ABSTRACT

Multiple sclerosis (MS) is a chronic disease that is characterized by central nervous system (CNS) inflammation, demyelination, and neurodegeneration. Although the pathophysiology of MS is not completely understood, it is clear that much of the underlying disease process is clinically silent and continues even when patients are not experiencing symptoms. Most patients initially present with relapsing/remitting MS, in which acute disease episodes are separated by a return to normal or near-normal neurologic function. Eventually, most patients transition to secondary progressive MS, which is defined by the gradual accumulation of irreversible neurologic impairment. A consensus has recently begun to emerge that the long-term progressive disability in patients with MS is due to irreversible neurodegeneration, and that inflammation is less prominent in the later stage of the disorder. MS lesions exhibit extensive axonal transection and degeneration, and may involve both gray matter and white matter. Demyelination alone does not appear to cause axonal injury, and most axons survive transitory demyelination. However, axons that are chronically demyelinated are at substantial risk of degeneration. This may reflect the loss of important nerve growth factors that are produced by surrounding oligodendrocytes and that are essential for axonal survival. The gradual accumulation of axonal injury probably contributes to the long-term atrophy of the CNS that is often observed in patients with chronic MS, and to the eventual progression of neurologic impairment. Early initiation of disease-modifying therapy may therefore help to slow long-term neurodegeneration and disease progression in patients with MS. (Adv Stud Med. 2009;9(2):37-41)
early period of relapsing/remitting MS (RRMS), patients experience discrete episodes of transient disability during periods when disease activity within the CNS exceeds a minimum threshold. These episodes usually resolve spontaneously over the course of a few weeks and may involve any portion of the CNS, including visual, sensory, or motor function. Most patients eventually enter a stage of secondary progressive MS (SPMS), which is characterized by irreversible and gradually progressing neurologic impairment.

It is now generally accepted that the early acute episodes of MS reflect the infiltration of immune cells into the white matter of the CNS and the loss of myelin. When viewed using magnetic resonance imaging (MRI), active MS lesions are revealed by the uptake of the contrast agent gadolinium, which occurs at sites where the integrity of the blood-brain barrier has been compromised. With time, the immune activity subsides, and many lesions enter a chronically active state of continued slow expansion. Some of these lesions, although not all, ring-enhance when viewed using MRI. These lesions may eventually become occupied by hypertrophic astrocytes, resulting in the formation of chronic "black holes" that are visible on T1-weighted MRI. Although inflammatory processes are thought to account for acute MS exacerbations, inflammation alone does not explain the long-term progression of disability in patients with progressive MS. Many patients with SPMS continue to exhibit long-term functional decline even in the absence of any visible ongoing inflammatory activity. In addition, these patients are much less likely to respond to anti-inflammatory therapies than patients with RRMS. A consensus has recently begun to emerge that the permanent neurologic disability in patients with MS is closely related to slowly evolving axonal loss and neurodegeneration.

**Axonal Loss in MS**

Studies of the histopathology of MS lesions have demonstrated that axons are transected as an indirect effect of inflammatory demyelination. Long-term effects of axonal transection on neurologic function are much more serious than demyelination. CNS neurons have only a limited capacity for repair and recovery following injury, and axonal transection often leads to the eventual death of the neuron. In contrast, demyelination within the CNS is often reversible as oligodendrocytes remyelinate surviving axons. Although the mechanism of transection is not completely understood, it is possible that demyelination within an acute MS lesion may increase the susceptibility of demyelinated axons to inflammatory cytokines or other inflammatory mediators that are present within the lesion.

Postmortem studies in which axon counts were performed within MS lesions have demonstrated that axonal injury in MS plaques is surprisingly extensive. These studies have found that there are approximately 11,000 transected axons per mm³ in active MS lesions, compared to approximately 1 transection per mm³ in white matter from healthy control subjects. It has been estimated that axonal loss in postmortem samples of the spinal cord from patients with severely disabling MS averages nearly 70% compared to normal values. Studies such as these demonstrate that MS is not simply a disorder of white-matter demyelination and that profound axonal degeneration is common.

