10 DISORDERS OF MYELIN

Myelin

Overview

Myelin is produced in the PNS by Schwann cells and in the CNS by oligodendrocytes. Both cells are embryologically derived from the neural crest. Each Schwann cell myelinates a single 1-mm segment of a PNS axon while each oligodendrocyte myelinates as many as 60 CNS axon segments. At birth, PNS myelination is almost complete, but CNS myelination continues after birth for a decade. In the PNS, loss of Schwann cells triggers regeneration of new Schwann cells, which then remyelinate the demyelinated axon. PNS remyelination is characterized by shorter-length intervals of myelin that have fewer whorls of compact myelin. Nevertheless, remyelination often results in return of normal nerve function. Remyelination can occur in the CNS but does so to a far lesser extent.

Myelin serves several important functions. A key function is to house axons and to provide for the axons' hollow tubular channels of extracellular matrix. In the PNS, unmyelinated axons are surrounded by Schwann cell cytoplasm, but in the CNS oligodendrocytes do not wrap around unmyelinated axons. Myelin provides physical strength to the axon. It also serves to insulate the axon from environmental toxins and prevents ephaptic transmission (direct axon-to-axon electrical transmission without a synapse). In addition, myelin allows saltatory conduction (the action potential moves down a myelinated nerve by jumping from node of Ranvier to node of Ranvier), increasing nerve conduction velocity as much as 100-fold. An unmyelinated peripheral sensory nerve has a conduction velocity of 0.5 to 1.0 m/s. A myelinated peripheral motor nerve conducts at 60 to 80 m/s. Myelination allows more efficient impulse propagation, requiring less energy. As such, myelinated axons can conduct at much faster frequencies for longer periods of time than unmyelinated axons.

Myelin contains about 70% lipid and 30% protein compared with normal cell membranes, which have only about 40% lipid. Some myelin proteins, such as myelin basic protein, myelin-associated glycoprotein, and myelin oligodendrocyte glycoprotein, are specific to myelin, can become immunogenetic, and may be the target of immune-mediated myelin damage.

Demyelinating diseases occur when the disease process primarily involves myelin sheaths, Schwann cells, or oligodendrocytes. Thus there is damage to myelin sheaths with relative sparing of

the underlying axon. Diseases such as strokes that destroy both myelin and axons are not considered demyelinating diseases. The disease process may involve CNS myelin, PNS myelin, or both. Causes of demyelinating disease include genetic (Charcot-Marie-Tooth neuropathy), toxic (diphtheric polyneuropathy), infectious (progressive multifocal leukoencephalopathy), immune-mediated (Guillain-Barré syndrome), and unknown (multiple sclerosis).

There are four major mechanisms of demyelination: (1) death of oligodendrocytes or Schwann cells, (2) interference with myelin synthesis, (3) interference with myelin turnover, and (4) immune-mediated destruction of myelin.

Signs and symptoms of demyelination are due to dysfunction of the underlying axon. In general, the longer the myelinated nerve tract, the greater the probability that a demyelinating disease will disrupt its function. In the CNS, tracts commonly involved include the corticospinal tract (weakness and spasticity), spinothalamic tract (sensory loss), visual pathway (visual disturbance), and spinocerebellar pathways (ataxia). Of note, demyelinating diseases seldom produce the signs of gray matter disease, such as early dementia and aphasia, basal ganglia deficits (parkinsonism or chorea), or seizures. In the PNS, motor and sensory (vibration sense) myelinated nerves are often mildly involved. Similarly, the sensations of pain and temperature (unmyelinated axons) are seldom impaired. In general, genetic and toxic causes of demyelination usually produce symmetrical signs, while immune-mediated and infectious causes of demyelination are often asymmetrical.

Multiple Sclerosis

Introduction

Multiple sclerosis (MS) is an enigmatic, relapsing, and often eventually a progressive disorder of CNS myelin. The classical definition of MS requires dissemination of CNS white matter lesions in time (multiple attacks) and space (involving different areas of CNS white matter). There is a female predominance of about 2:1. The disease usually begins in the third decade of life. Over 300,000 adults in the United States have the disorder. However, the prevalence varies from less than 5/100,000 to 30/100,000 adults around the world, with higher prevalences occurring the further north or south one lives from the equator.

