



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Diseases Involving Myelin

Susan M. Staugaitis, Bruce D. Trapp

OUTLINE

General Classification	692	Deficiencies of peripheral nerve myelin in common inherited human neuropathies are caused by mutations in a variety of genes	701
Myelin deficiency can result from failure of synthesis during development or from myelin breakdown after its formation	692		
Many of the biochemical changes associated with central nervous system (CNS) demyelination are similar regardless of etiology	692	Other Diseases Primarily Involving Myelin	701
		Myelin formation and stability are affected by a variety of other etiologies including developmental insults, nutritional deficiencies, therapeutic intervention and chemical and biological toxins	701
Acquired Immune-Mediated and/or Infectious Diseases of Myelin	692	Disorders Primarily Affecting Neurons with Secondary Involvement of Myelin	702
Nervous system damage in acquired demyelinating diseases is selectively against myelin or myelin-forming cells, but axons also are often affected	692	Many insults to the nervous system initially cause damage to neurons but eventually result in regions of demyelination as a consequence of neuronal degeneration	702
Multiple sclerosis (MS) is the most common demyelinating disease of the CNS in humans	692	Repair in Demyelinating Diseases	702
Box: Basic Aquaporin 4 and Neuroinflammation	693	The capacity for remyelination depends upon the presence of receptive axons and sufficient myelin-forming cells	702
Animal models are required to understand the pathogenesis of MS and test the efficacy of possible therapeutic interventions	696	Spontaneous remyelination of lesions of MS is well documented, but remyelination is usually incomplete	703
Other acquired disorders affecting CNS myelin have an immune-mediated or infectious pathogenesis	697	Remyelination in the CNS can be promoted by various treatments	703
Some human peripheral neuropathies involving demyelination are immune mediated	697	Acknowledgments	703
Genetically Determined Disorders of Myelin	699	References	703
The human leukodystrophies are inherited disorders of CNS white matter	699		

The integrity of myelin sheaths is dependent upon the normal functioning of myelin-forming oligodendrocytes in the central nervous system (CNS) and Schwann cells in the peripheral nervous system (PNS) as well as on the viability of the axons that they ensheath. Neuronal death inevitably leads to degeneration of axons and secondary degeneration of the myelin surrounding them. Primary diseases of myelin

or myelin-forming cells can result from a multitude of causes, including autoimmunity, viral infections, genetic defects, toxic agents, malnutrition, and mechanical trauma. Comprehensive descriptions of the clinical features, pathology, and pathogenesis of most of the diseases described in this chapter are available in specialized books (Lazzarini, 2004; Love et al., 2008; Ropper & Samuels, 2009). For a historical perspective

on the neurochemistry of myelin and its diseases, the reader is referred to the book *Myelin*, edited by Pierre Morell (1984, Plenum Press).

GENERAL CLASSIFICATION

Myelin deficiency can result from failure of synthesis during development or from myelin breakdown after its formation

Failure of synthesis of normal myelin proteins or lipids is usually referred to as *hypomyelination* or *dysmyelination*. Myelin forms initially, but it becomes progressively vulnerable to degeneration with age due to accumulation of metabolic intermediates. Diseases resulting from loss of normal myelin after it is formed, i.e., demyelination, can be subdivided into primary and secondary categories on the basis of morphological observations. *Primary demyelination* involves the destruction of myelin with relative sparing of axons, whereas *secondary demyelination* includes those disorders in which myelin is involved only after damage to neurons and axons occurs. However, in recent years it has become increasingly apparent that some diseases that had been classified as primary demyelination may involve more injury to axons than originally thought. This axonal damage could be caused by inflammation or loss of trophic support provided by myelinating cells to axons. This topic is described in more detail in the sections on multiple sclerosis and the acquired and inherited peripheral neuropathies.

Many of the biochemical changes associated with CNS demyelination are similar regardless of etiology

The most pronounced biochemical changes associated with CNS demyelination occur in white matter, where there is a marked increase in water content, a decrease of myelin proteins and lipids and/or the appearance of other lipids or proteins, such as cholesterol esters or glial fibrillary acidic protein (GFAP). Particularly noteworthy with regard to lipids are dramatic decreases in galactocerebroside, ethanolamine plasmalogens and cholesterol, all of which are enriched in myelin membranes (see Ch. 10). The major structural proteins of CNS myelin, myelin basic protein (MBP) and proteolipid protein (PLP), are also invariably decreased. These changes can be explained by the breakdown and gradual loss of myelin (which is relatively rich in solids) and its replacement by extracellular fluid, astrocytes and inflammatory cells (which are more hydrated, relatively lipid-poor and free of myelin-specific constituents). The frequent appearance of cholesterol esters in demyelinating diseases is related to the fact that cholesterol is not readily degraded and is esterified by phagocytes that often remain at the site of the lesion for some time. Since cholesterol esters are essentially absent from normal mature brain, their presence in myelin disorders is indicative of recent phagocytosis of myelin. In the CNS, GFAP is specific to astrocytes, and an increase of this protein during demyelination is due to reactive astrocytosis (see Ch. 6). The

magnitude of the changes mentioned above vary considerably from disease to disease and from specimen to specimen in the same disease, depending on the severity, location, duration and activity of the pathological processes.

ACQUIRED IMMUNE-MEDIATED AND/OR INFECTIOUS DISEASES OF MYELIN

Nervous system damage in acquired demyelinating diseases is selectively against myelin or myelin-forming cells, but axons also are often affected

Acquired immune-mediated diseases involve either CNS or PNS myelin, but not both. In most acquired or infectious disorders, the lesions are disseminated and characterized by perivenular demyelination and inflammation, macrophage-mediated phagocytosis of myelin lipids and proteins, and relative sparing of axons.

Multiple sclerosis (MS) is the most common demyelinating disease of the CNS in humans

Most often the disease begins in the third or fourth decade with neurological dysfunction, such as blurred or double vision, slurred speech, weakness in limbs, sensory deficits, and paresthesias (Compston & Coles, 2008). The most common initial course, referred to as relapsing–remitting MS, is characterized by acute episodes of one or more of these symptoms followed by subsequent recovery. Over time, the improvement after attacks may be incomplete and the relapsing–remitting course may evolve into one of increasing progression of disability, termed secondary progressive MS. Approximately 15% of patients develop a form of disease that begins as a slowly progressive process, which has been termed primary progressive MS. A few patients have a very aggressive course, which can even lead to death over a short period.

Neuromyelitis optica (Devic's disease) is a demyelinating disease characterized by transverse myelitis and optic neuritis that was considered to be a subtype of MS. Recently, antibodies to aquaporin 4, a water-channel protein of astrocytes, have been identified in patients with this disease (See Box). Astrocytes appear to be the primary autoimmune target, with oligodendrocyte, and myelin as secondary targets. Therefore, neuromyelitis optica is currently considered a distinct entity.

Diagnosis

The diagnosis of MS is dependent on evidence of CNS involvement separated in both time and space; i.e., there must be evidence that two areas of the CNS are involved and a history that this involvement occurred at two different times and without any other identifiable cause. A diagnosis can be made solely on clinical criteria, but this can result in long delays in diagnosis and treatment. The current criteria permit a diagnosis to be made with less clinical evidence if specific features are present on magnetic resonance imaging (MRI) (Polman et al., 2011). Results of cerebrospinal fluid analysis can also be

AQUAPORIN 4 AND NEUROINFLAMMATION

Susan M. Staugaitis, Bruce D. Trapp

The role of auto-antibodies to aquaporin 4 (AQP4) in neuro-myelitis optica was first suggested by studies in which human sera was reacted with mouse tissue sections. Sera from patients with NMO showed a pattern of immunoreactivity that highlighted CNS microvessels and the pia (Lennon et al., 2004). This and the pattern of immunoreactivity in kidney and stomach suggested that AQP4 was the target antigen, and this was proven to be the case (Lennon, et al., 2005). Studies on tissue from NMO patients showed that there is loss of AQP4 immunoreactivity and complement deposition in the lesions of inflammatory demyelination, but not in uninvolved tissue. At the time, AQP4 was known to be the predominant water channel in the brain and had a role in brain edema formation in response to a variety of etiologies. The possible involvement of AQP4 in neuroinflammation had never been investigated. Several groups explored the pathogenic role of antibodies to AQP4 in rodent models (see Li et al. 2011 for references). These studies showed that administration of anti-AQP4 antibodies to animals with EAE or along with complement to naïve animals produced pathology characteristic of NMO. When EAE was induced in AQP4 knockout mice, the animals had attenuated symptoms and CNS inflammation compared to wild-type controls. This group went on to perform a systematic exploration of the mechanism by which AQP4 deficiency protected animals from the inflammatory pathology

of EAE (Li et al., 2011). The major difference between the two groups was that the knockout mice showed a decreased inflammatory response to intracerebral injection with lipopolysaccharide (LPS). In vitro analysis of microglia-free astrocyte cultures showed that LPS induced secretion of TNF-alpha and IL-6 into the medium, but this was reduced in the knockout animals compared to controls. Transfection studies demonstrated that cytokine secretion was directly related to expression of AQP4 by cells. These recent data provide new hypotheses for investigating the role of the water permeability function of astrocytes in neuroinflammation.

