapsing-remitting MS. However, their duration was probably less than necessary to include the negative effect of neutralizing antibodies.

Side Effects The majority of the side effects associated with interferon-β use (Table 10.3) are most likely during first 3 to 6 months of treatment and decline in frequency thereafter. The frequency of side effects is similar with interferon-β-1a or β-1b, with two exceptions. A higher incidence exists of both local skin reactions and positive titers for neutralizing antibodies against interferon-β in interferon-β-1b–treated patients. Local skin reactions to interferon-β tend to decline with improved injection technique. Neutralizing antibodies have been associated with reduced levels of interferon-induced biologic markers, and probably affect the clinical and MR response in MS patients. They tend, however, to disapper over time.

Treatment Protocol In conclusion, a single weekly administration of interferon-β, although more attractive for patients, may be

less effective, or its effects might be delayed by at least 1 year from the start of treatment. It is important for patients to receive the best treatment with the quickest onset of beneficial effect, which in this case is most likely interferon-β given by multiple weekly injections. Arguments that neutralizing antibodies against interferon-β-1b deleteriously affect the eventual course of MS must be evaluated in long-term comparisons.

GLATIRAMER ACETATE

Randomized Trials The first large controlled trial, published by Johnson and coworkers in 1995, included 251 patients with an EDSS score between 0 and 5.5 and at least two relapses in the preceding 2 years, randomized to receive either placebo or 20 mg glatiramer acetate subcutaneous daily for up to 3 years. Using evidence-based medicine analysis, after 2 years glatiramer acetate reduced relapse rate (–29%; $p = 0.007$), the primary endpoint; and slowed unconfirmed 1.5-point EDSS progression (–28%; $p = 0.037$), compared to placebo. No MRI outcome measures were assessed as part of this trial. No trial monitoring by trained personnel is described.

A second short-duration European/Canadian trial, published by Comi and coworkers in 2001, was undertaken to look specifically at MRI measures. It involved 249 patients with EDSS scores between 0 and 5.0, at least one relapse in the previous 2 years, and one gadolinium-enhancing lesion on the screening MRI, randomized to receive either placebo or 20 mg glatiramer acetate for 9 months. Glatiramer acetate reduced the total number of enhancing lesions (the primary endpoint) (–35%; $p = 0.001$), relapse rate (–33%; $p = 0.012$), and the median change in T2 disease burden (–8.3%; $p =$

KEY POINTS

- Glatiramer acetate efficacy in RR-MS is less convincing than that of interferon-β. It should be reserved as second choice in case of intolerable side effects or toxicity of interferon-β.
- Glatiramer acetate at a dose of 20 mg subcutaneously daily reduces relapse rate, unconfirmed 1.5-point EDSS progression, the total number of MRI-enhancing lesions, and the median change in T2 disease burden.

TABLE 10.3 **The Most Common Side Effects of Interferon-β Treatment in MS (Percent Occurrence in Interferon- and Placebo-treated Patients [%/%]) and Their Management**

	Every-other-day interferon beta-1b Subcutaneous	Once-a-week interferon beta-1a Intramuscular	Three-times-weekly interferon beta-1a Subcutaneous	Management	Tolerability
Local skin reactions	85%/22%	15% /10%	46%/22%	Transient 50% dose reduction, improve injection technique	Good
Fever	49%/30%	23%/13%	35%/24%	Acetaminophen 500–1,000 mg, pentoxyphilline 1,200–1,500 mg	Good
Flu-like symptoms	52%/24%	61%/40%	56%/24%	Acetaminophen 500–1,000 mg, pentoxyphilline 1,200–1,500 mg	Good
Fatigue	37%/15%	21%/13%	23%/26%	Amantadine 100–200 mg	Poor
Leuko- or thrombocytopenia	40%/28%	8%/5%	20%/10%	Transient 50% dose reduction	Good
Increased liver enzymes	19%/18%	10%/8%	20%/8%	Transient 50% dose reduction	Good
Depression	16%/12%	10%/10%	24%/28%	Antidepressants	Poor
Skin necrosis	5%/0%	0%/0%	2%/0%	Improve injection technique, stop treatment	Poor
Thyroid alterations	1–2%/1%	1–2%/1%	1–2%/1%	Transient 50% dose reduction	Good

KEY POINTS

- The effect on MRI-enhancing lesions was delayed until 6 months after starting treatment, whereas studies with interferon-β demonstrated effects on MRI activity after only 1 or 2 months.
- Risk ratios, absolute risk reductions, and NNTs obtained for all outcome measures are not statistically significant.
- The efficacy of interferon-β in SP-MS is still controversial.

