The Virology of Demyelinating Diseases

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Infectious agents have been postulated as causes of multiple sclerosis for over a century. The possible role of a virus or viruses is supported by data that (1) a childhood exposure is involved and "viral" infections may precipitate exacerbations of disease, (2) experimental infections in animals and natural infections in humans can cause diseases with long incubation periods, remitting and relapsing courses, and demyelination, and (3) patients with multiple sclerosis have abnormal immune responses to viruses. The pathogenesis of three human demyelinating diseases of known viral etiology is discussed. In progressive multifocal leukoencephalopathy, a papovavirus selectively infects oligodendrocytes and causes focal areas of demyelination. In postmeasles encephalomyelitis, the virus is lymphotrophic and disrupts immune regulation that can result in an autoimmune perivenular demyelinating illness without evidence of infection of the central nervous system. In human immunodeficiency virus-encephalopathy and myelopathy virus is present in macrophages and microglia and the myelin abnormalities apparently are caused by soluble factors such as viral proteins, cytokines, or neurotoxins. These findings may have implications on how, when, and where to seek viruses in multiple sclerosis.

In 1868 Jean Martin Charcot described the clinical features of the first human demyelinating disease, multiple sclerosis, and postulated that the disease resulted from exposure to dampness or from injuries or emotional stress. Over the next two decades Koch and Pasteur blazed the new era of microbiology; therefore, it was a natural sign of the times that in 1884 Pierre Marie, one of Charcot's students and a successor to his chair in neurology at the University of Paris, postulated an infectious etiology for multiple sclerosis. Because a rabies vaccine had just been introduced by Pasteur, Marie believed a vaccine for multiple sclerosis would soon be produced [1].

Speculation of a viral etiology of multiple sclerosis has recurring throughout the past century. This speculation has been given credence by three areas of investigation. First, epidemiologic studies have indicated a childhood exposure factor (possibly an infectious agent) in the genesis of multiple sclerosis [2, 3] and also have suggested that infections may precipitate acute exacerbation in established disease [4, 5]. Second, studies in a wide variety of animal models (Table 1) and human diseases have shown that viruses can cause diseases with prolonged incubation periods, with remitting and relapsing courses, and with myelin destruction mediated by a variety of mechanisms. Third, studies of patients with multiple sclerosis consistently have shown higher levels of antibody against measles virus in serum and cerebrospinal fluid (CSF) than in controls and in some studies antibodies have been elevated to other viral agents as well (Table 2).

Subsequent to the description of multiple sclerosis three human demyelinating diseases have been defined in which viral causes are known. In each, the causative virus is from a different family and in each the pathogenesis of demyelination appears to be different.

**Progressive Multifocal Leukoencephalopathy**

Progressive multifocal leukoencephalopathy (PML) was originally described by Astrom and collaborators [21] in 1958 as a rare complication of leukemia and lymphoma. It was subsequently seen in a variety of immunodeficiency states caused by other diseases and medical therapy. Over the last decade, the disease has increased greatly in frequency as a complication of the acquired immunodeficiency syndrome (AIDS).

Clinically, against the background of immune deficiency, multifocal neurological signs develop and follow an ingarvescent course usually ending in death in less than 6 months. Very rare cases have stabilized or recovered [22, 23]. The CSF is usually normal. Neuropathology shows demyelinated foci, particularly in the subcortical white matter. Within these foci the oligodendrocytes are gone and astrocytes are enlarged, misshapen, and often multinucleated. Surrounding the foci many of the oligodendroglia are enlarged and contain intranuclear inclusions. The neurons and many of their axons coursing through the demyelinated areas appear normal.

