ABSTRACT

Although Charcot and others described many of the clinical and histopathologic features of multiple sclerosis (MS) as early as the 1860s, it was not until the end of the 20th century that immunomodulators emerged as potential disease-modifying therapies for MS. Recent research has increasingly demonstrated the importance of neurodegeneration at even the earliest stages of MS, which has prompted the focus on developing new neuroprotective therapies. Considerable evidence suggests that the clinical signs and symptoms of MS are the result of interactions between 2 distinct physiologic processes. Transient relapses are thought to reflect periods of acute central nervous system (CNS) inflammation, which become less frequent over time. Progressive disability is believed to reflect the gradual loss of CNS axons, which may begin even at the earliest stages of the disease. Studies of patients with MS have used magnetic resonance spectroscopy to reveal subtle and progressing abnormalities of CNS axons over time, even in patients without new T2 lesions or clinical relapses. These observations imply that neuroprotective therapies should be instituted as soon as possible after the diagnosis of MS in order to produce the greatest possible reduction in long-term disability. Some research suggests that glatiramer acetate may produce neuroprotective effects within the CNS, possibly by stimulating the release of neurotrophic factors from T lymphocytes or other cell populations. Interferon β may also produce neuroprotective effects in patients with MS, possibly as a result of suppressing inflammation. Several new neuroprotective therapies are now in development for the treatment of MS, and these agents are likely to significantly expand the number of options for MS care during the next few years. (Adv Stud Med. 2009;9(2):42-47)

In 1868, Jean-Martin Charcot first described many of the clinical and pathologic features of multiple sclerosis (MS) that we recognize today, including perivascular inflammation and demyelination, periventricular distribution of white-matter plaques, and the involvement of gray matter in some lesions. He also noted that axons were relatively preserved early in the course of the disease, but were lost in patients with advanced MS. Charcot and others identified these clinical and pathologic features of MS that we still consider to be important, yet it was not until the end of the 20th century that MS was recognized as an autoimmune reaction against myelin, and immunomodulators emerged as the principal treatment option to reduce the frequency of MS episodes. Although the use of immunomodulatory therapies has represented a significant advance in MS care, the management of MS is about to undergo another dramatic change. Recent research has increas-
ingly demonstrated the importance of neurodegeneration in the long-term course of MS disability, and potentially neuroprotective treatment options for MS are now being evaluated in clinical trials.

INFLAMMATION AND NEURODEGENERATION IN MS

As shown in Figure 1, patients with MS may exhibit several different patterns of clinical disability over time. Approximately 55% of patients have relapsing/remitting MS (RRMS), which is characterized by discrete episodes of transient functional impairment. Approximately 30% of patients have secondary progressive MS, in which an initial period of RRMS is followed by gradually progressing disability without clear episodes of exacerbation and improvement. Primary progressive MS, which accounts for approximately 10% of cases, is characterized by a pattern of gradual progression of disability from the earliest stages of the disease. Finally, approximately 5% of patients have progressive relapsing MS, which is defined by a pattern of progressive disability from the onset of disease that is punctuated by episodes of acute worsening of symptoms.

Until recently, inflammation was considered the primary pathophysiological event in MS, and demyelination and subsequent neurodegeneration were considered secondary events. However, it now appears that neurodegeneration occurs early in the course of the disease, perhaps preceding other events, such as demyelination and inflammation. Many researchers now believe that the clinical signs and symptoms of MS reflect the interaction of 2 distinct physiologic processes: acute periods of central nervous system (CNS) inflammation, which result in transient relapses and that become less frequent over time; and the gradual and irreversible loss of CNS axons and brain volume, which cause the irreversible progression of neurologic disability. This understanding of the pathophysiology of MS has crucial implications for the way that patients are treated. The identification of early subclinical axonal degeneration implies that neuroprotective treatment of patients soon after diagnosis may alter the long-term course of disease progression. If neuroprotective treatment is deferred until the onset of progressive disease, it may be too late to counteract the extensive axonal loss and neurodegeneration that have already occurred.