References

- Lennon, V. A., Kryzer, T. J., Pittock, S. J., Verkman, A. S., & Hinson, S. R. (2005). IgG marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *Journal of Experimental Medicine*, 202, 473–477.
- Lennon, V. A., Wingerchuk, D. M., Kryzer, T. J., Pittock, S. J., Lucchinetti, C. F., Fujihara, K., et al. (2004). A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet*, 364, 2106–2112.
- Li, L., Zhang, H., Varrin-Doyer, M., Zamvil, S. S., & Verkman, A. S. (2011). Proinflammatory role of aquaporin-4 in autoimmune neuroinflammation. *FASEB Journal*, 25, 1556–1566.

used to support the diagnosis of MS, but in most cases clinical and imaging data are sufficient.

There are a variety of MRI imaging protocols used in the diagnosis and monitoring of patients with MS (Fox, 2008). T2-weighted MRI is the most sensitive sequence for identification of lesions in brains of MS patients, but is not specific because both inflammatory demyelination and ischemic necrosis result in increased signal. T2-weighted images also cannot distinguish new from old lesions. T1-weighted imaging after the administration of gadolinium can identify new lesions in which the blood-brain barrier has been compromised. Serial studies of patients with early relapsing–remitting MS have shown that the first event in the development of a new MS lesion is the appearance of a gadolinium-enhanced lesion, which can occur during periods of clinical stability in many patients. Newer imaging techniques, such as magnetic resonance spectroscopy, magnetization transfer ratio, and diffusion tensor imaging, provide additional characterization of lesions over time, and correlations of MRI of postmortem brains with histopathology (e.g., Fisher et al., 2007), can validate the interpretations of lesions identified by different techniques and help to focus ongoing research.

Pathology

MS lesions can occur in all parts of the CNS. Areas of predilection are the periventricular white matter and subpial white matter of the brainstem and spinal cord. White matter

lesions typically are sharply demarcated from the surrounding tissue (Fig. 39-1). Microscopic examination shows loss of myelin with relative preservation of axons and inflammatory infiltrates composed of lymphocytes and myeloid lineage cells (macrophages and microglia). T-lymphocytes predominate, but B-lymphocytes and plasma cells are also present. Lesions commonly originate around venules, but this is not always the case (Lucchinetti et al., 2000). The activity of white-matter lesions can be classified as active, chronic active, or chronic inactive, based upon immunohistochemical staining patterns using antibodies to myelin proteins and myeloid cells. Active lesions are hypercellular due to the inflammatory infiltrates, whereas chronic lesions are hypocellular due to relative paucity of inflammation and oligodendrocyte loss. Detailed immunocytochemical studies of active lesions in biopsy and autopsy specimens suggest that MS lesions can be subdivided into four different patterns: T-cell-mediated demyelination, antibody-mediated demyelination, and primary oligodendrocyte death, with or without apoptosis (Lucchinetti et al., 2000). A recent report describes active MS lesions with areas of myelin phagocytosis and oligodendrocyte loss in the absence of lymphocytic inflammation, supporting the idea that primary oligodendrocyte degeneration may precede an inflammatory response (Henderson et al., 2009).

Gray matter lesions

There is increasing recognition of cerebral cortical demyelination in MS and the role that this pathology may play in

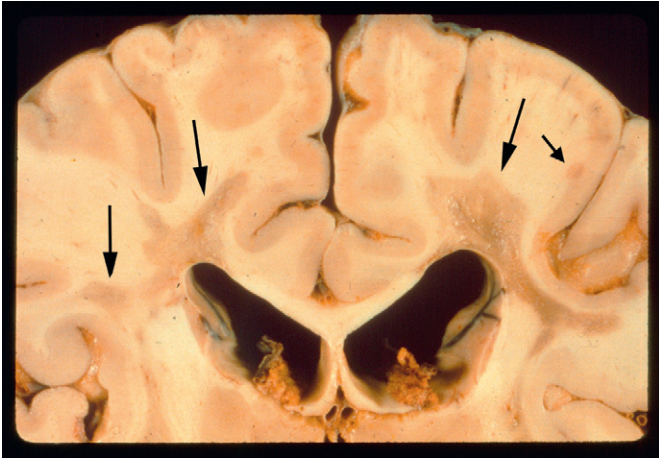


FIGURE 39-1 Coronal slice of brain from a patient who died with MS. Demyelinated plaques are clearly visible in the periventricular and subcortical white matter (large arrows). The periventricular lesions show focal cavitation consistent with axonal loss. A small plaque is also observed at the boundary between gray and white matter (small arrow). The generalized atrophy that is often seen in the brains of MS patients is illustrated by the enlarged lateral ventricles. Photograph courtesy of C. S. Raine.

the neurological dysfunction, including cognitive deficits, experienced by most MS patients. Several pathological classifications of cortical lesions have been proposed. One scheme describes three types (Peterson et al., 2001). Type I lesions are present at the leukocortical junction and involve both cortex and subcortical white matter. Type II lesions are located entirely within the cortex and are typically centered on blood vessels. Type III lesions appear to begin at the pial surface and extend into the superficial layers of cortex. A single type III lesion can involve several gyri, so the total lesion area can be quite extensive. Cortical demyelination occurs without significant influx of hematogenous leukocytes (Peterson et al., 2001; Trapp & Nave, 2008). Compared to white matter lesions, there are fewer lymphocytes and no perivascular cuffs. Phagocytic macrophages are extremely rare, but many activated microglia are present, and they are often more dense at the lesion edge. Cortical lesions are not detected by conventional MRI modalities.

Axonal and neuronal pathology

Although oligodendrocytes and myelin appear to be the primary targets in MS, neurons are also damaged in this disease. In fact, axonal transection is now considered to be the pathology underlying permanent disability in MS patients (Trapp & Nave, 2008). Axonal transection and degeneration occur in the setting of acute inflammatory demyelination and as a consequence of chronic demyelination. The frequency of transected axons in white matter lesions correlates with the degree of inflammation. Active highly inflamed lesions can contain more than 11,000 transected axons per mm^3 tissue, and the edge of chronic active lesions contain more than 3,000 transected axons per mm^3 tissue, whereas the core of chronic lesions contains on average 875 transected axons per mm^3 tissue (Trapp et al., 1998). Cortical lesions, which have little inflammation, contain

transected neurites (axons and dendrites) but their numbers are only 25–30% of that seen in active white matter lesions (Peterson et al., 2001; Trapp & Nave, 2008). Identification of apoptotic neurons in cortical lesions confirms that cortical demyelination can be lethal to neurons.

Axon loss and parenchymal atrophy are also features of the chronically demyelinated brain (Trapp & Nave, 2008) (Fig. 39-1). At this stage, there is usually minimal evidence of inflammation, so different mechanisms may be responsible for the axonal degeneration. Studies on animal models suggest that long-term axonal survival requires trophic support from oligodendrocytes. For example, removal of myelin proteins, such as myelin associated glycoprotein (MAG) or 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNP), in mice results in late-onset axonal degeneration without significant myelin pathology (Nave & Trapp, 2008; Trapp & Nave, 2008). While these data demonstrate that normal myelin is required for long-term axonal survival, the signaling mechanisms by which myelinating oligodendrocytes support the axon are unknown. An understanding of these mechanisms could aid in the development of neuroprotective therapies for MS patients. This is important because analysis of repeat MRIs in MS patients shows that brain atrophy is one of the most reliable predictors of clinical disease progression.

Biochemistry

The biochemistry of demyelination in MS has been reviewed in detail (Cuzner & Norton, 1996). Affected areas of MS white matter exhibit the expected decrease of myelin constituents and a buildup of cholesterol esters. For example, polyacrylamide gel electrophoresis of homogenates of macroscopically normal appearing white matter, outer periplaque, inner periplaque, and plaque shows the expected decline of MBP and PLP in going from the normal-appearing white matter to the center of the plaque in both chronic and acute lesions (Fig. 39-2). There is a virtual absence of these myelin proteins in the center of the chronic plaque and an accumulation of GFAP indicative of astrogliosis (Fig. 39-2B). A plaque from a more acute lesion is not completely demyelinated, as indicated by the presence of some MBP and PLP, and there is no accumulation of GFAP (Fig. 39-2C). The more acute plaque contains albumin as a result of breakdown of the blood-brain barrier. A number of biochemical studies have indicated that myelin constituents are significantly reduced even in some areas of macroscopically normal-appearing white matter of MS brain in comparison to control white matter, and this is most probably explained by the presence of microlesions throughout the affected brain.