**Figure 1. Axons in Spinal Cord Tissue from a Patient with SPMS and a Normal Control Subject**

Axons in spinal cord tissue samples obtained from a patient with SPMS (left) and from a normal control subject (right). Patients with SPMS exhibit a marked loss of spinal axons compared to control samples.

**GRAY-MATTER LESIONS**

Although MS has traditionally been described as a disorder of the white matter, recent research has demonstrated that many individuals with MS also exhibit marked cerebral pathology. Three types of demyelinating lesions involving the gray matter have been identified. Type I cortical lesions involve both the cortical white matter and the gray matter. Type II lesions are small perivascular areas of gray-matter demyelination. Type III lesions appear as a band of demyelinated cortex that extends downward from the pial surface through cortical layers 3 or 4, and often traversing several gyri. Although some researchers have suggested that cortical lesions may be more important than white-matter lesions in the pathogenesis of MS, it has been difficult to characterize the importance of gray-matter lesions because there is no simple way to identify them in living patients, and little is known about the dynamics of lesion formation in gray matter. The information that is available suggests that pathologic processes that occur in white matter also occur in gray matter, including transections of axons and neuronal degeneration. In one study, gray-matter lesions were examined histologically using tissue samples from the brains of 20 patients with MS that were obtained from a Norwegian MS tissue bank and from 7 patients without neurologic disease. Myelin staining of samples from standardized brain regions revealed mean demyelination of 24% of the frontal cortex, 11% of parietal cortex, 28% of temporal cortex, and 44% of cingulate gyrus. Although this study represents only a small sample of patients, the findings suggest that approximately 25% of the cerebral cortex may be demyelinated in patients with chronic MS.

Cortical lesions may be very important in the disability associated with MS, especially in association with factors such as cognitive impairment and fatigue. Fatigue is among the most common complaints among patients with MS, yet the causes of fatigue in these individuals are not well understood. Cortical lesion load has been proposed as an important predictor of fatigue in patients with MS.

**CHRONIC Demyelination and Neurodegeneration**

Demyelination itself does not directly cause neuronal loss, and the vast majority of demyelinated axons survive demyelination. Whereas the rapid onset of disability in the acute MS lesion probably reflects edema, the loss of myelin, and the diminished capacity of axons to convey action potentials, function may improve as inflammation resolves and sodium channels are redistributed from the nodes of Ranvier along the entire demyelinated axonal membrane. This redistribution of sodium channels restores at least some ability of the axon to propagate action potentials. However, axons that remain chronically demyelinated for long periods are at substantial risk of degeneration. It has been hypothesized that one reason for the degeneration of these chronically demyelinated axons is that the myelin sheath provides trophic support that is essential for long-term axonal survival.

The relationship between myelin loss and neurodegeneration has been difficult to study in patients with MS because it requires the ability to examine a particular lesion over time in a single patient. In practice, human MS lesions are usually studied histologically only at a single point in time using postmortem tissue. However, the results of animal studies strongly suggest that a particular myelin-derived protein—myelin-associated glycoprotein (MAG)—is important in axonal survival. MAG is present only in the portion of the oligodendrocyte membrane that makes direct contact with the underlying axon and was originally believed to be crucial in the process by which oligodendrocytes surround and myelinate CNS axons. This view was challenged by animal studies that demonstrated that mice in which MAG had been removed from the genome still exhibited normal-appearing CNS myelination during development. However, further analysis of these MAG-deficient mice revealed significant axonal degeneration once the mice reached adulthood. MAG may therefore be important in maintaining axon survival, rather than in the formation of axonal myelination, and the loss of MAG may be an important contributor to axonal degeneration in chronically demyelinated MS lesions.

