CHAPTER 37

Virus-Induced Demyelination

PETER W. LAMPERT* AND MOSES RODRIGUEZ†

Demyelination refers to a pathologic process that causes the destruction of myelin sheaths without injury to axons. According to etiology, the demyelinating diseases can be classified into genetic, nutritional, toxic, allergic, or virus-induced disorders. Clues to etiology are found by observing early ultrastructural alterations that may affect either myelin lamellae or the myelin supporting cells, i.e., oligodendrocytes or Schwann cells in the central or peripheral nervous system, respectively. Metabolic changes induced by nutritional deficiencies or intoxications may initially manifest themselves in the most distal extensions of the cytoplasm of the myelin-supporting cells, i.e., at nodes of Ranvier or at the inner glial loops of myelin sheaths (Fig. 1). In other conditions, myelin lamellae are primarily affected resulting in wide lamellar separation as seen in intoxications with hexachlorophene or triethyltin [1]. Early lysis of myelin lamellae without damage to the myelin-supporting cells is seen in allergic neuritis [2] and presumably also occurs in autoimmune encephalomyelitis in which the myelin lamellae rather than the myelin-supporting oligodendrocytes are the target of the allergic reaction. This review is concerned with virus infections of the central nervous system that cause demyelination by different mechanisms such as direct virus-induced lysis of oligodendrocytes, immune-mediated destruction of persistently infected cells, “bystander” demyelination accompanying nonspecific inflammatory reactions, and autoimmune demyelination occurring after virus-induced sensitization to myelin.

* University of California-San Diego, La Jolla, California.

† Mayo Clinic and Research Foundation, Rochester, Minnesota.

Fig. 1. Oligodendrocyte depicting connections with myelin sheaths, one of which is unwrapped to reveal the continuity of cytoplasm around compact myelin. Early ultrastructural changes provide clues to the etiology of demyelinating diseases. Nutritional deficiencies and intoxications may first affect myelin lamellae or glial cytoplasm in their most distal extensions. Virus-induced demyelination may begin with infection and lysis of oligodendrocytes or by primary injury to myelin lamellae similar to the mechanism of demyelination in experimental autoimmune encephalomyelitis (EAE).

Virus-Induced Lysis of Oligodendrocytes

This mechanism of demyelination is well documented in mice after acute infection with mouse hepatitis virus (MHV) and in humans in progressive multifocal leucoencephalopathy (PML) caused by infection with papova virus.

After inoculation with the JHM strain of MHV, a corona virus, mice develop an acute encephalomyelitis [3]. Depending on virus dosage, inoculation route, age, and strain of mice, the course of the disease can be attenuated with lesions restricted to the white matter [4]. Demyelination most consistently develops after infection of weanling Balb/c mice with a temperature sensitive mutant (*ts8*) [5]. The lesions develop within a week, are randomly scattered throughout the white matter and show no particular relation to vessels. Large plaques of demyelination involving the entire half of the spinal cord are observed in some mice 3 weeks after infection (Fig. 2). Inflammatory cells are rare at the onset of demyelination, but abundant macrophages are seen at later stages. The mortality of infected mice is enhanced by immunosuppressive measures, suggesting that the disease is not mediated by host immune responses but by the direct cytolytic effect of the virus [4].

Electron microscopy confirmed the presence of corona virus in oligodendrocytes (Fig. 2) [6]. The infected cells reveal hypertrophic changes prior to lysis. Their cytoplasm is filled with aggregates of viral protein that bud into cisterns of endoplasmic reticulum. The infected hypertrophic cells frequently show myelin lamellae arising from plasma membranes (Fig. 2), a

Fig. 2. Demyelination in mouse hepatitis virus encephalomyelitis caused by direct viral cytolysis in oligodendrocytes. A. Large area of demyelination in spinal cord 25 days after infection $\times 500$; B. Completely denuded axons, 21 days after infection

feature difficult to demonstrate in normal oligodendrocytes. After cytolysis, the myelin sheaths related to the necrotic cells are removed by macrophages that strip compact myelin sheaths off their axons. Abundant demyelinated axons interspersed by lipid-laden macrophages are seen 2 to 3 weeks after infection. Characteristically, even mice with large areas of demyelination recover rapidly. Oligodendrocytes proliferate and remyelinate the denuded axons [7]. Remyelination is remarkably effective, resulting in almost complete restoration of myelin sheaths within 2 to 3 months. The recovered mice remain persistently infected at a low titer and small foci of recurring demyelination have been detected in some mice many months after infection [5].

