ABSTRACT

Multiple sclerosis (MS) is a chronic inflammatory degenerative neurologic disorder that is usually characterized by episodic periods of acute exacerbations, gradual progressive deterioration of neurologic function, or combinations of both. Early diagnosis and treatment is crucial to delay disease progression and prevent future disability. This discussion explores the complex immunopathogenesis involved in MS, as well as current and emerging techniques used to diagnose/evaluate this condition. (Adv Stud Pharm. 2010;7(3):57-62)

Affecting over 400 000 Americans and 2.7 million individuals worldwide, MS is a chronic, inflammatory disease of the central nervous system (CNS). Eighty percent of patients with MS develop the condition at a young age (between 16 and 45 years), and women are 2 to 3 times more likely than men to be diagnosed with this disease. Symptoms vary widely among patients and may include numbness, fatigue, gait disturbances, bladder dysfunction, optic neuritis, dizziness, spasticity, visual disturbances, and/or depression. MS is the leading cause of disability in young women, and the second leading cause of disability in young men. Left untreated, 50% of patients with MS require ambulatory support within 15 years of disease onset and 30% eventually become wheelchair- or bed-bound.1

Because individuals often become symptomatic during their most productive years, the financial cost of MS can be staggering. Medication therapy typically costs between $20 000 and $30 000 per year, with an additional $13 000 needed to treat each disease flare-up. Taken together with indirect expenses due to absenteeism/unemployment, the costs of MS are estimated at $57 500 per patient, per year,1 or roughly $9.5 billion in total annual expenses.2

CLINICAL COURSE OF MS

The clinical course of MS may follow a variable pattern over time, but can usually be characterized by episodic periods of acute exacerbations, gradual progressive deterioration of neurologic function, or combinations of both. As such, clinicians have developed 4 categories of disease: relapsing-remitting MS (RRMS), primary progressive MS (PPMS), secondary progressive MS (SPMS), and relapsing progressive MS (Table).3 Approximately 80% of patients with MS require ambulatory support with 15 years of disease onset and 30% eventually become wheelchair- or bed-bound.1

Etiology and Pathogenesis of MS

Although its exact cause is unknown, several factors...
(ie, genetic predisposition, environmental conditions, and infections with *Chlamydia pneumoniae*, human herpes virus-6, or Epstein-Barr virus) are believed to be involved in the initial immunologic response in MS.\(^4,5\) Disability caused by inflammatory demyelination clinically dominates the early stages of RRMS and is potentially reversible. Axonal transection occurs at sites of inflammation and begins at disease onset; however, this process is clinically silent during early stage disease because the CNS compensates for neuronal loss via regeneration, which reflects an inherent cerebral reserve capacity. But once axonal loss bypasses a critical threshold, such compensatory mechanisms are lost, thereby triggering the conversion of RRMS to SPMS. Axonal degeneration in SPMS is caused by chronic demyelination and may be irreversibly progressive. Thus, early initiation of anti-inflammatory and neuroprotective therapy may help to delay disease progression and reduce disability.\(^6\)

**PROPOSED IMMUNOPATHOGENESIS**

The proposed immunopathogenesis of this disease is illustrated in the Figure.\(^7\) MS is thought to be an autoimmune disorder in which the body mounts an immune response that ultimately results in axonal destruction. This process is initially triggered by T-cell activation, which takes place when an antigen-presenting cell, in the groove of major histocompatibility complex, is recognized by a T-cell receptor. Upon antigen presentation, and in the presence of specific costimulatory molecules, the T cell undergoes clonal expansion and differentiation into effector cells.\(^4\) A subset of T cells bearing the CD4\(^+\) molecule on their surface can differentiate into 3 effector cell types (ie, T-helper [TH]1, TH2, and TH17); TH1 cells, which promote cell-mediated immunity, produce pro-inflammatory cytokines (ie, interleukin [IL]-2, IL-12, interferon [IFN]-\(\gamma\), and tumor necrosis factor [TNF]-\(\gamma\]), while TH2 cells release anti-inflammatory cytokines (ie, IL-4, IL-10, IL-13, and transforming growth factor-\(\alpha\)).\(^10\) Patients with MS tend to have an elevation of TH1 cytokines and a diminution of TH2 cytokines, which may explain the inflammatory nature of the disease.\(^8\) Similar to TH1 cells, TH17 cells produce pro-inflammatory cytokines (ie, IL-17), and have recently emerged as key players in the pathogenesis of MS.\(^9\)

The inflammatory demyelination seen in MS occurs when T cells cross the blood-brain barrier (BBB) and infiltrate the CNS. Although the BBB is
normally impermeable to immune cells, pro-inflammatory effector T cells can induce endothelial cells of the BBB to upregulate surface adhesion markers. Additionally, activated leukocytes secrete matrix metalloproteinases, which may promote transendothelial migration by degrading the BBB. Once they have entered the CNS, T cells activate macrophages and microglial cells; these cells enhance phagocytic activity, cytokine production, and the release of toxic mediators, thereby propagating demyelination and axonal loss. Although TH2 cells can help to regulate/suppress this process, consequent B-cell stimulation ultimately increases T-cell activation and initiates the complement cascade, thus perpetuating CNS inflammation and damage. Indeed, patients with PPMS and SPMS have been found to have pockets of B cells present in the intermeningeal space, which are directly associated with cortical lesions visible by magnetic resonance imaging (MRI).