0.0011). The effect on MRI-enhancing lesions was delayed until 6 months after starting treatment, whereas studies with interferon-β demonstrated effects on MRI activity after only 1 or 2 months. Details on randomization and sample size calculation are lacking in the clinical study, and the MRI study lasted only 9 months (see Tables 10.1 and 10.2). Neither investigator's specific training nor trial monitoring by trained personnel are described. Risk ratios, absolute risk reductions, and NNTs obtained for all outcome measures are not statistically significant. This includes MRI outcome measures, even though the study was specifically designed to test glatiramer acetate MRI effects.

Side Effects Glatiramer acetate is well tolerated. Only minor, short-lived local skin reactions are common (Table 10.4). Localized lipoatrophy at the site of injection has been, however, reported in as many as 45% patients, mostly women. In some cases, lipoatrophy occurred within months of therapy initiation. Lipoatrophy can be very disfiguring and is thought to be permanent; the psychological impact can be significant. It is, therefore, important that patients be aware of the possibility of lipoatrophy, be able to identify it, and discontinue injecting in areas where it is identified.

Once in every 1,000 injections, a systemic reaction may occur, with dyspnea, flushing, chest tightness, or palpitations, resolving in seconds or minutes without sequelae. This rare event seems benign, even though its exact nature and mechanism remains unknown.

The only protocol used for glatiramer acetate is 20 mg subcutaneously per day. The risk ratio, absolute risk reduction, and NNT values are less convincing than are those for interferon-β. They are not statistically significant for all outcome measures, both in the clinical as well as in the MRI study.

TREATMENT OF SECONDARY PROGRESSIVE MS

Interferon-β The effect of interferon-β in secondary progressive MS (SP-MS) is still controversial. The European Study Group on Interferon-β-1b in Secondary Progressive MS (EuSPMS) trial, published in 1998), which included 718 patients treated with either interferon-β-1b or placebo for 3 years, demonstrated a reduction in the rate of 1.0-point confirmed EDSS progression (–22%; $p = 0.0008$), the primary endpoint. Other trials with interferon-β-1b in North America or -1a failed to confirm this.

IMPACT investigators testing the efficacy of 60 μg once-weekly interferon-β-1a claimed a low sensitivity of the EDSS and also used an alternative outcome measure, the Multiple Sclerosis Functional Composite (MSFC) scale (see Chapter 9). MSFC assesses ambulatory function, plus arm and cognitive function. They demonstrated a significant 40% reduction of median MSFC worsening with interferon-β-1a treatment compared to placebo ($p < 0.033$). The composite evaluation of functions other than ambulation (the main function evaluated by EDSS) is certainly useful. The recently introduced MSFC scale, developed and validated by the same investigators who also performed IMPACT, consists of continuously distributed measures. It will need to be validated for statistical significance in comparison to discrete measures of function.

All trials with interferon-β in SP-MS are good quality trials (see Tables 10.1 and 10.2). Some of them were prematurely stopped. Evidence-based medicine measures from the published trials are statistically significant for both clinical and MRI endpoints in the EuSPMS trial, but only for MRI endpoints in the SPECTRIMS and IMPACT trials. It has been noted that patients in the unsuccessful trials had significantly fewer attacks than did those in the EuSPMS trial, and that perhaps interferon-β is more effective in the relapsing phase of the illness.