Recent research involving the biochemistry of MS has focused on the molecular mechanisms of damage in acute lesions and the chronically demyelinated axon (Trapp & Nave, 2008; Trapp & Stys, 2009). The inflammatory microenvironment in acute lesions contains a variety of substances, such as proteolytic enzymes, cytokines, oxidative products, and free radicals, which can directly injure cells. Other substances present in the inflammatory microenvironment can induce signal transduction events that ultimately result in injury or affect the migration of cells involved in damage or repair. The mechanism for neurodegeneration in chronic lesions has been proposed to represent an imbalance between axonal energy

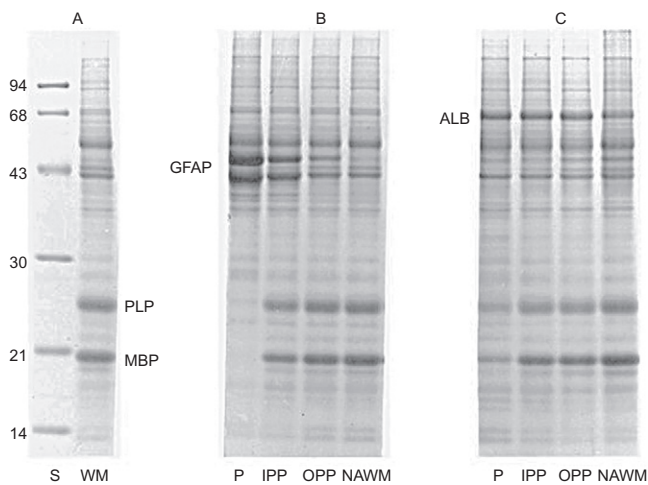


FIGURE 39-2 Polyacrylamide gel electrophoresis of proteins in control and MS tissue. Total proteins of the tissue samples were solubilized with a detergent (sodium dodecyl sulfate) and electrophoresed on a polyacrylamide gel system that separates proteins according to their size. After electrophoresis, the proteins were stained with Coomassie brilliant blue dye. **(A)** Molecular weight standards (S) labeled according to their molecular mass (kDa) and the proteins of control white matter (WM). **(B)** Samples from the region of a chronic MS plaque. **(C)** Samples from the region of an acute MS plaque. ALB, serum albumin; GFAP, glial fibrillary acidic protein; IPP, inner periplaque; MBP, myelin basic protein; NAWM, macroscopically normal appearing white matter near the plaque; OPP, outer periplaque; P, plaque center; PLP, proteolipid protein. (With permission from Johnson et al., 1986, *J. Neurochem.* 46:1086–1093.)

demand and limited energy supply (Trapp & Stys, 2009). Nerve conduction in nonmyelinated axons requires more ATP than myelinated axons. Recent analysis of MS brains showed that expression of nuclear encoded mitochondrial genes was reduced in non-lesion cortex, implying impaired mitochondrial energy production in MS brain. Impaired ATP production in axons can result in altered ionic gradients, including accumulation of axoplasmic Ca^{2+} and activation of Ca^{2+} -dependent proteolytic enzymes that can damage axons.

Therapy

Treatment of patients with MS includes management of symptoms and attempts to slow the course of the disease (Compston & Coles, 2008). There are several classes of therapies approved for patients with relapsing–remitting MS that are considered to be “disease modifying.” All of these are believed to affect inflammation-mediated injury. The beta-interferons approved for MS therapy have many immunomodulatory effects. The mechanism by which treatment reduces the number of relapses is unknown. Although interferon treatment delays disease progression, it does not stop it. Glatiramer acetate is a synthetic random polymer, composed of L-alanine, L-glutamic acid, L-lysine, and L-tyrosine, and is believed to block antigen presentation and promote Th2 anti-inflammatory responses. Mitoxantrone is a synthetic antineoplastic anthracycline that causes immunosuppression by inhibiting proliferation of B- and T-cells and macrophages. Although it has efficacy in reducing relapses and progressive disability, the risk

of cardiotoxicity and secondary leukemia limits its use. Another therapeutic approach is to inhibit migration of T-cells across the blood–brain barrier by natalizumab, a humanized monoclonal antibody that is directed against alpha 4-integrin and blocks its function. Natalizumab is highly effective in controlling relapses and reducing the appearance of new lesions on MRI. Unfortunately, treatment with natalizumab (and other monoclonal antibodies that interfere with leukocyte function) can result in progressive multifocal leukoencephalopathy (PML), a fatal viral-mediated demyelinating disease (see below). Currently, this drug is approved only for a subset of patients refractory to other therapies, and its use requires close surveillance for development of PML. The most recent drug approved for MS is fingolimod. Fingolimod is given orally, in contrast to the other agents which require injection or intravenous infusion. It induces internalization of the sphingosine-1-phosphate type 1 receptor on lymphocytes, which results in sequestration of lymphocytes in peripheral lymphoid organs. The long-term efficacy of fingolimod is still under investigation. Alternative approaches to therapy involve repair both by stimulating remyelination and by promoting the survival and regeneration of axons and are discussed in greater detail at the end of this chapter.

Etiology

Despite intensive research over many decades, the cause of MS is still unknown. The following paragraphs will summarize existing data on the susceptibility to developing MS that have served to formulate hypotheses on its etiology and ends with perspectives on how reconsideration of existing knowledge might be utilized to formulate new hypotheses for future research.

Epidemiology and natural history of MS

Descriptions of a clinical disease entity characteristic of MS were first clearly recorded early in the 19th century (Compston & Coles, 2008), and MS was first defined as a clinical/pathological entity by Charcot in 1868. Epidemiologic surveys in the 20th century show that MS is more prevalent in northern Europe and North America than in Africa and Asia. Correspondingly, MS is most prevalent among Caucasians, but the incidence of MS has been documented worldwide. Recent analyses of large clinical registries of MS patients have demonstrated that, while the clinical course of MS is quite variable in early stages of the disease, the later stages are more uniform in the rate of progression and the chronological age at which permanent disability milestones are achieved (see Compston, 2006).

Environmental factors

Several types of evidence indicate that environmental factors influence the risk of development of MS (Compston & Coles, 2008). Studies on geographical migration show that the risk of MS is highest among people who lived in high-prevalence areas prior to puberty. In addition, there have been reports of epidemics or clusters of increased MS incidence. Possible environmental exposures include infections, nutritional factors, and chemical toxicities. Among these a viral etiology has been the subject of the most intense investigation.

Candidate viruses include measles, rubella, mumps and the herpes viruses, including Epstein–Barr virus, Herpes simplex virus 1 and 2, Varicella zoster virus and human herpes virus 6. Much of this interest has been based upon the risk of acute disseminated encephalomyelitis following viral infections and vaccinations and the prevalence of seropositivity to certain viruses, such as Epstein–Barr virus, among MS patients.

Genetics

Although there is no evidence that risk for MS is attributable to classical Mendelian genetic inheritance, multiple studies have provided data that support a genetic component of susceptibility to the disease (Compston & Coles, 2008). First is the different prevalence of MS among ethnic groups. Second is the well-documented increased risk among first-degree relatives of individuals with the disease. Specifically, risk of MS is 20–30% between monozygotic twins compared to 2–5% among fraternal twins. More recently, genome-wide analysis of single-nucleotide polymorphisms has identified a number of genetic loci that are associated with increased risk of MS among the general population (Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene), 2009; De Jager et al., 2009). Many polymorphisms map to genes or genetic loci associated with immune regulation. The strongest association is with the HLA–DRB1 gene on chromosome 6p21 that accounts for 16–60% of genetic susceptibility to MS. The increasing number of genetic loci implicated in susceptibility to MS indicates that, if MS is a genetic disease, it is a complex genetic disorder in which multiple interacting polymorphic genes have low penetrance and exert a small effect on the overall disease risk (Ch. 41).

Immunology

The inflammatory histopathology of the demyelinating lesions in MS, the ability of myelin antigens to induce experimental allergic encephalomyelitis, and the response of patients with relapsing–remitting MS to anti-inflammatory treatments provide the basis for the hypothesis that MS is an autoimmune disease that arises in the setting of environmental and genetic risk factors. An autoimmune response could be induced by molecular mimicry to an infectious agent, but all efforts to identify a single responsible agent have been unsuccessful. It may be that several myelin antigens play a role in MS, and that the relative importance of different antigens varies among individuals depending on their immunogenetic background and environmental factors encountered during their life. Furthermore, the possibility that MS patients have autoantibodies that recognize complexes of two or more myelin antigens, as is the case in some patients with Guillain–Barré syndrome, has not been investigated.

Perspectives for future research

The preceding paragraphs summarized evidence for the role of multiple factors in the development of MS. This complexity has led some authors to question whether long-held hypotheses based upon this evidence should be re-evaluated, and new hypotheses proposed and investigated. For example, the recent research on the epidemiology (Compston, 2006) and pathology (Henderson et al., 2009) of MS raises the

possibility that MS could be a primary degenerative disease of oligodendrocytes with a secondary immune or inflammatory tissue response. Other research on the immunohistochemistry of actively demyelinating lesions has suggested that different pathogenetic mechanisms can give rise to the same clinical phenotype (Lucchinetti et al., 2000). Fortunately, the technology for biochemical analyses, including genomics, RNA expression profiling, and proteomics, is advancing rapidly, and research on small histologically defined regions within MS lesions from frozen and even fixed archival tissue is becoming feasible.