Pathophysiology

The pathologic hallmark of MS, the demyelinated plaque, consists of a well-demarcated hypocellular area characterized by the loss of myelin, relative preservation of axons, and the formation of astrocytic, glial scars (Figure 10-1). The lesions are usually oval and have a small- or medium-sized blood vessel near the center. Inflammatory cells (mainly lymphocytes and macrophages) are typically perivascular in location, but may infiltrate the lesion diffusely. Some plaques demonstrate partial remyelination while others do not. Plaques may occur anywhere in the CNS but not in the PNS. Common locations for plaques include the white matter of optic nerves, surrounding lateral ventricles, corpus callosum, brainstem, cerebellum, and spinal cord. Lesions involve both hemispheres and distribute asymmetrically. Recent studies suggest that there are 4 pathologic forms of MS. The 2 most-common forms appear to display primary

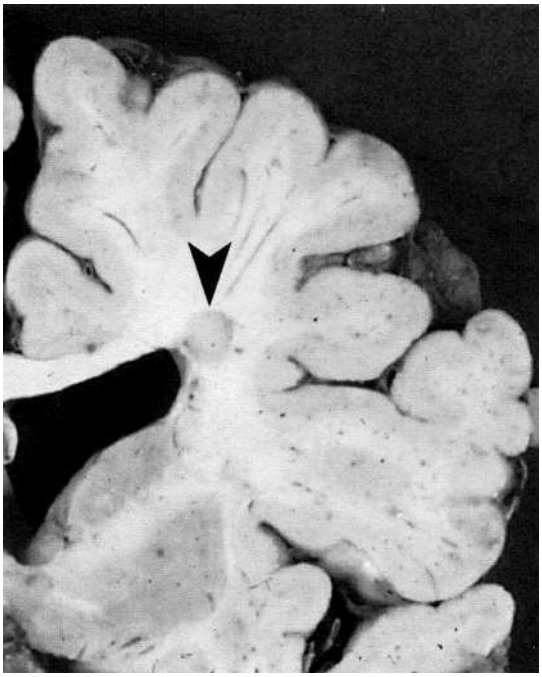

Figure 10-1 Pathologic specimen showing multiple sclerosis plaques. (Courtesy of Mario Kornfeld, MD)

damage to CNS myelin (the first form mediated by antibody, complement, and immune cells and the second mediated only by immune cells), while the other two forms appear to incur primary damage to the oligodendrocytes. Whether the 4 forms have different etiologies is unknown, but in the future may direct patient treatment.

The cause of MS remains mysterious. Extensive searches for an infectious agent or genetic cause have yet to identify a likely etiology. While there is mounting evidence that damage to CNS white matter develops from an immune-mediated process, the initial inciting antigen and how the immune process is maintained at irregular intervals for years remains unclear. Nevertheless, our most-successful treatments have been directed against modifying the immune process.

Major Clinical Features

The clinical features and rate of MS progression vary considerably from patient to patient. Neuroimaging has shown that plaques often appear in "silent" brain areas without producing clinical signs. In the early phase of MS, clinically apparent attacks develop about once or twice a year. The onset occurs over 1 to 2 days and does not have an identifiable trigger. Common clinical signs occur from damage to long CNS myelinated tracts. Thus, MS patients often develop hemiparesis or monoparesis (corticospinal tract), unilateral visual loss (optic nerve), sensory loss (posterior columns or spinothalamic tracts), ataxia (cerebellum or cerebellar pathways), and neurogenic bladder or paraparesis (spinal cord). Patients often complain of worsening of their symptoms in hot weather or when they are febrile.

