Demyelinating Diseases

Diseases with Autoimmune Pathogenesis
Diseases with Probable Autoimmune Pathogenesis

The primary degeneration of central nervous system (CNS) myelin characterizes a heterogeneous group of diseases (Table 8.1). Important diseases, affecting chiefly young adults, are immune-mediated; others, affecting chiefly children, are inherited; and still others are caused by viruses, metabolic disorders, toxins, and blood-vessel diseases. The immune-mediated diseases are presented here. Diseases with other etiologies are covered in other chapters.

DISEASES WITH AUTOIMMUNE PATHOGENESIS

Multiple Sclerosis

Multiple sclerosis (MS) is a multifocal inflammatory demyelinating disease affecting chiefly young individuals between 20 and 40 years of age; it rarely occurs earlier or later in life. It is a major, chronic, disabling disease among young adults, affecting women more often than it does men. Its prevalence varies geographically: It occurs more often—averaging 90 to 100 cases per 100,000 population—in countries with temperate and cold climates. The clinical presentation of MS is greatly diverse and variable. It correlates well with the multiplicity of the lesions and their distributions at various anatomical sites within the brain and spinal cord. (see Chapter 2, for chemical composition and pathology of myelin).

Pathology

Grossly, multiple focal areas of demyelination, called plaques, are the pathologic hallmark of the disease. The location, number, size, and shape of the plaques vary greatly from case to case. Plaques typically occur within the white matter, but may also be found within gray structures, such as the cerebral cortex, thalamus, and basal ganglia. Preferential sites are the optic nerves and chiasma, the periventricular and periaqueductal regions,
the floor of the fourth ventricle, and beneath the pia mater in the spinal cord. Acute plaques are poorly demarcated, soft, pinkish-yellow, and slightly granular. Chronic plaques are distinctly demarcated, firm, grayish, slightly retracted, and translucent or gelatinous (Figs. 8.1 through 8.4). Cerebral atrophy, not uncommon, is evidenced by a thinning of the cortical ribbon and corpus callosum, a reduction of the white matter, and the dilatation of the ventricles.

Histologically, three basic processes characterize plaque formation: inflammation, myelin breakdown, and astrocytic fibrillary gliosis.

Inflammation occurs with vasogenic edema and perivascular infiltrations with lymphocytes, chiefly T cells, some B cells, and macrophages (early in the course CD4 helper/inducer T-cell and later in the course CD8, cytotoxic/suppressor T-cells) (Fig. 8.5).

Myelin breaks down into neutral lipid globules, some of which immunoreact for myelin basic protein (MBP). The myelin globules are phagocytosed by macrophages and gradually removed to the perivascular and subarachnoid spaces (Fig. 8.5).

## TABLE 8.1.
**Diseases of Central Myelin**

<table>
<thead>
<tr>
<th>Etiologies</th>
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<tr>
<td>Autoimmune mechanism</td>
<td>Multiple sclerosis</td>
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<tr>
<td>Probably autoimmune mechanism</td>
<td>Postinfectious and postvaccination encephalomyelitis</td>
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<td>Viruses</td>
<td>Acute hemorrhagic leukoencephalitis</td>
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<tr>
<td>JC virus</td>
<td>Progressive multifocal leukoencephalopathy</td>
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<td>Measles virus</td>
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<td>Rubella virus</td>
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<td>Human immunodeficiency virus</td>
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<tr>
<td>Acquired metabolic</td>
<td>Central pontine myelinolysis</td>
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<td>Vitamin B12 deficiency</td>
<td>Marchiafava-Bignami disease</td>
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<tr>
<td>Inherited metabolic</td>
<td>Combined degeneration of the spinal cord</td>
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<tr>
<td>Vascular</td>
<td>Leukodystrophy</td>
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<tr>
<td>X-irradiation</td>
<td>Subcortical arteriosclerotic encephalopathy (Binswanger’s disease)</td>
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<tr>
<td>Toxins</td>
<td>Leukoencephalopathy</td>
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<tr>
<td>Solvent: Toluene</td>
<td>Spongiform leukoencephalopathy</td>
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<td>Carbon monoxide</td>
<td>Leukoencephalopathy</td>
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<tr>
<td>Drugs</td>
<td>Multifocal leukoencephalopathy</td>
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<tr>
<td>Amphotericin B</td>
<td>Necrotizing leukoencephalopathy</td>
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<tr>
<td>Methotrexate</td>
<td>Leukoencephalopathy</td>
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<tr>
<td>Chronic edema</td>
<td>Multifocal necrotizing leukoencephalopathy</td>
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<td>Immunosuppressed conditions</td>
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</table>

