Aaron Miller *Editor*

Handbook of Relapsing-Remitting Multiple Sclerosis

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This book is dedicated to Ellen, whose warmth, compassion, and empathy are a constant inspiration and whose love and unwavering support make everything possible.

Preface

In an era of ever greater specialization among health care providers, it has become increasingly difficult to stay abreast of the latest developments of any one particular field. Nowhere is this challenge more manifest than in the field of multiple sclerosis (MS), where advances in basic science, neuroimaging, and clinical care have shaped a landscape that might have seemed unrecognizable to neurologists practicing 50 years ago. The *Handbook of Relapsing-Remitting Multiple Sclerosis* is the culmination of an effort by MS specialists at a world-renowned medical institution to distill the current state of knowledge into a practical guide. Non-MS specialists wishing to learn more about MS will hopefully find this handbook a useful resource. We will describe the epidemiology and known genetic and environmental risk factors of MS; pathogenesis and clinical presentation; diagnosis and differential diagnosis; and treatment strategies, including goals of treatment, existing and emerging therapies, and symptom management.

New York, NY, USA — Aaron Miller

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Chapter 1
Multiple Sclerosis: An Overview

Robert Gross and Fred Lublin

1.1 Introduction

Multiple sclerosis (MS) is a chronic dysimmune disorder of the central nervous system (CNS). It is characterized pathologically by perivascular infiltrates of autoreactive lymphocytes and activated macrophages producing breakdown of the myelin sheaths that surround neurons. These inflammatory infiltrates form the characteristic plaques whose presence on autopsies led the nineteenth century French neurologist Jean-Martin Charcot, known as the founder of modern neurology, to coin the term *la sclérose en plaques*. Neurological symptoms associated with demyelinating plaques are varied and include vision impairment, dizziness, focal weakness and clumsiness, numbness and tingling, bowel and bladder dysfunction, incoordination, imbalance, gait impairment, fatigue, and cognitive dysfunction. In many instances, the location of the lesions predicts the clinical manifestation, though some symptoms (e.g., fatigue, cognitive dysfunction) are less localizable within the brain. Phenotypically,

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MS is heterogeneous: some patients are minimally or not at all affected, while others are extremely debilitated.

When characterizing the clinical course of MS, it is helpful to be familiar with standard nomenclature. A *relapse* or *exacerbation* is defined as an acute or subacute episode of new or increasing neurologic dysfunction followed by full or partial recovery, in the absence of fever or infection. Generally, relapses include neurologic symptoms or signs that persist for at least 24 h. *Progression* is a gradual, steady increase in neurologic dysfunction or disability without unequivocal recovery (fluctuations and periods of stability may occur).

Classification of patients into categories based on their clinical course has been essential for defining patient groups in natural history studies and for designing clinical trials, as well as for communicating with patients and other clinicians. In an effort to provide clear and consistent definitions of the different clinical subtypes laid out in earlier course descriptions, a committee of MS experts from around the world issued the consensus-based 2013 revisions [1]. The vast majority of patients (~85–90 %) begin their clinical course with a relapse, often occurring in late adolescence or young adulthood. An initial clinical episode suggestive of MS but without clinical or radiographic evidence establishing dissemination in time and/or space is termed *clinically isolated syndrome* (CIS). Classic examples of CIS include optic neuritis, brainstem attack (such as internuclear ophthalmoplegia), and partial transverse myelitis. Longitudinal studies have shown that patients with CIS who present with two or more lesions on brain MRI (some 50–70 % of adults with CIS [2]) have a high risk of a second attack and thus conversion to MS: after 20 years, 82 % of patients with CIS and abnormal brain MRIs will have converted to MS, compared to 21 % of those with normal baseline brain MRIs [3]. For many neurologists specializing in MS, the practical distinction between CIS with brain lesions and definite MS—in which dissemination in space *and* time has been established—has eroded in light of such natural history studies and the pivotal CIS drug trials that demonstrated improved outcomes with early treatment [4–10]. Positive cerebrospinal

fluid (CSF), commonly defined as either an elevated immunoglobulin G (IgG) index or the presence of oligoclonal bands, is also a risk factor for conversion from CIS to MS independently from MRI lesions, though perhaps not as helpful as brain lesions [11].

Relapsing-remitting MS (RRMS) is the most common disease subtype and consists of relapses separated by periods of remission of variable length. Chronic symptoms may persist in these otherwise quiescent periods, or may reappear transiently with increased body temperature as during an infection or vigorous exercise (i.e., Uhthoff's phenomenon), as a result of diminished signal transmission through demyelinated axons—these are not reflective of ongoing disease activity, per se. The decades of young adulthood following an MS diagnosis are the times when the disease tends to be the most active. Later in life, inflammation subsides, though relapses can still occur in one's 60s or 70s. Patients are generally followed with regular neurologic evaluations and periodic MRIs—best practice is to perform surveillance neuroimaging once a year in the absence of new symptoms. Evidence of disease activity, whether in the form of a new relapse or new lesions on the MRI, often prompts a discussion about changing treatments.

Natural history studies of multiple sclerosis suggest that approximately 50 % of patients with RRMS go on to transition to *secondary progressive* MS (SPMS), in which there is a gradual worsening with or without superimposed relapses after an initial relapsing-remitting course. Such estimations, though, are potentially misleading in the current context of widely available disease modifying treatments, which some believe may slow or prevent the transition to SPMS, though direct proof of this hypothesis is lacking. Some 10–15 % of patients initially present without relapses, but rather with slow deterioration; this is labeled *primary progressive* MS (PPMS) (Fig. 1.1).

When still accompanied by relapses or MRI markers of disease activity, SPMS and PPMS take on the added descriptor of "active." Additionally, as progressive disease does not always advance uniformly—some progressive patients may

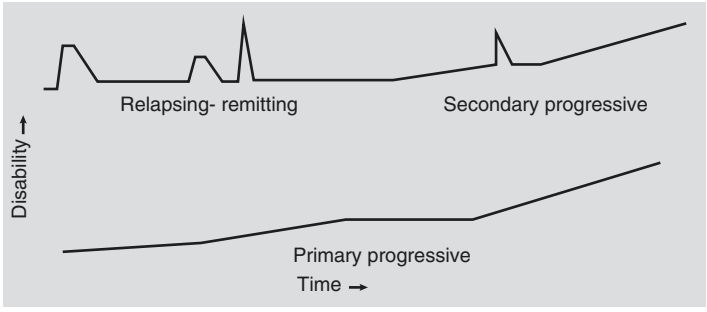

Figure 1.1 Disease courses of multiple sclerosis

remain relatively stable over a period of time—a full description of the clinical course according to the 2013 revisions includes a mention of whether or not the patient is progressing at that point. Thus, a patient with SPMS who has gradually worsened over the past year, during which time two new lesions appeared on an MRI, would be considered SPMS, active and progressing; on the other hand, a patient with PPMS who has a stable examination and no activity on an MRI would be characterized as having PPMS, not active and without progression. One or more attacks in a course initially characterized by progression and previously classified as progressive relapsing MS (PRMS) is by the 2013 consensus criteria deemed "PP-active."

Distinguishing clinically between disease activity and progression reflects the current view of MS as a disease involving both inflammation and neurodegeneration and is important for prognosis and management. While much has been learned about the mechanisms of immune dysregulation underlying relapsing forms of MS, less is known about progressive MS pathophysiology. Likewise, the numerous therapies that have emerged to treat relapsing forms of MS—all targeting some aspect of the immune system—have largely been unsuccessful, with one notable recent exception [12], in slowing or halting progressive forms of the disease, during which inflammatory activity is replaced by axonal loss and atrophy.

The fact that multiple trials of immunosuppressive and immunomodulatory agents with the ability to reduce MS-related inflammation have failed to convincingly halt progressive disease is a testament to its fundamentally distinct nature. In this way, SPMS behaves more like PPMS than like RRMS, from which it evolved. Whether or not neurodegeneration in progressive MS is a process driven by underlying inflammation that is not visible on conventional MRI is an open question. Therapies that curb progression and promote repair are sorely needed and are the focus of ongoing research.

The proliferation of incidentally discovered imaging findings that are suggestive of MS presents something of a dilemma for MS specialists. This situation, *radiologically isolated syndrome* (RIS), is technically not a subtype of MS; diagnostic criteria currently require clinical evidence of demyelinating disease. However, since the early 1960s, it has been recognized that individuals without clinical evidence of disease during their lifetime can, on autopsy, be found to have pathological changes consistent with MS [13]. Indeed, even among patients with established MS, "clinically silent" MRI lesions are known to occur with much greater frequency than symptom-producing lesions [14]. Adding to the confusion is the fact that not all "white spots" in the brain are equal; migraine, small vessel disease, and even aging can all produce white matter changes on MRI. It has been shown that family members of patients with MS are more likely than others to be found to have asymptomatic lesions [15, 16]. Proposed MRI diagnostic criteria for RIS include ovoid, well-circumscribed, and homogeneous lesions with or without corpus callosal involvement measuring at least 3 mm, in at least three of four characteristic neuroanatomical locations (juxtacortical, periventricular, infratentorial, spinal cord) [17]. About 34 % of patients with RIS meeting these criteria will have an attack in 5 years of follow-up [18]. Younger age at RIS identification, male gender, spinal cord lesions, contrast-enhancing lesions, and positive CSF are all risk factors for an eventual MS diagnosis [16, 17, 19].

1.2 Epidemiology and Risk Factors

About 400,000 people carry an MS diagnosis in the United States (1 in 750), though this figure is a rough estimate, as no centralized reporting mechanism exists for MS. Globally, the figure is thought to be around 2.5 million. The incidence of MS has been increasing in recent years, not solely due to an improvement in diagnostic capability, for reasons that remain unclear [20]. As in other autoimmune conditions, women are more affected than men; the sex ratio is between 2:1 and 3:1 women-to-men and has been increasing over the last century [21]. This gender disparity may involve hormonal differences, as pediatric MS—though rarer—is diagnosed more equally in boys and girls. Indeed, endogenous hormones are not only implicated in MS susceptibility, but also in disease activity, most notably in the observation that various hormones rise dramatically during pregnancy, when MS activity is generally suppressed, and plunge in the immediate post-partum period, which is often marked by rebound disease activity. Like the overall increasing incidence of MS, the increasing rates of the disease in women compared to men are inadequately understood but probably involve changing environmental (nonheritable) risk factors. The demographics of PPMS differ somewhat from those of RRMS, in that PPMS generally presents at a later age and has a more equal male-to-female incidence ratio.

Many researchers have hoped that by learning about what predisposes certain people to developing MS, we can discover new avenues of treatment, or even prevention. Several decades of MS research have given rise to the theory that MS occurs in genetically susceptible individuals upon exposure to certain environmental triggers. Thus, this chapter will review the environmental risk factors before discussing the genetic ones.

Regarding the global MS distribution, the *latitude gradient* is probably the single most recognized feature: regions farther from the equator generally have higher rates of MS. Sunlight exposure and, by extension, vitamin D levels,

which increase in relation to the duration and intensity of sunlight exposure, may be the primary driver of the latitude gradient. Evidence for the role of vitamin D deficiency in MS also comes from investigations of food consumption. In Scandinavia, for example, coastal fishing areas where diets are richer in vitamin D have a lower incidence of MS than inland regions [22]. It should be noted that many case-control trials that have found correlations between low vitamin D levels and MS are prone to biases, such as reverse causation and recall bias. For example, it may not be that low vitamin D levels cause MS, but rather that vitamin D levels (captured retrospectively after disease onset) are depressed in patients with MS because they choose to avoid sunlight. Munger et al. showed in a prospective nested case-control study that higher circulating levels of 25-hydroxy vitamin D were associated with a lower risk of MS [23]. A study drawing from two large prospective cohorts, the Nurses' Health Study and the Nurses' Health Study II, found a relative risk of developing MS of 0.67 when comparing those in the highest quintile of vitamin D intake to the lowest [24]. To be sure, not all studies have consistently shown an association between vitamin D deficiency and MS susceptibility. In fact, there may be differential effects of low vitamin D in different groups, the result of interactions with other environmental or genetic factors [25]. Vitamin D is known to have immunoregulatory and anti-inflammatory effects and can prevent the development of experimental autoimmune encephalomyelitis (EAE), the murine model of MS. Furthermore, fewer MRI lesions and relapses are observed in patients with MS and higher serum concentrations of vitamin D [26, 27]. Still, whether or not supplementation is an effective strategy to prevent MS, or even to reduce disease activity in patients with MS, has not been proven.

In addition to the increasing incidence of MS, another phenomenon that provides strong evidence for the influence of environmental factors is the presence of changing risk levels among migrants. When migrating from a low- to high-incidence region, individuals generally assume the risk level

of the new region if migration occurs prior to age 15 [28]. Besides sunlight and vitamin D, population-based epidemiological studies have looked for associations with a variety of environmental risk factors, including various infections, vaccinations, trauma, surgeries, and toxin exposures. Of these, two of the risk factors that have emerged with the highest degree of confidence are cigarette smoking and Epstein-Barr virus (EBV) infection (e.g., infectious mononucleosis [IM]) [29]. In areas where early childhood exposure to EBV is universal, MS is rare. Where EBV exposure occurs later, the incidence of both IM and MS increases. People who have had IM have about a 2.17-fold increased risk of developing MS, according to one meta-analysis [30]. While EBV seropositivity in adults is nearly as high in healthy controls as it is in patients with MS, the difference is more pronounced among pediatric cases and controls [31]. Overall, the evidence of EBV involvement in MS pathogenesis rests on these epidemiological data; a direct mechanism has not been proved; although, interestingly, researchers have found B cell follicles within the meninges of MS brains with EBV-encoded RNA [32], a finding that has not yet been replicated.

The *hygiene hypothesis* posits that living in areas with greater exposure to infections protects from, rather than induces, autoimmune diseases such as MS. Over the past several decades, allergies and autoimmune conditions have been on the rise in the developed world, where improved sanitation and vaccination have prevented many childhood illnesses. As an example of this phenomenon, the prevalence of one common human pathogen, the parasite *Trichuris trichiura*, is inversely correlated with MS risk; in developing regions where the *T. trichiura* prevalence exceeds 10 %, MS rates drop sharply [33]. Though seemingly at odds with the theory of an infectious trigger of MS, the hygiene hypothesis could be viewed as complementary, in that exposure to, for example, EBV in developed countries is delayed and not outright prevented. If the immune system is not "educated" by a certain age through exposure to a pathogen such as EBV, according to this line of reasoning, then autoimmunity is more likely to develop.

Cigarette smoking is a risk factor that has been consistently found to have an impact both on MS susceptibility, increasing the risk by about 50 % [34], and on disease course. A 3-year study of patients with CIS, abnormal brain MRI, and oligoclonal bands unique to the CSF (both indicative of a high risk for the conversion from CIS to MS) found that 75 % of smokers had converted to MS, compared to 51 % of nonsmokers [35]. In addition, smokers are more likely to be diagnosed with PPMS or transition from RRMS to SPMS [36–38].

In the search for modifiable risk factors, investigations have also pointed to a link between adolescent obesity and MS. In the developed world, the rates of obesity, including in children and adolescents, have been climbing in recent years, a trend that could in part explain the rising MS incidence. Langer-Gould et al. found an association between childhood obesity and MS in adolescent girls, but not in boys, and demonstrated an escalating risk level at higher weights, which were measured prior to disease onset [39]. Others have shown a correlation with juvenile obesity in both sexes [40, 41]. Another feature of the Western diet that has changed over the past century, salt intake, has garnered attention as a possible MS risk factor, with studies demonstrating the deleterious effects of salt on the immune system. In vivo experiments in mice and in humans showed that high salt conditions boost the induction of inflammatory T_H17 lymphocytes, which are pathogenic in MS and other autoimmune diseases [42]. As with other putative risk factors, high sodium consumption not only seems to affect the development of MS but also is associated with more active disease [43]. Despite their growing popularity among patients with MS, little is known about the impact of fad diets on MS susceptibility or disease course.

In parallel with environmental risk factors, scientists have investigated human genetics to better answer the question of "who gets MS?" Epidemiological observations about higher prevalence of the disease in certain ethnic groups have strongly suggested a genetic component. In the United States

and Europe, Caucasians, especially those of Northern European background, have the highest risk of MS, while other groups, such as those of African and Southeast Asian descent, have a lower risk. African-Americans, whose ancestry is largely a mix of Caucasian and African, have an intermediate risk of MS, but those who develop MS tend to have a more aggressive course [44, 45]. Sardinia, a semi-autonomous Mediterranean island, has a particularly high risk of MS in relation to its neighbors, owing to the disproportionate genetic burden found in its population [46, 47].

In addition to varying rates of MS in different ethnic groups, the recognition of MS as a disease with a strong genetic underpinning is demonstrated by the clustering of MS and other autoimmune diseases within families. Siblings and children of patients with MS have an increased risk of developing MS: the risk of MS in those with affected first-degree relatives is about 2–3 %, similar to the 2–5 % seen in dizygotic twins [48], while the concordance rate in monozygotic twins is roughly 25 % [49]. Mendelian (e.g., autosomal dominant or recessive) forms of MS have not been identified. Rather, it appears that numerous genetic variants common in the general population all individually contribute a small increase in risk to render a person genetically susceptible (rarer undiscovered variants with larger effect sizes may also increase risk in some people).

Though much of what is known about the genetic architecture of MS has been revealed in recent years, early linkage and candidate gene studies established correlations between genetic variants in the major histocompatibility complex (MHC) and MS risk. The MHC, encoded by a large gene family on chromosome 6, is a set of cell surface markers that display fragments of peptides broken down by the cell, allowing the body's immune cells to distinguish self from non-self. Different populations are very heterogeneous with respect to the distribution of MHC alleles. The degree of polymorphism and linkage disequilibrium (the tendency of different alleles to distribute together) within the MHC had previously made it difficult to identify the specific allele driving the association,

though recent studies have demonstrated that the allele with the largest strength of association and effect size is *HLA-DRB1*1501* [50, 51]. Not all genetic variants confer risk; *HLA-A*0201* exerts a protective effect.

Improvements in genotyping technology and the creation of large international consortia have facilitated the identification of 110 unique variants outside the MHC that are associated with MS susceptibility [51]. The vehicle for the discovery of these risk alleles was the Genome-Wide Association Study (GWAS), a case-control design in which hundreds of thousands of single nucleotide polymorphisms (SNPs) were genotyped in every subject. Large numbers of cases and controls are required to generate the statistical power needed for so many concurrent tests. Most risk alleles were found to be in regulatory, as opposed to coding, regions of the DNA, and likely influence gene expression on a tissue-specific level. While most of the loci are in or near genes associated with immune function, and several alleles have been linked to other autoimmune conditions, the functional consequences of most of them have yet to be worked out.

Through multiple GWASs as well as prior studies, we have learned that each risk allele exerts a very modest effect size: the odds ratio (OR) associated with possessing one copy of the *HLA-DRB1*1501* allele is roughly 3, while all other risk alleles outside of the MHC have ORs below 1.5. This underscores the difference between a risk allele and a genetic variant associated with a monogenic disorder, like cystic fibrosis, where possessing one or two copies determines that the phenotype will be expressed. In MS, possessing all the known genetic risk alleles does not guarantee development of the disease, though the creation of predictive models in healthy individuals is a focus of ongoing research.

The various MS risk factors probably exert their effects both individually and through interactions with other risk factors, both genetic and environmental. For example, case-control studies showed that smoking increased the risk of MS by 2.8 among subjects with the *HLA-DRB1*1501* and without the *HLA-A*0201* allele, while it only increased the risk

by 1.4 among those in the lower genetic risk category [52]. Similar studies found gene-environment interactions with adolescent obesity [53]. Recent research has tried to identify genetic variants associated with MS risk within the maternally inherited mitochondrial genome [54], of particular interest because of observations that mitochondrial dysfunction may underlie the bioenergetic failure seen in MS. Finally, scientists are looking at other sources of inter-individual variability—the epigenome [55] and the gut microbiome—in the hopes of explaining MS susceptibility and, ultimately, discovering targets for intervention.