MITOXANTRONE

Randomized Trials Mitoxantrone is a synthetic antineoplastic drug with long-lasting immunosuppressive effects. On the basis of two controlled studies, it was registered for the treatment of worsening progressive MS. Edan and coworkers, as published in 1997, studied 42 patients with an EDSS score of up to 6.0 and at least two relapses or disease progression assessed by an increase of two EDSS points in the preceding 12 months

TABLE 10.4 **The Most Common Side Effects of Glatiramer Acetate Treatment in MS (Percent Occurrence in Glatiramer Acetate- and Placebo-treated Patients [%/%]) and their Management**

	Frequency	Management	Tolerability
Local skin reactions:	90%/59%	Transient reactions,	Good
Pain	64%/36%	do not need treatment	
Erythema	57%/13%		
Pruritus	38%/4%		
Induration	27%/8%		
Necrosis	0%/0%		
Localized lypoatrophy	5–45%	Change injection site	Poor
Systemic reaction:	15%/3%	Transient reaction,	Good
Dyspnea	13%/2%	does not need treatment	
Flushing	8%/2%		
Chest pain	10%/2%		
Palpitation	5%/0%		
Laboratory abnormalities	0%/0%	—	—

KEY POINTS

- Mitoxantrone should be reserved for patients with a particularly aggressive and progressive disease. Its use requires careful monitoring of possible toxicity and must be of limited duration due to the cumulative toxicity of multiple doses.
- In patients with an EDSS score of up to 6.0 and at least two relapses or disease progression assessed by an increase of two EDSS points in the preceding 12 months and one new enhancing lesion on baseline monthly MRI, mitoxantrone at a dose of 20 mg intravenously monthly increased the proportion of patients with no new enhancing lesions, without relapses, and without confirmed 1.0-score EDSS worsening.

and one new enhancing lesion on baseline monthly MRIs. Patients were randomized to 20 mg mitoxantrone plus 1,000 mg methylprednisolone, or 1,000 mg methylprednisolone only, intravenously monthly for 6 months. Mitoxantrone treatment increased the proportion of patients with no new enhancing lesions (+200%, $p < 0.001$), the primary endpoint; without relapses (+103%, $p < 0.05$); and without confirmed 1.0-score EDSS worsening (+34%; $p < 0.01$). The follow-up lasted only 6 months, details on randomization are lacking, and only the MRI assessment was blind (see Tables 10.1 and 10.2). Despite the small sample size, the risk ratios, absolute risk reductions, and NNTs are statistically significant for both clinical and MRI outcome measures. Neither investigator's specific training nor trial monitoring by trained personnel are described; the trial was prematurely stopped.

In the MIMS study, published by Hartung and coworkers in 1998, 194 patients with an EDSS score between 3.0 and 6.0 and a documented progression of at least 1.0-EDSS point in the preceding 18 months were randomized to 12 or 5 mg/m^2 mitoxantrone intravenously, or placebo, every 3 months for 24 months. A significant treatment effect ($p < 0.0001$) for 12 mg/m^2 mitoxantrone compared to placebo was demonstrated on a composite primary outcome measure that included changes in EDSS plus other clinical indices, and on the number of relapses, and the time to first severe relapse. Mitoxantrone increased the proportion of patients without relapses (+58%, $p = 0.02$); without confirmed 1.0-point EDSS worsening (+17%, $p = 0.03$); and without enhancing lesions on MRI (+18%, $p = 0.02$). Details of randomization are lacking, and MRI studies were performed on only 57% of patients (see Tables 10.1 and 10.2). Neither independent ethics committee nor possibility of direct access to source data or documents are described. Concern about study blindness comes from the impossibility of keeping either the patient or the treating physician blind to the blue coloration of the sclera and urine that occurs with this treatment. Risk ratios, absolute risk reductions, and NNTs are statistically significant for both clinical and MRI outcome measures.