Spontaneous clinical return of function usually occurs within a month. In the relapsing–remitting form of MS (80% of patients), full return of function prevails but over time, attacks may leave some permanent dysfunction (Figure 10-2). Return of clinical function occurs when the demyelinated portion of the axon converts from permitting only saltatory conduction requiring myelin to an axon segment that has continuous conduction, like unmyelinated axons (Figure 10-3). Thus the conduction velocity slows but function returns. When brain temperature rises, some continuous-conducting axons develop temporary conduction blocks, which explain the worsening of a patient's symptoms in hot weather. Remyelination of demyelinated axons in a plaque is so limited that it probably does not result in significant clinical improvement. Permanent loss of function is associated with loss of the underlying axons.

After 5 to 10 years, relapsing–remitting patients often develop a slowly progressive illness called secondary progressive MS (Figure 10-2). A few percent of patients slowly progress without acute attacks (primary progressive MS). Over 30 years, about 1/2 of MS patients will develop sufficient ataxia or spasticity to require a wheelchair. Life expectancy shortens only slightly.

Major Laboratory Findings

There is no diagnostic test for MS. However, there are characteristic cerebrospinal fluid (CSF) changes

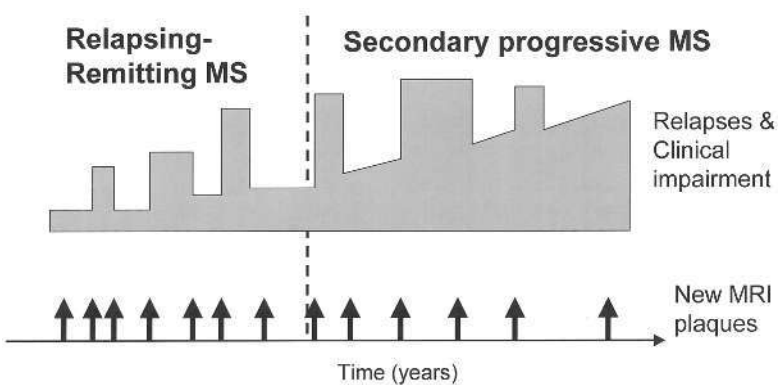

Figure 10-2 *Natural history of multiple sclerosis.*

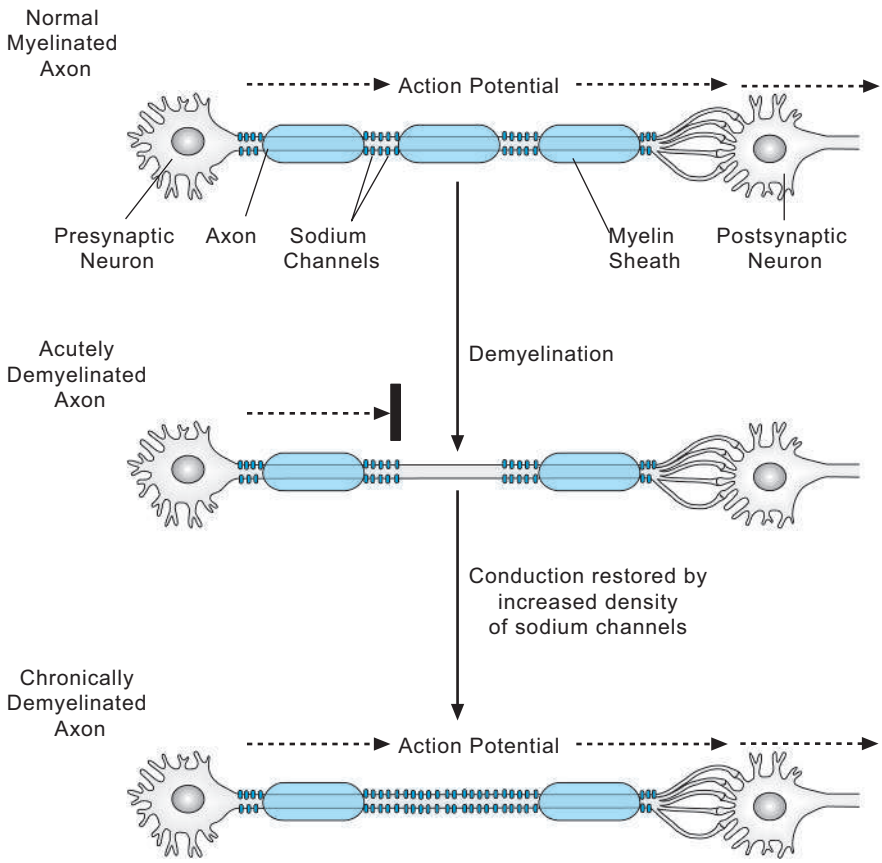

Figure 10-3 *Axonal changes in acute and chronic demyelination.*