## FIGURE 8.1
Acute MS plaques in cerebral hemispheric white matter are ill-defined, yellowish, and slightly granular.

Meanwhile, the astrocytes begin to proliferate, becoming plump with homogeneous eosinophilic cytoplasm and numerous fibrillary processes (Fig. 8.5). As the plaque matures, the edema and the inflammation resolve and the macrophages gradually disappear. The astrocytes produce more and more fibers and, ultimately, a dense and firm fibrillary gliosis (glial scar) fills the demyelinated plaque (astrocytic fibrillary gliosis).
These characteristic plaques prompted Charcot, a nineteenth-century French neurologist, to name the disease *sclerose en plaque* (sclerotic plaque or multiple sclerosis).

Concurrently, important alterations occur in the axons and oligodendrocytes and, to some extent, in the neurons:

In axonal changes, a variable number of nerve fibers are damaged, some reversibly and some permanently, probably by the inflammatory process and by being stripped of their myelin sheaths. They may be swollen, beaded, or thinned. In severe cases, they may be broken up (Fig. 8.7). Early damage to the axons is readily demonstrated by applying immunohistologic stain for β-amyloid precursor protein (β-APP). Disruption of structural integrity of the nerve fibers leads to wallerian degeneration in the distal segments.

In oligodendroglial changes, the number of oligodendrocytes within the plaques is variably reduced or totally absent (Fig. 8.8). Nevertheless, premyelinating oligodendrocytes and their migrating progenitor cells are evident in some plaques, as has been demonstrated using immunocytochemical techniques. These oligodendrocytes are credited with the potential of remyelinating the denuded nerve fibers under favorable conditions.

Within the plaques, the neurons may be unaffected, or they may show atrophy and some losses (Fig. 8.9). Neuronal losses outside the plaques have also been reported and are attributed to retrograde axonal degeneration.

There are three types of chronic plaques: an *inactive (burnt-out) chronic plaque* consists of a dense astrogliosis with a reduced number of astrocytic nuclei, sparse or absent oligodendrocytes, and variably damaged nerve fibers.

An *active chronic plaque*, by contrast, shows marginal perivascular lymphocytic cuffings, ongoing myelin destruction, macrophages, and a variable number of oligodendrocytes.
FIGURE 8.4
**FIGURE 8.5**
Histology of acute MS plaques: A. Perivascular lymphocytic infiltration (HE). B. Disintegration of myelin into oil-red-O–positive neutral lipid globules. C. Macrophages remove myelin debris (HE). D. Fibrous astrocytes produce fine fibrillary processes (Holzer stain).

**FIGURE 8.6**
Chronic MS plaques. (A) Demyelination and (B) dense astrocytic gliosis in a subcortical plaque. C. Extensive demyelination in the tegmentum and small demyelinated foci in the basis of the pons and D. Dense astrogliosis within demyelinated areas (LFB-CV and Holzer stains).
A shadow or remyelinating plaque shows reduced myelin density, thin and faintly staining myelin sheaths, and moderate to large number of oligodendrocytes.

**Etiology**

Despite a great interest in the disease and ample experimental and pathologic studies, the etiology remains elusive. A combination of genetic susceptibility and environmental factors are implicated in the etiology. Familial occurrences are recognized, and the disease has been reported in monozygotic and dizygotic twins. Certain major histocompatibility complexes (MHC)—HLA-DR2, HLA-A3, HLA-B7—are more frequent among MS patients than among the general population.

**FIGURE 8.7**

Nerve fiber changes within MS plaques. A. At the margin of a plaque, the myelin sheaths are sharply disrupted but a reduced number of nerve fibers is spared. B. Moderate and (C) total loss of nerve fibers in the center of a chronic plaque (Holmes stain).