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Chapter 2
The Pathophysiology and Clinical Presentation of Multiple Sclerosis

Sam Horng and Michelle Fabian

2.1 Introduction

Multiple sclerosis (MS) is a chronic disease of immunologic dysregulation. Histopathological and radiographic data demonstrate characteristic patterns of focal inflammatory lesion formation in the brain and spinal cord upon a background of accelerated brain atrophy, which in turn results in clinical deficits and disability [1, 2]. Symptom presentation, degree of disability, and the rate of disease progression vary across a spectrum, as does the therapeutic response to immunomodulatory therapies [3].

Though there is clinical heterogeneity in MS, unifying features of lesion distribution, pathology, and symptomatology suggest that it represents a single disease entity sharing common pathophysiologic mechanisms [4]. While genetic and environmental risk factors have been identified, the ultimate etiology of this disease, including the critical precipitating factor (or factors), remains a mystery. What is known is that the pathogenesis is complex and likely multifactorial, modulated by a diverse array of genetic, epigenetic, and environmental factors [5].

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Current thinking posits that MS involves two primary pathogenic processes. The first is an inflammatory, demyelinating process that underlies the most common, initial disease phenotype: a self-resolving, but recurrently relapsing pattern of focal lesion formation in the CNS [6]. The second is a neurodegenerative process that may include more longitudinal, simmering levels of inflammation and leads to a gradual accumulation of disability as documented in the progressive subclasses of the disease [7]. The interrelation between these two processes is not well understood, though this is an active area of investigation [8].

2.2 Etiology of Multiple Sclerosis

2.2.1 Autoimmunity

The leading hypothesis of the etiology of MS is that it is a result of an autoimmune attack on the central nervous system (CNS) [9]. An unknown factor, either foreign, for example, a virus, or native to the body stimulates a population of self-reactive T cells in the peripheral circulation. The factor accomplishes this activation either by its similarity to an endogenous protein (antigenic mimicry) or by its precipitation of an immune response that activates bystander self-reactive immune cells collaterally (bystander activation). The self-reactive T cells target some component of the CNS, functionally necessary for the integrity of the myelin sheath that insulates CNS neurons and the process of demyelination is initiated [5].

Support for the autoimmune model includes studies that show autoreactive T cells against myelin in the peripheral circulation of MS patients [10], and an expansion and activation of myelin basic protein-specific $CD4^+$ T cells in the periphery of patients prior to clinical relapses [11]. Whether failure of immune tolerance is involved and if so, whether it occurs centrally within the thymus or in the peripheral compartments of the immune system are unknown.

Extrinsic modulators likely contribute to the autoimmune cascade of signaling and cell activation in MS. Factors such as smoking [12], low vitamin D levels [13], female gender and the effects of pregnancy (e.g., a decrease of relapse rate during the third trimester of pregnancy and rebound in the post-partum period) suggest that toxic, nutritional, and hormonal signaling affects MS pathophysiology [14]. Exploratory work to investigate the possible contributions of the gut microbiome to immune dysfunction in MS is also underway [15]. The mechanisms by which these modulating factors act are largely unknown.

2.2.2 Genetics

Heritability studies reveal a genetic predisposition to developing MS, with lifetime risk increased from 0.1 % in the general population to 3 % for siblings and up to 25 % for monozygotic twins [16]. Linkage studies have revealed that human leukocyte antigen (HLA) alleles are associated with the largest genetic contribution to MS susceptibility [17]. The HLA-DR15 haplotype, an allelic cluster of closely linked major histocompatibility complex (MHC) class II genes, including DRB1*1501, is commonly inherited in patients with MS, and it is postulated that this cluster of alleles modulates the specificity and magnitude of antigen presentation in ways that encourage an aberrant autoimmune response [18, 19]. Additional risk factors, including single nucleotide polymorphisms in the genes for IL2Rα, interleukin-7 receptor (Il7R), and CD58, have also been implicated [20]. These data suggest that functional variants in antigen presentation, T-cell activation, and immune signaling could predispose to and exacerbate disease pathogenesis.

2.2.3 Infectious

An infectious etiology for MS has long been hypothesized based on the presence of various pathogenic proteins and nucleic acids in the post-mortem tissue of patients. Candidates

include, most prominently, Epstein–Barr virus as well as chlamydia and human herpesvirus 6 (HHV-6) [21–23]. These links have not yet been firmly established, as many of the studies have not been replicated.

2.2.4 Degenerative

In its progressive form, disability from MS develops differently, occurring gradually over months and years. The formation of new contrast-enhancing lesions is not as prominent while brain atrophy accelerates; therefore, a degenerative mechanism of disease has been inferred [8]. Post-mortem pathology reveals diffuse processes of axonal degeneration and cortical atrophy that are more prominent in patients with progressive disease, and thus progressive global changes may be distinctive in mechanism from the focal inflammatory lesions of relapsing disease [24]. Pathologic hallmarks of chronic inflammation are present in progressive disease [25]. Therefore, it is not clear whether a common inflammatory precipitant causes parallel pathways of focal inflammatory and diffuse degenerative disease or whether degeneration follows a focal inflammatory phase or whether these are two entirely separate pathological processes.

2.3 Pathophysiologic Mechanisms of Multiple Sclerosis

Our understanding of MS pathophysiology is informed (and limited) by the tools currently available to us:

- Traditional histopathology on post-mortem, or occasionally biopsied, human tissue
- Advanced MRI imaging with clinical correlation in living patients
- Animal models of MS, including experimental autoimmune encephalomyelitis (EAE), which resemble some but not all aspects of human disease [26]

Divergent pathophysiological mechanisms between the animal models and human MS may explain why some interventions improve deficits in EAE but not in humans. MS pathology, as classically described by J.M. Charcot at the end of the nineteenth century, focused on focal inflammatory demyelinating white matter lesions, termed plaques, and the surrounding reactive astrocyte scar, known as the glia limitans [2]. Partial axonal preservation was a simplified feature of this model. In the last two decades, more attention has been directed toward abnormalities of the grossly normal-appearing white matter (NAWM), the prevalence of gray matter lesions, different types of cortical demyelination, global brain atrophy, and variable degrees of axonal injury [27–29].

A unified model of how these various pathological features are causally related has not been formulated, although the commonality of these findings in all patients across the clinical spectrum of MS does support a fundamental disease process that involves recurrent flares of acute inflammation causing demyelination as well as axonal injury in both the white and gray matter [2]. A lower grade, insidious process of chronic inflammation with slowly progressive global cortical atrophy and diffuse white matter changes is also present, possibly contributing to the degenerative or progressive pathways of the disease [30]. Figure 2.1 illustrates the processes discussed below.

The underlying trigger is unknown, but may be autoimmune, environmentally stimulated or intrinsically degenerative. Whatever the initial precipitant, the innate immune response leads to a more targeted acquired immune response and subsequent inflammatory reaction. Within the CNS parenchyma, secretion of cytokines activates resident microglia, which in turn induces reactive astrocytes to release further inflammatory cytokines, opening up the BBB and allowing for the recruitment and infiltration of circulating leukocytes [31–33]. This inflammatory storm leads to the destruction of CNS tissue, with myelin degradation, metalloprotease digestion and phagocytosis by macrophages. This process in turn may release additional CNS autoantigens, including myelin oligodendrocyte glycoprotein (MOG),

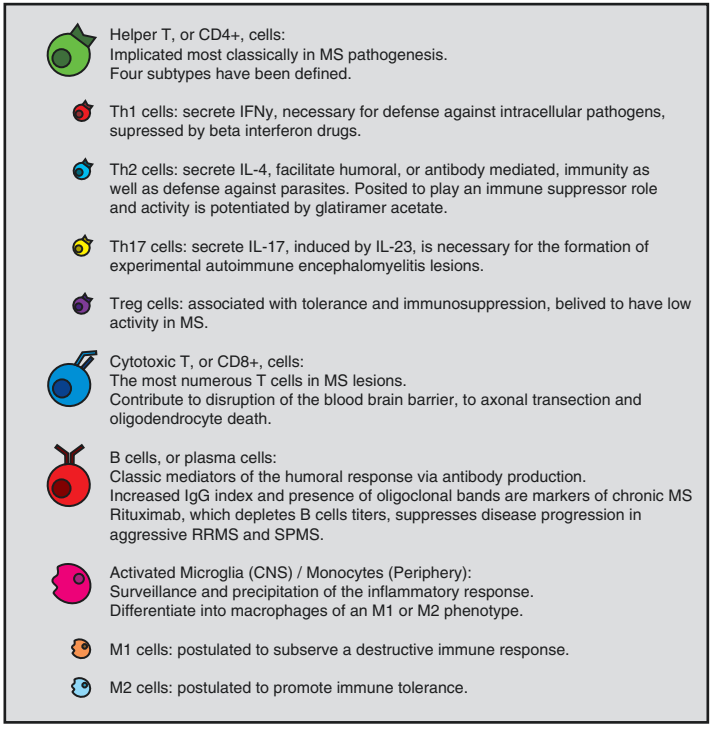

FIGURE 2.1 The immune players of multiple sclerosis

myelin basic protein (MBP), proteolipid protein (PLP) among others [34].

The pathophysiology of MS involves a variety of cellular players, as observed in human lesion pathology and in experimental animal models of MS. These different cell types are introduced in Fig. 2.2 and their functions are described in more detail below.

2.4 White Matter Plaque Formation

The classic histopathologic lesions found in MS are focal sclerotic white matter plaques. Though located throughout the CNS, they tend to appear in the optic nerve, periventricular

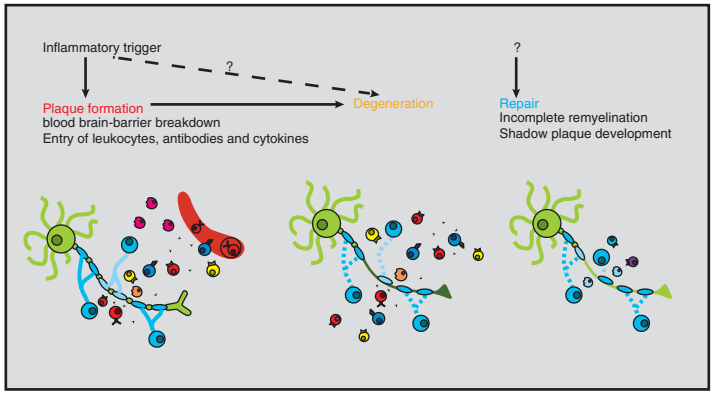

FIGURE 2.2 Pathogenesis of multiple sclerosis. An unknown trigger leads to an inflammatory response within the CNS parenchyma, in which resident microglia are activated, permeability of the blood-brain barrier increases and entry of leukocytes and soluble factors occurs. Both the myelin sheath and axon are damaged in this process leading to impaired electrical transmission down the nerve cell. Over time, neurodegeneration consisting of axonal transection and neuronal death develops. Unknown factors promote the incomplete remyelination and repair of some plaques, underlying a partial recovery of function and characteristic "shadow" appearance on pathology

white matter (particularly the corpus callosum), juxtacortical border, cerebellum, brainstem, and the cervical spine with longitudinal extension of no more than two vertebral segments and axial involvement of less than one-half [6]. It is not known why these locations are preferentially affected but they are so characteristic that diagnosis utilizing MRI criteria is based upon them [35].

White matter plaques are typically centered around large- or medium-sized veins, with areas of high venous density frequently affected. They exhibit a finger-like perivenular extension pattern, classically termed Dawson's fingers. Periventricular lesions may exhibit strip-like patterns of demyelination. In the spinal cord, lesions are fan-shaped with the tips located at the subpial surface. In cortical lesions, large subpial band-like lesions can be found. In sum, these patterns

suggest pathogenic factors emanating from the vasculature, meninges, or CSF [2].

White matter lesions in the acute phase of disease demonstrate the disruption of the blood-brain barrier (BBB), allowing for visualization with gadolinium contrast enhancement on MR imaging [36]. The formation of new white matter lesions acts as a radiologic sign for continued inflammatory disease activity and thus serves as a biomarker for assessing the efficacy of immunomodulatory therapy both in clinical trials and practice [37].

Lymphocyte activation is presumed to play a major role in the formation of white matter lesions [38, 39]. In active lesions, macrophages and activated microglial cells are the most numerous inflammatory cells [40], but the process is initiated by an initial wave of $CD8^+$ T cells, followed by $CD4^+$ T cells, B cells, plasma cells, and additional macrophages [6, 41, 42].

On post-mortem tissue, four different types of white matter lesion pathology have been described [2, 6]. Pattern 1 (present in 10 % of patients with MS, with higher incidence in those with <1 year disease history) shows sharply demarcated lesion edges with a perivascular T-cell infiltrate, active demyelination, activated microglia, and macrophages full of myelin. Pattern 2 (seen in 55 % of patients) shows more severe T-cell and macrophage infiltration, with IgG deposition and complement (C9neo) antigen in areas of demyelination. Pattern 3 (30 % of patients) has poorly defined borders, dying oligodendrocytes, inflamed vessels with loss of myelin associated glycoprotein (MAG) and CNPase reactivity and a rim of spared myelin. Pattern 4 is found only in PPMS patients and rarely at that (5 % of patients), characterized by infiltrating T cells and macrophages with oligodendrocyte degeneration in the white matter adjacent to the active lesion.

Disagreement over whether individual patients tend to have one type of lesion pathology exists, although over time, all four types become fully demyelinated and converge toward a final sclerotic endpoint. Whereas acute plaques exhibit uniform myelin destruction with macrophages laden

with myelin degradation products at early stages of digestion, more chronic plaques demonstrate an inactive center with a surrounding rim of macrophages engorged with early myelin degradation products [4]. Slowly expanding active lesions have an inactive center with surrounding macrophages, though the myelin digestion is advanced or complete in most of these cells. The acute and chronic plaques are found in early MS, whereas the slowly expanding active plaques are more common in progressive stages of MS [30, 43].

2.5 Blood-Brain Barrier Breakdown, Leukocyte Entry, Demyelination, and Axonal Injury

As noted, breakdown of the BBB, as detected by contrast permeability of gadolinium on MRI, precedes the formation of a lesion [44]. However, it is important to note that gadolinium enhancement is not sensitive in detecting small breaches of the BBB, which can be found with organic dyes on post-mortem tissue [45]. These breaches are widespread throughout chronic lesions and NAWM and, along with diffuse ultrastructural changes, suggest increased vascular permeability (including the separation of endothelial cells, increased transendothelial transport marker, dysferlin, and disorganization of astrocytic foot processes) [43]. Taken together, this supports the presence of widespread chronic inflammatory changes not limited to active lesions in the MS brain.

Inflammatory lesions are believed to be driven by peripheral activation of T cells demonstrating upregulated expression of α4 integrin, which mediates binding to vascular cell adhesion molecules (VCAMs) on endothelial cells and transmigration through the BBB [46]. Within the CNS parenchyma, T cells secrete pro-inflammatory cytokines which activate microglia, which then secrete additional cytokines drawing more T cells, macrophages, and dendritic cells to the lesion.

Active demyelination occurs as macrophages engulf myelin fragments and accumulate lysosomal myelin degradation products within days to weeks of lesion formation [47]. Variable degrees of axonal injury may be found alongside the disintegrated myelin sheaths and apoptotic cell death of oligodendrocytes may occur [2].

Demyelination is observed in all types of white matter lesions, though types I and II are characterized by damage to the myelin sheaths and types III and IV exhibit oligodendrocyte death [6, 48]. Damage to myelin sheaths may be secondary to toxic effects of activated macrophages or by autoantibody-mediated attack on myelin components. Autoantibodies are more commonly present in patients with RRMS, though specific autoantigens (such as anti-MOG) have not been shown to be unique to MS [49]. Death of oligodendrocytes is likely multifactorial and may be secondary to hypoxia, toxic injury from macrophages and mitochondrial failure [50, 51].

Contrary to classical medical teaching, axonal injury is found to occur in MS lesions, often as an early event [2, 8]. It has been proposed that two separate mechanisms are involved in axonal damage. The first is an early fulminant injury related to the mediators of the acute inflammatory reaction, possibly including cytotoxic T cells, macrophages, excitotoxic changes in the extracellular milieu or axonal membrane, or intrinsic neuronal changes induced by the denuded axon, leading to deficiencies in mitochondrial function and transport [52]. The second process involves a slow degeneration in chronic plaques that may be mitigated by remyelination [8].

2.6 Cortical Demyelination

Advanced imaging techniques and detailed pathological studies have established that cortical demyelination is common in MS and often is not correlated to the extent or locations of WM lesion load [24, 28]. Cortical lesions correlate clinically with cognitive deficits and increase the risk for

seizures to develop [53, 54]. It is not known whether cortical demyelination shares the same pathophysiologic precipitant as white matter disease, whether it occurs primarily from a distinctive demyelinating process, secondarily to remote changes of the white matter tracts or both. Cortical neuron loss does tend to appear globally rather than in regional areas correlating to white matter lesions [55].

Notably, though not readily apparent on MR imaging, GM lesions exhibit lymphocytic infiltration (including myelin-laden macrophages, T cells, and B cell follicular structures), BBB breakdown, and meningeal inflammation on post-mortem tissue, suggesting that inflammatory events underlie the formation of these lesions [56]. Indeed, the magnitude of active demyelination and neurodegeneration correlates with the amount of meningeal inflammation. Of note, cortical demyelination is present in RRMS though it becomes more prominent in PPMS and SPMS, and does not appear to be correlated with the extent and degree of white matter lesions [24].

2.7 Diffuse White Matter Changes, Global Atrophy, and Progressive Degeneration

Grossly normal-appearing white matter (NAWM) shows abnormal pathology as well, particularly in patients with SPMS and PPMS [27]. Changes consistent with a diffuse inflammatory process (activation of microglia cells and diffuse axonal injury independent of demyelination) have been described and these changes do not correlate with the focal white matter lesion load [24].

Progressive gray matter damage and cortical atrophy have also been described with an average of 10 % global cortical thinning in post-mortem MS brains compared to controls [57]. Retrograde degeneration of focal WM lesions may contribute to cortical atrophy but cannot fully explain the degree and location of diffuse cortical atrophy as it does not correlate with the white matter lesion burden. Similarly, the

regional distribution of cortical demyelinating plaques is likely insufficient to directly account for the widespread cortical changes [24].

Whether cortical atrophy causes global white matter changes or in turn, is a result of anterograde and retrograde degeneration of axons is not known. Both processes may occur in parallel.

As described elsewhere in this book, progressive forms of MS are characterized clinically by gradual accumulation of disability and a poor clinical response to available immunosuppressive and immunomodulatory therapies that are effective in RRMS. Pathologically, PPMS and SPMS exhibit fewer new focal white matter plaques and demonstrate more slowly expanding lesions, cortical demyelination, diffuse damage and axonal injury of the NAWM, with widespread microglial activation and brain atrophy [2]. Therefore, progressive MS may involve distinctive inflammatory mechanisms that are more widespread and insulated from immunotherapies of the systemic circulation.

2.8 Remyelination and Repair

Remyelination in plaques is demonstrated by the presence of pale thinly myelinated lesions, termed "shadow plaques" in post-mortem tissue [58]. These lesions are characterized by an increased number of oligodendrocyte precursor cells (OPC) and mature oligodendrocytes [59]. The presence of remyelinated plaques seems to occur in some patients but not in others, and the extent of remyelination may differ between lesions within an individual [2]. Cases with high levels of remyelination have been observed equally among patients with RRMS, SPMS, and PPMS, suggesting that inter-individual differences may determine the capacity for remyelination, though no genetic polymorphisms have yet been found [60].

In chronic MS, maturing oligodendrocytes are rare, suggesting that a block in differentiation exists. Possible deficits may be in failure to activate, failure to recruit, or failure to

differentiate. Several inhibitory factors have been identified, which prevent OPCs from contacting an axon, expressing myelin-specific genes and ensheathing an axon, key steps in the functional differentiation of OPCs [61, 62]. Interestingly, remyelination is more commonly observed in cortical lesions rather than subcortical, cerebellar, or spinal cord white matter lesions, suggesting that there is a more permissive environment in the cortex.

Remyelinated plaques are susceptible to subsequent new demyelinating attacks and appear to be more susceptible to new demyelination than normal-appearing white matter [58]. MR imaging is able to detect poorly myelinated lesions though there is no currently available neuroimaging marker to differentiate early demyelinating lesions from incompletely remyelinated plaques [63].