One consequence of axonal loss is the significant brain atrophy that has been observed in long-term MRI studies of patients with MS. A study at the Cleveland Clinic is currently conducting detailed pathologic assessments using CNS tissue samples from recently deceased patients with MS in a prospective brain donation and rapid autopsy program. A surprising finding of these studies was that many patients...
had extensive atrophy after a long history of MS, yet they exhibited no macroscopic evidence of demyelinated lesions in brain tissue samples. These observations suggest that chronically demyelinated axons had degenerated, resulting in CNS atrophy.

**Two-Component Model of MS Pathogenesis**

As described earlier, it is now clear that MS lesions are characterized by both the infiltration of immune cells from the periphery to the CNS and the gradual loss of CNS neurons. On the basis of these observations, a 2-component model has been proposed to account for the long-term histopathologic and clinical findings that are observed in patients with MS (Figure 2). Neurodegeneration may begin even at the earliest stages of the disease and well before clinical signs and symptoms of MS become apparent. A similar lack of early symptoms despite ongoing neurodegeneration is common to many chronic neurodegenerative disorders, and is thought to reflect the ability of the surviving tissue to compensate for early neuronal loss. While this clinically silent neurodegeneration is taking place, acute relapses and remissions occur due to transitory episodes of CNS inflammation. The gradual accumulation of neuronal loss continues until the intact neuronal systems can no longer compensate for the neurons that have been lost. At this point, the irreversible disability of MS begins to appear. Although compensation may be an important mechanism by which some neuronal function is restored, the additional metabolic demands on the remaining neurons may shorten their eventual lifespan and contribute to widening neurodegeneration later in the course of the disease.

This 2-component model of MS is supported by data from patient cohorts that have examined the long-term course of MS disability progression. For example, one study examined the time required for patients with MS to reach 2 clinical milestones. The first milestone was the time required to attain a score of 4 or more on the Expanded Disability Status Scale (EDSS), which corresponds to the appearance

![Figure 2. Two-Component Model of MS](image)

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Symptoms occur when disease activity within the CNS crosses a threshold (horizontal solid line). During the RRMS phase of the disease inflammatory activity is especially prominent. Neurodegeneration begins even at the earliest stages of the disease (dotted diagonal line). During the RRMS stage, MS symptoms occur as the result of transient episodes of CNS inflammation (dashed horizontal lines). As the patient transitions to SPMS, neurodegeneration becomes the principal factor driving disease progression and irreversible disability.

CNS = central nervous system; MRI = magnetic resonance imaging; MS = multiple sclerosis; RRMS = relapsing/remitting MS; SPMS = secondary progressive MS.


![Figure 3. Progression Rate of Neurologic Disability in Patients with MS](image)

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Progression of disability during the early stages of MS (ie, to an EDSS score of 4) is highly variable from patient to patient. This probably reflects varying degrees of compensation for the loss of CNS axons. However, once patients reach an EDSS score of 4, the time to reach an EDSS score of 7 is very consistent. This suggests that the rate of neurodegeneration in patients with MS is generally similar once the compensatory ability of the CNS has been exceeded.

CNS = central nervous system; EDSS = Expanded Disability Status Score; MS = multiple sclerosis.

Data from Confavreux et al.
of permanent disability. The second milestone was an EDSS score of 7, indicating the loss of the ability of to walk without support. The results of the study are illustrated in Figure 3. The time required for patients to reach an EDSS score of 4 was highly variable, with a range from less than 1 year to more than 31 years. However, once patients had reached the onset of permanent disability, the time required to progress to an EDSS score of 7 was very consistent from patient to patient. This suggests that the process of neurodegeneration is highly consistent once patients have reached a certain threshold of disability and can no longer compensate for accumulating neurologic injury.

**CONCLUSIONS**

Cortical demyelination and axonal transection occur in patients with MS, but without the extensive influx of inflammatory cells that are seen in lesions of the white matter. Better detection methods are important to visualize this aspect of MS, which is poorly understood, but that may cause a substantial portion of the disability associated with this disease. Axonal transection and neurodegeneration of MS are associated with early inflammatory changes within MS lesions. This observation implies that one way to prevent chronic neurodegeneration is to use anti-inflammatory disease-modifying therapies early in the course of MS.

**REFERENCES**