A similar mechanism of demyelination beginning with virus-induced cytolysis of oligodendrocytes is seen in humans afflicted with progressive multifocal leucoencephalopathy [8]. This rare demyelinating disease may develop in debilitated or immunosuppressed patients, particularly in patients suffering from leukemia or lymphoma. Multiple patches of demyelination are found in the brains of patients after a progressive neurologic illness that may last for months. The lesions show no relation to vessels and, except for macrophages, inflammatory infiltrates may be completely lacking. Oligodendrocytes with enlarged nuclei full of papova virus are pathognomonic. Astrocytes with great bizarre, hyperchromatic nuclei that also contain viral antigen are seen in more advanced lesions. It is not clear how this virus infects the brain or what might activate its proliferation in oligodendrocytes. Papova virus isolated from cases of PML has been most frequently identified as JC virus, which commonly infects humans [2].

Immune-Mediated Lysis of Virus-Infected Oligodendrocytes

In contrast to demyelination in PML or MHV, the pathogenesis of other virus-induced demyelinating disorders probably also involves interaction of virus or virus-infected cells with host immune responses. Subacute sclerosing panencephalitis (SSPE) and Theiler's mouse polioencephalomyelitis (TME) will serve as examples.

SSPE is caused by persistent infection with measles virus. It is a slowly progressive disease in children and young adults leading to death within months to a few years. The virus persists in both neurons and glial cells including oligodendrocytes, leading to demyelination. Characteristically, both the spinal fluid and the infected brain contain high titers of antimeasles antibodies and there are perivascular infiltrates of lymphocytes and plasma

×5000. C. Oligodendrocyte identified by connections with myelin lamellae (arrow) contains numerous virus particles within cisterns of endoplasmic reticulum (double arrows) ×15,000. D. Corona virus within a cistern of endoplasmic reticulum of an oligodendrocyte ×150,000. E. Enlargement of area marked by arrow in C to show connection of oligodendrocyte with a myelin lamella (arrow) ×100,000.

cells. Ultrastructural studies demonstrated that lysis of infected oligodendrocytes occurs in the presence of antibodies that bind to nucleocapsids of measles virus [9]. Although the persistently infected cells are eventually destroyed by competent host immune responses, one wonders how the virus can persist in the presence of specific antiviral antibodies. Morphologic studies show that persistently infected oligodendrocytes rarely reveal surface expression of viral antigen. Nucleocapsids are found within the nucleus and cytoplasm but no virus buds from the cell surface and there is no alignment of nucleocapsids beneath the plasma membrane. Experimentally, lysis of infected cells is induced by antibody and complement when virus is expressed on the cell surface. Viral antigen can be stripped off the cell membrane by antibody in the absence of complement, rendering the infected cell resistant to immunologic injury [9]. However, after removal of antibody, the cell will again express viral antigen on its surface and become vulnerable to immunologic injury. Survival or lysis of persistently infected cells in SSPE may thus depend on titer and ratio of complement and antibody within the affected brain, which may be subject to changes in the permeability of the blood brain barrier.

TME is a demyelinating disease that develops in mice 1 to 3 months after infection with the DA strain of Theiler's mouse encephalomyelitis virus (TMEV), a picorna virus [10,11]. The virus first affects neurons but a few weeks later perivascular demyelinating lesions develop in the spinal cord (Fig. 3). Demyelination is preceded by perivascular mononuclear cell infiltrates. Patchy perivascular demyelination associated with inflammatory infiltrates is seen for many months in persistently infected mice. Remyelination by oligodendrocytes occurs, but compared with efficient remyelination following MHV infection, the restoration of myelin sheaths is delayed, abortive, or incomplete. In some mice, however, Schwann cells enter the damaged cord via nerve roots and remyelinate axons more effectively [11].