2.9 The Clinical Presentation of Multiple Sclerosis

Variability is one of the hallmarks of the clinical picture of MS. Some patients have a mild course with little activity or progression over many decades, while for others the course may be aggressive with significant neurological decline over a few years. However, despite the unpredictable nature of symptom frequency and intensity, patients often experience comparable patterns of disease.

As described elsewhere, MS symptoms manifest in two major ways: through relapses or progressive disease. Lesions in the optic nerve, posterior fossa, and spinal cord most commonly cause a clinical relapse. Because of their inflammatory nature, they typically evolve over days to weeks, plateau, and then improve, again over days to weeks. While some relapses do leave a residual deficit, most often the symptom intensity is significantly less than at the peak of the relapse. It may take 1–2 years for a relapse to recover to the fullest extent. Relapses often occur in a focal manner; however, some patients with a very active inflammatory response may

present with multi-focal symptoms correlating to multiple lesions that have simultaneously formed. Progressive symptoms are quite different in that they occur as a result of neurodegeneration, and cause gradual worsening occurring over months and years. Throughout the course of their disease, many patients with MS also experience the subtle development of chronic symptoms that are related to the condition, yet are difficult to place into the relapsing or progressive categories.

2.10 Common Symptoms

2.10.1 Fatigue

Although the pathophysiology of MS fatigue is ill understood, this symptom is exceedingly common in MS, affecting up to 80 % of patients with MS. MS fatigue has been defined as a sense of exhaustion, lack of energy or tiredness out of proportion to what might be expected [64]. It can impact a patient's ability to work, to be physically active and to be involved in social activities. For some, it may be one of the most disabling features of the condition.

2.10.2 Cognitive Dysfunction

Cognitive dysfunction is one of the most challenging, yet underrecognized, symptoms of the condition. It spans the disease spectrum and may be present even at symptom onset. Overall, 35–65 % of patients with MS will experience cognitive dysfunction at some point in the condition. Cognitive dysfunction in MS results in slowed processing speed, decreased working memory and issues with attention. It may not be apparent to the examiner through normal examination methods. Neuropsychological testing may be helpful in elucidating deficits, and repeating the testing allows the practitioner to monitor a patient's trajectory over time.

2.10.3 Mood Symptoms

Psychiatric disorders are more common in multiple sclerosis than in the general population though it is unclear whether these symptoms are a direct reflection of the underlying pathology of MS. Depression is the most common psychiatric condition in patients with MS. At some point after an MS diagnosis, up to 50 % of patients will receive a diagnosis of depression [65], a rate that is higher than that of the general population or of patients with other chronic conditions. The prevalence of bipolar disorder is likely increased in the MS population. Though debated, suicide is thought to be more common in MS patients that the general population, and thus depression should be treated proactively. Anxiety is another common occurrence in MS.

2.10.4 Optic Neuritis

Optic neuritis (ON) is a common initial clinical presentation. As with all MS relapses, it typically evolves over the course of days to weeks as the lesion develops. Visual loss is usually unilateral and mild to moderate in severity. Classically, the patient will experience a central scotoma, though the pattern of visual loss may also be uniform throughout the entire field or more focal. Patients usually, but not always, experience pain with eye movement and loss of color discernment, more significantly in the red tones, termed loss of "red discrimination." Examination will reveal an afferent pupillary defect (APD) in most patients with a healthy contralateral optic nerve. In the majority of cases in which the lesion is in a retrobulbar location, the optic nerve will appear normal on ophthalmologic examination, and only in a minority of cases where the lesion is located distally will there be papillitis. Further testing could reveal loss of color discrimination with Ishihara plates and abnormal results both with visual evoked potentials (VEPs) and optical coherence tomography (OCT).

2.10.5 Brainstem and Cerebellar Symptoms

Symptoms resulting from the disruption of *cranial nerve pathways* or *connections* are common in MS. Internuclear ophthlamoplegia (INO), especially when it is bilateral, is a classic finding. An INO in its classical form is characterized by the loss of, or delay in, adduction of one eye with nystagmus of the contralateral abducting eye. An INO is produced by a lesion in the medial longitudinal fasciculus (MLF). Although some patients with an INO may complain of diplopia, many do not, and often it is incidentally found on examination. Diplopia resulting from lesions affecting the function of the VIth, IIIrd, or rarely IVth cranial nerves may occur. Facial weakness from a brainstem lesion may also occur. Depending on the location, the lesion may have the appearance of an upper motor neuron lesion or a lower motor neuron lesion. Dysguesia, dysarthria, and dysphagia may also occur, with the latter two occasionally occurring as a result of a relapse, but more commonly developing insidiously over the course of the disease.

Vertigo is a frequent symptom in MS. Before a patient has a diagnosis of MS, vertigo may often be erroneously chalked up to a peripheral cause, and thus the examiner should carefully ask about previous episodes in the initial history. Because vertigo from MS is central, it is often continuous in nature though sometimes worsened by positional change. It may accompany other brainstem symptoms during a relapse.

Nystagmus is commonly seen in MS and represents dysfunction in the vestibulo-ocular tracts. Although MS patients may have many different types of nystagmus, pendular nystagmus in particular is a characteristic finding. Pendular nystagmus is sinusoidal in waveform and may be unilateral or bilateral. In some patients, it is hard to detect and may be only found by closely examining the retina.

Dysmetria and ataxia both arise secondary to cerebellar pathway dysfunction. Patients may complain of clumsiness, incoordination, and/or tremor. Upon examination, there may be dysmetria with finger-to-nose and heel-to-shin

testing, as well as presence of dysdiadichokinesis with rapid alternating movements. The gait may appear wide-based and unsteady and the patient will be unable to perform tandem gait. Patients with the most severe cerebellar symptoms may have normal strength on formal testing, yet the limbs are essentially useless because of severe dysmetria.

2.10.6 Sensory Disturbances

Sensory symptoms are the most common initial MS symptom. The area of sensory abnormality will correlate to lesion location. Though uncommon, a brain lesion could cause unilateral symptoms involving the face, arm, and leg. More typically, a brainstem lesion could cause hemi-facial symptoms. A spinal cord lesion could produce symptoms in a hemi-body, radicular, or bilateral (with a level) distribution.

Patients may report that they have decreased sensation, tingling, hypersensitivity, temperature aberrations, pain, or swelling in the affected areas. Sensory examination may be normal or may mirror the symptoms including loss of pin-prick and/or temperature discrimination, loss of vibration sense and/or proprioception, and rarely, loss of stereognosis. The examiner should look for a spinal cord level when appropriate.

2.10.7 Motor Symptoms

A motor relapse may rarely involve one limb, or cause a hemi- or paraparesis. In addition to limb weakness, the examiner may find hyperreflexia and an extensor response. Subtle signs such as mild weakness of the intrinsic hand muscles, pronator drift, and decreased ability to walk on heels or toes may be elicited. Importantly, recovery from even the most severe motor relapse is typically quite good. Motor symptoms are almost, though not always, a feature of progressive MS. In this case, they usually take the course of a gradually worsening hemi-paresis or para-

paresis, with the most advanced patients progressing to quadriplegia. In addition to the motor findings above, spasticity is common and worsens as the disease progresses.

2.10.8 Bladder, Bowel, and Sexual Dysfunction

It is important for the practitioner to directly ask about bladder, bowel, and sexual symptoms, as a patient may not complain of their presence out of feelings of embarrassment. However, the negative impact of these symptoms on quality of life may be immense.

Urinary dysfunction in MS can take multiple forms. While some patients may experience symptoms of overactivity causing frequency, urgency, and nocturia, others may experience underactivity resulting in hesitancy and retention. Still others may experience a mixed picture combining both states.

Similarly, bowel dysfunction is common, though it differs from patient to patient. Constipation is the most common problem. This is largely secondary to spinal cord dysfunction, but lack of mobility and dehydration resulting from restricted fluid intake for fear of urinary frequency can make this worse. Conversely, some patients with MS experience bowel urgency and, rarely, incontinence. This is understandably a large source of anxiety for some patients.

Lastly, sexual dysfunction is common in patients with MS. The range of sexual problems for both men and women is wide, with multifactorial etiologies. Spinal cord pathology again is responsible for the majority of organic sexual issues, mainly erectile dysfunction in men and decreased ability to orgasm in women. However, psychological factors may also be a factor with issues such as loss of libido and decreased self-esteem contributing to the situation.

2.11 Conclusion

In conclusion, all forms of MS, including early and late, relapsing and progressive forms, exhibit pathological signs of inflammation, microglial activation, leukocyte infiltration,

and active demyelination. While there are distinctive types of white matter and cortical lesions, variants appear in no specific pattern in the 3 clinical subtypes of MS. Relapsing and progressive forms appear to differ in the prominence of active white matter lesions and lower grade cortical and white matter changes, respectively, though the presence of these pathological features are generally shared, pointing to a common disease process. The etiology of this process is still a mystery and while both autoimmune and infectious theories have been proposed, with the autoimmune model most favored based on animal models (EAE) and related CNS inflammatory diseases, such as neuromyelitis optica (NMO), the specific pathogenic factors remain to be elucidated. The widespread injury to the CNS through both inflammatory and neurodegenerative process results in varied symptomatic presentations.

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Chapter 3
Assessment and Diagnosis of Relapsing Multiple Sclerosis

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3.1 Introduction

No single definitive test is available for multiple sclerosis (MS), but rather a diagnosis is made when the physician determines the patient fulfills diagnostic criteria. Various iterations of diagnostic criteria for MS have been proposed over the years, but the underlying principle of diagnosing relapsing–remitting MS (RRMS) has remained the same: the patient's disease must fulfill criteria for dissemination in time and space, meaning that the patient must have experienced neurologic events at various time points and in various parts of the central nervous system. What has changed over the years is the means by which patients are able to fulfill these criteria. According to all criteria, the presenting neurologic symptoms must not have a better alternative explanation.

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3.2 Patient History and Clinical Relapses in Establishing a Diagnosis

Early MS diagnostic criteria relied largely on clinical history and neurologic examination for establishing dissemination in time and space [1]. Indeed, a history of at least one relapse (synonymous with the terms "attack" or "exacerbation") remains essential for a diagnosis of relapsing MS. Attacks are defined as patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, current or historical, with a duration of at least 24 h in the absence of fever of infection [2]. When considering an MS diagnosis, a careful history of the presenting complaint should be obtained and a neurologic examination to assess for objective signs (though not always present) should be undertaken.

While, in theory, MS may produce a variety of neurologic symptoms, in practice, certain events are "typical of MS." These include optic neuritis, brainstem symptoms such as diplopia, ataxia, vertigo or facial weakness, or sensory or motor symptoms suggesting a partial myelitis. Symptom onset is typically acute to subacute (hours to days); after reaching maximal intensity, symptoms may remit completely, partially, or not at all. The patient should be interrogated for a history of prior unexplained neurologic events, or events for which an explanation is not entirely satisfactory (e.g., a history of carpal tunnel syndrome in which symptoms did not fit the distribution of the median nerve). A history of two or more such events, separated by at least 30 days, and localizing to different parts of the CNS, would meet criteria for dissemination in time and space, presuming there was no better alternative explanation for these events. The situation in which only one event suggestive of MS has occurred is referred to as clinically isolated syndrome (CIS).

3.3 Role of MRI in Establishing a Diagnosis

MRI is the single most useful ancillary test in establishing a diagnosis and should be performed in all patients for whom a diagnosis of MS is being considered. Modern diagnostic

criteria, starting with the McDonald criteria of 2001, still require at least one clinical relapse but allow for both dissemination in space and dissemination in time criteria to be met by means of MRI findings. Just as typical clinical symptoms are suggestive of MS, the demyelinating lesions of MS have characteristic appearances and locations that are thought to result from the perivenular histopathology of the disease. Typical lesions include ovoid-shaped periventricular and callosal lesions oriented perpendicularly to the long axes of the lateral ventricles; lesions to the juxtacortical white matter; and lesions to the brainstem, cerebellum, and spinal cord—most typically the cervical cord. Barkhof et al. proposed four sensitive and specific imaging parameters that best predicted conversion to clinically definite MS [3, 4]:

- A gadolinium(Gd)-enhancing lesion or ≥9 T2 lesions
- One infratentorial lesion
- One juxtacortical lesion
- Three or more periventricular lesions

Based on these findings, the McDonald 2001 criteria allowed dissemination in space to be established if at least three of the four Barkhof criteria were met. The McDonald criteria also allowed for the use of MRI in establishing dissemination in time. A gadolinium-enhancing lesion appearing more than 3 months after CIS onset or a new T2 lesion with reference to a baseline scan obtained at least 1 month after CIS onset allowed for a patient with CIS to meet dissemination in time criteria [5].

Subsequent revisions to the McDonald criteria simplified the criteria by which dissemination in space and time can be met by MRI [2, 6]. The most recent iteration, the McDonald 2010 criteria, allows for dissemination in space to be met by as few as one lesion in each of two characteristic CNS locations (periventricular, juxtacortical, infratentorial, or spinal cord). Dissemination in time criteria can be met if there is simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time or if a new T2 lesion develops at any time after a baseline scan (Table 3.1) [2]. These new criteria allow patients with CIS to potentially meet dissemination in space and time criteria with a single

Table 3.1 2010 Revisions to the McDonald criteria

MRI criteria for demonstration of dissemination in space	One or more T2 lesions in at least two out of four CNS areas: (a) Periventricular (b) Juxtacortical (c) Infratentorial (d) Spinal cord If a patient has a brainstem syndrome or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not contribute to lesion count
MRI criteria for demonstration of dissemination in time	(a) A new T2 and/or Gd-enhancing lesion with reference to a baseline scan, irrespective of the timing of the baseline MRI (b) Simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions at any time

Gd gadolinium. Adapted with permission from Polman et al. [2] ©Wiley

enhanced MRI scan. This has allowed for increased sensitivity and earlier diagnosis of MS, which is increasingly a priority in the age of effective medications for relapse prevention, with little sacrifice of specificity [7].

3.4 Patients Who Do Not Meet Full Diagnostic Criteria: Clinically Isolated Syndrome and Radiologically Isolated Syndrome

3.4.1 Clinically Isolated Syndrome

Despite the increased sensitivity of the McDonald 2010 criteria, some patients with CIS suggestive of MS do not meet criteria for an official MS diagnosis. These patients remain with a diagnosis of CIS until definitive criteria for MS are met

either clinically or via MRI. Many practitioners will treat these patients with disease-modifying therapy (DMT) based on the fact that several randomized controlled studies showed that intervention with DMTs in patients with CIS who have at least two MRI lesions consistent with MS prolonged time to a second clinical event [8–13]. Although not included as part of the most recent 2010 McDonald criteria, CSF findings of oligoclonal bands or elevated immunoglobulin G (IgG) index may be an additional factor that could sway a practitioner to treat a patient. Regardless of whether a patient is treated, patients with CIS should be followed closely with periodic clinical evaluation and MRIs.

3.4.2 Radiologically Isolated Syndrome

With increased availability and use of modern neuroimaging, MRIs performed for reasons unrelated to a potential diagnosis of MS (e.g., headaches or trauma) have been found to reveal incidental white matter lesions suggestive of MS. The term radiologically isolated syndrome (RIS) is used for such individuals who lack the clinical symptomatology of MS but have MRI abnormalities suggestive of demyelinating pathology, without an alternative explanation [14, 15]. Longitudinal follow-up shows that approximately one-third of these patients will go on to develop clinical symptoms within the next 5 years and so, as with CIS, these patients should continue to be monitored [15].

3.5 Role of Ancillary Testing in Establishing a Diagnosis (CSF Analysis and Evoked Potentials)

Paraclinical tests including CSF examination and evoked potentials are frequently abnormal in patients with MS. Under prior diagnostic criteria [1, 5, 6], these ancillary tests were incorporated into diagnostic criteria for relapsing MS, and

could be helpful for establishing a diagnosis if space and time requirements were not met clinically. Typically, CSF shows evidence of intrathecal synthesis of IgG as indicated by the presence of oligoclonal bands or elevated IgG index. Testing for oligoclonal bands, meaning two or more IgG bands in the CSF that do not appear in the serum, is a sensitive screening tool for MS and is reported to be positive in over 95 % of patients with MS [16], although in the authors' experience, using commercial laboratories, this seems to be true in perhaps 60–70 %. However, this finding is nonspecific and can be seen in a host of inflammatory, infectious, neoplastic, hereditary, and vascular disorders. An elevated IgG index (CSF IgG–CSF albumin ratio compared to the serum IgG–serum albumin ratio) is similarly elevated in about 70–80 % of patients with MS, but rarely in oligoclonal band-negative patients [16, 17].

However, reliance on MRI has increasingly replaced the role of paraclinical testing for diagnosing relapsing MS (positive CSF can still be used to meet criteria for diagnosis of MS with progression from the start). However, these tests may be particularly useful in certain circumstances. In the scenario where a patient has CIS but does not meet MS criteria either clinically or via MRI, CSF with positive immunological markers can be helpful at predicting future conversion to MS independent of MRI characteristics [18, 19] and may influence the decision on whether to begin immunomodulatory treatment.

Perhaps most importantly, CSF analysis can be useful in ruling out alternative disease etiologies. The diagnosis of MS is often challenging because of the requirement that no better explanation for the neurologic symptoms be available. The extent and nature of additional testing that should be undertaken is highly case dependent. CSF analysis may be useful in excluding infectious or neoplastic etiologies. CSF that is highly cellular (>50 white blood cells [WBCs]/cubic μL) has a neutrophilic predominance, or a protein concentration greater than 100 mg/dL should raise suspicion for an alternative process.

Though less sensitive than MRI and no longer incorporated in diagnostic criteria, evoked potentials may be used to

detect evidence of subclinical demyelination [20, 21]. Visually evoked potentials may show conduction delays and conduction blocks of the P100 potential in up to 75 % of patients with MS [22]. The N13 and N20 potentials of the median nerve and the P37 potential of the tibial nerve may be prolonged in somatosensory evoked potentials. Wave I–V latency may be prolonged in brainstem auditory-evoked potentials.

3.6 Assessment Scales

The most widely used scale for the measurement of the severity of neurologic disability in patients with MS is the Kurtzke Expanded Disability Status Scale (EDSS) [23]. This nonlinear ordinal scale rates patients on overall disability level in 0.5-point intervals ranging from 0 (no disability) to 10 (death due to MS) using a combination of neurologic signs, patient-reported symptoms, and measures of ambulation. It includes measures of severity of disability on seven functional/anatomic systems: visual, brainstem, pyramidal, cerebellar, sensory, bowel and bladder, and cognitive. Scores on these functional systems are combined in a non-additive way, along with measures of ambulation and reports of activities of daily living to obtain an overall EDSS score. Patients obtain scores of 0–3.5 based on combinations of functional system impairments, scores of 4.0–7.0 based primarily on limitations in ambulation, and scores of 7.5–10 based primarily on reports on activities of daily living. The EDSS is an imperfect measure for several reasons including its nonlinear nature (quantitative differences between consecutive scores are not equal or well-defined), strong emphasis on ambulation, and limited reliability and sensitivity to clinical change in the mid to upper ends of the scale [24, 25]. Despite these limitations, the EDSS is the most frequently used endpoint measure in MS clinical trials.

The Multiple Sclerosis Functional Composite (MSFC) is another frequently used measure of disability in clinical trials

[26]. Objective quantitative measures of three different functional domains are assessed; lower extremity function/ambulation is measured by a timed 25-foot walk test; upper extremity function is measured by a 9-hole peg test; and cognition is measured by a 3-second paced auditory serial addition task. Scores on each measure are converted to standard scores (z-scores) and averaged to form a single MSFC score. This measure addresses some of the limitations of the EDSS by placing less emphasis on ambulation, having improved psychometric properties, and being more sensitive to small clinical changes. Limitations include the fact that vision and bowel/bladder function are not assessed.

