CHAPTER 24

Virus-induced Autoimmune Demyelinating Disease of the Central Nervous System

RICHARD T. JOHNSON AND DIANE E. GRIFFIN

Acute perivenular demyelinating disease of the brain and spinal cord can complicate a number of human viral infections. It has been most frequent late in the course of the exanthematous viral infections, particularly measles and vaccinia, and, to a lesser extent, varicella and rubella. The discontinuation of vaccination against smallpox and the successful immunization against measles and rubella in the United States have decreased the incidences of these infections and their parainfectious complications. Currently, postinfectious encephalomyelitis in the United States is most frequent after varicella, where mortality and morbidity rates are low, and after upper respiratory infections, where the etiologic agent is usually undetermined [1].

Nevertheless, measles is not controlled in most of the world; 1.5 million children still die annually from measles. Although most measles-associated deaths result from virus dissemination and secondary infections, encephalomyelitis occurs in about 1:1000 children [2] and remains a significant cause of mortality and the major cause of permanent neurological morbidity. Encephalomyelitis after vaccinia virus inoculation was highly variable; incidence rates ranged from 1 to 63 in one Dutch experience to 1 in 300,000 in a national survey in the United States. The reason for this variability has never been explained. Although postvaccinal encephalomyelitis appeared of only historical interest after the worldwide eradication of smallpox, this complication has assumed new importance. One of the most promising strategies for future vaccines is the use of recombinant vaccinia virus carrying sequences coding for multiple virus antigens [3]. A better understanding of the determinants of the postvaccinal encephalomyelitis will be critical before clinical trials of these vaccines are initiated.

Unfortunately, there is no animal model for acute postinfectious encephalomyelitis. The experimental disease that best simulates the acute periven-

A. L. Notkins et al. (eds.), *Concepts in Viral Pathogenesis II*

ular demyelination is experimental allergic encephalomyelitis. Subacute or chronic coronavirus infections of rat nervous system do lead to probable autoimmune-mediated demyelination [4]; however, studies of measles encephalomyelitis in humans indicate that neurotropism or direct infection of the nervous system may not be prerequisites to the development of acute demyelinating disease [5].

Similarities of Postinfectious Encephalomyelitis to Experimental Allergic Encephalitis

Postinfectious encephalomyelitis is remarkably similar clinically and pathologically to the neuroparalytic complications observed after multiple injections of rabies virus vaccine prepared in adult animal brains. This similarity led Rivers and Schwentker [6] to inoculate monkeys with homogenates of normal brain in an attempt to reproduce this disease. This resulted in the first induction of experimental allergic encephalomyelitis, the prototype autoimmune disease. Extensive studies of experimental allergic encephalomyelitis have shown that the encephalitogenic antigen is the basic protein of central nervous system myelin, and that the disease can be passively transferred by sensitized lymphocytes of the T-helper subset [7].

The parallels between the three diseases are remarkable (Table 24.1). In experimental allergic encephalomyelitis and post-rabies-vaccine encephalomyelitis, lymphocytes show lymphoproliferative responses to myelin basic protein. Similar responses have been observed in lymphocytes from patients with postinfectious encephalomyelitis following measles, varicella, and upper respiratory infections [5,8].

The inexplicable factor in these comparisons is how viruses can induce sensitization to neural proteins. Certainly, normal individuals have immune cells capable of reacting against myelin proteins. Expresssion of this reactivity is normally actively suppressed, but this suppression can be overcome by injection of excess antigen, as in experimental allergic encephalomyelitis and postrabies encephalomyelitis. Possibly, viral infections overcome this suppression by modification of myelin, by release of myelin products into the general circulation, or by disruption of immune regulation.

Coronavirus-induced Autoimmune Demyelination in Mice

One potential mechanism for autoimmune demyelinating disease induced by viruses comes from studies of a coronavirus, the JHM strain of mouse hepatitis virus. This virus was originally isolated from a spontaneous paralytic disease of mice. The virus causes acute demyelinating encephalitis by selective infection of oligodendrocytes [9]. The virus persists in the nervous system of mice, and late subclinical inflammatory demyelinating foci develop.

Table 24.1. Comparisons of experimental allergic encephalomyelitis with encephalomyelitis after rabies vaccine or viral infections.

	Experimental allergic encephalomyelitis	Post-rabies-vaccine encephalomyelitis	Postinfectious encephalomyelitis
Inducing event	Inoculation with CNS tissue or myelin basic protein	Inoculation with CNS tissue	Infection with enveloped viruses
Latency	10–21 days	10–41 days	10–40 days[a]
Clinical features			
Acute onset	+	+	+
Monophasic	+	+	+
Occasional Chronic or relapsing	+	+	+
Pathologic findings			
Perivenular lympohocytic infiltrates	+	+	+
Perivenular demyelination	+	+	+
Immunologic studies			
Lymphocytes stimulated in vitro by myelin basic protein	+	+	+
In vitro demyelination by lymphocytes	+		+

[a] From beginning of incubation period
Source: Modified from ref. 20.