Animal models are required to understand the pathogenesis of MS and test the efficacy of possible therapeutic interventions

All of the treatments tested for use in MS patients have been selected based upon their efficacy in animal models. Because the primary etiology of MS is unknown, the models employed in research have been developed to replicate different aspects of MS pathology, but no single model replicates the disease as it is manifested in humans (Denic et al., 2011). Therefore, any data from animal models must be critically evaluated in view of how results can be generalized to MS patients.

Viral models

A number of naturally occurring viral diseases in humans and animals cause demyelination (Fazakerley & Walker, 2003). These diseases provide a basis for the hypothesis that MS may be initiated by a viral infection. The best examples in humans are progressive multifocal leukoencephalopathy (discussed below) and subacute sclerosing panencephalitis caused by measles virus. Canine distemper virus causes a demyelinating disease, and the lesions in dog brain show a strong inflammatory response with some similarities to acute disseminated encephalomyelitis in humans (discussed below). Visna is a slowly progressive demyelinating disease of sheep caused by a retrovirus.

Other models of MS use intracerebral injections of mice with neurotropic viruses. JHM is a neurotropic strain of coronavirus mouse hepatitis virus that infects oligodendrocytes and produces acute and chronic inflammatory demyelination in rodents (Bergmann et al., 2006). Theiler's virus is a picornavirus that infects many neural cell types and induces a chronic encephalomyelitis (Sato et al., 2011). Investigation of animal models such as these has revealed several mechanisms by which viral infections can cause demyelination, including (1) a direct infection of oligodendrocytes resulting in cell death; (2) a virus-specific inflammatory response in which cytokines or other immune mediators damage oligodendrocytes/myelin indirectly as a 'bystander' effect; and (3) activation of an immune response directed at components of oligodendrocytes/myelin by molecular mimicry or epitope spreading. Molecular mimicry occurs when a viral antigen has structural homology to a myelin/oligodendrocyte component, resulting in cross-reactivity, and epitope spreading results from host immune cell processing of myelin/oligodendrocyte antigens released following tissue injury.

Experimental allergic encephalomyelitis

Experimental allergic encephalomyelitis (EAE) is an animal model used in the study of the autoimmune hypothesis of MS. The EAE model was initially identified through efforts to understand the cause of encephalomyelitis after inoculation of patients with the Pasteur rabies vaccine, which was prepared from virus-infected nervous tissue. It was noted that even control experimental animals inoculated with uninfected neural tissue developed an encephalomyelitis. Since its discovery, EAE has been induced in a number of species by a variety of techniques and includes models representing both acute and chronic relapsing aspects of inflammatory demyelinating disease. Usually EAE is induced by immunization with a myelin protein or peptide, most notably MBP, PLP or myelinoligodendrocyte glycoprotein (MOG). The classical form of the disease is mediated primarily by CD4-positive major histocompatibility complex (MHC) class II restricted T-cells that are stimulated in the periphery and enter the CNS. Transfer of these T-cells to naive animals can induce disease. Although these data document the importance of CD4 lymphocytes for EAE induction, studies of MS tissues show that CD8-positive T-cells are the predominant lymphocyte population. There is considerable variation in susceptibility of various animals, and this variation is largely due to the genetic background, especially that of MHC genes. This observation is relevant to the genetic association of MHC genes identified in MS patients (Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene), 2009; De Jager et al., 2009).

The most characteristic component of the EAE lesion is perivascular inflammation; the extent of demyelination varies between species and the identity of the immunogen used to induce the disease. Evidence from studying EAE in the rat or mouse indicates that activated T-cells, regardless of specificity, can cross the blood–brain barrier and enter the nervous system. If the T-cell encounters its antigen, the cell will be further activated and begin production of proinflammatory cytokines, such as gamma-interferon and tumor necrosis factor-alpha. This in turn activates the endothelial cells to upregulate cell adhesion molecules (see Ch. 9) and promotes entry of additional inflammatory cells into the CNS. The outcome of this process, at least in some animals, is myelin damage. The actual effector mechanisms for myelin damage include a direct toxic effect of tumor necrosis factor-alpha or nitric oxide on oligodendrocytes or damage mediated by macrophages and microglial cells. The latter possibility can be enhanced by the presence of antibodies, which bind to myelin and provide a ligand for activated monocytes. Indeed, demyelination associated with EAE in several animals, including the rat, mouse, and marmoset, is increased by the presence of antibodies to surface components of myelin, such as galactocerebroside or MOG. In fact, immunization of rodents with MOG alone has been shown to induce a relapsing–remitting demyelinating disease with both cellular and humoral immunity to this glycoprotein.

Toxins

Toxins such as cuprizone and lysolecithin can induce demyelination in animals (Denic et al., 2011). Cuprizone is a copper-chelating agent that when orally administered induces demyelination. The demyelination induced by cuprizone

is dependent upon continuous exposure because spontaneous remyelination occurs following cessation of treatment. Lysolecithin activates phospholipase A2. Focal demyelination occurs when lysolecithin is administered by intracerebral injection. Neither of these models reproduce the inflammatory component of demyelination observed in MS lesions. Therefore, both of these models are most useful for research on mechanisms of remyelination. Because the demyelination produced by the cuprizone model involves large areas of the CNS, this model is most amenable to biochemical analysis.

Other acquired disorders affecting CNS myelin have an immune-mediated or infectious pathogenesis

Acute disseminated encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is a rare condition following a viral infection, of which major examples are measles, rubella, and varicella (Sonneville et al., 2010). The incidence of ADEM following bacterial infections and vaccinations has also been well documented. Pathologically, ADEM is characterized by multiple small perivenular foci of demyelination (Love et al., 2008). Acute hemorrhagic encephalomyelitis is a more severe form of ADEM characterized by fibrinoid necrosis of parenchymal vessels that results in multifocal hemorrhage. Typically, there is leukocytosis and increased protein in cerebrospinal fluid, consistent with compromise of the blood–brain barrier. The demyelination occurring in these conditions is likely to be mediated at least in part by immune mechanisms, since T-cells sensitized to MBP are detected in many of these patients. Immunomodulatory treatments (steroids, intravenous immunoglobulin) are typically administered in addition to supportive therapy, but controlled clinical trials assessing the efficacy of these treatments are few.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease caused by infection of oligodendrocytes with the JC papovavirus. Most people are infected by JC virus, but the immune system prevents this virus from causing disease in healthy individuals. However, people who are immunosuppressed, because of disorders of the reticuloendothelial system, human immunodeficiency virus infection, or therapeutic immunosuppression for autoimmune diseases or organ transplants, are susceptible (Tan & Koralnick, 2010). The disease progresses rapidly, and areas of demyelination can be large and show evidence of tissue destruction. Lymphocytic infiltrates may be present, but usually are not a prominent feature. PML has been identified in a number of patients with MS (and other autoimmune diseases) treated with monoclonal antibodies to antigens that mediate CNS immune cell surveillance and trafficking (see above).

Some human peripheral neuropathies involving demyelination are immune mediated

There are three major categories of acquired peripheral neuropathies involving demyelination. These are paraproteinemic

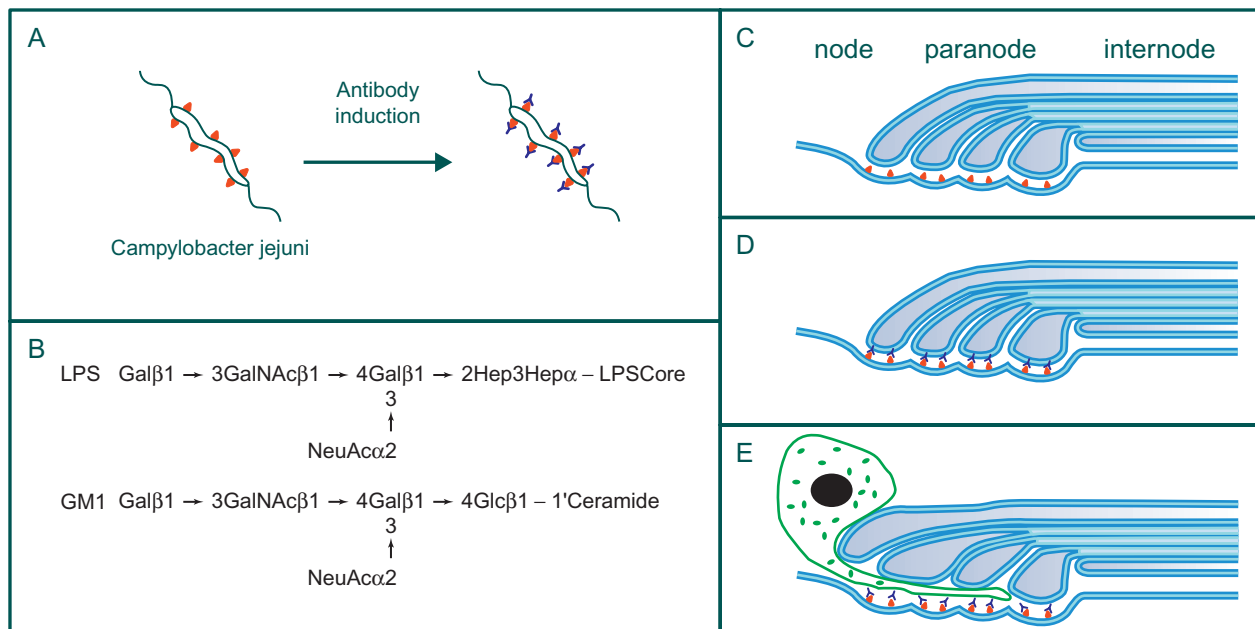


FIGURE 39-3 Molecular mimicry in subsets of patients with acute axonal motor neuropathy (AMAN) type of Guillain-Barré syndrome. (A) *Campylobacter jejuni* infection elicits an antibody response (blue) to antigens (red) displayed by lipopolysaccharide (LPS) on some strains of *Campylobacter jejuni*. (B–D) These antibodies also bind to the GM1 ganglioside on neural membranes. The antigenic similarity between LPS and GM1 is illustrated in panel B. (E) Axonal pathology is most likely mediated by binding of macrophages to these antibodies.