3.7 Patient Counseling and Education

When making a diagnosis of MS, it is important that the physician is supportive and provides education and counseling about the new diagnosis. Patients will naturally ask about their prognosis; although it may be difficult to predict the course of a given individual, an element of hope should always be emphasized. The physician can state that many patients do quite well and there are a significant number of effective medications that were not available as recently as a generation ago. Emphasizing that establishing the diagnosis provides an opportunity to intervene before significant (or any) disability develops may also be helpful. Referrals to mental health professionals can be extremely useful for issues such as anxiety or depression surrounding the diagnosis, and social workers can aid in matters such as issues of disclosure or, when appropriate, disability accommodations. Patients should also be counseled regarding reliable sources of information and should be urged to avoid unfiltered sources, particularly from the internet, which tend to portray worst-case scenarios and provide misleading, or potentially dangerous, advice. Patients can be referred to resources such as the National MS Society (in the United States) or the MS International Federation as reliable, balanced sources of information should

they have questions. These societies can also assist in locating resources such as support groups, MS-specific exercise groups, and mental health professionals familiar with MS.

Patients should be counseled about the relapsing nature of the disease. They should be instructed to contact their physician if they experience new neurologic symptoms that last for over 24 h as this may be a relapse and may warrant an intervention such as steroids. Brief, transient symptoms do not usually indicate an acute MS exacerbation. Patients should be warned that prior or existing symptoms may resurface or worsen should they become overheated, tired, or ill, and that this is a transient physiologic phenomenon rather than meaningful new disease activity.

Patients almost inevitably have questions regarding what lifestyle modifications, if any, they should be undertaking. For those patients who smoke, this is a good opportunity to emphasize smoking cessation and the information that smoking is specifically "bad for MS" may be a powerful motivator for quitting. Patients should also be advised to supplement their vitamin D intake so as to keep it within a normal range. Patients should be counseled that, despite many claims, there are no particular dietary modifications that have been proven to help patients with MS and that a well-balanced, heart-healthy diet and an active lifestyle are recommended for patients with MS, as they are for the rest of the population. It may also be helpful to advise the patient not to allow MS to dominate his or her life in ways that are not necessary. Nonetheless, if a patient states that a particular dietary or lifestyle intervention (i.e., gluten-free diet, vegetarian diet, and water aerobics) is helpful with subjective symptoms (fatigue, pain, and stiffness), this decision should be supported, provided the intervention is not otherwise unhealthy.

3.8 Differential Diagnosis

Part of what makes the diagnosis of MS so challenging is that a diagnosis requires that no better explanation for the neurologic symptoms be available. The extent and nature of

additional testing that should be undertaken is highly case dependent. When a patient presents with a typical relapsing course of characteristic symptoms and with typical MRI findings, little, if any, additional testing is necessary. However "red flags" in the clinical history, radiologic findings, or CSF could necessitate an extensive workup. In general, the differential diagnosis for MS is broad and includes infectious, vascular, neoplastic, genetic, and toxic/metabolic diseases as well as other non-MS idiopathic demyelinating disease such as neuromyelitis optica (NMO) and acute disseminated encephalomyelitis (ADEM).

Typical MS presentations include myelitis, brainstem or cerebellar syndromes, and optic neuritis (ON). MS myelopathy typically presents as a subacute partial myelitis with evolution of sensory and/or motor symptoms over hours to a few days. Lesions to the dorsal cord, the most typical cord location, may or may not be associated with a Lhermitte's sign (or the barber chair phenomenon), an electric sensation traveling down the back and/or limbs elicited by neck flexion. Radiologically, spinal cord lesions are typically short, extending the length of no more than two spinal segments. When MS presents as a posterior fossa syndrome, typical presenting signs include internuclear ophthalmoplegia, sixth nerve palsies, facial numbness, vertigo, ataxia, and/or dysarthria. The ON of MS is typically unilateral and mild-to-severe (though rarely so severe as to eliminate all light perception); decreased acuity is usually associated with a cecocentral scotoma and decreased color saturation. ON is usually associated with pain on eye movements. Upon examination, an afferent pupillary defect is frequently seen (though it may be absent if the ON is mild or if the other eye was previously affected). The optic disc is typically normal in appearance though it may initially appear swollen. Hemorrhages and exudates are rare, as is optic pallor on initial presentation.

Regardless of the type of presenting syndrome, MS relapses have a natural history in which the symptoms evolve over hours to days, reach their peak, and then begin to

stabilize or remit. On MRI, the acute lesion may enhance for up to 4–6 weeks and then leave a T2 hyperintense lesion. Clinical evolution over a different time course (hyperacute or slowly progressive) or persistent contrast enhancement on MRI are often clues to an alternate diagnosis. Below are some of the most frequent presenting MS syndromes and some atypical features that could alert one to an alternate diagnosis (Tables 3.2, 3.3, 3.4 and 3.5).

Included in the differential for MS may be other primary demyelinating diseases including neuromyelitis optica spectrum disorders (NMOSD) and ADEM. These are important to distinguish from MS because of differences in treatment strategies and anticipated disease course.

3.9 Neuromyelitis Optica Spectrum Disorders

Neuromyelitis optica is an inflammatory demyelinating disease resulting from autoantibodies against aquaporin-4 water channels in the CNS. It is less common than MS and, compared to MS, is even more disproportionately found in women and is overly represented among non-Caucasians. It is characterized by acute relapses that affect predominantly the optic nerves and spinal cord. These relapses may be difficult to distinguish from those of MS; however, they tend to be more severe and leave more residual impairment. NMO is thought to be almost invariably relapsing in nature and unlike MS, does not typically transition into a gradually progressive phenotype. Thus, unlike in MS, the majority of the disability accrues from relapses. Optic neuritis in NMO is more frequently bilateral, and the myelitis that occurs in NMO is more likely to be complete rather than partial. On MRI, longitudinally extensive lesions that span three or more spinal cord segments are typically present. Brain MRI is frequently unremarkable or may show lesions that do not meet Barkhof criteria. When cerebral presentations do occur, they may consist of intractable nausea, vomiting, and hiccups

Table 3.2 Differential diagnosis of a multiple sclerosis myelopathy

Disease category	Diagnoses to consider	Clinical and radiologic "red flags"
Vascular	Infarct Vascular malformation	Hyperacute onset (infarct) Gradually progressive onset (vascular malformation) Older age Vascular territory (i.e., dorsal column-sparing) Persistently enhancing lesion (vascular malformation)
Infectious	Lyme disease Syphilis Tuberculosis Human T-lymphotropic virus (HTLV) HIV Other viral infections (e.g., VZV, CMV, EBV)	Fevers/constitutional symptoms Meningeal symptoms Persistently enhancing lesion
Inflammatory	Sarcoidosis Lupus Sjögren's syndrome Neuromyelitis (NMO)	Meningeal symptoms Extra-CNS disease Complete transverse myelitis Longitudinally extensive transverse myelitis (for NMO) Persistently enhancing lesion

Neoplastic	Medullary cord tumor (ependymoma, astrocytoma, metastatic) Extramedullary cord tumor (meningioma, nerve sheath tumors)	Gradually progressive onset Known primary tumor Persistent enhancement
Compressive	Cervical spondylosis Herniated disc Compressive spinal tumor	Localized tenderness Radicular symptoms
Toxic/metabolic	Vitamin B_{12} or copper deficiency Nitrous oxide or zinc toxicity	Gradually progressive onset Symmetric, affecting dorsolateral columns diffusely
Genetic	Hereditary spastic paraplegia Adrenoleukodystrophy	Family history Neuropathy

CMV cytomegalovirus, *CNS* central nervous system, *EBV* Epstein–Barr virus, *HTLV* human T-lymphotropic virus, *VZV* Varicella zoster virus

Table 3.3 Differential diagnosis of a multiple sclerosis brainstem syndrome

Disease category	Diagnoses to consider	Clinical
Vascular	Infarct Vascular malformation	Hyperacute onset (infarct) Vascular territory (i.e., lateral medullary syndrome) Older age Persistent enhancement (vascular malformation)
Infectious	Lyme disease Syphilis Tuberculosis (TB) Viral (VZV, CMV, EBV)	Fever Constitutional symptoms Multiple cranial neuropathies (Lyme, TB) Persistent enhancement
Inflammatory	Sarcoidosis Lupus Neuromyelitis optica (NMO) Behçet's disease Histiocytosis Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)	Extra-CNS disease Rheumatologic symptoms Intractable nausea/vomiting/hiccups (for NMO) Multiple cranial neuropathies (for sarcoidosis) Persistent enhancement

Neoplastic	Lymphoma Glioma	Gradually progressive onset Older age Immunosuppression Constitutional symptoms Persistent enhancement
Toxic/metabolic	Central pontine myelinolysis	History of rapid correction of hyponatremia Central pontine location

CMV cytomegalovirus, *CNS* central nervous system, *EBV* Epstein–Barr virus, *HTLV* human T-lymphotropic virus, *VZV* Varicella zoster virus

Table 3.4 Differential diagnosis of MS optic neuritis

Disease category	Diagnoses to consider	Clinical
Vascular	Ischemic optic neuropathies: anterior ischemic optic neuropathy, posterior ischemic optic neuropathy Giant cell arteritis	Hyperacute onset Older age Painless (except giant cell arteritis) Altitudinal field defect Swollen optic disc (except posterior ischemic optic neuropathy)
Infectious	Syphilis Tuberculosis (TB) Lyme Cat-scratch Viral	Gradual onset Severe disc edema
Inflammatory	Neuromyelitis optica (NMO) ADEM Neuroretinitis Chronic relapsing inflammatory optic neuropathy (CRION) Wegener granulomatosis Susac's syndrome Sarcoidosis Lupus Behçet's disease	Gradual onset (vasculitis) Severe, bilateral optic neuritis Poor recovery (NMO) Extra-CNS manifestations (Sarcoid, Lupus, Behcet, Wegener) Swollen optic disc and macular star (neuroretinitis) Recurrence following steroid withdrawal (CRION)
Neoplastic	Compressive tumors: meningioma, glioma Pituitary tumors	Painless, progressive vision loss Pale optic disc

Table 3.4 (continued)

Disease category	Diagnoses to consider	Clinical
Toxic/metabolic	Vitamin B_{12} deficiency Methanol	Megalocytic anemia History of exposure
Genetic	Leber hereditary optic neuropathy	Painless progressive, sequential bilateral vision loss Family history

ADEM acute disseminated encephalomyelitis, *CNS* central nervous system

Table 3.5 Differential diagnosis of multiple sclerosis cerebral lesions

Disease category	Diagnoses to consider	Clinical and radiologic "red flags"
Vascular	Infarct Chronic microvascular disease	Hyperacute onset (infarct) Gradually progressive onset (microvascular disease), vascular territory, aphasia, unilateral lesions (carotid disease), deep gray matter lesions, lesions to cortical–subcortical junction (embolic infarcts)

(continued)

Table 3.5 (continued)

Disease category	Diagnoses to consider	Clinical and radiologic "red flags"
Infectious	Lyme Syphilis Tuberculosis HIV Other viral infections (VZV, CMV, EBV), PML	Fever Constitutional symptoms Meningeal symptoms History of immunosuppression (PML) Persistently enhancing lesions
Inflammatory	Sarcoidosis Lupus Sjögren's syndrome Systemic vasculitis Primary CNS vasculitis Susac's syndrome Acute disseminated encephalomyelitis (ADEM)	Extra-CNS symptoms Rheumatologic symptoms Headache, fevers/ constitutional symptoms/ rash/peripheral neuropathies (systemic vasculitis) Hearing loss/branch retinal artery occlusion (Susac's) Encephalopathy, post-infectious/post-vaccination (ADEM) Persistently enhancing lesions Simultaneously enhancing lesions Cortical infarcts Hemorrhages Central collosal lesions (Susac's)

Table 3.5 (continued)

Disease category	Diagnoses to consider	Clinical and radiologic "red flags"
Neoplastic	Primary CNS lymphoma Glioma Paraneoplastic Metastatic	Gradually progressive onset Headache Known primary tumor Immunosuppression Systemic symptoms Persistent enhancement Simultaneously enhancing lesions Complete ring-enhancing lesions Lesions to cortical–subcortical junction (metastases)
Genetic	Leukodystrophies Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Family history Peripheral neuropathies (some leukodystrophies) Diffuse, confluent white matter lesions (leukodystrophy) Anterior temporal lobe lesions/external capsule lesions (CADASIL)
Toxic/metabolic	Cranial irradiation Chemotherapy (e.g., methotrexate) Carmustine Heroin inhalation Carbon monoxide Toluene Methanol, metronidazole	History of exposure Altered mental status Cerebellar, peripheral nerve, hepatic, cardiac, or hematologic involvement

ADEM acute disseminated encephalomyelitis, *CMV* cytomegalovirus, *CNS* central nervous system, *EBV* Epstein–Barr virus, *HTLV* human T-lymphotropic virus, *PML* progressive multifocal leukoencephalopathy, *VZV* Varicella zoster virus

caused by lesions in the area postrema of the medulla, or narcolepsy and altered consciousness caused by lesions to the diencephalon.

Unlike MS, where the pathogenesis remains unknown, the antibody against the aquaporin 4 (AQP4) water channels has been identified as the cause of NMO [27, 28]. In all patients for whom a diagnosis of NMO is being considered, a serologic test for the AQP4-Ab should be undertaken. AQP4-Ab testing is approximately 64 %–77 % sensitive and highly specific (>95 %); testing for the AQP4-Ab by means of a cell-based assay has been found to be both more sensitive and more specific than testing via protein-based assays [29, 30]. A subset of AQ4-Ab negative NMO patients tests positive for myelin oligodendrocyte glycoprotein (MOG) Abs, though this assay is not currently commercially available [31]. Criteria for NMO can still be met in AQP4-Ab negative patients, although clinical and radiological criteria are more stringent in these patients. The most recent diagnostic criteria, as defined by the International Panel for NMO Diagnosis in 2015, are outlined in Table 3.6 (previous criteria distinguished between NMO and NMO spectrum disorders, whereas, according to the most recent criteria, the unifying term of NMO spectrum disorders is used and is subcategorized further as NMOSD with or without AQP4-Ab) [30, 32].

Immunosuppressive therapies such as azathioprine, mycophenolate mofetil, or rituximab are typically used for treatment of NMO, although randomized, controlled studies documenting effectiveness are lacking. Several MS therapies have been suggested to aggravate NMO [33, 34], underscoring the importance of correct diagnosis. In situations where the distinction between MS and NMO is difficult, an immunosuppressive strategy that may have benefit in either condition is favored.

Table 3.6 Neuromyelitis optica spectrum disorder diagnostic (NMOSD) criteria [30]

Diagnostic criteria for NMOSD with AQP4-IgG
At least one core clinical characteristic
Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
Exclusion of alternative diagnosis
Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status
At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all the following requirements
(a) At least one core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
(b) Dissemination in space (two or more different core clinical characteristics)
(c) Fulfillment of additional MRI requirements as applicable
Negative test for AQP4-IgG using best available detection method or testing unavailable
Exclusion of alternative diagnoses
Core clinical characteristics
Optic neuritis
Acute myelitis
Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
Acute brainstem syndrome
Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic lesions
Symptomatic cerebral syndrome with NMOSD-typical brain lesions

(continued)

Table 3.6 (continued)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown Ab status
Acute optic neuritis: requires brain MRI showing Normal findings or only nonspecific white matter lesions OR Optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm
Acute myelitis: requires associated intramedullary MRI lesion extending ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with a history compatible with acute myelitis
Area postrema syndrome: requires associated dorsal medulla/area postrema lesions
Acute brainstem syndrome: requires associated periependymal brainstem lesions

AQP-4 aquaporin-4, *IgG* immunoglobulin G, *LETM* longitudinally extensive transverse myelitis

3.10 Acute Disseminated Encephalomyelitis

ADEM is a rare inflammatory demyelinating syndrome characterized by the simultaneous occurrence of multiple symptoms originating from different regions of the CNS. It frequently results in encephalopathy (behavioral changes or alterations in consciousness) and, though controversial, some criteria require encephalopathy for definitive diagnosis [35]. ADEM is most common during childhood and is distributed equally between the sexes. It is often preceded by vaccination or infection, leading to theories that myelin-reactive T cells may provoke a CNS autoimmune response by molecular mimicry. Radiologically, typical ADEM lesions tend to be larger, more confluent, and more poorly defined than MS lesions. They are more likely than MS lesions to be found in the deep gray matter, and less likely to be found periventricularly, juxtacortically, or in the corpus callosum [36]. ADEM is treated acutely with IV steroids, though long-term treatment is not required because the course is typically monophasic.

Recently, a multiphasic form has been recognized, but this occurs infrequently [36].

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Chapter 4
Treatment Strategies in Multiple Sclerosis

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4.1 Introduction

Multiple sclerosis (MS) is one of the leading causes of disability among young adults and presents a major health burden in the USA and other Western countries. Disease-modifying therapies (DMTs) for MS are primarily aimed at reducing relapse rate and disability accumulation over time, and have been shown to significantly decrease disease activity clinically as well as radiographically on MRI. In the past several years, the number of therapies for this debilitating disease has greatly increased, offering the ability to tailor treatment plans based on severity of disease, personal preference, risk tolerance, and comorbidities. However, new treatments also come with new safety concerns and monitoring requirements with which physicians must familiarize themselves. This chapter will review the data regarding the treatment options currently available. Finally, while the armamentarium of treatment options for relapsing forms of MS has expanded over the past few years, no currently available therapy has been efficacious in the treatment of (primary or secondary) progressive MS

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without relapses, and emerging treatment strategies are aimed at addressing this issue (see Chap. 5).

4.2 Initiating Therapy

Accurate diagnosis and early treatment with DMTs are imperative in the management of MS. The increased availability of MRI over the last decades has allowed for the diagnosis of MS earlier in the disease course (see McDonald Criteria in Chap. 3), often after only a single clinical attack. Moreover, even in patients with clinically isolated syndrome (CIS) who fall short of formal MRI criteria for the diagnosis of MS, the presence of characteristic brain MRI lesions portends a high risk of conversion to clinically definite MS (CDMS) [1]. Numerous studies have shown that early initiation of DMTs in these high-risk patients with CIS leads to a robust delay in conversion to CDMS, conversion to MS (via McDonald Criteria), and development of new MRI lesions [2–6]. Furthermore, earlier treatment with interferon (IFN) β-1b led to sustained benefit in cognitive performance [7]. Therefore, it is widely accepted that high-risk CIS patients should be treated early with a DMT.

Conversely, in the case of a patient with CIS and no lesions on MRI, the risk of CDMS is relatively low, and most providers would opt to forgo treatment in favor of close monitoring with serial exams and MRIs. However, because the presence of oligoclonal bands (OCBs) in the CSF, low serum vitamin D levels, and abnormalities on ocular coherence tomography (OCT) have all been shown to be predictors of conversion from CIS to MS independent of MRI lesion burden, some authors have more recently argued that these factors should also be used in stratifying risk of CDMS in CIS patients to inform the decision of whether to start a DMT [8–10]. Finally, as MRI utilization has increased, so, too, has the occurrence of incidentally discovered lesions suggestive of MS, termed radiologically isolated syndrome (RIS) (see Chaps. 1 and 3). There is a relative lack of data available to guide the management of

patients with RIS and, therefore, high variability in the viewpoint as to whether to begin a DMT in this population. Most clinicians opt for close monitoring of these patients for evidence of disease activity, while others use ancillary data, such as the presence of OCBs, to guide their decision.

Once the decision has been made to initiate therapy, DMT choice should be tailored to consider comorbidities, disease severity, risk tolerance, and the patient's personal preference. Available therapies have different risk profiles, monitoring requirements, and routes of administration. The clinician and patient should have a thorough discussion of the risks and benefits of each DMT prior to initiation.

4.3 Disease-Modifying Therapies

4.3.1 Interferons

IFN β-1b, approved by the US Food and Drug Administration in 1993, was the first injectable DMT available on the market. Currently, the IFN group includes two available subtypes: IFN β-1b and IFN β-1a, and each formulation has its own dosing frequency and route of administration (Table 4.1). Beta IFNs are cytokines that have both antiviral and anti-inflammatory effects, and their efficacy in MS is believed to be mediated by a reduction of T-cell activation and IFN-γ production, modulation of the blood–brain barrier, and promotion of an anti-inflammatory immune system profile [11].