Dr Guthrie: It has always been my understanding that glatiramer acetate treats MS by promoting a shift from TH1 to TH2 cells, thereby producing an anti-inflammatory response. But is the corresponding increase in B-cell activation detrimental?

Dr Miravalle: The increase in B-cell activation may explain why the medication is only partially effective. However, glatiramer acetate is not just an anti-inflammatory agent; it is one of the few products that also impede neuronal degeneration.

Dr Guthrie: What is the role of TH17 cells in MS?

Dr Miravalle: Patients with MS have differing immunologic profiles, and those with high levels of TH17 (and IL-17) may not respond to the same drug therapy (ie, IFNβ) as other individuals. Thus, TH17 may act as a biomarker for a specific type of inflammation that certain patients have.

HISTOPATHOLOGY OF MS

The sclerotic plaques characteristic of MS may present as 1 of 4 types, each of which represents a unique pattern of demyelination. These plaque types are defined on the basis of myelin protein loss, geography and extension, patterns of oligodendrocyte destruction, and immunopathological evidence of complement activation. Specifically, type I and II lesions are inflammatory in nature; type I lesions are T-cell–mediated, whereas type II lesions are both T-cell and B-cell (antibody)–mediated. Type III and IV lesions are less inflammatory and involve a primary oligodendrocyte dystrophy.

DEMYELINATION AND AXONAL LOSS/NEURODEGENERATION

There currently exist 2 theories describing neurodegeneration (loss of neuron structure/function) in MS. The classical theory, or the outside-in model, suggests that chronic inflammatory demyelination leads to secondary axonal swelling and degeneration. Axonal survival is dependent on trophic support from oligodendrocytes, and in the absence of such support, chronic demyelination may lead to Wallerian degeneration (axonal degeneration distal to the site of transection). Conversely, the inside-out model suggests that selective axonal degeneration is later followed by demyelination. In actuality, it is likely that both of these mechanisms play a role in the pathogenesis of MS.

There are many possible causes of axonal loss in MS. Direct inflammatory causes include cell-mediated cytotoxicity, antibody-mediated cytotoxicity, TNF toxicity, and glutamate toxicity, whereas indirect inflammatory causes include astrocyte-mediated TNF production and upregulation of inducible nitric oxide synthase. A variety of secondary causes (ie, loss of trophic support, delayed axonal transport, loss of synaptic connections, inadequate neuronal discharge rates, genetic variations in repair capability, disuse atrophy, and aging in a brain with no reserve capacity) also have been implicated; these represent direct/indirect consequences of the inflammatory attack on the CNS.

ROLE OF MRI IN ASSESSING NEURODEGENERATION

Magnetic resonance imaging is commonly used to assess MS-related neurodegeneration, which is the best prognostic indicator of future disability. T2-hyperintense lesions, which present as bright areas, represent increased tissue water content due to inflammatory demyelination. These lesions appear early in the course of disease, and research indicates that a higher initial lesion burden (during the first 5 years of disease) correlates well with future disability and progression to SPMS. Indeed, one study following patients with clinically probable or definite MS over 14 years found that patients with a higher T2 lesion volume at presentation typically experienced greater long-term disability. T2 lesions tend to accumulate over time, but early intervention can help to prevent disease exacerbations, thereby preserving patients’ functional ability.

T1-hypointense lesions (ie, black holes), which appear as dark areas, indicate sustained axonal loss. Cortical atrophy also increases over time, resulting in a
loss of brain volume. T1 lesions and brain volume are excellent markers of neuronal degeneration and have been seen early in the course of the disease.

Gadolinium is a contrast material that can be used to highlight areas of inflammation on MRI. Gadolinium enhancement requires disruption of the BBB, so it may only be used to discern active (ie, enlarging or enhancing) lesions. It is an important tool that is commonly used to increase MRI sensitivity for evaluating disease activity; indeed, data indicate that it may double the number of detectable active lesions. Gadolinium enhancement requires disruption of the BBB, so it may only be used to discern active (ie, enlarging or enhancing) lesions. It is an important tool that is commonly used to increase MRI sensitivity for evaluating disease activity; indeed, data indicate that it may double the number of detectable active lesions.