**FIGURE 8.8**

Oligodendrocytes within chronic MS plaques. A. Oligodendrocytes are sparse among large fibrillary astrocytes. B. Plaque depleted of oligodendrocytes (HE).

**FIGURE 8.9**

Preservation of neurons within MS plaque (LFB-CV).

**FIGURE 8.10**

MRI of acute MS plaques in a 48-year-old man with relapsing MS. Gadolinium-enhanced T1-weighted axial image shows one ring-like enhancing and few homogenously enhancing lesions.
Individuals with HLA-DR2 on chromosome 6 are particularly susceptible to developing MS.

Epidemiologic data indicate a higher incidence of MS in certain geographic areas and among particular ethnic groups. The incidence is higher in northern Europe, the northern United States, and Canada. It is also higher in people of Anglo-Saxon and Scandinavian descent, and lower among Japanese and Chinese. In the United States, the incidence is lower among African American than it is among whites.

Exposure to an as yet unidentified infectious agent probably occurs during the early years of life. As mentioned, the incidence of the disease is higher in cold and temperate climates. Studies indicate that persons who migrate from a cold climate to a warm climate after 15 years of age keep the higher risk of their native locality. Conversely, persons who migrate before age 15 years acquire the lower risk of their new locality.

Pathogenesis

Current views favor an autoimmune-mediated reaction against the myelin (immunologic attack against self-antigen) involving both cellular and humoral immunity. This autoimmune mechanism is supported by similarities between the pathology of MS and the experimental allergic encephalomyelitis (EAE) induced by immunization with brain and spinal cord myelin extracts.

The cellular immune reaction is mediated by T lymphocytes. Simplistically, activated CD4+ T lymphocytes possessing antigen-specific receptors cross the blood–brain barrier and react with myelin and/or oligodendroglia antigen. Cytokines released by T lymphocytes activate macrophages expressing MHC class II antigen. These macrophages present the myelin antigens to the T cells and, in time, remove the products of myelin disintegration. MBP, proteolipid protein, and myelin oligodendrocyte glycoprotein are major target antigens. The humoral immune reaction is mediated by activated B lymphocytes that secrete myelin-specific antibodies. Several pathogens have been postulated to trigger the immune reaction: measles virus, Epstein-Barr virus, human herpes virus 6, retroviruses, canine distemper virus, and Chlamydia pneumoniae. None has yet been confirmed.

An alternative view regarding the pathogenesis of MS implicates apoptotic oligodendroglial deaths and subsequent microglial activation as early events in plaque formation.

Clinical Features

The multiplicity of MS plaques and their locations at various anatomic sites account for the great variability of clinical symptoms and signs (Table 8.2). Visual impairment, varying from diminished visual acuity to total blindness in one or both eyes, orbital pain, and frontal headaches are often the presenting symptoms. However, any cerebral or spinal cord dysfunction may introduce the disease.

Among diagnostic tests, magnetic resonance imaging (MRI) is particularly valuable in supporting the diagnosis (Figs. 8.10–8.12). It shows the typical periventricular plaques and also plaques as small as 3 to 4 mm. Using contrast material, MRI identifies acute plaques and is helpful in monitoring therapeutic efficacy. MS plaques are hypointense (black holes) on T1-weighted images and hyperintense on T2-weighted images. Proton-density images better delineate the periventricular lesions,

<table>
<thead>
<tr>
<th>Table 8.2. Multiple Sclerosis: Common Symptoms and Signs</th>
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<tr>
<td><strong>Ocular</strong></td>
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<tr>
<td>Optic/retrobulbar neuritis</td>
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<td>Scotomas</td>
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<td>Temporal pallor of optic disc</td>
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<td>Diplopia</td>
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<tr>
<td>Internuclear ophthalmoplegia</td>
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<tr>
<td>Nystagmus</td>
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<tr>
<td><strong>Cranial nerves</strong></td>
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<tr>
<td>Facial numbness</td>
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<tr>
<td>Facial palsy</td>
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<tr>
<td>Trigeminal neuralgia</td>
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<tr>
<td>Vertigo</td>
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<tr>
<td><strong>Motor</strong></td>
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<tr>
<td>Weakness,</td>
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<tr>
<td>Ataxia</td>
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<tr>
<td>Tremor</td>
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<tr>
<td>Spasticity</td>
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<tr>
<td>Reflex changes</td>
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<td><strong>Pathologic reflexes</strong></td>
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because the CSF is darker here than on T2-weighted images. The plaques are often oriented perpendicularly to the ventricular surface (Dawson’s fingers). Magnetic resonance spectroscopy (MRS) is useful in demonstrating axonal injury. By measuring the concentration of N-acetyl aspartate (NAA), a neuron-specific marker, MRS monitors axonal dysfunction, which correlates with clinical disability. NAA levels are decreased in acute and chronic plaques. A temporary decrease in acute plaques is associated with reversible neurologic deficits. An increase in choline, a cellular membrane marker, indicates myelin breakdown.