Abundant data from multiple trials and almost two decades of clinical use are available regarding the efficacy and safety of the IFNs, and the major trials are listed in Table 4.1. These trials used annualized relapse rate (ARR) reduction, proportion of relapse-free patients, and sustained accumulation of disability (SAD) as the main outcomes. The IFN β Study Group Trial demonstrated that subcutaneous (SC) administration of 0.25 mg of IFN β-1b every other day (Betaseron®) decreased the ARR by 34 % compared to placebo, but a statistically significant effect on SAD was not

Table 4.1 FDA-approved disease-modifying therapies for relapsing-remitting multiple sclerosis

Disease-modifying agent		ROA and frequency	Mechanism of action	Major clinical trials	Major adverse events	Monitoring requirements
Interferons (IFN)	IFN β-1b (Betaseron®, Extavia®)	0.25 mg SC every other day	Immunomodulation, reduction of T-cell activation and IFN-γ production	IFN β Study Group	Injection site reactions; flu-like symptoms; depression; mild lymphopenia; transaminitis	CBC and LFT every 3 months
	IFN β-1a (Avonex®)	30 μg IM weekly		MS Collaborative Research Group		
	IFN β-1a (Rebif®)	44 μg SC three times a week		PRISMS		
	Peginterferon β-1a (Plegridy™)	125 μg SC every 14 days		ADVANCE		
Glatiramer Acetate (Copaxone®)		20 mg SC daily	Competition with myelin antigens, anergy of cytotoxic T cells	Copolymer 1 MS Study Group	Injection site reactions; immediate post-injection systemic reaction	No monitoring requirements
		40 mg SC three times a week		GALA		

Natalizumab (Tysabri®)	300 mg IV infusion every 28 days	Antibody to alpha4 integrin, inhibition of lymphocyte adhesion and transmigration to CNS	AFFIRM, SENTINEL	PML; possible disease rebound upon drug withdrawal; infusion reactions	JCV Ab every 6 months
Fingolimod (Gilenya®)	0.5 mg PO daily	Downregulation of $S1P_1$ receptor, sequestration of T cells in lymphatic tissues	FREEDOMS, TRANSFORMS	HTN; transient bradycardia; transient AV block; minimal increase in risk of skin cancers; PML; disseminated zoster	Varicella status prior to rx; cardiac monitoring at first dose; baseline and serial CBC, LFT, ophthalmological and dermatological exams

(continued)

Table 4.1 (continued)

Disease-modifying agent	ROA and frequency	Mechanism of action	Major clinical trials	Major adverse events	Monitoring requirements
Teriflunomide (Aubagio®)	14 mg PO daily	Inhibition of DHODH, reduction in pyrimidine synthesis, cytostatic effect on lymphocytes	TEMSO, TOWER, TENERE	Mild diarrhea and nausea; hair thinning; transaminitis; intestinal TB; teratogenicity	Baseline CBC, LFT, quantiferon gold; monthly LFT for 6 months; serial LFT and CBC during rx
Dimethyl fumarate (Tecfidera®)	240 mg PO twice daily	Activation of Nrf2 antioxidant pathway	DEFINE, CONFIRM	GI sx; flushing; lymphopenia; PML	CBC every 3 months

Alemtuzumab (Lemtrada™)	12 mg IV infusion daily × 5 days, then 12 mg IV infusion daily × 3 days 12 months after initial treatment	Antibody to CD52, pulsed administration leads to rapid long-lasting depletion of lymphocytes	CARE-MS I, CARE-MS II	Infusion-related reactions; infections: URIs, UTIs, HSV; autoimmune: thyroid disease, ITP, GN, AIHA; melanoma	Monthly CBC, Cr, UA, and TFTs at baseline and every 3 months until 48 months after last dose; baseline and yearly dermatological exams

AIHA autoimmune hemolytic anemia, *CBC* complete blood count, *Cr* creatinine, *DHODH* dihydroorotate dehydrogenase, *GN* glomerulonephritis, *HSV* herpes simplex virus, *IM* intramuscular, *ITP* idiopathic thrombocytopenic purpura, *IV* intravenous, *JCV Ab* John Cunningham virus antibodies, *LFT* liver function test, *PO* oral, *rx* treatment, *ROA* route of administration, *SC* subcutaneous, *sx* symptoms, *TFT* thyroid function test, *UA* urinalysis, *URI* upper respiratory infection, *UTI* urinary tract infection

seen [12]. The MS Collaborative Research Group Trial compared the efficacy of weekly intramuscular (IM) administration of 30 mcg IFN β-1a (Avonex®) with that of placebo, and showed an 18 % reduction in ARR and a 37 % reduction in SAD [13]. The PRISMS trial revealed that treatment with 44 mcg of IFN β-1a SC three times a week (Rebif®) led to a 32 % reduction in relapse rate, and a 78 % reduction in new T2 lesions on MRI, as well as a significant reduction in SAD [14]. The 22 mcg dose also significantly reduced the ARR and new lesions on MRI, albeit less robustly than the higher dose. More recently, a new pegylated IFN was developed, allowing for biweekly dosing. The recent ADVANCE trial showed a significant reduction in ARR with SC administration of 125 mcg of peg-IFN β-1a dosed every 2 weeks (Plegridy™) compared to placebo, as well as a reduction in SAD and new T2 hyperintense lesions on MRI [15]. While these findings are similar to those of other IFN studies, a direct comparison cannot be made as the study did not include an active comparator arm. Comparative studies have not provided conclusive evidence regarding possible differences in efficacy among the IFN formulations. Large retrospective studies (such as the Quality Assessment in Multiple Sclerosis Study) showed no difference between the IFN therapies, while some smaller prospective studies (EVIDENCE, INCOMIN) suggested improved efficacy with higher frequency IFN formulations such as INF β-1b every other day and SC INF β-1a three times a week, compared to weekly IM INF β-1a [16–18]. It is generally accepted that these higher-dose, higher-frequency IFNs are likely more effective than weekly intramuscular IFN β-1a, and it is unclear where pegylated IFN β-1a falls on that spectrum.

The IFNs have a favorable safety profile, but tolerability issues are common. The most frequent adverse events (AEs) are injection site reactions and influenza-like symptoms. Up to 60 % of patients in clinical trials reported injection site reactions including pain, bruising, and erythema. Flu-like symptoms consisted of fever, chills, headaches, and myalgias

and were reported by approximately 50 % of patients. In susceptible patients, IFNs may also worsen depression [19]. Side effects generally improve after the first 3 months but in some patients can be persistent. Injection site reactions are often ameliorated with nursing visits aimed at improving injection technique, and flu-like symptoms are often managed with acetaminophen or ibuprofen.

In clinical trials, mild and asymptomatic lymphopenia was present in 80 % of patients and mild neutropenia, anemia, thrombocytopenia, or transaminitis was present in 20 % [12–14]. It is rare for laboratory disturbances related to IFNs to reach clinical significance; however, it is recommended to monitor complete blood counts (CBCs) and hepatic function tests (LFTs) every 3 months. IFNs should be used with caution in patients with liver disease and the drug should be discontinued if liver enzymes reach five times the upper limit of normal or if clinical symptoms of liver dysfunction occur [20–22].

During treatment with IFNs, neutralizing antibodies (NAbs) can develop. NAbs usually appear between 6 and 18 months of treatment, and the incidence is variable, ranging from 2 to 45 % in clinical trials [23]. While the presence of NAbs is associated with decreased efficacy of IFNs, the clinical utility of testing for them is unclear because failure of an IFN would necessitate a change in DMT regardless of etiology.

4.3.2 Glatiramer Acetate

Glatiramer acetate (GA), a short polypeptide copolymer that is antigenically similar to myelin basic protein (MBP), is another commonly used injectable DMT. Its function in MS is thought to be mediated by its ability to bind to HLA-DR2 and compete with various myelin antigens for their presentation to T cells. GA causes anergy of MBP-reactive T cells and induction of anti-inflammatory T helper type 2 cells [11]. It is administered SC at a dose of 20 mg daily or at the more recently approved dosing of 40 mg three times a week.

The efficacy and safety of GA was evaluated in several placebo-controlled trials. The copolymer 1 MS Study Group trial showed that SC administration of 20 mg GA daily over 2 years led to a 29 % reduction in ARR [24], with an extension trial demonstrating sustained ARR reduction of 32 % over up to 35 months [25]. In addition, more patients in the placebo group had progression in disability as assessed by a standardized version of the neurological examination. Subsequently, a European/Canadian multicenter placebo-controlled study corroborated the beneficial effect of GA, showing a 33 % ARR reduction in GA-treated patients [26]. This study also demonstrated a statistically significant benefit with regard to MRI markers of disease activity, such as lesion volume and number of new T2 and enhancing lesions. More recently, a new dosing regimen of GA (40 mg SC three times a week) showed a comparable 34 % reduction in ARR compared to placebo [27] and was shown to reduce injection-related AEs when compared to the old regimen [28]. Finally, three trials have directly compared the efficacy of GA to that of IFN β-1a (REGARD) and IFN β-1b (BECOME, BEYOND), and found no statistically significant differences in ARR [29–31].

GA has the most favorable safety profile of all the DMTs. In clinical trials, the most common AEs were mild injection site reactions, consisting of pain and erythema, occurring in 90 % of patients. Focal lipoatrophy at injection sites occurs commonly after prolonged medication use but likely occurs less frequently with the new dosing schedule available [28]. The most notable AE in trials was a transient immediate post-injection reaction that was experienced at least once by 16 % of patients, occurring within minutes after an injection, and consisting of flushing, chest pressure, palpitations, shortness of breath, and anxiety. This reaction is of unknown etiology but is benign and resolves spontaneously within 30 min [32]. Finally, unique among all the DMTs, patients on GA are not required to undergo regular monitoring of laboratory values. No hematologic abnormalities have been encountered and drug-induced liver injury has only been reported in isolated cases as an idiosyncratic drug reaction and is exceedingly rare [33].

4.3.3 Natalizumab

Natalizumab is a humanized monoclonal antibody against α4 integrin, a glycoprotein expressed on the surface of lymphocytes that allows for adhesion to the endothelial vessel wall. By blocking adhesion and subsequent transmigration of lymphocytes into the central nervous system (CNS), natalizumab prevents CNS inflammation. It is administered as a 300 mg IV infusion every 28 days.

Natalizumab was approved for relapsing MS in 2004 on the basis of two Phase III trials. The randomized placebo-controlled AFFIRM study demonstrated a 68 % reduction in ARR and a 42 % reduction of SAD at 2 years in the treatment arm compared to placebo. It also showed a remarkable 83 % reduction in new/enlarging T2 lesions and a 92 % reduction in contrast-enhancing lesions [34]. An additional study, SENTINEL, enrolled patients who, despite treatment with weekly IFN β-1a, had experienced at least one relapse in the prior year. The study found that natalizumab added to INF β-1a 30 μg IM weekly was significantly more effective than IFN β-1a alone, with a 54 % reduction in ARR at 1 year and a 24 % decrease in the risk of SAD [35].

However, natalizumab was temporarily withdrawn from the market in 2005 after discovery of three cases of progressive multifocal leukoencephalopathy (PML), a potentially lethal opportunistic infection of CNS oligodendrocytes caused by reactivation of the John Cunningham polyomavirus (JCV). Natalizumab was reintroduced to the market in 2006 with the stipulation that it be only used as monotherapy and with the implementation of an extensive risk evaluation and monitoring program, Tysabri Outreach: Unified Commitment to Health (TOUCH). A better understanding of the risk factors for developing PML has emerged since re-introduction, and the drug is now FDA-approved as monotherapy for any patient with relapsing MS. The major risk factors include the presence of JCV antibodies (Ab) in the serum (which indicates prior exposure, essentially a prerequisite for developing PML), use of prior immunosuppressive therapy, and cumula-

tive duration of therapy [36]. The estimated probabilities of developing PML after accounting for known risk factors are detailed in Table 4.2. It is recommended to check JCV Ab prior to initiating therapy and at 6-month intervals during treatment because there is a seroconversion rate of 1–2 % per year [37]. Consideration of PML risk factors is useful for informing appropriate patient selection, and many practitioners feel comfortable prescribing natalizumab in Ab-negative patients. However, in the seropositive population, most clinicians will limit duration of exposure to the drug, or will restrict use of the drug to those who have failed other therapies or have especially active disease.

Another concern with natalizumab is that cessation of the medication has, in several studies, been associated with rebound inflammation [38]. However, other studies have failed to show that post-natalizumab inflammatory activity is higher than activity prior to treatment [39], arguing against a true rebound effect. Given the possibility of rebound inflammation after stopping natalizumab, long "washout periods" after discontinuation of the drug have fallen out of favor. Although there is no consensus regarding the optimal timing

Table 4.2 Estimated US incidence of PML stratified by risk factor

		Anti-JCV antibody positive	
Anti-JCV antibody negative	**TYSABRI exposure**	**No prior immunosuppressant use**	**Prior immunosuppressant use**
	49–72 months	**6/1000**	**13/1000**
<1/1000	1–24 months	<1/1000	1/1000
	25–48 months	3/1000	12/1000
	49–72 months	6/1000	13/1000

The risk estimates are based on post-marketing data in the USA from approximately 69,000 patients exposed to natalizumab (Tysabri; http://www.tysabri.com/about/safety)

for starting a DMT after natalizumab cessation, MS subspecialists increasingly recommend initiating alternative therapy by around 2 months after discontinuation of natalizumab.

Aside from PML, natalizumab is well tolerated and generally safe. In trials, there was no increased risk for other infections with natalizumab. However, the current prescribing information indicates an increased risk of encephalitis and meningitis caused by herpes simplex or varicella zoster virus. Allergic reactions occurred in 1–4 % of patients and were generally mild, and fatigue occurred more often than with placebo. A small number of patients (6 %) developed neutralizing Abs to natalizumab, which were associated with an increase in infusion-related AEs as well as a loss of efficacy [34].

4.3.4 Fingolimod

The first oral agent for relapsing forms of MS was approved by the FDA in 2010 [40]. Fingolimod is a nonselective sphingosine-1-phosphate (S1P) receptor modulator that is metabolized by sphingosine kinase to the active metabolite fingolimod-phosphate. The $S1P_1$ receptor on lymphocytes is responsible for T lymphocyte circulation, exit from lymph nodes, and differentiation. Fingolimod-phosphate causes internalization and degradation of this receptor, leading to sequestration of T cells in secondary lymphatic tissues, in turn bringing about a reduction of MS-related inflammation [41]. Fingolimod is administered as a once daily 0.5 mg capsule.

Several large Phase III trials have studied the efficacy and safety of fingolimod. The first trial, FREEDOMS, was a 24-month study that compared two doses of fingolimod (0.5 mg and 1.25 mg daily) with placebo. Patients receiving fingolimod showed a significantly decreased ARR compared to placebo (0.16 on 1.25 mg, 0.18 on 0.5 mg, 0.40 on placebo), and fingolimod use led to a reduction of the number of new/enlarged T2 lesions, T1-enhancing lesions, and brain-volume

loss on MRI. In this study, fingolimod significantly reduced SAD [42], and an extension of the trial showed sustained effect after 4 years [43]. The second trial, TRANSFORMS, was a 12-month long study comparing the same two doses of fingolimod (0.5 mg and 1.25 mg daily) to weekly intramuscular IFN β-1a (30 mcg). The two groups receiving fingolimod exhibited a lower ARR (0.20 on 1.25 mg, 0.16 on 0.5 mg, 0.33 on IFN) and had fewer new/enlarged T2 lesions and T1 enhancing lesions. Disability progression was infrequent in all three groups, and, unlike in FREEDOMS, there was no statistical difference in SAD [44]. The 1.25 mg dose of fingolimod failed to provide additional benefit compared to the 0.5 mg dose in both studies, leading to approval of only the 0.5 mg dose.

In both trials, AEs occurred at similar rates in all arms and were generally mild to moderate. The most common serious AEs were bradycardia and atrioventricular block after the initial dose, as well as macular edema. There were two deaths in the TRANSFORMS study, both in the group receiving 1.25 mg of fingolimod. One was due to disseminated primary zoster infection in a patient without history of chicken pox, while the other was secondary to herpes simplex encephalitis. However, infections as a whole occurred with similar rates in all arms. Cardiovascular side effects, such as hypertension, bradycardia, and AV block, were largely asymptomatic and are thought to be related to the presence of $S1P_1$ and $S1P_2$ receptors in the heart [45]. Hypertension occurred in 3 %–6 % of patients and was mild. Bradycardia was seen in 2–3 % of patients and was temporary, occurring within 1 h of initial fingolimod administration, and beginning to resolve within 6 h of administration. Heart block was infrequent, transient, and largely asymptomatic, occurring in 0.5 % of patients after initial administration. No further effects on heart rate or conduction were observed with continued administration of the drug during the clinical trials. Consistent with the drug's mechanism of action, peripheral lymphocyte counts decreased by 73–77 % over the first month of treatment with fingolimod in both

Phase III studies, and remained stable thereafter. Given an increased risk of skin cancers in the Phase II study of fingolimod [46], patients underwent close dermatological monitoring in Phase III trials. Five cases of basal cell carcinoma and three of melanoma occurred in the TRANSFORMS fingolimod treatment arms, and only one in the IFN group. FREEDOMS, on the other hand, showed a higher rate of malignancies in the placebo group. In a more recent Phase III trial, FREEDOMS II, there was a slight increase in incidence of basal cell carcinoma (3 % with 0.5 mg fingolimod vs. 1 % in placebo) [47]. Finally, while trials did not show any risk of PML in patients taking fingolimod, to date, there have been rare cases of PML in the absence of prior exposure to natalizumab among the >125,000 patients treated with fingolimod [48]. No PML risk stratification has been established for patients taking fingolimod, but currently the overall risk seems to be quite low.

Based on FDA recommendations, all patients should undergo evaluation with baseline ECG, blood pressure, complete blood count (CBC), liver function tests (LFTs), and ophthalmological and dermatological exams prior to starting fingolimod and regularly during treatment [49]. Varicella antibody should be tested in patients without a history of chicken pox or varicella immunization; those who are seronegative should be vaccinated before initiation of fingolimod, and treatment should be postponed for at least 30 days. Fingolimod is contraindicated in those with recent myocardial infarction, severe heart failure, unstable angina, prolonged QTc >500 ms, or history of Mobitz Type II 2nd or 3rd degree atrioventricular block or sick sinus syndrome unless a pacemaker is present. Patients should undergo observation and cardiac monitoring for at least 6 h after receiving the first dose of fingolimod, with a repeat electrocardiogram (ECG) at the end of observation. Those at higher risk of cardiac complications should be observed overnight. If treatment is interrupted for over 2 weeks, the observation and cardiac monitoring period has to be repeated upon restarting fingolimod [49].

4.3.5 Teriflunomide

The second oral agent for MS, teriflunomide, was approved by the FDA in the USA in 2012. Teriflunomide reversibly inhibits the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), leading to a decrease in de novo pyrimidine synthesis, a crucial step in DNA/RNA synthesis. In this manner, teriflunomide exerts a cytostatic effect on B and T cells [50]. The drug is administered as a once daily 7 mg or 14 mg dose.

Teriflunomide has been studied in several Phase III clinical trials in RRMS. TEMSO and TOWER both evaluated the efficacy and safety of the drug compared to placebo [51, 52]. Both trials included two treatment arms (7 mg and 14 mg doses) and used ARR as the primary outcome and SAD as a secondary outcome. In TEMSO, ARR was significantly reduced in both treatment arms when compared to placebo (ARR 0.37 for teriflunomide at either 7 mg or 14 mg vs. 0.54 for placebo). In TOWER, there was also reduction in ARR in both treatment arms (0.39 and 0.32 for teriflunomide at 7 mg and 14 mg, respectively, vs. 0.50 for placebo). The higher treatment dose in both trials reduced the risk of SAD (29.8 % reduction in TEMSO and 31.5 % in TOWER). MRI endpoints were also met. Based on these data, both the 7 and 14 mg doses were approved by the FDA; however, in practice, the 7 mg dose is rarely used and is not licensed in most countries outside of the USA. Finally, in another recent Phase III study, TENERE, teriflunomide was noninferior, but failed to show superiority, over three times weekly IFN β-1a in reducing risk of treatment failure [53].

In the Phase III trials, the most common AEs associated with teriflunomide were diarrhea, nausea, hair thinning, and transaminitis, each occurring in more than 10 % of patients. However, these were generally mild and rarely led to the discontinuation of the drug. Teriflunomide was not associated with an overall higher risk of infections; however, one case of intestinal tuberculosis occurred in the 14 mg treatment arm in the TOWER trial. Mean reductions in neutrophil and lym-

phocyte counts were generally mild and mostly occurred within 12 weeks of treatment. A small percentage of patients in the teriflunomide arms developed serious neutropenia, which was asymptomatic, and which resolved during continued treatment with the drug or after discontinuation [51, 52].