Despite the paucity of inflammation, Richardson [24] postulated that this disease might be a viral infection of the brain in an immunocompromised host. In
Table 1. Animal Models of Acute and Chronic Viral Demyelinating Diseases

| Virus          | Description                                                                 |
|----------------|-----------------------------------------------------------------------------|
| Papovavirus    | SV 40 in macaque monkeys [6]                                                |
| Paramyxovirus  | Canine distemper virus [7]                                                  |
| Coronavirus     | JHM strain mouse hepatitis virus [8]                                        |
| Picornavirus   | Theiler’s virus in mice [9]                                                  |
| Togavirus      | Semliki Forest virus in mice [11]                                            |
| Rhabdovirus    | Chandipura                                                                  |
| Lentivirus     | Visna virus in sheep                                                        |
|                | Caprine arthritis-encephalitis virus [14]                                    |
| Ross virus     | Encephalomyocarditis virus in mice [10]                                      |
| SV 3 virus     | Ross River virus in mice [12]                                                |
| Semliki virus  | Encephalomyocarditis virus in mice [10]                                      |
| Forest virus   | Encephalomyocarditis virus in mice [10]                                      |

Table 2. Higher Anti-Viral Antibodies in Multiple Sclerosis Patients Than in Controls

| Serum                | CSF                        |
|----------------------|----------------------------|
| Measles              | Measles                    |
| Parainfluenza 3      | Parainfluenza 1, 2, 3      |
| Influenza C          | Influenza A, B             |
| Varicella            | Varicella                  |
| Herpes simplex       | Herpes simplex             |
| Rubella              | Rubella                    |
| Epstein-Barr         | Epstein-Barr               |
| Mumps                | Respiratory syncytial      |
| Coronaviruses        | Adenoviruses               |
| HTLV-I (gag)         | HTLV-I (gag)               |
| HTLV-II              | Simian virus 5             |

Data are from [15–20].

CSF = cerebrospinal fluid; HTLV = human T-cell lymphotropic virus.

1964 ZuRhein and Chou [25] examined inclusions ultrastructurally and found pseudocrystalline assays of virulike particles characteristic of papovaviruses, a seemingly bizarre observation considering that the only human papovaviruses known at that time was the virus of warts. Armed with the knowledge of the type of virus to seek, methods were developed and a previously unknown papovavirus called JC was found to be the etiologic agent [26–28]. This virus is ubiquitous, usually causes infection of the human populations during childhood, and is not associated with disease. The development of human fetal glial cultures was necessary to make its recovery possible.

The bizarre forms and mitoses in astrocytes are described in the original study as being “ordinarily met with only in neoplastic processes” [21]. Indeed, many of these astrocytes contain viral DNA and express tumor antigen (T antigen), while relatively smaller numbers express viral antigen or contain virions [29]. This suggests a semipermissive infection of astrocytes. In contrast the pathogenesis of demyelination in PML appears straightforward; selective productive and lytic infection of oligodendrocytes causes demyelination and neurons are not susceptible, hence there is preservation of the axons. This selective vulnerability of the cells maintaining the myelin provides a mechanism many of us naïvely thought might explain all human demyelinating diseases [30]. Other disease mechanisms have not proved as straightforward.

Postinfectious Encephalomyelitis

Postinfectious encephalomyelitis (aka acute disseminated encephalomyelitis, postexanthematous encephalomyelitis, and perivenular leukoencephalitis) is a perivenular demyelinating disease that occurs as an unusual complication of a variety of viral infections. It was most common following measles and vaccination with vaccinia virus [31, 32]. The clinical and pathological disease was defined in clinical–pathological reports in the 1920s and was differentiated from typical acute encephalomyelitis with cortial inflammation and neurophagia. This syndrome characteristically follows a febrile illness and is characterized by perivenular demyelination. Postmeasles encephalomyelitis, the commonest form that still occurs, will be discussed.