Side Effects Mild transient nausea, alopecia, and menstrual disorders occur in over 50% cases; secondary amenorrhea in 10% (Table 10.5). Granulocytopenia is the main dose-limiting toxic effect, occurring in about 6% cases, peaking 8 to 14 days after drug administration and persisting for 4 to

KEY POINTS

- Dose-dependent, usually irreversible, cardiac toxicity may occur, exceptionally leading to congestive heart failure. Acute leukemia has been reported in 2 multiple sclerosis patients 1.3–5 years after discontinuing mitoxantrone.
- Use of mitoxantrone requires careful monitoring for possible toxicity.

10 days. Dose-dependent, usually irreversible, cardiac toxicity also may occur, exceptionally leading to congestive heart failure (2 of 452 patients). Acute leukemia also has been reported 1.3 to 5 years after discontinuing mitoxantrone.

Treatment Protocol Mitoxantrone is administered at the dose of 5 to 12 mg/m^2 every 1 to 3 months intravenously. The total cumulative dose should not exceed 160 mg (see Table 10.5). Because of concerns about such potential cardiac toxicity, a cumulative dose of mitoxantrone of more than 140 mg/m^2 is not recommended for treatment of MS, although doses of up to 96 mg/m^2 seem to be safe. At a dose of 12 mg/m^2 administered every 3 months, this limitation (140 mg/m^2) translates to a maximum duration of therapy of only 2 to 3 years. Such a therapeutic approach may be inadequate in a disease that will likely require ongoing treatment over many years. Moreover, the optimal way to monitor patients for potential cardiotoxicity (e.g., multiple-gated acquisition [MUGA] scans, echocardiograms) is unknown, as are the risks of long-term cardiac toxicity from short-term treatment. Similarly, whether the limit of 140 mg/m^2 is safe for all patients or whether a bell-shaped curve exists for individual susceptibility to such toxicity remains to be determined.

NATALIZUMAB

Natalizumab is a recombinant humanized IgG4K antibody produced in murine myeloma cells. On November 2004, it was approved by the U.S. Food and Drug Administration (FDA) as Tysabri for treatment of MS. The approval was based on two randomized, double-blind, placebo-controlled trials with over 2,000 subjects. Subjects were enrolled if they had experienced at least one relapse during the prior year and had a score of between 0 and 5.0 on the EDSS. In both studies, neurologic evaluations were performed every 12 weeks

TABLE 10.5 **The Most Common Side Effects of Mitoxantrone Treatment in MS (Percent Occurrence in Mitoxantrone- and Placebo-treated Patients [%/%]) and Their Management**

	Frequency	Management	Tolerability
Nausea	76%/20%	Give always intravenous antiemetics before infusions	Good
Alopecia	61%/31%	Transient, no treatment	Good
Menstrual disorders (secondary amenorrhea)	60%/26% (10%/0%)	Transient, no treatment (hormonal replacement)	Good (may be irreversible)
Urinary tract infection	32%/13%	Antibiotics (check white blood cell count)	Good
Leukopenia (granulocytopenia)	19%/0% (6%/2%)	White blood cell count 3–6 days before and every 10 days after infusions (50% dose reduction if neutrophil count <1,500/mm^3)	Good
Increased liver enzymes	15%/8%	Usually transient, 50% dose reduction if >fivefold baseline	Good
Cardiac toxicity	2%/0%	Echocardiogram every 6 months or above 100 mg cumulative dose; stop if left ventricular ejection fraction drops by 10% or below 50% or above 160 mg cumulative dose	May progress even after stopping treatment
Acute leukemia	Exceptional	—	May occur even after stopping treatment