Based on FDA guidelines [54], patients should be evaluated with baseline CBC, LFTs, and TB testing prior to initiation of teriflunomide. LFTs should be monitored monthly for the first 6 months after starting the drug, and a CBC should be repeated regularly during treatment. Based on animal studies suggesting that use of teriflunomide can cause significant fetal malformations, it has been classified as pregnancy category X under the current FDA rating system. Women of childbearing age should be using reliable contraception and pregnancy should be ruled out prior to beginning treatment. In addition, since teriflunomide is present in low levels in semen, the FDA recommends that a man should not father a child while taking the drug, though this is not part of the European prescribing information. As teriflunomide is cleared slowly from plasma (an average of 8 months is necessary to achieve negligible drug levels), an accelerated elimination protocol consisting of either activated charcoal or cholestyramine followed by laboratory testing to ensure drug clearance should be implemented if reproduction is planned or if drug removal is necessary for another reason.

4.3.6 Dimethyl Fumarate

Dimethyl fumarate (DMF), the third oral agent for MS, was approved by the FDA in 2013 but related fumaric acid esters have been used in Europe since 1994 for treatment of psoriasis. Administered as a twice-daily 240 mg capsule, DMF is thought to function by reducing inflammation and neurodegeneration via activation of the nuclear factor-like 2 (Nrf2) antioxidant pathway.

Two Phase III trials have evaluated DMF in active RRMS. The DEFINE trial compared DMF 240 mg twice

daily, DMF 240 mg three times daily, and placebo, with the primary endpoint being the proportion of relapse-free patients at 2 years. The proportion of patients with relapses was lower in both treatment arms (27 % in the twice-daily group and 26 % in the thrice-daily group) when compared to the placebo group (46 %) [55]. In addition, DMF led to a reduction in ARR (by 53 % in the twice-daily group, 48 % in the thrice-daily group), SAD (by 38 % and 34 %, respectively), and the number of new/enlarging T2 lesions and T1-enhancing lesions [55]. The CONFIRM study also compared 240 mg DMF twice-daily and thrice-daily to placebo. However, this trial also included GA as an active comparator, though subjects in this group were not blinded and the study was not powered for a direct comparison of DMF with GA. The study demonstrated a reduction in ARR of 44 % with twice-daily DMF, 51 % with thrice-daily DMF compared to placebo, and 29 % compared to placebo. In addition, all treatment arms showed a favorable effect on MRI markers of disease. However, unlike the DEFINE study, CONFIRM did not demonstrate a statistically significant reduction in risk of SAD between treatment and placebo arms [56].

A mild decrease in total white blood cell (WBC) count and absolute lymphocyte count (ALC) can occur with DMF. In the trials above, WBC and ALC declined by an average of 11 % and 30 % within the first year and then stabilized. A WBC of less than 3.0×10^9/L or ALC of less than 0.5×10^9/L was infrequent, seen in under 5 % of patients. It is recommended to check a CBC prior to starting treatment, and many clinicians routinely check counts every 3 months during treatment as was done in the clinical trials.

While the initial trials showed no increased rate of infections with DMF, to date there have been four cases of PML reported among >155,000 patients treated with DMF. Three of these patients exhibited prolonged lymphopenia of less than 0.5×10^9/L [57] and the fourth patient showed a rapidly falling lymphocyte count. While prolonged severe lymphopenia might increase the risk of PML, a case has been reported with compounded DMF in the absence of this risk factor [58].

Nonetheless, discontinuation of DMF for persistently low ALC seems likely to be a reasonable strategy.

Finally, although they are not dangerous, gastrointestinal (GI) side effects (nausea, vomiting, diarrhea, or abdominal pain) and flushing (erythema of the upper body or face) can limit tolerability of DMF. In the clinical trials, 25 %–30 % of subjects experienced flushing and 20 %–25 % experienced GI side effects within the first month of treatment, though the majority of these AEs were mild to moderate and abated shortly thereafter. Flushing or GI upset rarely resulted in discontinuation of therapy during the clinical trial (in 2 %–4 % and 2 %–5 %, respectively). Post-marketing experience has shown that taking DMF with food can ameliorate side effects and aspirin prior to dosing may decrease flushing.

4.3.7 Alemtuzumab

Alemtuzumab, approved in the USA in 2014, is generally reserved for those patients who have failed two or more DMTs or have very aggressive MS because of its side effect profile and associated monitoring program. Alemtuzumab is a recombinant humanized monoclonal antibody to CD52, a cell-surface molecule present on T and B lymphocytes, natural killer cells, monocytes, and macrophages. Pulsed administration results in a rapid, long-lasting depletion of lymphocytes from the circulation via antibody- and complement-mediated cytolysis. Alemtuzumab is administered via an IV infusion consisting of 12 mg daily for five consecutive days (60 mg total) at the initiation of treatment, followed by 12 mg daily for three consecutive days (36 mg total) 12 months after the first treatment course [59]. Benefits may last for years, and patients are typically re-treated only if they exhibit new disease activity.

Two randomized Phase III trials, CARE-MS I and CARE-MS II, have evaluated treatment with alemtuzumab versus IFN β-1a 44 mcg three times weekly [60, 61]. CARE-MS I was a 2-year rater-blind trial that demonstrated a 54.9 % reduction in

ARR with alemtuzumab compared to IFN β-1a and showed a significant improvement in the percentage of patients who were relapse-free at the conclusion of the study. The study failed to show a significant improvement on the rate of SAD, possibly related to a lower than expected SAD rate in the IFN group. In contrast to CARE-MS I, which studied treatment-naive patients, CARE-MS II recruited only those who had exhibited a relapse on another MS therapy. Patients were once again randomized to either IFN β-1a or alemtuzumab. Alemtuzumab led to a 49.4 % reduction in ARR, as well as an increase in the percentage of patients who were relapse-free at the end of the trial (65 % vs. 47 %). In this trial, alemtuzumab also led to a significant decrease in the rate of SAD (13 % vs. 20 %).

The incidence of AEs was similar across both studies. Ninety percent of patients receiving alemtuzumab had infusion-related reactions, but only a small minority of reactions were serious. Infections occurred at a higher rate with alemtuzumab compared to IFN β-1a (67 % vs. 45 % in CARE-MS I, 77 % vs. 66 % in CARE-MS II), but the vast majority were mild to moderate. The most common infections in the alemtuzumab arms were URIs, UTIs, and herpesvirus infections. Herpes prophylaxis was subsequently added to the protocol and the incidence of these infections decreased.

Perhaps the biggest concern with alemtuzumab is the potential for emergent autoimmune disorders. Autoimmune AEs mostly consisted of mild to moderate autoimmune thyroid disease (16 %–18 %). In addition, immune thrombocytopenic purpura (ITP) occurred in 1.3 % of patients and autoimmune glomerulonephritis, hemolytic anemia, and pancytopenia were each observed in <1 % of patients. Two patients treated with alemtuzumab in CARE-MS I and one patient in CARE-MS II developed thyroid cancer. Finally, there have been case reports of melanoma in patients treated with alemtuzumab, with the manufacturer reporting that 0.3 % of alemtuzumab-treated patients developed melanoma in uncontrolled studies [59].

Despite the remarkable efficacy of alemtuzumab, its safety profile prevents the drug from being a first-line therapy for most patients. Prescribing information in the USA recom-

mends use only for those who have failed two or more agents, though this is not included on the European label. In the USA, treatment with alemtuzumab requires special registration through a restricted distribution program. To minimize the risk of infusion reactions, patients receiving alemtuzumab should be premedicated with corticosteroids prior to the infusion for the first 3 days of each course of treatment. Antihistamines and antipyretics may also be used. Herpetic prophylaxis with oral acyclovir 200 mg twice daily should be initiated on the first day of alemtuzumab dosing and continued for a minimum of 2 months after completion of the drug and until the CD4+ lymphocyte count is >200/mL. Regular monitoring includes monthly CBC, serum creatinine levels, and urinalysis for 48 months after the last dose. The possibility of secondary autoimmunity should be discussed with the patient. Thyroid function tests should be obtained at baseline and every 3 months until 48 months after the last infusion. Finally, patients should undergo baseline and yearly dermatological evaluation [59].

4.3.8 Mitoxantrone

Approved by the FDA in 2000, mitoxantrone is a second-line agent that is administered as an IV infusion of 12 mg/m^2 every 3 months, with a maximum dose of 140 mg/m^2. Due to cumulative dose-associated safety concerns (12 % incidence of systolic dysfunction, 0.4 % incidence of congestive heart failure, and 0.8 % of acute leukemia) and the growing availability of alternative agents, mitoxantrone has fallen out of favor as an MS treatment [62].

4.4 Switching Disease-Modifying Therapies

Evidence-based guidelines on criteria for switching DMTs in MS are limited, and decisions to change therapy are often based on observational reports and clinical judgment. Many

factors can motivate the decision to switch DMTs, from suboptimal efficacy, problems with tolerability, safety concerns, (as in a JCV Ab positive patient on natalizumab), and personal preference (as in a switch from an injectable to oral medication). Before treatment failure can be addressed, other possible reasons for a suboptimal response to therapy, such as poor compliance, should be investigated. The ultimate goal for therapy is the concept of "no evidence of disease activity" (NEDA), which refers to the absence of clinical relapses and disability worsening in combination with the absence of new/enlarging T2 lesions or contrast-enhancing lesions on MRI. However, in a recent cohort study, while 46 % of patients with MS met NEDA status after the first year, only 8 % maintained NEDA after 7 years [63]. Therefore, NEDA may not be a realistic goal with the current treatment options available. Because all DMTs are incompletely effective in reducing relapse rates and MRI activity, it is difficult to define treatment failure, and standardized definitions for suboptimal response still remain to be established. However, most clinicians would initiate a DMT switch in a patient with ongoing relapses, worsening disability, or significant MRI activity.

4.5 Acute Treatment of Relapses

While there has been considerable advancement made with regards to chronic treatment with DMTs, treatment of acute relapses has largely remained constant over the years. Acute exacerbations are typically treated with IV infusion of 1 g methylprednisolone daily for 3–5 days as this has been shown to hasten relapse recovery [64]. While a recent study demonstrated that high-dose oral methylprednisolone is not inferior to the IV form [65], use of oral steroids for relapses is not yet commonplace. If the symptoms are purely sensory and/or not impairing function, acute treatment may not be necessary. Practice differs on whether an oral prednisone taper should be included at the end of IV treatment, but there is no

evidence that this practice improves outcomes. ACTH or plasmapheresis can in some cases be used as a second-line treatment for severe attacks if steroids are contraindicated or response is suboptimal [66, 67]. While a short course of high-dose methylprednisolone is associated with few side effects in most patients, hyperglycemia, and dyspepsia can occur; therefore, glucose monitoring and gastrointestinal prophylaxis with H2 antagonists or proton pump inhibitors during treatment is common practice [68]. Avascular necrosis of the femoral head is a less common but severe potential complication of repeated short-course corticosteroid use in MS, and vigilance is key to preventing delayed diagnosis of this condition [69].

4.6 Treatment of Multiple Sclerosis During Pregnancy

As MS affects many women of childbearing age, management of MS during pregnancy is a crucial topic. Outcomes of pregnancy in patients with MS are usually no different than in the general population. Pregnancy is thought to be protective in terms of relapses and in the PRIMS study was associated with an increasingly robust reduction in relapse frequency, reaching 70 % in the third trimester [70]. However, the first 3 months postpartum are associated with a corresponding rebound increase in relapse risk. The etiology of this phenomenon is unclear.

The classical recommendation has been to stop any DMTs prior to conception. However, small pregnancy studies of exposure to GA and IFN in humans have shown no clear evidence of fetal harm [71, 72]. Many clinicians weigh the risk of relapse off DMTs while patients try to conceive with the purely theoretical risk of harm from GA or IFN exposure during early pregnancy. The risks and benefits of continuing GA or IFN therapy until conception should be discussed on a case-by-case basis between the clinician and patient [73]. The risk of the newer DMTs in pregnancy is even less well

elucidated, and current recommendation is to stop these medications prior to conception, the timing of which depends on the half-life of the individual agents. There are limited data on whether breastfeeding itself may be somewhat protective for MS, as well as on the safety of breastfeeding while on DMTs. Decisions regarding breastfeeding and the timing of DMT initiation should be discussed on a case-by-case basis, taking into account both individual preferences and MS disease severity.

4.7 Treatment of Pediatric Multiple Sclerosis

Management of MS in the pediatric population is an important issue and it is similar to that of adult patients. A detailed discussion is beyond the scope of this chapter, but a comprehensive review is available elsewhere [74].

4.8 Conclusion

In the past several years, the number of medications for the treatment of MS has grown significantly. With an increasing availability of choices comes an improved ability to tailor therapies to individual patient characteristics and preferences. This necessitates a thorough knowledge of each available DMT on the part of the clinician. While a large body of literature on the long-term safety and efficacy of the GA and IFN β preparations exists, relatively little is available on the long-term efficacy and potential complications of therapy with the newer agents. Vigilance is necessary with regard to existing and emerging safety issues. With an abundance of clinical trials currently underway, the treatment of MS will only become more complex in the coming years.

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Chapter 5
Emerging Therapies in Multiple Sclerosis

Sylvia Klineova and Stephen Krieger

5.1 Introduction

The field of multiple sclerosis (MS) therapeutics, particularly for relapsing-remitting MS (RRMS), is rapidly evolving. Many agents are currently in various stages of clinical trials, with several medications presently under regulatory review. New treatments for MS pose exciting opportunities for disease control of relapsing MS; however, new mechanisms of action carry the potential for new side effects, novel adverse events, and the need for vigilant monitoring to ensure their safe and effective use. This chapter will review several promising emerging MS therapies, with an emphasis on two agents that have completed Phase III studies (daclizumab and ocrelizumab), as well as new approaches of great interest to patients with MS: remyelination therapy and the potential use of stem cells.

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5.2 New Monoclonal Antibodies

Several new monoclonal antibodies are currently in the developmental pipeline for relapsing MS (Table 5.1). This chapter will review two of them, daclizumab and ocrelizumab, in further detail.

5.2.1 Daclizumab

Daclizumab, a humanized monoclonal antibody (Ab) targeting the CD25 subunit of the interleukin (IL)-2 receptor, is currently approved by the FDA for use in rheumatoid arthritis and other autoimmune diseases. Initially thought to decrease T-cell expansion via a reduction in IL-2 signaling, daclizumab was subsequently found to increase the levels of circulating $CD56^{bright}$ natural killer (NK) cells. The contact dependent inhibitory effect of NK cells on T-cell survival is the proposed mechanism of action in relapsing MS [1]. It has been studied as a once-monthly subcutaneous injection.

After a successful Phase II study (SELECT) [2] and its 1 year extension (SELECTION) [3], the efficacy of daclizumab (monthly 150 mg subcutaneous injection) in RRMS was further assessed in a Phase III, randomized, multicenter, double-blind study, using the weekly intramuscular interferon (IFN) β-1a as an active comparator (DECIDE trial). The DECIDE trial enrolled over 1800 patients and successfully met its primary outcome by demonstrating a 45 % annualized relapse rate (ARR) reduction compared to weekly IFN β-1a ($P<0.0001$). Secondary endpoints included the number of new or newly enlarging T2 lesions and the proportion of relapse-free patients. The majority of secondary endpoints were also met with statistically significant 54 % reduction in the number of new/enlarging T2 MRI lesions at week 96. The second-ordered secondary endpoint of disability progression confirmed at 12 weeks was not statistically different between the two groups. At 144 weeks, 16 % in the daclizumab high-yield process (HYP) group and 20 % in the IFN β-1a group

Table 5.1 New monoclonal antibodies

Drug	Molecule	Mechanism of action	Main trials	Side effects
Daclizumab	Humanized monoclonal antibody of CD25 subunit of IL-2 receptor	Increase of the CD56 NK cell levels	1. *SELECT* Phase II 2. *SELECTION* Phase II extension 3. *DECIDE* Phase III ARR reduction 45 %	Infections Cutaneous reactions LFT elevation
Rituximab	Human-mouse chimeric anti-CD20 monoclonal antibody	B-cell depletion	1. *HERMES* Phase II RRMS 91 % reduction in total T1 Gd+lesions 2. *OLYMPUS* Phase II/III PPMS Delayed time to CDP in younger individuals	Infusion-associated reactions (fever, chills, hypotension, rigors) UTI Sinusitis
Ocrelizumab	Recombinant humanized anti-CD20 monoclonal antibody		1. *Phase II trial* *600 mg and 2000 mg* 89 % and 96 % reduction in total T1 Gd+lesions ARR reduction 80 and 73 % 2. *OPERA I and II* Phase III: ARR reduction 46 % vs. interferon, 95 % reduction in T1 Gd+lesions	Infusion-associated reactions
Ofatumumab	Fully human anti-CD20 antibody		1. *Phase II trial* >99 % reduction in total T1 Gd+lesions	Bronchospasm Rash Pharyngeal edema Erythema

ARR annualized relapse rate, *Gd* gadolinium, *IL-2* interleukin-2, *LFT* liver function test, *NK* natural killer, *UTI* urinary tract infection

had progressed. Although 67 % of patients were relapse-free in the daclizumab treatment arm (compared to 51 % in IFN arm) at 144 weeks, translating into relative reduction of 41 %, this was not considered significant on the basis of the pre-specified hierarchical testing plan.

The adverse events and side effects reported in the DECIDE study included serious infections, which were reported in 4 % of patients (compared to 2 % in IFN arm). Patients in the daclizumab arm also had a higher incidence of cutaneous adverse events (37 % vs. 19 %) and serious cutaneous reactions (2 % vs. 1 %). Significant elevation of liver enzymes was observed in 6 % of daclizumab-treated patients (3 % in the IFN arm) [4]. It remains to be seen what type of monitoring, including liver function tests, will be recommended. The Biologics License Application requesting marketing approval of daclizumab for RRMS is currently in review process by the Food and Drug Administration (FDA) in the United States and has now been approved by the European Medicines Agency (EMA).

5.2.2 Ocrelizumab

Ocrelizumab is a B-cell depleting monoclonal Ab with binding affinity towards a specific epitope of the common B-cell surface marker CD20. As a recombinant humanized Ab, ocrelizumab is less immunogenic than the human-mouse chimeric rituximab with repeated infusions, resulting in a potentially lower rate of infusion- associated adverse reactions. Compared to rituximab, in vitro studies also suggested that ocrelizumab had greater B-cell depleting capacity. This agent is given by intravenous infusion, with cycles given every 6 months.

The Phase II, multicenter, randomized, double-blind, dose-finding study assessed efficacy and safety of ocrelizumab in 220 patients with RRMS. Two ocrelizumab dosing regimens (600 mg and 2000 mg) were compared to placebo and the study also included an active, open label, rater-masked,

control weekly IFN β-1a treatment arm. Both ocrelizumab doses had statistically significant impact on the total number of gadolinium-enhancing T1 lesions, the primary outcome of this study, showing relative reduction by 89 % at 600 mg and 96 % at 2000 mg dose. Compared to placebo and IFN treatment arms, a higher proportion of participants in both ocrelizumab treatment arms remained free of gadolinium-enhancing lesions (77 % and 88 %). The ARR at 24 weeks was 80 and 73 % lower in 600 and 2000 mg ocrelizumab arms vs. placebo.

With regard to adverse events, serious infection rates were similar across all four arms. Most infusion-associated reactions were mild to moderate and occurred with greater frequency in both ocrelizumab arms (35 % in 600 mg, 44 % at 2000 mg) than in placebo (9 %), but this difference was observed only during the first infusion [5]. One patient in the ocrelizumab 2000 mg group died of a systemic inflammatory response of unknown etiology.

The OPERA I and II Phase III trials, were multicenter, randomized double-blind, double-dummy studies comparing 600 mg dose of ocrelizumab, administered intravenously every 6 months to three-times weekly IFN β-1a in patients with RRMS. Both studies successfully met the primary outcome and showed 46 % and 47 % reduction of the ARR over a 2-year period when compared to IFN β-1a. The majority of the secondary outcomes were also met; specifically, the 43 % and 37 % reduction in confirmed disability progression at 24 months and reduction in total number of gadolinium T1-enhancing lesions (94 and 95 %), as well as reduction in total number of new and/or enlarging T2H lesions (77 and 83 %).