Postinfectious encephalomyelitis complicates clinical measles in approximately 1 per 1,000 cases. It is less frequent in children under 2 years of age. Following uncomplicated measles in otherwise healthy children, the disease typically comes on 4 to 5 days after the rash. The rash coincides with the onset of the immune response and the clearance of virus. After the rash abates and the child is returning to activities outside the house, there is a sudden recurrence of fever, decrease in consciousness, often seizures, and multifocal neurological signs. The disease has an abrupt onset, often reaching its nadir within the first 24 hours. Mortality is approximately 20%, and sequelae persist in the majority of survivors. The electroencephalogram is slow but nonspecific, and the CSF usually shows a mild elevation of protein and some mononuclear cells, but in about one-third of the patients the CSF is entirely normal. Neuropathologic examination shows diffuse perivenular infiltration of mononuclear cells with demyelination. Inflammation of the meninges is limited or absent. Histologically the lesions resemble those that were subsequently induced experimentally by injection of animals with myelin proteins with adjuvant, that is, experimental autoimmune encephalomyelitis. Indeed, the pattern of myelin loss in the lesions is the same as that seen in the experimental autoimmune disease [33].

Because the encephalomyelitis develops after the acute exanthem and because of the unusual pathological changes, it was postulated that this was not the
direct virus invasion of the nervous system but some toxic reaction. Subsequent to the discovery of experimental autoimmune encephalomyelitis in animals in the 1930s it has been assumed that this disease represented an autoimmune response induced by viral infection.

Historically, approximately one-third of the cases of encephalitis were thought to be of this form, but with the elimination of vaccination to prevent smallpox and the widespread use of measles vaccine, few cases are seen in North America. Cases continue in much of the world where measles continues partially or totally unabated. Indeed, measles remains one of the three major killing infectious diseases worldwide, causing about 1.5 million childhood deaths per year [34]. The majority of these deaths are not due to encephalomyelitis, however, but to opportunistic infections that complicate the decreased immune responses seen for several weeks following the measles rash. Thus, in contrast to PML, measles virus appears to induce the immune deficiency, and opportunistic infections lead to death. This immunodeficiency was first observed in 1908 by von Pirquet [35] who found that children converted their tuberculin reactions at the time of rash and over subsequent weeks. Indeed, this was the first documented virus-induced acquired immunodeficiency syndrome.

A paradox is evident. The majority of measles deaths are due to immunodeficiency and opportunistic infections, whereas 1 in 1,000 patients encephalomyelitis develops, which is thought to have an autoimmune mechanism. In studies of patients with uncomplicated measles, measles with pneumonia, and encephalomyelitis, the degree of nonresponsiveness of lymphocytes to mitogens is equal [36]. In all three groups similar leukopenia develops with maintenance of the normal T4/T8 ratios [37]. All lose their cutaneous tuberculin reactions; those with infectious complications remain negative for a longer period of time [38]. It is clear, however, that these findings do not represent simple immunosuppression. There is activation of lymphoid cells and spontaneous proliferation of lymphocytes (T4, T8, and B cells) (Table 3). Rather than immunosuppression, measles virus produces an activation of lymphocytes and macrophages stimulating immunoresponsive cells such as those responsive to myelin basic protein; proliferation of culture lymphocytes in the presence of myelin basic protein was found in 15% of the cases of measles without neurological findings and in 47% of those who developed encephalomyelitis [46].

Evidence suggests that measles virus may not directly invade the nervous system. Virus has only rarely been isolated from the central nervous system and our isolation attempts have failed. In studies of CSF we found no intrathecal synthesis of antibody in postmeasles encephalomyelitis to suggest antigenic stimulation within the nervous system [46], and interferon levels were not elevated in CSF as they are in the serum during the prodrome of measles or in CSF of herpes encephalitis [44, 47]. On the other hand, neopterin, a product released by activated macrophages is elevated in CSF of measles encephalomyelitis patients [48]. Immunocytochemistry and in situ hybridization for viral proteins and viral RNA, in brains of patients dying with encephalomyelitis, have been consistently negative [49]. In acute fatal measles, antigen can be demonstrated in macrophages, lymphoid organs, skin, systemic vascular endothelium, and epithelial cells of lung, gut, bile duct, and bladder, but no measles antigen was found in cerebrovascular endothelial cells or neural cells [49, 50]. Thus, this demyelinating disease does not appear to be caused by selective vulnerability of any cells of the nervous system but by infection of the lymphoid organs, leading to the activation of lymphocytes including, in some patients, lymphocytes that are reactive against myelin basic protein and possibly other myelin constituents. These activated cells may then selectively home to the central nervous system, causing an autoimmune encephalitis after the virus has been cleared from lymphoid organs.