polyneuropathy, Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. An immune-mediated pathogenesis is implicated by identification of serum antibodies to PNS antigens and the efficacy of intravenous immunoglobulin and plasma exchange in the treatment of these disorders, as well as by experimental studies in animal models. Like many other diseases involving primary demyelination, secondary axonal injury and degeneration may be the critical factors in permanent disability. In addition, axonal damage may be primary in some patients with immune-mediated peripheral neuropathy.

Paraproteinemic polyneuropathy

Up to 10% of patients with peripheral neuropathy have a monoclonal gammopathy (paraproteinemia) in which there is expansion of a clone of plasma cells leading to large amounts of a monoclonal antibody in the patient's serum (Zivkovic et al., 2009). Some of these patients have a hematologic malignancy such as multiple myeloma or lymphoma at the time of diagnosis, but most have a premalignant condition called "monoclonal gammopathy of undetermined significance." Nerve conduction studies show that the majority of patients have a demyelinating neuropathy, and Western blot analysis demonstrates that the patients' sera contain IgM antibodies to MAG (Niermeijer et al., 2010). The anti-MAG antibodies in these patients react with a carbohydrate epitope (HNK-1) that is shared with other myelin glycoproteins, including P0 and peripheral myelin protein-22 (PMP-22), and sulfate-3-glucuronyl paragloboside, a glycolipid that is present in much larger amounts in the mature PNS than the CNS. Pathologically, patients with anti-MAG IgM antibodies have disruption of compact myelin at the intraperiod line. Several animal models

strongly suggest that this disease is caused by the antibodies, but the relative roles of the potential glycoprotein and glycolipid target antigens in contributing to the pathology remains to be established.

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) includes a wide spectrum of clinical phenotypes. Initial descriptions were that of a monophasic polyneuropathy that frequently occurred following a bacterial or viral infection and was characterized histologically by segmental demyelination and perivascular lymphocytic infiltrates (Lazzarini, 2004; Winer, 2011) (see also Ch. 38). Over the decades additional clinical phenotypes were identified, and today the GBS spectrum includes a number of additional entities including acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy, Bickerstaff's brainstem encephalitis, and Miller-Fisher syndrome (Winer, 2011). The immunopathogenesis of the GBS spectrum is best understood for AMAN (Hughes & Cornblath, 2005; Kaida & Kusunoki, 2010). Serum antibodies to gangliosides, including GM1, GD1a and GalNAcGD1a, were identified in these patients, and they also had antecedent intestinal infection with *Campylobacter jejuni*. Subsequent research demonstrated cross-immunoreactivity of serum antibodies with *C. jejuni* lipooligosaccharides and gangliosides present in myelinated axons (Fig. 39-3). These antibodies elicit activation of complement with subsequent nerve injury by phagocytosis. AMAN represents the best evidence for molecular mimicry between immunogens expressed by antecedent infectious agents and neural epitopes in the pathogenesis of nervous system disease. The precise cellular localization of immune-mediated injury has not been identified, but the node of Ranvier is a likely target.

Additional studies have demonstrated that sera from patients with GBS contain antibodies that react more strongly with complexes of two gangliosides than with individual gangliosides (Kaida & Kusunoki, 2010), indicating that heterodimeric interaction of two gangliosides, presumably within lipid rafts, produces new pathogenic epitopes. As a result, an increased number of patients with GBS and antiganglioside antibodies have been identified, including patients with demyelination identified by nerve conduction studies. The presence of antiganglioside complex antibodies has also been correlated with clinical severity. Laboratory diagnostic techniques that enable detection of antiganglioside complex antibodies have been developed that will enable high-throughput analysis of patient serum (Rinaldi et al., 2009). Applications of such advances are likely to facilitate research into our understanding of immune-mediated peripheral neuropathies as well as acquired immune-mediated diseases of the CNS.

Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is a progressive or relapsing–remitting disease with a duration of many months or years (Hughes, et al., 2006). Histologically, it is characterized by onion bulbs similar to those seen in inherited polyneuropathies. An immune-mediated pathogenesis is implicated by the presence of lymphocytes in nerve biopsy specimens and moderate degrees of clinical improvement in patients following immunomodulatory therapies. The pathogenesis of CIDP is not as well understood as the acute immune-mediated polyneuropathies. Current evidence indicates that the cellular immune response plays a greater role in the pathogenesis of CIDP than in paraproteinemic polyneuropathy or GBS.

GENETICALLY DETERMINED DISORDERS OF MYELIN

The human leukodystrophies are inherited disorders of CNS white matter

The term *leukodystrophy* refers to disorders involving CNS white matter. A more comprehensive description of genetic diseases that involve CNS white matter (leukodystrophy or leukoencephalopathy) can be found in neuropathology texts (Love et al., 2008), and the reader is referred to the Online Mendelian Inheritance in Man website (<http://www.ncbi.nlm.nih.gov/omim/>) supported by the National Center for Biotechnology Information for up-to-date information about the genetics of specific disorders (see Table 39-1). Because many of these disorders affect lipid metabolism in general, many of the leukodystrophies are also associated with dysfunction of peripheral nerve myelin and other organs with high levels of lipid metabolism (Ch. 43).

It is common to think of leukodystrophies as developmental disorders with onset in childhood, but recognition of adult-onset leukodystrophy is increasing (Costello et al., 2009). Children with leukodystrophy typically present with regression of previously acquired motor skills, but personality

and neurocognitive changes can also be present and may precede motor signs. Cognitive or neuropsychiatric symptoms are frequently more prominent features in adults and may be the reason that the patient seeks medical attention. In the absence of a family history, a leukodystrophy may not be considered initially. Symptomatic patients are often referred for brain MRI to evaluate for possible acquired infectious, neoplastic, and toxic diseases. In this setting, identification of diffuse symmetric abnormal signals in cerebral white matter leads to the consideration of leukodystrophy and subsequent solicitation of additional family history and appropriate biochemical and/or genetic testing. Because the genetic alteration for many leukodystrophies is known, it is possible that gene or cell-based therapies can treat or cure patients with these diseases. Preliminary results have demonstrated that the effectiveness of such therapies depends upon early (presymptomatic) diagnosis and intervention.

There have been few papers in recent decades on the neurochemical abnormalities in tissues of patients with different and newly described leukodystrophies. This is because diagnosis of specific leukodystrophies is now commonly made during life, and few of these patients have autopsy examination at centers capable of suitable research analyses of these tissues.

In some cases, magnetic resonance spectroscopy provides radiographic correlates of abnormal neurochemical metabolites. Older research has shown that the composition of myelin in the genetically determined disorders can be normal, have a specific alteration reflecting the genetic lesion, or show a nonspecific pathological composition that has much more cholesterol, less cerebroside and less phosphatidyl ethanolamine than does normal myelin (Lazzarini, 2004).

X-linked adrenoleukodystrophy is the most prevalent leukodystrophy (Costello et al., 2009). Biochemically, it is characterized by the accumulation of very-long-chain fatty acids. It is caused by an alteration in a gene called ABCD1 on chromosome Xq28. This gene encodes a peroxisomal membrane protein that is a member of the ATP-binding cassette (ABC) transporter superfamily. Members of this superfamily are responsible for transporting a variety of molecules across cell membranes, but the exact mechanism by which an alteration in the ABCD1 gene causes accumulation of very long chain fatty acids is still unknown (Lazzarini, 2004). There are two major clinical phenotypes: cerebral leukodystrophy and adrenomyeloneuropathy. A minority of patients presents with adrenal insufficiency or are asymptomatic. Up to 50% of female carriers can be symptomatic. The pathology of the cerebral form is unique among leukodystrophies in that there is marked perivascular lymphocytic inflammation and it can resemble the inflammatory demyelination of MS histologically. This observation demonstrates that inflammation can occur secondary to a primary disease of oligodendrocytes.