Visual, somatosensory, and brainstem evoked potentials demonstrate a delay or a block in the conduction of nervous impulses and detect clinically silent plaques. CSF abnormalities are not specific, but an increase in γ-globulin fraction and the presence of oligoclonal IgG bands further support the diagnosis. An acute solitary plaque, by producing edema with mass effect, may mimic a space-occupying lesion requiring a diagnostic brain biopsy. The definite diagnosis of MS is based on (a) two or more episodes of neurologic deficits separated in time by at least 1 month, (b) two or more noncontiguous anatomic lesions on MRI, and (c) the absence of an alternative clinical diagnosis.

Although the course of MS is not predictable, two major forms are distinguished: remitting-relapsing and progressive—either from the onset (primary) or after a remitting-relapsing course (secondary). The outcome of an attack is defined by the anatomic and functional relationships between the myelin sheath and its axon, and between the myelin and the myelin-forming oligodendroglia. The severity and extent of axonal injury largely determines the degree of recovery or the persistence of neurologic deficits. Briefly, after the inflammation has resolved and the myelin debris has been removed,
the conduction of the neural impulses is reestablished in the denuded nerve fibers. This results in remission with full or partial recovery of neurologic deficits. If remyelination of nerve fibers occurs, this also contributes to remission. New plaques, which may develop at any time throughout the course of the disease, account for relapses. New attacks of myelin destruction, with a further reduction in nerve fibers within and around an established plaque (active chronic plaque) account for the progression of existing neurologic deficits. The disability becomes permanent when the structural continuity of the nerve fibers is disrupted and wallerian degeneration develops.

The average duration of the disease is 25 to 30 years. Approximately one-third of patients have a benign course, with little disability for 15 years. Death is usually due to an intercurrent infection.

**Variants of Multiple Sclerosis**

*Neuromyelitis optica or Devic's disease* is characterized by an acute inflammatory demyelination confined to the optic nerves and spinal cord, often the cervical segments. The demyelination, in severe cases, progresses to necrosis and even cavitation (Fig. 8.13).

*Charcot classic type MS* shows the typical clinical features and course of MS.

*Marburg type MS* has an acute onset and rapid progression. Death usually occurs within 1 to 6 months of onset.

*Baló's concentric sclerosis* is characterized by concentric zones of demyelination alternating with zones of intact myelin, believed to represent remyelination.
Schilder’s disease refers to extensive demyelination in the cerebral hemispheres, with sudanophilic breakdown products (Fig. 8.15). The disease affects both children and adults.

The association of MS with inflammatory demyelinating polyradiculopathy is rare. A few cases have been documented using MRI, electrophysiologic studies, and nerve biopsy.

**DISEASES WITH PROBABLE AUTOIMMUNE PATHOGENESIS**

**Acute Disseminated Postinfectious and Postvaccination Encephalomyelitis**

Acute disseminated postinfectious and postvaccination encephalomyelitis develops 1 to 3 weeks following a viral or bacterial infection such as measles, varicella, rubella, influenza, mumps, infectious mononucleosis, or scarlet fever, or it develops following vaccination for smallpox, measles, typhoid, and paratyphoid.

The onset is acute with headaches, fever, meningeal signs, focal neurologic deficits, and often seizures. The disease resolves within several weeks, and the course is monophasic. The outcome varies from full recovery through variable residual neurologic impairment to death, which occurs in about 20% to 30% of cases.

Grossly, the brain and spinal cord are swollen and congested. The histology is characterized by perivenous inflammatory demyelination. Lymphocytes and lipid-laden macrophages fill the demyelinated zones (Fig. 8.16).