Wantanabe and co-workers [4] inoculated rats with this murine virus and described a subacute demyelinating encephalomyelitis that developed several weeks to two months later. Viral antigen was found primarily in glial cells in the neighborhood of demyelinating plaques. Most rats subsequently recovered despite the persistence of virus. Lymphocytes from sick rats were cultivated in vitro in the presence of myelin basic protein, and these lymphocytes were transferred passively to syngeneic rats. In four to five days, mild clinical disease was seen in many recipients, and the white matter lesions resembled experimental allergic encephalomyelitis. Thus, viral infection of the oligodendrocytes appears capable of inducing an autoimmune response against myelin proteins produced by the oligodendrocytes. This might occur by incorporation of the oligodendrocyte membranes into the virus envelope, by release of myelin from damaged cells, or by modification of myelin proteins.

Postmeasles Encephalomyelitis in Humans

Alternate mechanisms have been suggested in human studies of postmeasles encephalomyelitis. Measles is seldom isolated from the nervous system, and the cerebrospinal fluid shows no evidence of intrathecal immunoglobulin synthesis, as seen in most viral encephalitides associated with direct virus invasion of the nervous system [5]. Finally, immunocytochemical studies have failed to demonstrate viral antigen in the brains of patients with acute measles encephalomyelitis [10]. Measles virus infections are known for their striking immunosuppressive effects [11]. Thus, there is a paradox in that the secondary infections causing pneumonia and gastrointestinal disease are thought to be secondary to the immunosuppressive effect, whereas the encephalomyelitis is presumed to be a hypersensitivity response.

Studies of a number of immune parameters during measles and measles encephalomyelitis show a variety of abnormal immune responses with suppression of some responses on one hand and release of normal inhibition on the other (Table 24.2). Most patients with measles show prolonged suppression of lymphoproliferative responses to mitogens, which is similar in uncomplicated measles, measles pneumonia, and encephalomyelitis. Many patients who are exposed to measles nevertheless show normal lymphocyte responses to mitogens. Despite the normal ratio of lymphoctyes bearing T helper–inducer and T suppressor–cytotoxic surface markers, functional studies show an increase in spontaneous suppressor cell activity [12]. C-reactive proteins are elevated during acute measles and show an apparent secondary elevation during postmeasles encephalomyelitis [13]. In patients with measles, and particularly with encephalomyelitis, serum IgE is elevated; this immunoglobulin is normally down-regulated by suppressor cells [14]. Significantly, lymphocytes cultivated from patients with measles may show proliferative responses to normal human myelin basic protein, and this response is more frequent in lymphocytes from patients with encephalomyelitis [5]. A variety of abnormalities in immune regulation occur, rather than simply "immunosuppression."

Because there is no evidence that virus regularly invades the nervous system and because there is abnormal immune regulation, the hypothesis arises that a deregulation of autoreactive cells may occur secondary to viral infection of lymphoid cells.

Unanswered Issues

Attempts to devise an animal model for postinfectious encephalomyelitis to facilitate studies of pathogenesis have remained unsuccessful. Therefore, studies require human investigation.

Two interrelated questions remain unanswered: Why are only a small number of individuals affected, and why is the central nervous system the

Table 24.2. Immunologic studies in patients with acute measles and measles encephalomyelitis.

Findings in uncomplicated measles	Comparison of encephalomyelitis	Reference
Antibody responses to nucleoprotein, fusion, hemagglutinin proteins of virus in all patients; low responses in one-half of patients to matrix protein	same response	21
Prolonged suppression of lymphoproliferative responses to mitogens	same suppression of similar duration	12
Decreased T cells but no change in helper/suppressor ratios	ND[a]	12
Spontaneous suppressor activity in cultured lymphocytes	ND	12
Elevated serum C-reactive protein levels	apparent second elevation at onset	13
Elevated serum IgE levels	prolonged	14
Lymphoproliferative responses to myelin basic protein	more frequent (47%)	5

[a] ND: not done.

Source: Modified from ref. 1.

sole target organ? If the disease is mediated by viral invasion of the central nervous system, then the answer to both may be that virus infects the brain only infrequently and then triggers the disease. To date, in measles it has been difficult to find virus in the brain, but more sensitive techniques or examinations of tissue taken at earlier times in the disease may be necessary. If this disease is autoimmune, then genetic susceptibility of the host to autoimmune disease may be important. Multiple sclerosis, for instance, is associated with the presence of the DR2 or DW2 allotypes [15]. In a limited study, we found no evidence for an increase in these or other HLA types in postmeasles encephalitis. Such an association could be revealed with the study of larger numbers of patients or it may be that other unstudied background genes are important for susceptibility, as they are in determining the susceptibility of mice to experimental allergic encephalomyelitis [16] or demyelination following Theiler's virus infection ([17]; see also Lipton et al., Chapter 29, this volume). The central nervous system could be targeted because of antigenic similarities between myelin proteins and viral proteins. Sequence data suggest regions of homology between myelin basic protein and numerous polypeptides from viruses that are or are not associated with postinfectious encephalomyelitis, so the biological significance of this finding is not yet clear ([18,19]; see Oldstone and Notkins, Chapter 23, this volume). Because the CNS is relatively isolated, alterations in access to the systemic immune response may occur during infection. Virus may increase permeability by infecting vascular endothelium or the infectious process with attendant immune responses may indirectly damage the normal blood–brain barrier by release of lymphokines, vasoactive amines, or other factors affecting permeability.