and at time of suspected relapse. MRI evaluations for T1-weighted gadolinium (Gd)-enhancing lesions and T2-hyperintense lesions were performed annually. In the AFFIRM study, all 942 subjects enrolled had not received any interferon-β or glatiramer acetate for at least the previous 6 months. The median age was 37, with a median disease duration of 5 years. Subjects were randomized to receive natalizumab (300 mg intravenous [IV] infusion) or placebo every 4 weeks for up to 28 months. The 1-year results showed that subjects who received natalizumab had a 66% reduction of annualized relapse rate compared with subjects taking placebo. The proportion of patients with sustained disability progression was 17% in the natalizumab-treated group compared with 29% in the placebo group (41% reduction). Seventy-six percent of subjects taking Natalizumab had remained relapse free, compared with 53% of subjects taking placebo (30% increase). In the SENTINEL study, all 1,171 subjects enrolled in the study had experienced one or more relapses while on treatment with IFN-β-1a (30 μg intramuscularly) once weekly during the year prior to study entry. The median age was 39, with a median disease duration of 7 years. Subjects were randomized to receive natalizumab (300 mg IV infusion) or placebo every 4 weeks for up to 28 months. Subjects continued taking interferon-β-1a at their normal dosing once weekly. The 1-year results showed that subjects who received natalizumab had a relapse rate of 0.36 compared with 0.78 for subjects taking placebo (53% decrease). Data demonstrated that 67% of subjects taking natalizumab remained relapse free, compared with 46% of subjects taking placebo (31% increase).

Side Effects The most frequently reported serious adverse reactions at the moment of the approval were infections, including pneumonia; temporary hypersensitivity reactions (such as rash, fever, low blood pressure, and chest pain); depression; and cholelithiasis. These serious adverse reactions were uncommon. Common adverse reactions were generally mild and included nonserious infections (such as urinary tract, lower respiratory tract, GI system, and vaginal infections), headache, depression, joint pains, and menstrual disorders.

Unexpectedly, in February 2005, the drug was suspended from marketing. The FDA received a report from Biogen Idec, the manufacturer of Tysabri, of one confirmed fatal case and one possible case, later confirmed, of progressive multifocal leukoencephalopathy (PML) in patients receiving natalizumab for MS. PML is a lethal opportunistic infection of the central nervous system (CNS) for which no specific treatment exists. It is caused by reactivation of a clinically latent JC polyomavirus infection. This virus infects and destroys oligodendrocytes, leading to multifocal areas of demyelination and associated neurologic dysfunction. The occurrence of PML in this setting was totally unexpected, because it almost invariably occurs in the context of profoundly impaired cell-mediated immunity in patients with acquired immune deficiency syndrome (AIDS) or leukemia or in organ transplant recipients. Although the relationship between natalizumab and PML was not known at that time, because of the serious and often fatal nature of PML, the FDA concurred with the company that the drug be voluntarily withdrawn from marketing and that the use of natalizumab in clinical trials be suspended until more was known. After the drug suspension from marketing, a third case of PML, of a patient treated with natalizumab within a Crohn disease trial, has been reported. The retrospective MRI analysis of all the treated patients is ongoing and focused on finding other possible cases of PML. No new cases have been found.

SUMMARY

Several other immunomodulatory agents have been tested for the treatment of RR-MS or SP-MS in randomized controlled trials over the last few years. Unfortunately, some trials were stopped due to severe drug toxicity, whereas others did not yield significant results.

Using the evidence-based medicine paradigm, interferon-βs represent the best therapeutic option, based on the evidence to date, particularly if given at high doses and with multiple injections per week. In partially responding patients, it might be appropriate to gradually increase the dose. Glatiramer

KEY POINTS

- Natalizumab at a dose of 300 mg intravenously once monthly reduces relapse rate, sustained disability progression, and the number of MRI enhancing lesions.
- Natalizumab treatment has been associated with rare cases of PML, a lethal viral encephalopathy. It has therefore been approved for treatment of MS with a warning about PML.

KEY POINT

- Using EBM parameters, interferon β represents the best treatment, particularly at high doses and multiple weekly injections. Glatiramer acetate is a second choice drug; and mitoxantrone should be reserved for particularly aggressive forms of MS with frequent monitoring for possible toxicity.

acetate should be reserved as second choice in case of intolerable side effects or toxicity of interferon-β. Mitoxantrone should be reserved for patients with a particularly aggressive and progressive disease. Its use requires careful monitoring of possible toxicity and must be of limited duration due to the cumulative toxicity of multiple doses. It is hoped that some of the oral medications being tested at present in experimental trials, either as inhibitors of blood–brain barrier (BBB) transgression or as immunosuppressors will end up improving our management tools, which remain rather poor.

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