Magnet strength is another important factor to consider when assessing MRI visibility because lesions may be more clearly defined when viewed under a stronger magnetic field. For instance, a 7- or 8-Tesla (T) magnet may be able to distinguish lesions that are undetectable under a 1.5- or 3-T magnet; thus, it is important to maintain consistency of magnet strength when assessing T2 lesion load, particularly when evaluating disease progression. Cortical lesions, which are often difficult to visualize using conventional MRI techniques, also may be identified through the use of higher magnet strengths.

Dr Rich: Are 7- and 8-T magnets commercially available?

Dr Miravalle: No, due to safety concerns (ie, dizziness and vertigo), they are only used for investigational purposes at this time. However, they are valuable research tools because they demonstrate the presence of lesions that have been neglected for many years.

**Case Study (cont’d)**

Based on her history and symptomatic presentation, RE is evaluated via MRI and is diagnosed with early stage MS. Although black holes have not yet developed, 3 active lesions are detected in her brain. Should RE be given drug therapy, or should treatment be held off until her symptoms progress?

**Recent MRI Advances in MS**

Diffusion tensor imaging (DTI) is a relatively new MRI technique that uses water diffusion to characterize brain tissue microstructure and white-matter tracts. The direction of highest diffusivity coincides with the tissue’s fiber tract axis, a principle that allows fiber direction to be determined. DTI may be a valuable tool for evaluating MS. Under normal conditions, water mobility through white-matter tracts is restricted by axons oriented along the fibers; conversely, axonal loss or demyelination in patients with MS allows water to diffuse more quickly. Disease progression may thus be assessed, based on the fact that a higher level of diffusivity correlates with increased axonal loss. This may be a promising way to compare remyelination and axonal sprouting before and after administering drug therapy designed to enhance regeneration.

Magnetization transfer, a new technique for improving image contrast in MRI, is based on application of off-resonance radiofrequency pulses and observing their effects on the images, as well as measuring the signal intensity with and without application of the pulses (ie, magnetization transfer ratio [MTR]). MTRs can be used to detect changes in the structural status of brain parenchyma that may or may not be visible with standard imaging techniques. Normal white matter has a high MTR, whereas demyelinated lesions typically have reduced MTRs. Moreover, normal-appearing white matter tends to have a lower MTR in patients with MS than in healthy individuals; this suggests that MTR measurement may enable detection of early disease that cannot be imaged with standard techniques.

Functional MRI (fMRI) is another newly emerging diagnostic tool used to evaluate MS. In order to perform a given task, patients with MS often compensate for structural brain injury, even early in the course of disease. Specifically, they recruit additional cerebral networks that are not typically activated by healthy individuals, thereby limiting clinical manifestations of disease. By measuring hemodynamic response (ie, change in blood flow) related to neural activity, fMRI may be used to reveal the presence of these functional cortical changes. This is a promising tool that may provide further insight into the neurodegenerative processes underlying MS.

Dr Lipsy: Is there a concern that these improved detection techniques will result in unnecessary drug therapy?

Dr Miravalle: Treatment is usually warranted because administering drug therapy during the first 5 years of disease onset is crucial to preventing future disability.

Dr Guthrie: Additionally, improved detection techniques will allow patients to be referred to MS specialists earlier in the course of disease, which would result in long-term cost savings.
CASE STUDY (cont’d)

RE should be referred to a specialist if necessary, but drug therapy should be initiated as soon as possible, to delay disease progression and reduce disability.

CURRENT AND EMERGING THERAPEUTIC TARGETS

Based on the pathogenesis of MS, current and future therapeutic targets include dendritic cells, macrophages, natural killer cells, T cells, B cells, microglia, astrocytes, oligodendrocytes, and neurons. Agents designed to target these constituents include IFNβ, alemtuzumab, natalizumab, mitoxantrone, glatiramer acetate, daclizumab, altered peptide ligand, rituximab, calcium channel blockers, and glutamate antagonists.31

Dr Bainbridge: Is LINGO-1 (leucine-rich repeats and Ig domain-containing, neurite outgrowth inhibitor receptor-interacting protein-1) another therapeutic target?

Dr Miravalle: LINGO-1 inhibits axonal sprouting and remyelination, which may become pathologic in excess. Thus, LINGO-1 is a potential target for neuroprotective therapy in that antagonists may promote remyelination in diseases such as MS.

CONCLUSIONS

Multiple sclerosis is an inflammatory, degenerative disease of the CNS. Involving both T and B cells, it is typically characterized by episodic periods of acute exacerbations, gradual progressive deterioration of neurologic function, or combinations of both. Although early inflammatory demyelination may be reversible, the eventual loss of CNS compensation results in irreversible, progressive disease; thus, early initiation of anti-inflammatory and neuroprotective therapy is essential to delay disease progression and reduce future disability. MRI, which detects both new and old lesions, is currently the standard technique used to diagnose MS. Recent technologic advances such as DTI, MTR, and fMRI may also prove valuable in improving detection and evaluation of this disease.

REFERENCES

1. Rocky Mountain MS Center. MS: the basics. Available at: http://www.mscenter.org/content/view/145/180/.