The incidence of serious adverse events including infections did not differ between the active and comparative treatment arms (6.9 % vs. 8.7 %) and the most frequent adverse events were mild-to-moderate infusion-associated reactions (34.3 % vs. 9.7 %). The data has been submitted for review to US and EU regulatory authorities and ocrelizumab has been designated a “breakthrough therapy” by the FDA [6].

5.3 Remyelination and Repair

5.3.1 Anti-LINGO-1

While existing immunomodulatory treatment agents reduce disease activity in patients with RRMS, they are not able to facilitate repair mechanisms. Anti-LINGO-1 Ab is the first agent directed towards the repair of the existing damage in MS rather than preventing new injury. The oligodendrocytic leucine and rich repeat (LRR) and immunoglobulin-like (Ig) domain-containing neurite outgrowth inhibitor (Nogo) receptor interacting protein (LINGO-1) negatively regulates oligodendrocyte differentiation and myelination [7]. In animal studies, application of an Ab against LINGO-1 resulted in remyelination. The encouraging pre-clinical data supported further advancement into Phase II and later Phase II human studies RENEW and SYNERGY.

The RENEW study assessed the remyelination potential of anti-LINGO-1 treatment in acute optic neuritis (ON). This randomized, double-blind, placebo-controlled trial enrolled 82 patients with a first unilateral episode of ON. After completing treatment with high-dose steroids, participants in the active arm received 100 mg/kg of anti-LINGO-1 Ab intravenously every 4 weeks for six doses total. The trial met its primary outcome and demonstrated 34 % improvement in the recovery of optic nerve latency as measured by full-field visual evoked potential relative to placebo in the per protocol population ($P = 0.0504$) [8]. Severity and incidence of adverse events were comparable across the treatment arms. The serious adverse event profile included hypersensitivity reactions close to the time of infusion (two patients) and an asymptomatic elevation of LFTs (one patient) [8].

Another Phase II dose-finding, efficacy, and safety study of anti-LINGO-1 in patients with active RRMS and secondary progressive MS (SPMS) treated also with IFN β-1a (SYNERGY trial) is currently underway. A total of 396 patients with active RRMS or SPMS are being randomized to the active arm with intravenous anti-LINGO-1 treatment or

placebo for 72 weeks as an add-on to weekly intramuscular IFN β-1a. The trial aims to evaluate sustained improvement in neurophysical and/or cognitive function for 3 months as the primary outcome; sustained worsening in function for 3 months is the key secondary outcome. Conventional and nonconventional MRI outcomes are exploratory efficacy imaging endpoints. Results of this study will inform decisions on further clinical development of anti-LINGO-1 for CNS remyelination and/or neuroaxonal protection [9]. If investigations of anti-LINGO-1 prove successful, this agent may be utilized in combination with existing disease-modifying agents for relapsing MS, to both prevent new disease activity and foster myelin repair.

5.4 Stem Cell Therapeutics

Stem cell transplantation-based therapies in MS either seek to remove disease-causing immune cells and induce a reset of the immune system, or use multipotent stem cells with neuroprotective and restorative capabilities. After encouraging results from early studies, three main concepts of stem cell therapies are currently under investigation: hematopoietic stem cell transplantation (HSCT), mesenchymal stem cell transplantation, and glial progenitor cell transplantation (Table 5.2).

5.4.1 Hematopoietic Stem Cell Transplantation

The goal of HSCT therapy is to replace the existing immune system with another one, either derived from the individual with MS (autologous) or another individual (allogeneic) [10]. This approach consists of the initial application of high-dose immunosuppressive therapy (HDIT; usually chemotherapy) to ablate the original immune system, followed by subsequent HSCT. Several groups have reported the results of this treatment in patients with active RRMS or progressive MS.

Table 5.2 Stem cell therapeutics

Stem cell transplantation	Rationale/method	Main trials	Side effects
Hematopoietic Autologous Allogeneic	Replacement of the existing immune system Application of HDIT with subsequent HSCT	*1. Observational Swedish study* 87 % relapse-free patients at 5 years 85 % MRI activity-free patients at 5 years *2. ASTIMS* Phase II 79 % new T2 lesions reduction *3. HALT-MS* Phase II 78.4 % disease-free patients at 3 years *4. Nonmyeloablative HSCT* Case series 50 and 64 % patients with EDSS improvement ≥ 1.0 at years 2 and 4	*Immediate*: alopecia, cytopenias *Late*: herpes zoster reactivation, thyroid disease Febrile neutropenia Gastrointestinal events Cytopenias Infections Gastrointestinal events *Late*: herpes zoster reactivation Post-transplant immune dysfunction (immune-mediated thrombocytopenia, hyper- or hypothyroidism)

Mesenchymal Intravenous Intrathecal	Mesenchymal stem cells exhibit immunomodulatory and neuroprotective properties Cells harvesting, in vitro expansion and subsequent administration – intravenous or intrathecal	*1. Phase IIa study* Intravenous MSCs administration Improvement of VEP latency and amplitude *2. Phase IIa study* Single intrathecal MSCs administration No effect on disease course at 12 months *3. Phase I study* Repeated intrathecal MSCs administration Ongoing study	*Late*: URI, UTI Low grade fever Nausea/vomiting Headache No adverse events
Glial progenitor	Transplanted OPC exhibit remyelinating and oligodendrocyte generating properties in animal models	1. Initiated first clinical trial of human OPC transplantation in patients with chronic progressive MS	

EDSS Expanded Disability Status Scale, *HDIT* high-dose immunosuppressive therapy, *HSCT* hematopoietic stem cell transplantation, *MS* multiple sclerosis, *MSCs* mesenchymal stem cells, *OPC* oligodentrocyte progenitor cells, *URI* upper respiratory infection, *UTI* urinary tract infection, *VEP* visual evoked potential

An observational study conducted in Sweden reported the outcomes of HSCT treatment in 41 patients treated between May 2004 and April 2013. In this study, patients with either RRMS ($n=34$) or progressive MS ($n=7$) and mean ARR of 4.1 the year prior to HSCT were followed for 47.7 months on average. At 5 years, 87 % of patients were relapse-free and 85 % of patients were MRI disease activity free. Additionally, the study showed EDSS score progression-free survival of 77 % and disease-free survival of 68 %.

Immediate side effects (alopecia and various cytopenias) were related to the known acute toxicity of the treatment and were experienced by a majority of patients. Late side effects, including herpes zoster reactivation and thyroid disease, were observed in 17 % and 8.3 % of patients, respectively [11].

The Autologous Haematopoietic Stem Cell Transplantation trial in MS (ASTIMS) was a multicenter, randomized, Phase II study comparing the effect of autologous HSCT vs. mitoxantrone (MTX) on disease activity, measured by MRI. The study enrolled 21 patients with either RRMS (33 %) or SPMS (67 %); 9 were randomized into the HSCT arm. The ASTIMS study met the primary outcome by demonstrating 79 % fewer new T2 lesions in the HSCT arm as compared to the MTX arm. Febrile neutropenia and gastrointestinal side effects were the most frequently observed adverse events and occurred only in the HSCT arm [12].

The Hematopoietic Cell Transplantation for Relapsing-Remitting Multiple Sclerosis (HALT-MS) study is a prospective, open-label, single arm, multicenter Phase II trial investigating the efficacy of HDIT/HSCT in 25 patients with RRMS with breakthrough disease on conventional therapy. The primary endpoint of this study is the time to treatment failure, defined as death from any cause or disease activity (clinical or imaging). The 3-year interim analysis showed no disease activity in 78.4 % participants [13]. Treatment failed in five patients and there were two deaths, one caused by MS progression more than 2.5 years after transplant, the other

caused by worsening of pre-existing asthma. Cytopenia, infection, and gastrointestinal events were the most frequently observed adverse events; no early treatment-related mortality or organ failure occurred. The final report on the efficacy and safety of the HDIT/HSCT is planned after a total of 5 years follow-up [13].

A slightly different approach, using nonmyeloablative regimen, thus bypassing potential toxicity and late complications associated with myeloablative regimens, was used in a study conducted by Burt and colleagues [14]. This case series of 151 patients with MS (123 RRMS and 28 SPMS) aimed to evaluate association between nonmyeloablative HSCT (using conditioning regimen of cyclophosphamide in combination with either alemtuzumab or thymoglobulin) and disability progression in MS. The primary outcome of this study was reversal or progression of disability measured as change in Expanded Disability Status Scale (EDSS) score by 1.0 or more, secondary endpoints also included relapse-free and progression-free survival and disease activity measured by MRI.

Of 151 patients treated with HSCT, 55 were treated on the study protocol and 96 received the treatment on compassionate use. Patients were followed-up for a median of 2 years (range: 6 months to 5 years). The use of HSCT was associated with statistically significant improvement in EDSS score by $\geq$1.0 in 50 % and 64 % of patients at years 2 and 4, respectively. The relapse-free survival was 89 % at year 2 and 80 % at year 4; progression-free survival was 92 % and 87 %, respectively [14].

There were no deaths related to treatment. Post-transplant immune dysfunction (immune-mediated thrombocytopenia, hyper- or hypothyroidism) was observed in 22.7 % of patients receiving alemtuzumab compared to 6.9 % of patients given thymoglobulin [14]. Four patients developed late reactivation of dermatomal zoster. Despite the obvious limitations of the uncontrolled case series, the intriguing results do warrant further confirmation in randomized trials.

5.4.2 Mesenchymal Stem Cell Transplantation

Intravenous Mesenchymal Stem Cell Application

Mesenchymal stem cells (MSCs) are multipotent adult stem cells present in nearly all human tissues. The rationale behind their use as a novel MS therapy stems from exhibited immunomodulatory and neuroprotective properties as well as from relatively easy isolation from tissues and in vitro cell line expansion [15].

In a Phase IIa, open label, proof-of-concept study, safety, and efficacy of intravenously administered autologous mesenchymal stem cells on visual function was studied in 10 patients with SPMS. The results showed improvement of visual evoked potential latency and amplitude; imaging measures showed an increase in optic nerve area after treatment. No adverse events were recorded during the treatment, but two benign infections (upper respiratory and urinary) occurred 1 month after treatment [16].

Intrathecal Mesenchymal Stem Cell Application

The approach of intrathecal application of the MSCs is based on known neurorestorative and neuroprotective ability of these cells. In a Phase II, open-label study, the safety and efficacy of one intrathecal injection of autologous MSCs was studied in 22 patients with progressive MS. The injection-related side effects included low-grade fever, nausea/vomiting, and headache. At 6 months post-treatment, the disease course in 72.8 % of patients was stable, as measured by EDSS; however, this effect was lost at 12 months. The authors concluded that this vanishing effect could be related to insufficient treatment frequency [17].

In order to overcome this limitation, the latest Phase I study seeks to evaluate the safety and efficacy of repeated intrathecal MSC-neuroprogenitor cell injections in 20 patients with progressive MS. A recently presented interim analysis reported no adverse events in nine patients who have received this treatment so far [18]. While safety data might provide

initial reassurance, only further, larger studies, designed specifically to evaluate efficacy, will provide much needed guidance on this currently experimental treatment in MS.

5.4.3 Glial Progenitor Cell Transplantation

The concept of glial cell transplantation, specifically oligodentrocyte transplantation, as a therapeutic approach in MS stems from our recognition of the value of oligodendroglial replacement in demyelinating disorders. Oligodendrocytes are instrumental for intact neural transmission through myelin production and for neurons themselves through trophic support [19]. The understanding of neural cell developmental processes allowed the production of autologous oligodendrocyte progenitor cells (OPC) using induced pluripotent stem cells for myelin repair. OPC are then able to produce myelin and generate mature oligodendrocytes [20]. After successful OPC transplantation in hypomyelinated animals, a recent clinical trial of human OPC transplantation in patients with chronic progressive MS was initiated. This 4-year project is the first attempt at human OPC transplantation [21].

At the time of this writing, no commercially available stem cell treatments for MS have garnered regulatory approval. Given the substantial risks associated with these treatment strategies, patients should be advised that these approaches should only be pursued in the context of legitimate research protocols.

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Chapter 6
Symptom Management in Multiple Sclerosis

Aliza Bitton Ben-Zacharia and Gretchen Mathewson

6.1 Introduction

Multiple sclerosis (MS) is a progressive neurodegenerative disease leading to multiple neurological deficits affecting quality of life (QoL) [1]. The goals in MS care are minimizing the risk of relapses, delaying progression of the disease, and managing the daily symptoms of patients. The symptoms may be divided into several categories that include sensory/pain, motor/balance, visual, and neuropsychological features (Fig. 6.1). Further, MS symptoms may be categorized as primary, secondary, tertiary, and quaternary. Primary symptoms are directly related to pathological processes of the disease: demyelination and axonal loss. Secondary symptoms stem from the primary deficits, such as dysuria due to urinary tract infections resulting from a neurogenic bladder and falls related to weakness and impaired balance. Tertiary symptoms occur as a result of the whole disease process (e.g., social isolation and reactive depression). Finally, quaternary symptoms are consequences of unnecessary or excessive interventions of health systems and MS care (Fig. 6.2).

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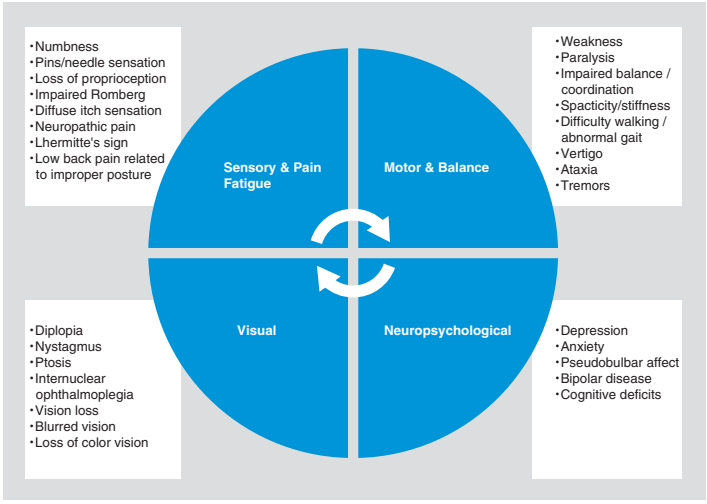

FIGURE 6.1 The categories of symptoms in multiple sclerosis

MS symptoms may be classified as acute, subacute, or chronic. Acute symptoms are of new onset and may represent a relapse in the absence of infection or of neurological changes related to Uhthoff's phenomenon, which reflects a physiological impairment of nerve function related to increased body temperature. Acute neurological signs or symptoms in the context of relapse may be managed with a 3- to 5-day course of high-dose (e.g., 1000 mg methylprednisolone) intravenous or oral steroid treatment, or subcutaneous or intramuscular adrenocorticotropic hormone therapy (ACTH), based on the severity of the relapse. In contrast, subacute symptoms are those lasting less than 6 months, while chronic symptoms, such as urinary urgency or neuropathic pain, last more than 6 months. Symptoms may be persistent or intermittent, or they may occur in brief, repeating stereotypical patterns classified as paroxysmal episodes. MS symptoms may be related to each other and interdependent [2].

In MS, symptom management is no less important than disease-modifying therapies (DMTs). Key factors include

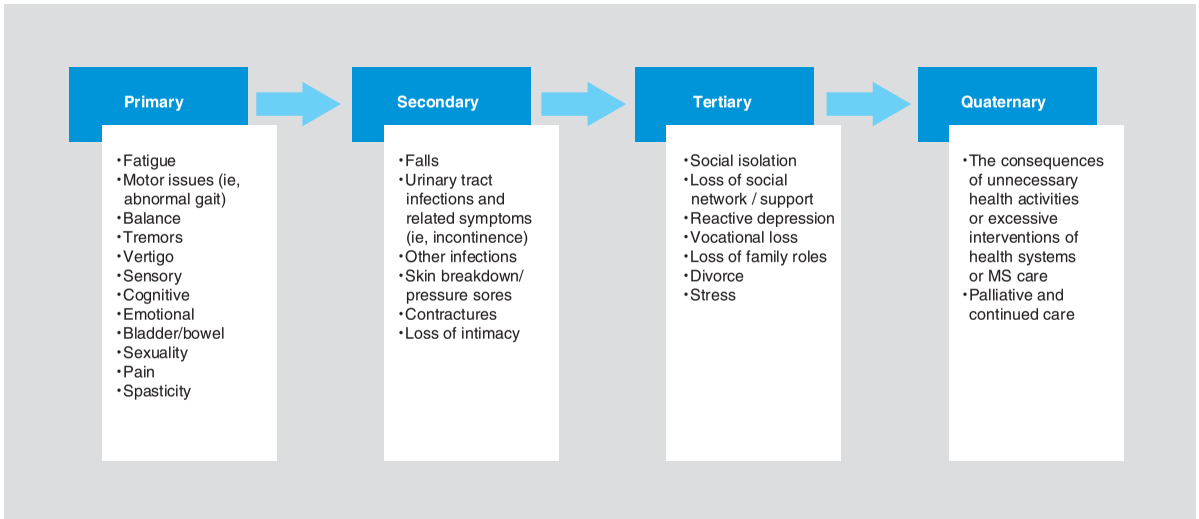

FIGURE 6.2 Primary, secondary, tertiary, and quaternary symptoms in multiple sclerosis

identifying and managing symptoms while prioritizing and strategizing care. Steps of symptom management have been characterized in the acronym ICAP [3]: *identification* of symptoms; understanding *causation* of symptoms as primary, secondary, tertiary or quaternary; *alleviation* of symptoms; and *prevention* of complications (Fig. 6.3).

A key element of assessment is to rule out causes unrelated to MS. A challenge in clinical care is distinguishing between primary MS symptoms and symptoms that are due to unrelated conditions, and often recognizing combinations of the two. For example, fatigue may be due to MS but may also be related to other causes, such as thyroid disease or anemia. Furthermore, polypharmacy is frequent in MS as it is in other chronic illnesses. As a result, often symptoms experienced by patients may be considered side effects of their medications. The role of the clinician is to perform a thorough

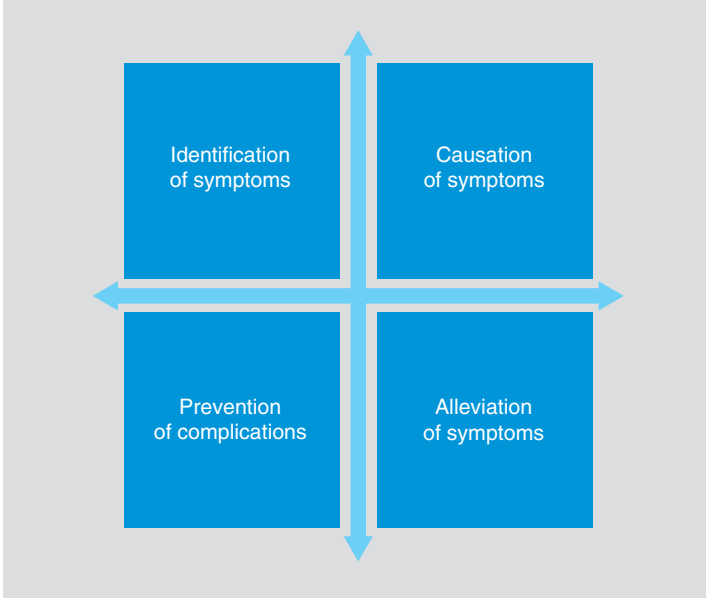

FIGURE 6.3 ICAP model (Adapted with permission from Cohen [1])

assessment identifying potential barriers and unnecessary quaternary measures of care.

The care of MS symptoms includes patients and their families as partners at the center of the MS team. Goals of care have to be discussed and shared during the initial steps of the plan. MS symptoms are often alleviated by non-pharmacological methods, such as rehabilitation, exercise, yoga and meditation, in addition to pharmacotherapy. The priority is to address the MS symptoms in conservative rehabilitative ways unless it is important to intervene with medical treatment, for example, in addressing a symptom, such as urinary burning and incontinence, which may imply an infectious process. Conservative measures include stretching exercises for spasticity, physical therapy for an impaired gait, cognitive remediation for difficulties in processing information, and other approaches. Symptom management requires ongoing education of patients and their families and/or caregivers. The education entails assessing symptoms, prioritizing, and planning long-term care.