Acknowledgement

These studies were supported in part by grants from the Rockefeller Foundation and NIH (PO1 N21916-01).

References

1. Johnson RT, Griffin DE, Gendelman HE (1985) Postinfectious encephalomyelitis. Semin Neurol 5:180–190
2. Miller HG, Stanton JB, Gibbons JL (1956) Parainfectious encephalomyelitis and related syndromes. Quart J Med 25:427–505
3. Perkus ME, Piccini A, Lipinskas BR, Paoletti E (1985) Recombinant vaccinia virus: Immunization against multiple pathogens. Science 229:981–984
4. Watanabe R, Wege H, ter Meulen V (1983) Adoptive transfer of EAE-like lesions from rats with coronavirus-induced demyelinating encephalomyelitis. Nature 305: 150–152

5. Johnson RT, Griffin DE, Hirsch RL, Wolinsky JS, Roedenbeck S, Lindo de Soriano I, Vaisberg A (1984) Measles encephalomyelitis: Clinical and immunological studies. New Engl J Med 310:137–141
6. Rivers TM, Schwentker FF (1935) Encephalomyelitis accompanied by myelin destruction experimentally produced in monkeys. J Exp Med 61:689–702
7. Hashim GA (1985) Neural antigens and the development of autoimmunity. J Immunol 135:838s–842s
8. Lisak RP, Zweiman B (1977) In vitro cell-mediated immunity of cerebrospinal fluid lymphocytes to myelin basic protein in primary demyelinating diseases. N Engl J Med 297:850–853
9. Weiner LP (1973) Pathogenesis of demyelination induced by mouse hepatitis virus (JHM virus) Arch Neurol 28:298–303
10. Gendelman HE, Wolinsky JS, Johnson RT, Pressman NJ, Pezeshkpour GH, Boisset GF (1984) Measles encephalomyelitis: Lack of evidence of viral invasion of the central nervous system and quantitative study on the nature of demyelination. Ann Neurol 15:353–360
11. Casali P, Rice GPA, Oldstone MBA (1984) Viruses disrupt functions of human lymphocytes: Effects of measles virus and influenza virus on lymphoctye-mediated killing and antibody production. J Exp Med 159:1322–1337
12. Hirsch RL, Griffin DE, Johnson RT, Cooper SJ, Lindo de Soriano I, Roedenbeck S, Vaisberg A (1984) Cellular immune responses during complicated and uncomplicated measles virus infections of man. Clin Immunol Immunopathol 31:1–12
13. Griffin DE, Hirsh RL, Johnson RT, Lindo de Soriano I, Roedenbeck S, Vaisburg A (1983) Changes in serum C-reactive protein during complicated and uncomplicated measles virus infections. Infect Immun 41:861–864
14. Griffin DE, Cooper SJ, Hirsch RL, Johnson RT, Lindo de Sorinao I, Roedenbeck S, Vaisberg A (1985) Changes in plasma IgE levels during complicated and uncomplicated measles virus infections. J Allergy Clin Immunol 76:206–213
15. Spielman RS, Nathanson N (1982) The genetics of susceptibility to multiple sclerosis. Epidemiol Rev 4:45–65
16. Linthicum DS, Frelinger JA (1982) Acute autoimmune encephalomyelitis in mice. II. Susceptibility is controlled by the combination of H2 and histamine sensitization genes. J Exp Med 155:31–39
17. Melvold RM, Knobler R, Lipton H (1986) Linkage between Theiler's virus demyelinating disease and T-cell receptor beta chain (constant region) gene. J Immunol (in press)
18. Fujinami RS, Oldstone MBA (1985) Amino acid homology and immune responses between the encephalitogenic site of myelin basic protein and virus: A mechanism for autoimmunity. Science 230:1043–1045
19. Jahnke U, Fischer EH, Alvord EC (1985) Sequence homology between certain viral proteins and proteins related to encephalomyelitis and neuritis. Science 229:282–284
20. Johnson RT (1982) Viral Infections of the Nervous System. Raven Press, New York
21. Graves M, Griffin DE, Johnson RT, Hirsch RL, Lindo de Soriano I, Roedenbeck S, Vaisberg A (1984) Development of antibody to measles virus polypeptides during complicated and uncomplicated measles virus infections. J Virol 49:409–412