Lysosomal storage diseases

Two well-characterized leukodystrophies, metachromatic leukodystrophy and Krabbe disease, are lysosomal storage diseases (Costello et al., 2009) (Ch. 43). Both of these diseases are due to genetic alterations in single enzymes involved in lipid metabolism and so preferentially affect myelin. Metachromatic leukodystrophy results from a genetic alteration in the

TABLE 39-1 List of most commonly recognized genetically determined disorders of myelin

Disorder (OMIM* ID #)	Inheritance	Genetic lesion (OMIM ID #)	Comments
Adrenoleukodystrophy (300100)	X-linked	ABCD1 (300371), Peroxisomal membrane protein in the ABC transporter family	Decreased peroxidation of saturated, very-long-chain fatty acids, causing their accumulation in brain, adrenal glands and other tissues.
Aicardi–Goutieres syndrome. AGS1 (225750), AGS2 (610181), AGS3 (610329), AGS4 (610333) AGS5 (612952)	AR*	Heterogeneous: AGS1, TREX1 (606609); AGS2 (610181), subunit B of ribonuclease H2 (RNASEH2B; 610326); AGS3, RNASEH2C (610330); AGS4 RNASEH2A (606034); AGS5, SAMHD1 gene (606754)	Genes involved are ubiquitously expressed.
Alexander disease (203450)	AD*	glial fibrillary acidic protein (GFAP, 137780)	Usually results from de novo heterozygous mutations.
Canavan's disease (271900)	AR	Aspartoacylase (608034)	Widespread white matter edema with diminished myelin; <i>N</i> -acetylaspartic aciduria.
Charcot–Marie–Tooth disease and other inherited neuropathies	AD, AR or X-linked	PMP-22, P0, connexin-32 and other genes See text and references therein.	Variable degrees of myelin deficiency specific to the PNS.
Krabbe disease (245200)	AR	Galactocylceramidase (606890)	Macrophages (globoid cells) contain galactocerebroside.
Maple syrup urine disease (248600)	AR	Branched-chain keto acid dehydrogenase e1, alpha (608348) or beta (248611) polypeptide; dihydrolipoamide branched-chain transacylase (248610); dihydrolipoamide dehydrogenase (238331)	Impaired catabolism of the branched-chain amino acids, leucine, isoleucine and valine.
Megalencephalic leukoencephalopathy with subcortical cysts (604004)	AR	Megalencephalic leukoencephalopathy with subcortical cysts gene 1 (MLC1, 605908)	Function of MLC1 is unknown.
Metachromatic leukodystrophy (250100)	AR	Arylsulfatase A (607574)	Accumulation of sulfatide in brain
Pelizaeus–Merzbacher disease (312080)	X-linked	PLP1 (300401)	Variable degrees of hypomyelination due to different alterations in the major structural protein of CNS myelin. Similar to the <i>jimmy</i> mouse.
Phenylketonuria (216600)	AR	Phenylalanine hydroxylase (612349)	Hypomyelination may be caused by inhibition of amino acid transport and/or protein synthesis by the high level of phenylalanine that accumulates.
Vanishing white matter disease	AR	Eukaryotic initiation factor 2B (eIF2B)	Genes involved are ubiquitously expressed.

*OMIM, Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/omim/>); AR, autosomal recessive; AD, autosomal dominant.

arylsulfatase A gene, and there is an accumulation of sulfatide, which cannot be metabolized. In Krabbe disease, there is an alteration in the galactocylceramidase gene. This enzyme hydrolyzes galactose ester bonds, which are present in several glycolipids, including galactocerebroside, which is abundant in myelin, and galactosylsphingosine (psychosine). Galactocerebroside does not accumulate, most likely because oligodendrocytes die as a result of psychosine toxicity.

Pelizaeus–Merzbacher disease is the only known human leukodystrophy that can be attributed to a defect in a gene encoding a myelin structural protein, PLP (PLP1, Xq22). The majority of patients have a duplication in the PLP1 gene, indicating that gene dosage is important in pathogenesis, but a

number of alterations have been described. Depending on the nature of the alteration, patients can have a severe form (termed congenital), the intermediate phenotype of classical PMD, or a mild phenotype of spastic paraplegia. It is noteworthy that some mutations of the PLP1 gene also cause a peripheral neuropathy (Scherer et al., 2008), very probably related to the expression of low levels of PLP in peripheral nerve (see Ch. 4).

Several disorders of amino acid metabolism (aminoacidopathies) are associated with myelin deficiency (Ch. 42). These are aspartylase deficiency (Canavan disease), phenylketonuria, and maple syrup urine disease. Pathologically, all of these disorders demonstrate a spongy myelinopathy. Routine histology demonstrates vacuolization of the white matter, and

ultrastructural analysis shows splitting of the myelin sheath at the interperiod line.

Alexander disease has been typically classified as a leukodystrophy because cerebral white matter loss can be quite extensive, particularly in the infantile form. Research in the last decade has demonstrated that most cases of Alexander disease are associated with a mutation in the GFAP gene (Quinlan et al., 2007), and the mechanism by which a primary disease of astrocytes causes myelin pathology has not been determined.

Other leukodystrophies

There are a number of other genetic diseases that are associated with leukodystrophy. These are very rare, and their pathogenesis is not understood. Some, such as vanishing white matter disease and Aicardi–Goutieres syndrome, are associated with alterations in proteins expressed in all cells (see Table 39-1). Others, such as megalencephalic leukoencephalopathy with subcortical cysts, have been associated with defects in genes with unknown function. Further advances in the understanding of the pathogenesis of these diseases will require concerted efforts on the part of researchers to obtain post mortem tissues for analyses.

Deficiencies of peripheral nerve myelin in common inherited human neuropathies are caused by mutations in a variety of genes

There are a number of inherited peripheral neuropathies, and the nomenclature to classify them has evolved over the years (Shy et al., 2002; Suter & Scherer, 2003; Lazzarini, 2004; Scherer & Wrabetz, 2008) (Ch. 38). From a historical perspective, the most common inherited peripheral neuropathies were divided into two forms of Charcot–Marie–Tooth disease (CMT) largely on the basis of electrophysiology: type 1 (CMT1), which primarily affects myelin, and type 2 (CMT2), which primarily affects axons. There are a number of less-common diseases limited to peripheral neuropathy that vary in clinical severity, ranging from hereditary neuropathy with liability to pressure palsies to Dejerine–Sottas syndrome and congenital hypomyelinating neuropathy, as well as genetic syndromes that include peripheral neuropathy as a component (Scherer et al., 2008). This section will focus on the inherited neuropathies that have a demyelinating phenotype. The most common forms of CMT1 are caused by autosomal dominant mutations in genes encoding compact myelin proteins, PMP-22 in CMT1A and P0 protein in CMT1B, but over 20 other genes have been associated with demyelinating neuropathies. We have learned that the same clinical phenotype can result from alterations in different genes and that different alterations in the same gene can cause different clinical phenotypes.

Genetic alterations identified in inherited peripheral neuropathies include alterations in myelin structural proteins, transcription factors regulating the expression of myelin structural protein genes, membrane receptors, signaling molecules, and mitochondrial proteins. An emerging general concept is that gene dosage is a critical factor impacting the severity of clinical phenotype. This is supported by research on transgenic and knockout animal models that illustrate the importance of dosage of some myelin proteins for myelin

stability (see Ch. 10). For example, CMT1A is usually due to duplication of the PMP-22 gene with onset in the second or third decade of life and is characterized by segmental demyelination, remyelination, and onion bulb formation. Hereditary neuropathy with liability to pressure palsies is a milder neuropathy brought on by pressure or trauma to an affected nerve and is caused by a heterozygous deletion of PMP-22. Some more severe forms of CMT1A and Dejerine–Sottas syndrome have missense mutations in transmembrane regions of PMP-22 similar to the murine *trembler* mutations (see Ch. 10). CMT1B and some forms of Dejerine–Sottas syndrome are caused by a variety of mutations in the major P0 glycoprotein of compact myelin, presumably impairing its capacity to stabilize the intraperiod and/or major dense lines or interfering with a function in signal transduction (see Ch. 10).

There are other forms of inherited neuropathy affecting myelin that are caused by mutations of genes that alter Schwann cell proteins not localized in compact myelin. Some examples include (1) an X-linked form (CMT1X) caused by mutations of the gap junction protein connexin 32 (CX32), which is localized in paranodal loops and incisures where it probably forms gap junctions between adjacent layers of myelin membranes; (2) a recessive form (CMT4F) caused by mutations of periaxin, which is part of a protein complex linking the extracellular basal lamina to the actin cytoskeleton of Schwann cells; (3) a dominant form of CMT1 caused by mutations of a zinc finger transcription factor (EGR2, also called Krox 20); and (4) recessive forms involving signaling molecules, such as the myotubularin-related phosphatases (CMT4B1 and CMT4B1). The involvement of transcription factors and signaling molecules in demyelinating neuropathies also support the importance of gene dosage. For example, alterations in EGR2 often result in severe phenotypes because Krox20 is known to activate expression of a number of genes known to cause inherited neuropathies (P0, PMP22, Cx32, periaxin). Similarly, signaling molecules participate in numerous cellular pathways. It is clear that genetic alterations in a variety of Schwann cell functions can cause myelin deficiencies. Our understanding of the pathogenic mechanisms of the different alterations in genes known to be involved in inherited neuropathies is advancing, but far from complete. Furthermore, as is the case for disorders of CNS myelin, it is becoming increasingly apparent that axonal pathology and degeneration are often responsible for much of the neurological impairment in these inherited disorders caused by Schwann cell-specific defects, possibly due to altered Schwann cell–axon interactions (Ch. 38).