6.2 Fatigue

Fatigue, one of the hallmark symptoms of MS, has been defined as a feeling of physical and emotional tiredness and lack of energy [4]. Mechanisms of MS fatigue are not completely understood but are likely related to central nervous system (CNS) inflammation and the burden of lesions affecting nerve signals along the thalamus, basal ganglia, and frontal cortex. Studies have been unable to demonstrate an association between MS-related fatigue and the level of disability, clinical disease subtype, or gender, although recent data show an association between MS-related fatigue, depression, and QoL [5].

The management of fatigue includes non-pharmacological and pharmacological modalities. Occupational therapy offers energy conservation techniques by teaching patients how to pace and prioritize activities. Physical therapy and a

regular exercise plan including daily activities may boost energy. Sleep hygiene and preventing sleep disruption have a profound effect on energy level and fatigue. Pharmacological interventions include medications to increase energy level. These consist of amantadine, selective serotonin reuptake inhibitors (SSRIs), modafinil, armodafinil and, less commonly, the cautious use of stimulants such as methylphenidate or amphetamine preparations.

6.3 Sensory Deficits and Pain

Sensory symptoms and pain are very common in MS. These encompass numbness, pins-and-needles sensations, itching, burning, electrical and vibrating manifestations as well as a variety of other sensory perceptions experienced by patients with MS. These sensory deficits may be intermittent, repetitive paroxysmal or persistent episodes. Often, patients will experience positive sensations such as paresthesias and increased sensitivity rather than negative symptoms such as diminished sensation.

Pain in MS may be acute or chronic. It may be a primary symptom related to signal aberrations or a secondary symptom related to posture changes resulting in joint disease or lumbosacral spine abnormalities. Pain also may be experienced as a tertiary or quaternary symptom related to the overall impact of the illness or to unnecessary treatment. Acute pain in MS may result from Lhermitte's phenomenon (acute electrical sensation radiating down the torso or extremities when the neck is flexed in a patient with a cervical spine lesion), trigeminal neuralgia (severe acute unilateral facial pain associated with brain stem lesion), or optic neuritis (unilateral inflammation around the optic nerve). Chronic pain usually includes unpleasant (dysesthetic) tingling sensations and secondary symptoms, such as back pain.

Neuropathic pain management consists mainly of the use of anticonvulsant medications. Gabapentin, pregabalin, and

carbamazepine are considered first-line treatments for neuropathic pain because of their efficacy and relatively benign side effect profile. Additionally, tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), such as duloxetine HCL, and cannabinoids may be used for neuropathic pain management [6]. Opiates are not recommended because of their addictive properties, and their effects on cognitive function and bowel function. Often, a referral to a pain specialist is recommended for patients with severe and chronic pain.

6.4 Motor and Balance Issues

Motor symptoms include weakness, difficulty with fine and gross motor functions, and stiffness or spasticity. Static and dynamic balance issues include incoordination, ataxia, and difficulty performing activities of daily living (ADLs), such as showering, bathing, toileting, grooming, and others. Upper-extremity weakness leads to functional deficits and the inability to perform basic ADLs. Lower-extremity weakness is common in MS, leading to difficulty ambulating independently and safely. Falls are a major risk in patients with mobility deficits [7]. Many neurological deficits, such as spasticity, weakness, fatigue, sensory loss, visual loss, vestibular symptoms (i.e., vertigo and imbalance), ataxia, and incoordination contribute to gait and mobility issues in MS.

The main therapy for patients with these symptoms is rehabilitation. Referral to a physiatrist, physical therapist, and/or an occupational therapist is warranted. The physiatrist assesses the patient and then makes referrals to appropriate rehabilitation professionals (e.g., physical or occupational therapist). Physical therapy focuses on gait and balance training and orthotic fitting as needed, such as ankle-foot-orthosis (AFO) or an electrical stimulation device. Often, patients will require assistive devices such as a cane, crutches, or a walker. Occupational therapy promotes strengthening of upper extremities for ADLs, such as showering or transferring to

the toilet. Physical or occupational therapy may also be used in conjunction with other therapies to promote independence and preserve daily functioning. The goal of rehabilitation is to improve flexibility and endurance, and to evaluate the need for assistive devices and durable equipment to promote proper posture, range of motion and safety while performing ADLs.

The only available pharmacological treatment for walking difficulty in MS is dalfampridine, an oral medication taken every 12 h, which is appropriate for patients who do not have a history of seizures or renal disease [8]. Dalfampridine works as a potassium channel blocker that enhances conduction in injured nerve fibers [9]. Two randomized placebo-control trials have been conducted in patients with MS. The primary measure of efficacy in the studies was walking speed as measured by the Timed 25-Foot Walk (T25FW), using a responder analysis. A significantly greater proportion of patients taking dalfampridine were responders in both trials compared to patients taking placebo: 34.8 % vs. 8.3 % in the first trial, and 42.9 % vs. 9.3 % in the second [7, 9]. Furthermore, patients with an expanded disability status scale (EDSS) (Fig. 6.4) score higher than 6.0, exhibiting spasticity, muscle weakness, and severe walking impairment including spastic paretic gait, are as likely to benefit from prolonged-release fampridine as patients with less disability, with 31–32 % of fampridine-treated patients responding, compared to 12–15 % of placebo-treated patients [10]. Common side effects with this medication include dizziness, nervousness, and nausea. More serious adverse events include urinary tract infections and seizures in some patients taking more than the recommended dose [10–13]. Gait issues in MS need to be identified, assessed, and managed early, using a multimodal approach that views gait from several vintage points [14].

Spasticity in MS is a velocity-dependent increase in muscle reflexes as a result of damage to descending motor pathways that leads to increased tone and rigidity [15]. Spasticity afflicts approximately 75 % of patients with MS [2] and is a major cause of spasms, pain, gait abnormality, and postural

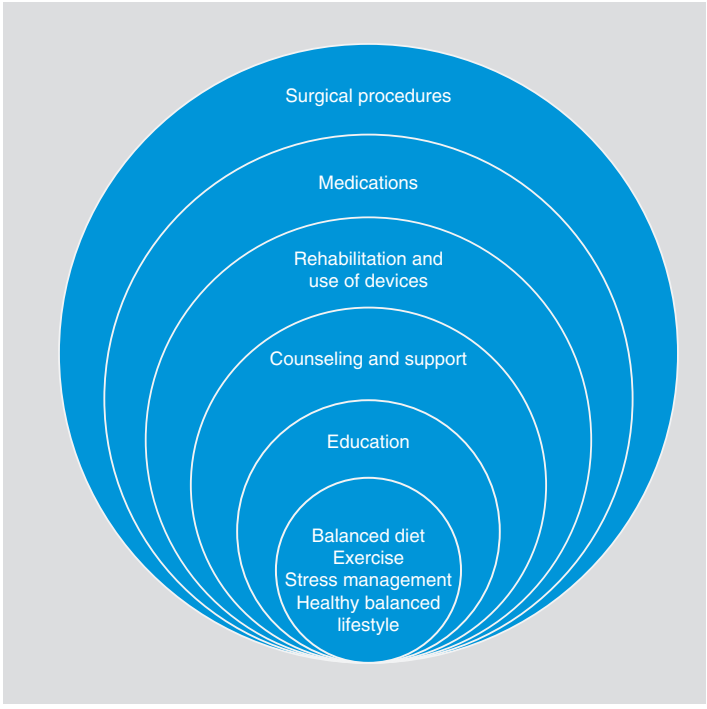

FIGURE 6.4 Symptom management in multiple sclerosis

changes. One-third of patients with MS modify their daily activities as a result of spasticity [16]. Spasticity treatment can significantly affect QoL by reducing spasms, pain, and fatigue. This includes physical therapy, stretching exercises, oral medications, injections, and/or use of an intrathecal baclofen pump.

First-line therapies for spasticity in clinical practice include baclofen and tizanidine [6]. The rule of thumb, as with all medications, is to start a new medication at a low dose and increase it as tolerated. Often patients benefit from frequent dosing throughout the day [15]. Frequently, the anti-spasticity oral medications can lead to sedation and weakness, requiring clinicians to consider other medications. For patients with

severe spasticity, the baclofen pump can provide the medication intrathecally (directly into the spinal subarachnoid space), delivering it continuously in small doses. The use of these intrathecal pumps can increase the therapeutic benefits with fewer and less severe side effects than oral anti-spasticity medications. Other oral medications include gabapentin and benzodiazepines (e.g., diazepam and clonazepam), which are considered to be second- and third-line therapies.

Other treatments for spasticity include botulinum toxin and cannabinoids. Botulinum toxin is injected into an affected muscle group to promote stretching and muscle relaxation. It may improve positioning and mobility, and alleviate pain [17]. Randomized, placebo-controlled trials of oral cannabinoid therapy detected no improvement for MS-related spasticity as measured by the Ashworth scale [18]. However, patients reported subjective benefit, raising questions about the sensitivity and validity of current instruments for measuring objective outcomes [18]. Further research is warranted to show the benefits of cannabinoids in MS. In addition, surgical procedures (e.g., selective dorsal rhizotomy) may be considered when all other anti-spasticity treatments have failed to alleviate spasticity or to prevent complications, such as contractures.

Balance, ataxia, and incoordination issues are common in patients with MS who have posterior fossa lesions. Balance and ataxia management include rehabilitation techniques and medications. Antiepileptics, beta-blockers, and benzodiazepines have been used, but with minimal effect.

6.5 Visual Deficits

Visual symptoms occurring in MS include loss of vision, blurred vision, color desaturation and, more rarely, visual field cuts. Posterior fossa lesions cause visual changes including diplopia, nystagmus, and internuclear ophthalmoplegia. Visual spatial rehabilitation and devices such as eye patches or prism glasses may improve vision.

Medical treatment for acute vision changes may include intravenous steroids, as found in the optic neuritis treatment trial (ONTT) [19]. Intravenous steroids provide a quicker recovery of vision than oral steroids, but after 1 month, there was no significant difference between intravenous and oral steroids in visual acuity, visual fields, color vision, or contrast sensitivity [19]. Similar findings have been reported in other studies. Therefore, some clinicians will use oral steroids, especially in patients with poor intravenous access. Furthermore, in clinical practice, some providers will use subcutaneous or intramuscular ACTH if corticosteroids are contraindicated or known to be inefficacious, or if patients have poor intravenous access. Chronic vision changes are treated with medications, such as gabapentin for nystagmus or others.

6.6 Bladder, Bowel, and Sexual Issues

Bladder issues are present in 70–80 % of patients with MS [20]. Urinary dysfunction may be classified into three types:

- Detrusor hyperreflexia (failure to store), which is managed with anticholinergic and non-selective muscarinic agents
- Hyporeflexia (failure to empty), which is managed with an intermittent catheterization program
- Detrusor-sphincter dyssynergia (DSD, a failure to store and empty properly), which is treated with an intermittent catheterization program, anticholinergic, and α-adrenergic agents

In general, the non-selective muscarinic agents, such as oxybutynin, tolterodine, and trospium, ought to be avoided in patients with cognitive issues since these agents may cross the blood–brain barrier (BBB) and exacerbate cognitive deficits; selective muscarinic agents, such as darifenacin and solifenacin, are preferable in patients with cognitive dysfunction [20]. In addition, the standard care for lower urinary tract symptoms includes other medications, such as

5-phosphodiesterase inhibitors (PDE5i) and β3-adrenoreceptor agonists (i.e., mirabegron) [21]. Recent studies have shown that PDE5is such as tadalafil have improved urinary flow and sexual function simultaneously, and stimulation of the β3-adrenoreceptor have increased bladder capacity without interference in micturition pressure, post-void residual (PVR), or voiding contraction [21]. Furthermore, clinical trials in patients with MS with urinary incontinence not adequately treated with oral medications have shown that intradetrusor onabotulinumtoxin A 200 U produced significantly greater reductions from baseline in urinary incontinence than placebo. Similar significant benefits of intradetrusor onabotulinumtoxin A 200 U when compared to placebo were observed on health-related QoL and treatment satisfaction endpoints [22].

Bowel dysfunction, mainly constipation or incontinence, is found in 50–70 % of patients with MS. While constipation is more common, many patients experience bowel incontinence as an ongoing problem affecting their quality of life. There is some evidence that lesions in the frontal lobes, brainstem, and spinal cord disrupt afferent and efferent pathways related to autonomic and voluntary bowel control [20]. Bowel management includes non-pharmacological methods such as a timed bowel routine, dietary changes, adequate hydration, exercise and physical activity, and biofeedback. Pharmacological agents include stool softeners, laxatives, rectal stimulants (i.e., glycerin suppositories) and mini-enemas.

Sexual dysfunction in MS is common in both men (~50–90 %) and women (~40–85 %) [20]. The origin of sexual dysfunction in MS is multifactorial. Primary causes may be related to demyelinating lesions and axonal loss; secondary causes may be related to other symptoms of MS (i.e., fatigue, bladder or bowel issues); tertiary sexual causes are related to the overall impact of the illness (i.e., social isolation); quaternary causes are related to consequences of MS interventions, such as the side effects of medications. Sexual dysfunction in men includes reduced libido, erectile impotence, and premature ejaculation [4, 6]. Sexual dysfunction in women includes

reduced libido, decreased vaginal lubrication and sensation, and reduced orgasms [6].

Non-pharmacological strategies for sexual dysfunction incorporate counseling, couple therapy that works on enhancing communication, and treatment of secondary symptoms to improve intimacy. The main pharmacological therapy for erectile dysfunction includes the phosphodiesterase-5 inhibitors (i.e., sildenafil and tadalafil). Two double-blind, randomized, placebo-controlled studies in men with MS showed modest positive results in improving erection. Patients have reported improved erections based on the Global Assessment Questionnaire among 33 % of those taking sildenafil as compared with 18 % of those receiving placebo ($P = .04$) but other studies have shown better effect of sildenafil on the ability to achieve an erection [23, 24]. Alternative male options include intracavernosal injections or different devices to improve erection and maintain it throughout intercourse.

A recently approved therapy, flibanserin, is the only medication to enhance libido in women by binding with serotonin receptors in the brain. The mechanism of action of flibanserin is similar to that of SSRIs. Studies have shown that flibanserin (100 mg) at bedtime resulted in significant improvements in sexual desire vs. placebo [25]. Furthermore, flibanserin was associated with significant reductions in distress associated with sexual dysfunction and low sexual desire [25]. The major side effect of flibanserin is hypotension and syncopal episodes if taken with other drugs. SSRIs such as fluoxetine and citalopram and SNRIs such as duloxetine HCL and bupropion HCL (the only norepinephrine-dopamine reuptake inhibitor [NDRI]) may alleviate depression, increase libido, and preserve open communication.

6.7 Neuropsychological Issues

Neuropsychological changes in MS include both psychiatric disorders and cognitive deficits. Depression and anxiety are both very common in MS. Predictors for improving depression

and anxiety in MS were social or emotional support and humor; factors worsening mood symptoms were excessive emotional ventilation and denial [26]. Other studies have shown that unhealthy habits and behaviors, such as drug use, smoking, lack of exercise, and psychological factors (e.g., low optimism and avoidance) have predicted depression and anxiety in MS [27]. These data might assist MS providers in determining which patients are at greatest risk for developing anxiety and depression [27]. Other serious mental disturbances (i.e., bipolar disorder) have been associated with MS [28]. It is clinically important to treat mood disorders because of the high risk of suicide among patients with MS. Death certificate-based reviews have indicated that suicide might be the cause of death for 15 % of patients attending MS clinics [29]. Because depression has been a major risk factor for suicide [28], it is essential to screen for it routinely and manage it appropriately.

Patients with MS may also experience disorders of affect, typically an expression of feelings that is not representative of a person's underlying emotions. Some patients with MS may laugh or cry out of proportion to or in the absence of an expected feeling; this condition is variably referred to as pseudobulbar affect (PBA) or pathological laughing and crying. A recently approved medication to treat PBA is a combination of dextromethorphan hydrobromide and quinidine sulfate. Other methods to treat PBA include SSRIs and SNRIs.

Mood management in MS may include psychotherapy, cognitive behavioral therapy (CBT), psychodynamic therapy, and medications such as antidepressants and anxiolytics. In addition, exercise and physical activity may help alleviate mood issues.

Cognitive deficits in MS include slowed information processing, impaired problem solving, reduced word-finding ability, decreased attention and concentration, memory loss, reduced visuospatial abilities, and reduced executive functioning [30]. Approximately 50 % of patients with MS have cognitive dysfunction over the course of their illness [15].

Studies have shown that disease-modifying medications can have an impact on clinical and MRI disease activity by altering the cerebral demyelinating process and, perhaps, reducing axonal loss, which leads to a slower decline in cognitive functions and improved ADLs for patients with MS [31].

Cognitive remediation, retraining, and rehabilitation are the mainstays of cognitive management. Medications such as acetylcholinesterase inhibitors (i.e., donepezil), memantine (a *N*-methyl-D-aspartic acid [NMDA] receptor antagonist), and rivastigmine tartrate have shown modest or no effects in patients with MS [32, 33]. While these medications have been approved for Alzheimer's disease, they have not been approved for MS, highlighting the fact that cognitive dysfunction in MS has a different pathological process [34, 35].

6.8 Comprehensive Care and Team Approach

MS is a chronic illness and, as such, requires an interdisciplinary team approach, which is best provided by comprehensive MS centers. MS may result in a wide variety of motor, sensory, and cognitive symptoms, emphasizing the need for a wide-ranging management approach [36]. To provide comprehensive care, an understanding of the pathophysiology and the increasingly complex medical management of MS is necessary [37]. Ideally, the comprehensive care team is housed within a single center. Although not every practice is equipped to provide full comprehensive care, it is possible to structure patient assistance in a way to provide both optimal care and a support network for the patient. In the absence of full support at one point of care, networking with other sites, providing referrals to other providers, and MS organizations can help fill the gaps in care. A large practice has to address the risk of spreading patient care to a network that is too extensive and risk losing the patient in the process. However, smaller or more general practices can be quickly overwhelmed by the sheer magnitude of patient needs. The right

balance of providing adequate resources and tracking patients can be found by applying a few basic principles: refer appropriately; give the patient responsibility according to his or her abilities; and delegate appropriate tasks to other providers and services when possible.

Empowering patients and their families to take responsibility for their own care is a critical skill for individual providers and groups alike. The goal of care in MS is to maximize the patient's physical, emotional, social, and vocational independence [36]. Through the interdisciplinary efforts of numerous health care workers, in cooperation and communication with the patient and family, this goal can be attained [38].

An interdisciplinary team approach can best manage both acute temporary disability and, often later, progressive physical and, occasionally, mental disability. The team typically involves a neurologist, nurse, social worker, and other health care professionals [39]. The nurse or nurse practitioner plays a key role in patient care. It is often up to the nurse to provide symptom management and to coordinate the other components of the care team. Mental health specialists such as psychologists, neuropsychologists, and social workers may assist patients with the emotional, cognitive, and social challenges (e.g., disclosure, job loss, relationship issues, changing roles within the family, depression) that they often face. Furthermore, referral to others is recommended based on the individual needs of each patient. Patients with MS are often referred to rehabilitation specialists: physiatrists, physical therapists, occupational therapists, and a speech/language pathologist, who are involved in the evaluation of the varying levels of physical/language deficits that the person with MS can exhibit [39]. In addition, the holistic and complex management of MS requires coordination of care by the primary care provider (PCP). The PCP monitors the patient's general health. This is critically important, as MS is just one of many potential disease processes that require routine follow-up of patients. Creating a dynamic team to help the patient may be the most rewarding and productive approach

to care. Finally, research suggests that a comprehensive care approach to MS management results in better clinical outcomes and lower costs [36].

6.9 Conclusion

Symptom management in MS has implications for patients' daily functioning and QoL. MS symptom management involves a thorough assessment and multiple-modality treatment that involve both non-pharmacological and pharmacological strategies. Complementary and supplementary approaches such as yoga, acupuncture, Feldenkrais, and relaxation techniques (e.g., deep breathing exercises) assist patients with MS address the daily fluctuations and challenges of the illness. An individualized and prioritized plan is vital in MS care because every individual is unique.

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