458 Multiple Sclerosis and Other Demyelinating Diseases

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Demyelinating disorders are immune-mediated conditions characterized by preferential destruction of central nervous system (CNS) myelin. The peripheral nervous system (PNS) is spared, and most patients have no evidence of an associated systemic illness. Multiple sclerosis, the most common disease in this category, is second only to trauma as a cause of neurologic disability beginning in early to middle adulthood.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disease of the CNS characterized by chronic inflammation, demyelination, gliosis (scarring), and neuronal loss; the course can be relapsing-remitting or progressive. Lesions of MS typically develop at different times and in different CNS locations (i.e., MS is said to be disseminated in time and space). Approximately 350,000 individuals in the United States and 2.5 million individuals worldwide are affected. The clinical course can be extremely variable, ranging from a benign condition to a rapidly evolving and incapacitating disease requiring profound lifestyle adjustments.

PATHOGENESIS

Pathology New MS lesions begin with perivenular cuffing by inflammatory mononuclear cells, predominantly T cells and macrophages, which also infiltrate the surrounding white matter. At sites of inflammation, the blood-brain barrier (BBB) is disrupted, but unlike vasculitis, the vessel wall is preserved. Involvement of the humoral immune system is also evident; small numbers of B lymphocytes also infiltrate the nervous system, myelin-specific autoantibodies are present on degenerating myelin sheaths, and complement is activated. Demyelination is the hallmark of the pathology, and evidence of myelin degeneration is found at the earliest time points of tissue injury. A remarkable feature of MS plaques is that oligodendrocyte precursor cells survive—and in many lesions are present in even greater numbers than in normal tissue—but these cells fail to differentiate into mature myelin-producing cells. In some lesions, surviving oligodendrocytes or those that differentiate from precursor cells partially remyelinate the surviving naked axons, producing so-called *shadow plaques*. As lesions evolve, there is prominent astrocytic proliferation (gliosis). Over time, ectopic lymphocyte follicle-like structures, consisting of aggregates of T and B cells resembling secondary lymphoid tissue, appear in the meninges and especially overlying deep cortical sulci and also in perivascular spaces. Although relative sparing of axons is typical of MS, partial or total axonal destruction can also occur, especially within highly inflammatory lesions. Thus MS is not solely a disease of myelin, and neuronal pathology is increasingly recognized as a major contributor to irreversible neurologic disability. Inflammation, demyelination, and plaque formation are also present in the cerebral cortex, and significant axon loss indicating death of neurons is widespread, especially in advanced cases (see "Neurodegeneration," below).

Physiology Nerve conduction in myelinated axons occurs in a saltatory manner, with the nerve impulse jumping from one node of Ranvier to the next without depolarization of the axonal membrane underlying the myelin sheath between nodes (Fig. 458-1). This produces considerably faster conduction velocities (~70 m/s) than the slow velocities (~1 m/s) produced by continuous propagation in unmyelinated nerves. Conduction block occurs when the nerve impulse is unable to traverse the demyelinated segment. This can happen when the resting axon membrane becomes hyperpolarized due to the exposure of voltage-dependent potassium channels that are normally buried underneath the myelin sheath. A temporary conduction block often follows a demyelinating event before sodium channels (originally concentrated at the nodes) redistribute along the naked axon (Fig. 458-1). This redistribution ultimately allows continuous propagation of nerve action potentials through the demyelinated segment. Conduction block may be incomplete, affecting high- but not low-frequency volleys of impulses. Variable conduction block can occur with raised body temperature or metabolic alterations and may explain clinical fluctuations that vary from hour to hour or appear with fever or exercise. Conduction slowing occurs when the demyelinated segments of the axonal membrane are reorganized to support continuous (slow) nerve impulse propagation.

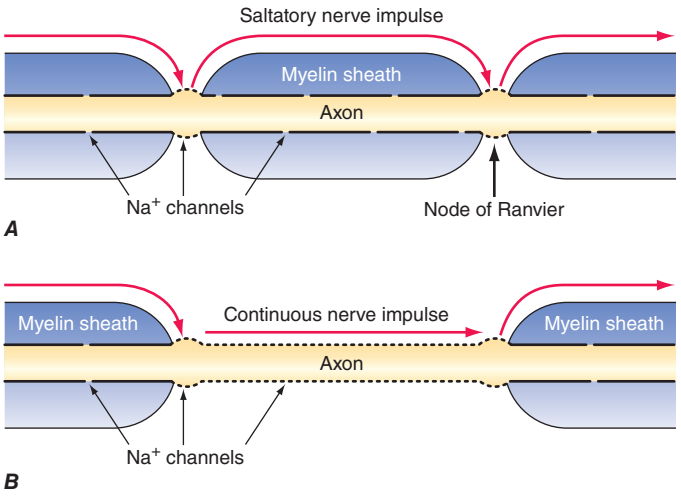

FIGURE 458-1 Nerve conduction in myelinated and demyelinated axons. ***A.*** Saltatory nerve conduction in myelinated axons occurs with the nerve impulse jumping from one node of Ranvier to the next. Sodium channels (shown as breaks in the solid black line) are concentrated at the nodes where axonal depolarization occurs. ***B.*** Following demyelination, additional sodium channels are redistributed along the axon itself, thereby allowing continuous propagation of the nerve action potential despite the absence of myelin.

Epidemiology MS is approximately threefold more common in women than men. The age of onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the lifespan. Approximately 10% of cases begin before age 18 years of age, and a small percentage of cases begin before the age of 10 years.

Geographical gradients have been repeatedly observed in MS, with the highest known prevalence for MS (250 per 100,000) in the Orkney Islands, located north of Scotland. In other temperate zone areas (e.g., northern North America, northern Europe, southern Australia, and southern New Zealand), the prevalence of MS is 0.1–0.2%. By contrast, in the tropics (e.g., Asia, equatorial Africa, and the Middle East), the prevalence is often 10- to 20-fold less.

The prevalence of MS has increased steadily (and dramatically) in several regions around the world over the past half-century, presumably reflecting the impact of some environmental shift. Moreover, the fact that this increase has occurred primarily (or exclusively) in women indicates that women are more responsive to this environmental change.

Well-established risk factors for MS include vitamin D deficiency, exposure to Epstein-Barr virus (EBV) after early childhood, and cigarette smoking.

Vitamin D deficiency is associated with an increase in MS risk, and data suggest that ongoing deficiency may also increase disease activity after MS begins. Immunoregulatory effects of vitamin D could explain these apparent relationships. Exposure of the skin to ultraviolet-B (UVB) radiation from the sun is essential for the biosynthesis of vitamin D, and this endogenous production is the most important source of vitamin D in most individuals; a diet rich in fatty fish represents another source of vitamin D. At high latitudes, the amount of UVB radiation reaching the earth's surface is often insufficient, particularly during winter months, and consequently, low serum levels of vitamin D are common in temperate zones. The common practice to avoid direct