that occur in most patients. The CSF usually shows an increased IgG synthesis rate (IgG index) and several oligoclonal bands. This indicates migration of B lymphocytes and plasmacytes from blood to brain plaques with subsequent local homogenous antibody production that then leaks into CSF. It is not known what antigen the MS antibody is directed against. The CSF may contain a small number of lymphocytes but should have a normal glucose level. Routine blood tests are normal.

MRI scans are sensitive, but not specific, indicators for myelin plaques. FLAIR and T2-weighted MRI lesions reflect inflammation, edema, demyelination, and gliosis (Figure 10-4). T1-weighted lesions ("black holes") often reflect marked axonal loss in the plaque (Figure 10-4). Gadolinium-enhancing lesions on T1-weighted images suggest disruption in the blood–brain barrier from active inflammation and demyelination. Neuroimaging lesions occur in the same locations found at autopsy and are commonly seen as perpendicular ovals in the white matter around the lateral ventricles, corpus callosum, cerebellum, and spinal cord.

MS is a clinical diagnosis with laboratory support. Patients should be young adults, have at least one definite clinical attack characteristic for MS, and have definite signs or MRI lesions distributed in several areas of the white matter of the brain and the spinal cord. The clinical diagnosis is supported by the presence of CSF oligoclonal bands and increased IgG synthesis. No other diagnosis for the clinical signs should be apparent.

Principles of Management and Prognosis

Treatment of MS is divided into treatment of acute lesions, rehabilitation of the patient with chronic disease, and prevention of future plaques. Acute relapses are often treated with short courses of high-dose corticosteroids. While spontaneous

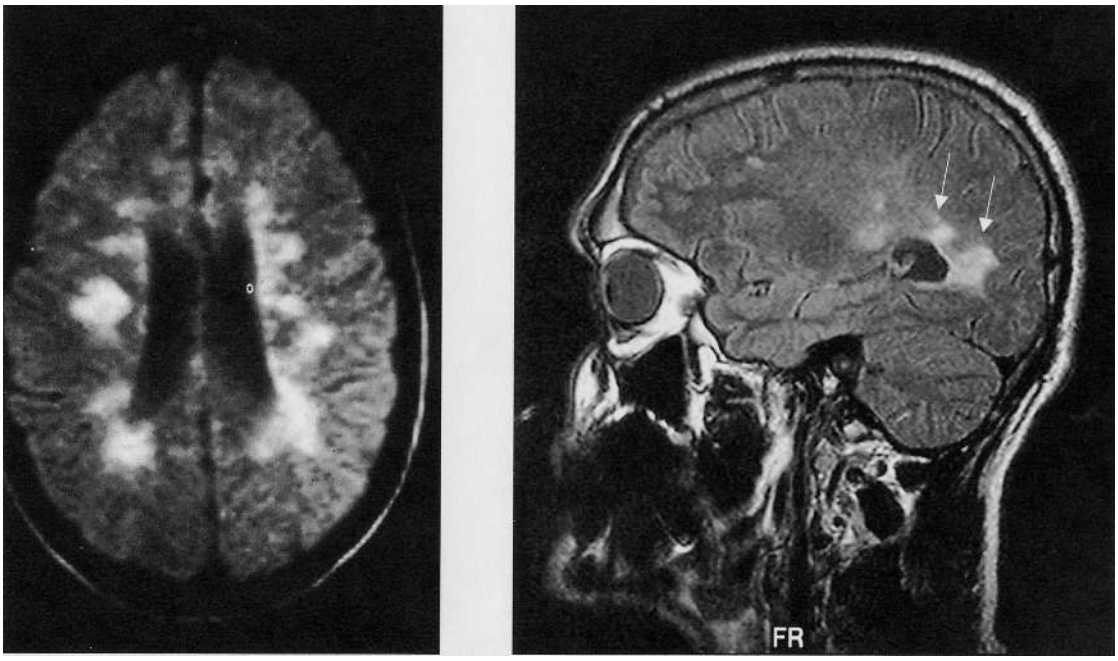

Figure 10-4 FLAIR magnetic resonance imaging scan of multiple sclerosis plaques. (Courtesy of Coley Ford, MD)