OTHER DISEASES PRIMARILY INVOLVING MYELIN

Myelin formation and stability are affected by a variety of other etiologies including developmental insults, nutritional deficiencies, therapeutic intervention and chemical and biological toxins

Much of the CNS myelin in mammals is formed during a relatively restricted time period of rapid development in the

last trimester of prenatal development and the first year of life (Ch. 31). During this period, a large portion of the brain's metabolic activity and synthetic capacity are involved in cerebral myelinogenesis. The most vulnerable period appears to be the time of oligodendroglial proliferation and differentiation. Therefore, any metabolic insult during this 'vulnerable period' may lead to a preferential reduction in myelin formation (Love et al., 2008). The most common disorder is periventricular leukomalacia. This disorder is usually a consequence of hypoxic/ischemic injury resulting in disruption of oligodendrocyte maturation. The pathology can be variable, ranging from focal cavitory necrosis to generalized cerebral hypomyelination. Specific nutritional deficiencies and acquired toxicities are known to cause pathology in mature myelin. Descriptions of the pathology of many of these disorders are found in older literature. Today, most patients with neurologic symptoms have MRIs early in the course of their disease and effective treatments are initiated at a stage that results in a positive clinical outcome.

Vitamin B12 deficiency can result in demyelination of the dorsal and lateral columns of the spinal cord (subacute degeneration of the spinal cord). A peripheral neuropathy is also associated with B12 deficiency, but most evidence indicates that this is an axonopathy. The pathology of spinal cord lesions is myelinolysis, which is characterized by light microscopy as vacuolization of white matter and by electron microscopy as splitting of myelin at the intraperiod line. Presently, B12 deficiency is less frequent due to the vitamin supplementation of most processed foods and clinical surveillance and treatment of patients at risk for primary deficiency (vegans) or impaired gastric absorption (e.g., individuals with pernicious anemia).

Central pontine myelinolysis is most consistently associated with rapid correction of hyponatremia (low serum sodium), but this pathology has been associated with other metabolic derangements in the absence of hyponatremia (Love et al., 2008; Ropper et al., 2009). The prevalence of this disease in chronic alcoholics is related to losses of sodium due to vomiting or to intestinal sodium loss following treatment with lactulose for hepatic encephalopathy. The acute pathology is characterized by a disruption of compact myelin at the intraperiod line, but macrophage-mediated demyelination and necrosis ensue in the absence of prompt appropriate treatment. Although the pons is characteristically involved, other CNS regions that contain an intermixture of myelinated axons and neuronal nuclei, such as basal ganglia, lateral geniculate nucleus, external capsule and cerebellum, can also be affected (Love et al., 2008). Radiotherapy and chemotherapy for neoplastic disease can cause white matter pathology (Filley & Kleinschmidt-DeMasters, 2001; Love et al., 2008). Because both endothelial cells and oligodendrocytes are susceptible to damage by these agents, the pathogenesis of the resulting leukoencephalopathy may be multifactorial. Generalized radiation-induced leukoencephalopathy is less common because of advancements in stereotactic radiotherapy. A number of chemotherapeutic agents used to treat cancer patients have also been implicated in white matter toxicity. Most notable is methotrexate, which is often used to treat MS patients.

A variety of toxins have been associated with leukoencephalopathy (Filley & Kleinschmidt-DeMasters, 2001; Love

et al. 2008). Poisoning with trimethyltin and therapeutic use of hexachlorophene have been correlated with myelinolytic pathology. Lead is also known to cause hypomyelination and demyelination. Diphtheritic neuropathy is a possible complication of *Corynebacterium diphtheriae* infection and is characterized by segmental demyelination (Love et al., 2008). Marchiafava–Bignami disease is a disorder initially described in Italian chronic alcoholics who consumed large quantities of red wine. It is characterized by lesions in the corpus callosum, and most diagnoses reported in recent literature have been based upon MRI. It is unclear whether the etiology is toxic or a vitamin deficiency.

DISORDERS PRIMARILY AFFECTING NEURONS WITH SECONDARY INVOLVEMENT OF MYELIN

Many insults to the nervous system initially cause damage to neurons but eventually result in regions of demyelination as a consequence of neuronal degeneration

The archetypical model for secondary demyelination is Wallerian degeneration (see Ch. 32). When a peripheral nerve or a myelinated tract in the CNS is cut or crushed, axons and myelin in the distal segment degenerate, demonstrating that the integrity of the myelin sheath depends on continued contact with a viable axon. During Wallerian degeneration in the PNS, there is a rapid loss of myelin-specific lipids and proteins within a week or two, with a concomitant increase in lysosomal enzymes. Between the second and fourth week after nerve section, most of the myelin debris has been removed by Schwann cells and macrophages, and remyelination of regenerating axons begins. Degeneration of CNS myelin is a much slower process than in the PNS and takes place primarily within macrophages/microglia (not within the myelin-synthesizing cells, as in the PNS).

Secondary demyelination occurs in a variety of acquired and genetic CNS disorders that initially affect neurons, including mechanical trauma, infarcts, tumors, motor neuron disease, and sphingolipidoses such as Tay–Sachs disease, generalized gangliosidosis and Niemann–Pick disease (see Chs. 41 and 43). The isolated myelin from these diseases is usually of the 'non-specific pathological type' that was discussed earlier in the context of some inherited primary demyelinating disorders.

REPAIR IN DEMYELINATING DISEASES

The capacity for remyelination depends upon the presence of receptive axons and sufficient myelin-forming cells

Much of this chapter has considered biochemical and cell biological mechanisms of myelin loss, but the capacity of nervous tissue to repair damage is also an important factor in the eventual clinical outcome of disorders affecting myelin. Because myelin always degenerates secondary to

axonal degeneration, the capacity for remyelination in this setting depends upon successful regeneration of axons. This is much more successful in the PNS than in the CNS. If the motor and sensory neurons that extend into the PNS regenerate successfully, Schwann cells rapidly proliferate and form new myelin.

Additional factors affect the capacity for myelin repair in primary diseases of myelin. Most important is the nature and persistence of the pathogenic insult. For example, the demyelination in mice treated with cuprizone is rapidly reversed when administration of this toxin is stopped. Successful remyelination in acquired immune-mediated peripheral neuropathies can also occur if treatment of the inflammatory pathogenesis is successful. Similarly, for genetic diseases, gene or cell-based therapies have shown promise if the intervention takes place before the patient demonstrates symptoms of the disease.

Spontaneous remyelination of lesions of MS is well documented, but remyelination is usually incomplete

There are a number of barriers to effective remyelination in MS. Like the PNS, remyelination is dependent upon production of new myelinating cells (Franklin & ffrench-Constant, 2008). Oligodendrocytes in the CNS differentiate from progenitor cells named for their expression of the NG2 chondroitin sulfate proteoglycan (NG2 glia). NG2 glia have the ability to proliferate and migrate, and these cells have been identified within chronic MS lesions. NG2 glia differentiate into premyelinating oligodendrocytes, which are multiprocess-bearing cells that express PLP. Premyelinating oligodendrocytes produce myelin internodes when they contact receptive axons. In the demyelinated lesions of MS, many axons are transected or dystrophic (Chang et al., 2002). Therefore, even if premyelinating oligodendrocytes are present in MS lesions, their ability to produce new myelin may be inhibited because the axons they contact are abnormal. In addition, molecules in the extracellular environment may inhibit proliferation and/differentiation of oligodendrocyte lineage cells (Franklin & ffrench-Constant, 2008). Finally, as noted above, inducing remyelination could be futile if ongoing demyelination exceeds the capacity for repair. Understanding the role of the different inflammatory infiltrates and associated molecules in MS lesions is important in this regard because most therapies target inflammation, and some aspects of inflammation may promote repair.

Remyelination in the CNS can be promoted by various treatments

There are multiple therapeutic targets for promoting remyelination in the CNS (Franklin & ffrench-Constant, 2008). These include increasing the number and differentiation of oligodendrocyte lineage cells, promoting an extracellular environment that promotes myelination, and protecting the health of the demyelinated axons. The number of oligodendrocyte lineage cells could be increased by a variety of growth factors (Ch. 29), such as epidermal growth factor, basic fibroblast growth factor,

platelet derived growth factor, ciliary neurotrophic factor and insulin-like growth factor, which are known to affect the survival, proliferation, migration and differentiation of oligodendrocyte progenitors. Alternatively, cells with a capacity to myelinate could be transplanted into specific lesions (cell replacement therapy). A number of candidates have been investigated, including NG2 glia, less differentiated progenitor cells, and other cells with stem cell properties. A number of inhibitors of oligodendrocyte differentiation have been identified, and interference with these inhibitors could create an environment that promotes myelination. For example, LINGO-1 is an oligodendrocyte membrane protein that inhibits oligodendrocyte differentiation and myelination. Antibodies to LINGO-1 promoted remyelination in several models of demyelination.