**FIGURE 8.14**

Balo’s concentric sclerosis shows zones of myelin losses alternating with zones of intact myelin in a circular fashion (myelin stain).

**FIGURE 8.15**

Schilder’s disease in a 40-year-old woman. Extensive demyelination in one frontal lobe extends into the corpus callosum (PTAH).

**FIGURE 8.16**

Acute disseminated perivenous encephalomyelitis. A and B. Spinal cord showing demyelination along radially oriented veins (myelin stain). C. Dense infiltrations with neutrophils, lymphocytes, and macrophages in the demyelinated zones (cresyl violet).
Acute Hemorrhagic Leukoencephalitis

Acute hemorrhagic leukoencephalitis or Hurst’s disease usually develops after a nonspecific upper respiratory infection. The onset is acute, the course fulminant, and the mortality high. Mental changes, focal neurologic deficits, and seizures are common.

Grossly, the brain is swollen and congested, and the white matter displays multiple confluent petechial hemorrhages. Characteristic histological features are fibrinoid necrosis of the arterioles and capillaries, ring- and ball-shaped petechial hemorrhages, and perivascular infiltrations with neutrophils, lymphocytes, and macrophages (Fig. 8.17).

**BIBLIOGRAPHY**


**FIGURE 8.17**

Acute hemorrhagic leukoencephalitis. A 42-year-old man, with a 3-week history of muscle and stomach aches and cough, suddenly developed headaches, neck pain, fever, and left hemiparesis. Four days later, he became hemiplegic and comatose. Six days after the headaches began, he died. Grossly, the hemispheric white matter displayed multiple petechial hemorrhages. Histologic section shows fibrinoid necrosis of a small vessel, dense perivascular and diffuse parenchymal infiltrations with neutrophils and lymphocytes, and small hemorrhages (HE).

**Review Questions**

1. Neurologic manifestations commonly encountered in patients with multiple sclerosis (MS) are:
   A. Paresthesias in extremities
   B. Internuclear ophthalmoplegia
   C. Difficulty with balance
   D. Sudden loss of vision
   E. Urinary retention

2. The histologic features of an acute MS plaque include all of the following except:
   A. Perivascular lymphocytic infiltrations
   B. Breakdown of myelin
   C. Axonal swelling
   D. Capillary proliferation
   E. Lipid-laden macrophages
3. Early axonal damage in MS plaque is best revealed in paraffin section with:
   A. Luxol fast blue
   B. Antibodies to β-APP
   C. Phosphotungstic acid hematoxylin (PTAH)
   D. Cresyl violet
   E. None of these

4. The current view on the pathogenesis of MS is:
   A. Reactivation of a dormant viral infection
   B. An autoimmune reaction to myelin
   C. Acute infection with papovavirus
   D. All of these
   E. None of these

5. The severity of neurologic deficits best correlates with:
   A. Virulence of an infective virus
   B. Degeneration of axons
   C. Loss of astrocytes
   D. Loss of oligodendrocytes
   E. Loss of myelin

6. The term shadow plaque refers to:
   A. Partially demyelinated plaque
   B. Remyelinating plaque
   C. Chronic inactive plaque
   D. None of these
   E. All of these

7. Potential risk factors for MS include:
   A. Familial occurrence
   B. Infection with varicella-zoster virus
   C. Association with HLA-DR2
   D. All of these
   E. None of these

8. Encephalitis that develops following smallpox vaccination is characterized by all the following except:
   A. It presents with perivenous demyelination.
   B. It presents with perivenous inflammation.
   C. It has a remitting-relapsing course.
   D. It has a monophasic course.
   E. It is more common in women.

9. Devic disease is characterized by demyelination predominantly in the:
   A. Pons and spinal cord
   B. Optic nerves and spinal cord
   C. Optic nerves and pons
   D. Pons and cerebellum
   E. Optic nerves and cerebral hemispheres

10. The MRI features of MS plaques include:
    A. They appear as hyperintense lesions on T2-weighted images.
    B. They appear as black holes on T1-weighted images.
    C. Acute plaques enhance with contrast.
    D. The lesions are not specific.
    E. Periventricular distribution is common.

(Answers are provided in the Appendix.)