NEURODEGENERATION WITHOUT INFLAMMATION

Several lines of evidence suggest that neurodegeneration is an important aspect of the pathophysiology of MS even in the absence of inflammation or autoimmunity. In 2004, Barnett and Prineas published a case report describing a patient with MS who died very quickly after developing a new brainstem lesion. The histopathologic analysis of this very early lesion was intriguing because it demonstrated the loss of oligodendrocytes despite the absence of an inflammatory infiltrate. This observation suggested that inflammation may actually follow earlier pathologic events. Similarly, Luchinetti et al have described 4 pathologic subtypes of MS, one of which resembles a primary oligodendroglialopathy that is followed by a secondary immune response and CNS inflammation.
Data from the magnetic resonance imaging (MRI) literature also support a primary neurodegenerative pathogenesis of MS. Several studies have examined axonal degeneration in MS using magnetic resonance spectroscopy (MRS), in which magnetic resonance signals are used to identify specific molecular signatures within the brain parenchyma. N-acetylaspartate (NAA) is a brain biomarker that is relatively specific to axons, and that has been used to noninvasively evaluate axon integrity in patients with MS. Compared with normal control subjects, patients with MS exhibit significantly lower levels of brain NAA, suggesting the loss of CNS axons. This loss of NAA is especially striking in regions with T1 black holes on conventional MRI, but is also present even in regions of white matter that appear normal when viewed using conventional MRI. Other MRS studies have also demonstrated that diffuse axonal injury is present in patients with MS who have few cerebral lesions and no disability, that measurable axonal injury occurs over time in the absence of new T2 lesion or clinical relapses, and that axonal damage is evident even at the earliest stages of MS. Studies such as these suggest that axonal degeneration is not a late-occurring response to CNS inflammation, but may be present from the onset of MS.

**NEUROPROTECTIVE EFFECTS OF DISEASE-MODIFYING THERAPIES**

Although these observations have generated considerable interest in the use of neuroprotective strategies in MS therapy, there is no generally accepted measure of neuroprotection. Some researchers have argued that any agent that promotes neuronal survival should be considered neuroprotective, regardless of the mechanism by which it acts. Others have suggested that only agents that directly affect neurons should be considered neuroprotective. Medications that are currently used for the treatment of MS may possess both direct and indirect neuroprotective effects. First-line immunomodulatory therapies not only reduce relapses, but they also slow the long-term progression of MS when administered to patients with relapsing forms of the disorder. In addition, all 3 interferon (IFN) β formulations (IFNβ-1a subcutaneous, IFNβ-1a intramuscular, and IFNβ-1b) and glatiramer acetate (GA) have been shown to significantly delay the conversion to definite MS when administered to patients with evidence of a single demyelinating event, a presentation that has been referred to as a clinically isolated syndrome.

Much of the research examining the neuroprotective effects of MS therapies has focused on the role of the neurotrophins, which are a family of proteins that are produced by immune cells and neurons of the CNS. Many neurotrophins have been identified in the CNS, including brain-derived neurotrophic factor (BDNF), nerve growth factor, neurophin-3 (NT-3), and glial-cell–derived neurotrophic factor. Neurotrophins are growth factors that support the survival and integrity of injured axons and neurons, and also produce other effects that are of potential benefit in MS. For example, BDNF and NT-3 have been shown to induce oligodendrocyte proliferation and remyelination of demyelinated axons in the spinal cord. Neurotrophins may also have immunoregulatory effects, including the suppression of microglia or monocyte activity. In mice, treatment with GA causes the accumulation of GA-specific T cells in the brain, and these cells have been shown to secrete BDNF. Although these results suggest a potential neuroprotective role of GA, it is not yet clear whether these neurotrophin-secreting T cells significantly alter the course of the disease in patients with MS. Azoulay et al retrospectively compared BDNF levels in serum samples from 74 patients with MS who were treated with either GA, IFNβ, or no treatment. Mean BDNF values for the 3 patient groups and for a group of 28 healthy control subjects are shown in Figure 2. The mean serum BDNF concentration of the GA-treated patients was similar to healthy control subjects, and was significantly greater than in patients with MS who were treated with IFNβ or patients with MS who did not receive disease-modifying therapy. No difference in BDNF concentration was observed between patients with MS who received IFNβ versus those who were untreated.