With the increasing awareness that substantial axonal degeneration occurs in many diseases that had previously been thought to affect primarily myelin and that this may account for much of the permanent neurological deficit, increasing attention is being given to therapies that promote axonal survival and regeneration. Various growth factors are likely to be beneficial in this regard. However, a complicating factor is that myelin contains a number of inhibitors of axonal regeneration (Cao et al., 2010) (see Ch. 32). This is important because the highest density of transected axons is present in acute lesions that also contain abundant myelin debris. Three well-characterized molecules, Nogo, MAG and OMgp, function through the same receptor, NgR1, so it may be feasible to block the effects of all three simultaneously.

In conclusion, therapy for myelin disorders in the future will likely involve a combination of approaches aimed at preventing myelin loss, while at the same time promoting the survival, regeneration and remyelination of axons.

Acknowledgments

We thank Christopher Nelson, Ph.D., for editorial assistance.

References

- Australia and New Zealand Multiple Sclerosis Genetics Consortium (ANZgene) (2009) Genome-wide association study identifies new multiple sclerosis susceptibility loci on chromosomes 12 and 20. *Nature Genetics*, 41, 824–828.
- Bergmann, C. C., Lane, T. E., & Stohlman, S. A. (2006). Coronavirus infection of the central nervous system: Host–virus stand-off. *Nature Reviews Microbiology*, 4, 121–132.
- Cao, Z., Gao, Y., Deng, K., Williams, G., Doherty, P., & Walsh, F. S. (2010). Receptors for myelin inhibitors: Structures and therapeutic opportunities. *Molecular and Cellular Neurosciences*, 43, 1–14.
- Chang, A., Tourtellotte, W. W., Rudick, R., & Trapp, B. D. (2002). Premyelinating oligodendrocytes in chronic lesions of multiple sclerosis. *The New England Journal of Medicine*, 346, 165–173.
- Compston, A. (2006). Making progress on the natural history of multiple sclerosis. *Brain*, 129, 561–563.
- Compston, A., & Coles, A. (2008). Multiple sclerosis. *Lancet*, 372, 1502–1517.
- Costello, D. J., Eichler, A. F., & Eichler, F. S. (2009). Leukodystrophies: Classification, diagnosis, and treatment. *Neurologist*, 15, 319–328.
- Cuzner, M. L., & Norton, W. T. (1996). Biochemistry of demyelination. *Brain Pathology*, 6, 231–242.

- De Jager, P. L., Jia, X., Wang, J., de Bakker, P. I., Ottoboni, L., Aggarwal, N. T., et al. (2009). Meta-analysis of genome scans and replication identify CD6, IRF8 and TNFRSF1A as new multiple sclerosis susceptibility loci. *Nature Genetics*, *41*, 776–782.
- Denic, A., Johnson, A. J., Bieber, A. J., Warrington, A. E., Rodriguez, M., & Pirko, I. (2011). The relevance of animal models in multiple sclerosis research. *Pathophysiology*, *18*, 21–29.
- Fazakerley, J. K., & Walker, R. (2003). Virus demyelination. *Journal of Neurovirology*, *9*, 148–164.
- Filley, C. M., & Kleinschmidt–DeMasters, B. K. (2001). Toxic leukoencephalopathy. *The New England Journal of Medicine*, *345*, 425–432.
- Fisher, E., Chang, A., Fox, R. J., Tkach, J. A., Svarovsky, T., Nakamura, K., et al. (2007). Imaging correlates of axonal swelling in chronic multiple sclerosis brains. *Annals of Neurology*, *62*, 219–228.
- Fox, R. J. (2008). Picturing multiple sclerosis: Conventional and diffusion tensor imaging. *Seminars in Neurology*, *28*, 453–466.
- Franklin, R. J., & ffrench–Constant, C. (2008). Remyelination in the CNS: From biology to therapy. *Nature Reviews Neuroscience*, *9*, 839–855.
- Henderson, A. P., Barnett, M. H., Parratt, J. D., & Prineas, J. W. (2009). Multiple sclerosis: Distribution of inflammatory cells in newly forming lesions. *Annals of Neurology*, *66*, 739–753.
- Hughes, R. A., Allen, D., Makowska, A., & Gregson, N. A. (2006). Pathogenesis of chronic inflammatory demyelinating polyradiculoneuropathy. *Journal of the Peripheral Nervous System*, *11*, 30–46.
- Hughes, R. A., & Cornblath, D. R. (2005). Guillain–Barré syndrome. *Lancet*, *366*, 1653–1666.
- Kaida, K., & Kusunoki, S. (2010). Antibodies to gangliosides and ganglioside complexes in Guillain–Barré syndrome and Fisher syndrome: Mini-review. *Journal of Neuroimmunology*, *223*, 5–12.
- Lazzarini, R. A. (2004). *Myelin biology and disorders*. San Diego, CA: Elsevier Academic.
- Love, S., Louis, D. N., & Ellison, D. W. (2008). *Greenfield's neuropathology* (8th ed.). New York: Oxford University Press.
- Lucchinetti, C., Bruck, W., Parisi, J., Scheithauer, B., Rodriguez, M., & Lassmann, H. (2000). Heterogeneity of multiple sclerosis lesions: Implications for the pathogenesis of demyelination. *Annals of Neurology*, *47*, 707–717.
- Nave, K. A., & Trapp, B. D. (2008). Axon–glial signaling and the glial support of axon function. *Annual Review of Neuroscience*, *31*, 535–561.
- Niermeijer, J. M., Fischer, K., Eurelings, M., Franssen, H., Wokke, J. H., & Notermans, N. C. (2010). Prognosis of polyneuropathy due to IgM monoclonal gammopathy: A prospective cohort study. *Neurology*, *74*, 406–412.
- Peterson, J. W., Bo, L., Mork, S., Chang, A., & Trapp, B. D. (2001). Transected neurites, apoptotic neurons, and reduced inflammation in cortical multiple sclerosis lesions. *Annals of Neurology*, *50*, 389–400.
- Polman, C. H., Reingold, S. C., Banwell, B., Clanet, M., Cohen, J. A., Filippi, M., et al. (2011). Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Annals of Neurology*, *69*, 292–302.
- Quinlan, R. A., Brenner, M., Goldman, J. E., & Messing, A. (2007). GFAP and its role in Alexander disease. *Experimental Cell Research*, *313*, 2077–2087.
- Rinaldi, S., Brennan, K. M., Goodyear, C. S., O'Leary, C., Schiavo, G., Crocker, P. R., et al. (2009). Analysis of lectin binding to glycolipid complexes using combinatorial glycoarrays. *Glycobiology*, *19*, 789–796.
- Ropper, A. H., & Samuels, M. A. (2009). *Adams and Victor's principles of neurology* (9th ed.). New York: McGraw-Hill Medical.
- Sato, F., Tanaka, H., Hasanovic, F., & Tsunoda, I. (2011). Theiler's virus infection: Pathophysiology of demyelination and neurodegeneration. *Pathophysiology*, *18*, 31–34.
- Scherer, S. S., & Wrabetz, L. (2008). Molecular mechanisms of inherited demyelinating neuropathies. *Glia*, *56*, 1578–1589.
- Shy, M. E., Garbern, J. Y., & Kamholz, J. (2002). Hereditary motor and sensory neuropathies: A biological perspective. *Lancet Neurology*, *1*, 110–118.
- Sonneville, R., Klein, I. F., & Wolff, M. (2010). Update on investigation and management of postinfectious encephalitis. *Current Opinion in Neurology*, *23*, 300–304.
- Suter, U., & Scherer, S. S. (2003). Disease mechanisms in inherited neuropathies. *Nature Reviews Neuroscience*, *4*, 714–726.
- Tan, C. S., & Koralnik, I. J. (2010). Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: Clinical features and pathogenesis. *Lancet Neurology*, *9*, 425–437.
- Trapp, B. D., & Nave, K. A. (2008). Multiple sclerosis: An immune or neurodegenerative disorder?. *Annual Review of Neuroscience*, *31*, 247–269.
- Trapp, B. D., Peterson, J., Ransohoff, R. M., Rudick, R., Mork, S., & Bo, L. (1998). Axonal transection in the lesions of multiple sclerosis. *The New England Journal of Medicine*, *338*, 278–285.
- Trapp, B. D., & Stys, P. K. (2009). Virtual hypoxia and chronic necrosis of demyelinated axons in multiple sclerosis. *Lancet Neurology*, *8*, 280–291.
- Winer, J. B. (2011). Guillain–Barré syndrome: Clinical variants and their pathogenesis. *Journal of Neuroimmunology*, *231*, 70–72.
- Zivkovic, S. A., Lacomis, D., & Lentzsch, S. (2009). Paraproteinemic neuropathy. *Leukemia & Lymphoma*, *50*, 1422–1433.