clinical recovery takes about 4 weeks, steroids appear to shorten the time to recovery by 1 to 2 weeks. However, steroids do not improve the extent of recovery or change the course of the disease. Chronic treatment with steroids has not been shown to prevent subsequent relapses.

Rehabilitation aims at maximizing patient functioning. Patients commonly become depressed, requiring counseling and antidepressant medication. Fatigue becomes a problem and is difficult to treat. Bladder spasticity with urinary incontinence may develop, requiring treatment. Ataxia and spasticity affect gait, balance, and coordination, interfering with activities of daily living.

Several drugs have been found effective in reducing the frequency of new lesions in relapsing–remitting MS. Interferon β–1b, interferon β–1a, and glatiramer acetate all reduce the frequency of relapses by about 30%. Serial neuroimaging studies show these drugs reduce new T2-weighted lesions by about 60%. While these drugs in short-term studies have shown a trend toward delaying progression of disability, they have not reached statistical significance. The mechanisms by which interferon and glatiramer acetate work are uncertain, but studies suggest the drugs affect the immune-mediated attack to white matter. Both the interferons and glatiramer acetate require daily or weekly administration injections, have a moderate number of local and systemic side effects, and are expensive (about $10,000/yr). It is currently unknown how long these drugs should be taken. Mixantrone, a chemotherapeutic drug, remains the only medication indicated for primary or secondarily progressive MS.

Guillain-Barré Syndrome

Introduction

Guillain-Barré syndrome (GBS) is a monophasic disease involving only myelinated nerves in the PNS. The most common form (>80% in the United States), called acute inflammatory demyelinating polyneuropathy (AIDP), appears to be due to an immune-mediated attack of peripheral myelin. Acute motor axonal neuropathy (AMAN) clinically is more severe than AIDP. The immune attack in AMAN appears directed against the PNS myelinated axon exposed at the node of Ranvier. The annual incidence of GBS in the United States

is about 1 to 2 cases per 100,000 persons. The incidence increases with age, and males slightly predominate. Patients with partial immunosuppression are at an increased risk for GBS.

Pathophysiology

GBS occurs in the setting of an antecedent illness in about 60% of patients. Upper respiratory and gastroenterologic infections are frequent, with the most common being viruses (cytomegalovirus and Epstein–Barr) and bacteria *(Campylobacter jejuni).* It is proposed that via molecular mimicry the patient develops an immune response against the infecting agent that cross-reacts with antigens on the patient's peripheral nerve myelin or axons.

In AIDP, nerve damage results from lymphocytic immune responses against peripheral nerve myelin, with antibodies playing an unclear role. The pathology shows patchy lymphocytic infiltrates, particularly around venules and capillaries within the endoneurium, and macrophages around the myelinated nerves. Hematogenous macrophages adhere to nerve fibers, where they penetrate the Schwann cell basal lamina, extending processes that amputate myelin lamellae and "strip" myelin away from the axon. This process produces segmental demyelination. The most heavily affected part of the nerve is the proximal root. Multiple peripheral nerves are involved in a uniform and generally symmetrical fashion. Central nervous myelin is not affected. Clinical recovery occurs over weeks when the demyelination stimulates abundant Schwann cell proliferation with subsequent remyelination of the naked axonal segment. Remyelination produces short-length myelin segments that are thinner than the original myelin.