Some evidence also suggests a potential neuroprotective role of IFNβ in patients with MS, which may reflect a secondary effect of suppressing inflammation. For example, an examination of the effects of IFNβ therapy on brain atrophy found that the rate of atrophy decreased over the course of 3 years of treatment. In a second study, determination of brain NAA levels demonstrated a significant loss of axons over a 1-year period in patients with MS who were untreated. In contrast, the NAA concentration increased over time in patients who were treated with IFNβ-1a.
**Future Directions in Neuroprotection for MS**

It is likely that the management of MS will soon become much more complex. Many new and potentially neuroprotective compounds are currently being evaluated in randomized clinical trials, and it is anticipated that several new agents will become available during the next 3 to 5 years. These emerging agents act by many different mechanisms, and each possesses its own unique efficacy and safety profile. Clinicians and patients will therefore face many new decisions as they attempt to balance the efficacy, safety, tolerability, and convenience of new MS therapies.

Fingolimod (FTY 720) is an example of a new class of oral once-daily MS therapies that is currently in phase III clinical trials. Fingolimod causes thymocytes and lymphocytes to internalize and inactivate a specific cell surface receptor (the sphingosine-1-phosphate-1 [S1P1] receptor) that these cells need to exit lymphoid tissues. These immune cells therefore are unable to enter the CNS and cause inflammatory demyelination. Fingolimod may also act at S1P receptors belonging to the same family that are expressed on neurons, astrocytes, and oligodendrocytes within the CNS. Fingolimod has been shown to protect oligodendrocyte precursor cells from cell-killing effects of certain cytokines, such as tumor necrosis factor-α and IFN-γ (Figure 3), which may help to promote remyelination and repair following episodes of inflammatory demyelination.

Sodium channel blockers are another class of potentially neuroprotective medications that may be useful in the treatment of MS. Axonal demyelination often causes the redistribution of sodium ion channels from the nodes of Ranvier to the entire cell membrane. This redistribution of sodium channels is part of a compensatory mechanism that can help axons to restore the conduction of action potential along demyelinated axons. However, the increased sodium transport across the cell membrane as a whole is accompanied by excessive influx of calcium from the extracellular fluid to the interior of the axon, which can result in neuronal toxicity due to intracellular calcium overload. Although the sodium channel blocker lamotrigine has been shown to reduce CNS injury in an animal model of inflammatory demyelination, a similar study using the sodium channel blocker phenytoin has raised some
Figure 4. Clinical Disease in Mice Is Prevented During Administration of Phenytoin, but Rebounds Rapidly After Phenytoin Discontinuation

Withdrawal of phenytoin exacerbated clinical disability in a mouse model of inflammatory demyelination that resembles multiple sclerosis in humans (EAE). Black diamonds indicate untreated animals with EAE; open circles represent animals with EAE that were treated with phenytoin. Gray squares represent animals that were treated with phenytoin for the first 28 days, after which phenytoin was discontinued. EAE = experimental allergic encephalomyelitis.

concerns about the clinical usefulness of these agents. In this study, mice with experimentally induced demyelination exhibited a significant reduction in neurologic disability while they were treated with phenytoin, but disability rapidly returned when phenytoin was withdrawn (Figure 4). The use of sodium channel blockers in clinical trials of patients with MS will require careful monitoring to understand how the blockade of sodium channels affects the long-term course of disease.

CONCLUSIONS

Neurodegeneration occurring early in the course of MS has recently been recognized as an important contributor to the long-term progression of permanent disability. The identification of the role of early axonal degeneration has suggested new approaches to the management of MS, including the importance of early treatment and the use of potentially neuroprotective agents. Future clinical trials will examine novel agents that act to protect the survival of neurons and oligodendrocytes, and will use new imaging techniques as surrogate measures of disease activity. Oral medica-

REFERENCES