The biphasic course of the disease, as well as the perivascular demyelination occurring within mononuclear cell infiltrates, suggested an autoimmune pathogenesis following host sensitization by the initial virus invasion of the brain. This view is supported by observations indicating that immunosuppressive measures prevented the development of the demyelinating lesions [12]. However, at present no convincing evidence exists to prove that the demyelinating disease can be transferred to uninfected mice much like the transfer of experimental autoimmune encephalomyelitis that is induced by sensitization to myelin. On the other hand, there are reports indicating that virus persists at low titers within the spinal cord and that glial cells (in particular, oligodendrocytes) are persistently infected in this chronic recurrent demyelinating disease (Fig. 3) [13,14]. These observations favor the interpretation of immune-mediated injury to persistently infected oligodendrocytes. Ultrastructural studies confirmed the presence of degenerating oligodendrocytes and the stripping of myelin from axons by invading macrophages.

Fig. 3. Theiler's mouse virus encephalomyelitis characterized by a biphasic course that involves first neurons and later glial cells in the white matter resulting in demyelination. A. Viral antigen is localized in nerve cells in the spinal cord of a SJL mouse 7 days after infection. Immunoperoxidase $\times 1000$. B. Paracrystalline array of picorna virus particles in a nerve cell 4 days after neonatal infection $\times 30,000$. C. Perivascular demyelination associated with mononuclear cell infiltrates in the spinal cord 110 days after infection $\times 250$. D. Demyelinated axons in the spinal cord 45 days after infection $\times 2000$. E. Viral antigen localized in inner and outer glial cells in the white matter of the spinal cord 45 days after infection. Arrow points to connections with myelin sheaths. Immunoperoxidase $\times 1000$. F. Viral antigen localized in oligodendroglial loops of a myelin sheath in the spinal cord 360 days after infection. Immunoperoxidase $\times 160,000$.

“Bystander” Demyelination

It has been proposed that inflammatory cells participating in immunologic reactions may release substances capable of causing nonspecific demyelination. This idea runs counter to neuropathologic observations showing that in most inflammatory diseases of the brain, demyelination is not a prominent feature. However, experimental studies suggest that demyelination may occur within the inflammatory infiltrate of delayed hypersensitivity reactions [15]. Local injections of purified protein derivative (PPD) into the spinal cord of guinea pigs sensitized to this antigen induce a mononuclear cell infiltrate associated with demyelination. Based on this observation, it has been postulated that demyelination in virus infections may represent a nonspecific “bystander” effect triggered by an immunologic reaction directed against the virus. *In vitro* studies of myelinated tissue cultures showed that demyelination can be induced by neutral proteinases, such as plasminogen activator, which are secreted by activated macrophages [16]. Other studies indicate, however, that the “bystander” effect may account only for minor demyelination in nonspecific inflammation, whereas more widespread demyelination is induced when the inflammatory reaction is associated with the recruitment of lymphocytes sensitized against myelin components or when antimyelin antibodies permeate the lesion (HC Powell, 1984, personal communication). The local production of a delayed hypersensitivity reaction in the peripheral nerve in rabbits by means of purified protein derivative is associated with significant demyelination when antigalactocerebroside antibody is elevated in the serum. Similarly, rats sensitized to PPD and galactocerebroside show demyelination of the peripheral nerve after local injection of PPD, whereas rats sensitized only to PPD show no or only minor demyelination in advanced stages. “Bystander” demyelination in virus infection could therefore be quite significant in a host with latent hypersensitivity to myelin, because stimulation of immunocompetent cells by virus may simultaneously turn on cells sensitized to myelin. This mechanism of nonspecific recruitment of cells or antibody directed against myelin might explain demyelination in infections with completely different viruses such as paramyxo-, rhabdo-, arbo-, retro-, and herpes virus [11].