In AMAN, antibodies (especially those associated with *Campylobacter jejuni*) appear to attack axon antigens located at the internodal axolemma. In a variant of AMAN called Miller Fisher syndrome (ataxia, areflexia, and internal and external ophthalmoparesis), the responsible antigen appears to be a GQ1b-like epitope that is shared by some bacteria and axons. The nerve pathology is largely noninflammatory and dominated by wallerian-like degeneration of nerve fibers, which accounts for the poorer prognosis of AMAN. Another uncommon variant called chronic inflammatory demyelinating polyneuropathy (CIDP) appears to be an antibody-mediated chronic disease of myelinated peripheral nerves that shares many similarities with GBS and responds to plasmaphoresis, corticosteroids, and immunosuppressive agents.

Major Clinical Features

Flaccid weakness is the hallmark of GBS. Leg weakness is often the earliest sign but usually the weakness involves all extremities. The weakness is both proximal and distal and may also involve motor cranial nerves, producing facial weakness and trouble swallowing and chewing. About 50% of patients experience a reduced vital capacity and about 25% require ventilator assistance. The weakness progresses over 1 to 3 weeks and then plateaus. Clinical involvement of the myelinated autonomic nerve system is common and may be life threatening. Complex supraventricular tachycardias, abrupt bradycardia, and bouts of hypertension or hypotension may occur spontaneously, follow minor adjustments in posture, or occur during painful stimuli. Most patients become areflexic during the first week even if weakness is minor. Diminished vibration sense in the feet is common, but loss of touch, pain, and temperature rarely occurs. Loss of bladder or bowel control is uncommon. Mentation remains normal.

In most cases the diagnosis is based on typical clinical signs. For atypical cases, the differential diagnosis includes acute intermittent porphyria, lead poisoning, tick paralysis, diphtheric polyneuropathy, and critical illness neuropathy.

The weakness progresses over the first 1 to 3 weeks, with subsequent stabilization and recovery. In mild cases of AIDP, motor recovery can occur over a few weeks. For AIDP patients who cannot walk, ambulation often takes 4 to 6 months. In severe cases, recovery may continue for up to 2 years. In AIDP, about 85% of patients fully recovery and 15% are left with minor sequelae such as loss of reflexes. In AMAN, up to 1/2 of patients are left with neurologic sequelae. Death following cardiac arrhythmias or infectious complications still occurs in 2% to 3% of patients with GBS.

Major Laboratory Findings

Major blood tests are normal. The CSF becomes abnormal during the first week. CSF protein elevates to levels of 100 to 400 mg/dL but CSF IgG

synthesis does not increase and oligoclonal bands do not develop. The CSF has a normal glucose level and normal WBC count. If a CSF pleocytosis exists, other diagnoses such as HIV infection, poliomyelitis, West Nile viral myelitis, or meningeal carcinomatosis should be considered. Neuroimaging of the spinal cord should be normal.

Nerve-conduction study results become abnormal in AIDP by the end of the first week. Mean values for compound motor action potential (CMAP) amplitude following nerve stimulation reduces to about 25% to 50% of normal, implying conduction blockage in the majority of motor axons. The motor nerve conduction velocity reduces to 50% to 70% of normal after several weeks, reflecting the segmental demyelination. Variable evidence of muscle denervation may be found on electromyography beginning after 2 to 3 weeks. In AMAN, the motor nerve conduction velocity does not fall markedly, but the amplitude of the CMAP does, as there is widespread evidence of muscle denervation, reflecting that pathologic damage primarily occurs in axons.

Principles of Management and Prognosis

The key to successful management is excellent nursing care. Patients usually require hospitalization and placement in a critical care setting. About 1/4 of patients require a ventilator. Cardiac monitoring is recommended because patients may be prone to severe arrhythmias that may require electrical cardioversion and medication.

Plasmaphoresis or human immune globulin is beneficial if given early in the course of AIDP. Both equally shorten the time to recovery and likely prevent progression of disease to more severe stages. In contrast, use of corticosteroids is not beneficial. Presently, it is unclear which treatments for AMAN may be beneficial. During recovery, physical therapy often improves function.

RECOMMENDED READING

Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;343:938–952. *(Excellent recent review of genetic and pathologic features, immunology, and treatment of MS.)*