Virus-Induced Autoimmune Demyelination

Human post-infectious encephalomyelitis generally develops a few weeks after a virus infection and shows morphologic features that resemble acute experimental autoimmune encephalomyelitis [2]. These findings prompted speculations that the initial invasion of the brain by virus may alter myelin or oligodendrocytes. Sensitization against the altered membranes may evoke immune responses against myelin, leading to autoimmune demyelination. Experimentally it is indeed possible to demonstrate both cellular and hu-

moral antimyelin sensitivity after virus infections, e.g., after infections with distemper or Marek's disease virus [2,11,17]. Another theory suggests that sensitization to myelin occurs because the peptide sequences of some viruses mimic those of myelin proteins. There is evidence indicating that cross-reactivity of antibody exists against measles virus and myelin basic protein [18]. Further, pertinent in this regard is the fact that following vaccination with killed virus, the host may develop a demyelinating disease that resembles post-infectious or autoimmune encephalomyelitis. As mentioned above, virus could also nonspecifically alter the immune system and thus permit the emergence of latent hypersensitivity to myelin. This idea is supported by the finding that recurrence of experimental autoimmune encephalomyelitis is precipitated by herpes virus infection [19].

Acknowledgment. The work described in this paper was supported by US PHS Grants NS-09053, 12428, and 07078.

References

1. Lampert PW (1983) Multiple sclerosis: The patient, treatment and pathology. In Hallpike J, Adams CWM, Tourtellotte WW (eds) Chapman Hall, London
2. Lampert PW (1978) Autoimmune and virus-induced demyelinating disease. A review. *Am J Pathol* 91:176-208
3. Cheaver FS, Daniels JB, Pappenheimer AM, Bailey OT (1949) A murine virus (JHM) causing disseminated encephalomyelitis with extensive destruction of myelin. 1. Isolation and biological properties of the virus. *J Exp Med* 90:181-194
4. Weiner LP (1973) Pathogenesis of demyelination induced by mouse hepatitis virus (JHM virus). *Arch Neurol* 28:298-303
5. Knobler RL, Tunison LA, Lampert PW, Oldstone MBA (1982) Selected mutants of mouse hepatitis virus type 4 (JHM strain) induce different CNS diseases. *Am J Pathol* 109:157-168
6. Lampert PW, Sims JK, Kniazeff AJ (1973) Mechanism of demyelination in JHM virus encephalomyelitis *Acta Neuropathol* 24:76-85
7. Herndon RM, Price DL, Weiner LP (1977) Regeneration of oligodendroglia during recovery from demyelinating disease. *Science* 195:693-694
8. Zu Rhein GM (1969) Association of papova-virus with a human demyelinating disease (progressive multifocal leukoencephalopathy). *Prog Med Virol* 11:185-247
9. Lampert PW, Joseph BS, Oldstone MBA (1976) Morphological changes of cells infected with measles or related viruses. In Zimmerman HM (ed) *Progress in Neuropathology*. Grune and Stratton, New York, 3:51-68
10. Lipton HL (1975) Theiler's virus infection in mice: An unusual biphasic disease process leading to demyelination. *Infect Immunol* 11:1147-1145
11. Dal Canto MC, Rabinowitz SG (1982) Experimental models of virus induced demyelination of the central nervous system *Ann Neurol* 11:109-127
12. Lipton HL, Dal Canto MC (1976) Theiler's virus induced demyelination: Prevention by immunosuppression *Science* 192:62-64
13. Brahic M, Stroop WG, Baringer JR (1981) Theiler's virus persists in glial cells during demyelinating disease *Cell* 26:123-128

14. Rodriguez M, Leibowitz JL, Lampert PW (1983) Persistent infection of oligodendrocytes in Theiler's virus induced encephalomyelitis. *Ann Neurol* 13:426–433
15. Wisniewski HM, Bloom BR (1975) Primary demyelination as a non-specific consequence of a cell mediated immune reaction. *J Exp Med* 141:346–359
16. Cammer W, Bloom BR, Norton WT, Gordon S (1978) Degradation of basic protein in myelin by neutral proteases secreted by stimulated macrophages: A possible mechanism of inflammatory demyelination. *Proc Nat Acad Sci USA* 75:1554–1558
17. Pepose JS, Stevens JG, Cook ML, Lampert PW (1981) Marek's disease as a model for the Landry–Guillain–Barre Syndrome. *Am J Pathol* 103:309–320
18. Panitch HS, Swoveland P, Johnson KP (1979) Antibodies to measles virus react with myelin basic protein. *Neurology* 29:548–549
19. Hochberg FH, Lehrich JR, Arnason BGW (1977) Herpes simplex infection and experimental model system for reactivation of EAE. *Neurology (Minneapolis)* 27:584