**Table 3. Altered Lymphocyte Function with Measles Virus Infection**

| Normal responses | Depressed responses |
|------------------|---------------------|
| Antibody responses to NP, F, and HA proteins [39] | Tuberculin skin test [38] |
| Lymphoproliferative responses to mitogens [36] | Elevated plasma IgE levels [42] |
| Lymphopenia (with normal T4/T8 ratio) [37] | Elevated C-reactive proteins [43] |

Evidence of activation

- Spontaneous proliferation of T4, T8, and B lymphocytes [40, 41]
- Spontaneous suppressor cell activity [36]
- Elevated plasma IgE levels [42]
- Elevated C-reactive proteins [43]
- Increased lymphocyte activation markers (T10, II-2 receptor) [37]
- Elevated levels of soluble IL-2 and CD8 [40]
- Elevated plasma levels of interferon-γ and neopterin and CSF levels of neopterin but not interferon in encephalitis [44]
- Increased monocyte activation (increased II-1B) [45]
- Lymphoproliferative response to myelin basic protein (15% uncomplicated; 47% encephalomyelitis) [46]

**IL-2** = interleukin-2; **CSF** = cerebrospinal fluid.

**Human Immunodeficiency Virus Encephalopathy and Myelopathy**

The acquired immunodeficiency syndrome was identified in the summer of 1981 with the unusual appearance of Kaposi's sarcoma and pneumocystis pneumonia in otherwise healthy, gay young men [51, 52]. Initial neurological interest focused solely on opportunistic infections of the central nervous system, but in
1985 it became evident that there was direct infection of the nervous system that might lead to neurological diseases. In 1985, multiple laboratories isolated human immunodeficiency virus (HIV) from brain tissue, CSF, and peripheral nerve of patients with neurological disease [53, 54]. HIV DNA and RNA were localized in brain tissue [55], and intrathecal synthesis of antibody against HIV was documented [56]. A further important finding the same year was the establishment that HIV was a lentivirus, not an oncavirus as previously suspected, and therefore, belonged to a family of viruses all of which produce chronic encephalopathies [57].

Subsequently, a variety of diseases of the central and peripheral nervous system and muscle have been described as complications of HIV infection [58, 59]. These occur at varying times. An acute meningitis or an acute demyelinating polyneuropathy may occur at the time of seroconversion; HIV encephalopathy and myelopathy usually evolve years later with full-blown AIDS. These different syndromes show very varied pathological changes, and in all probability have different mechanisms of pathogenesis. In several syndromes, demyelination is a prominent feature both early in disease, when a neuropathy resembling Guillain-Barré syndrome is usually seen, and accompanying AIDS, when unusual myelin changes are seen in the encephalopathy and myelopathy.

AIDS dementia and myelopathy usually evolve insidiously after the patient has developed an AIDS-defining illness. Dementia is the AIDS-defining disease in about 3% of the patients, is evident in 15 to 20% of ambulatory AIDS patients [58], and may develop in more than 50% by the time of death [60]. AIDS dementia is a so-called subcortical dementia with apathy, memory loss, and withdrawal, and with few features of cortical dementia such as behavioral problems and disorders of language and perception.

Signs of a myelopathy are evident in approximately 20% of patients by the time of death. This often accompanies the encephalopathy but can occur independently. Patients develop weakness, spasticity of the legs, and prominent loss of posterior column function [61].

Three distinctive white matter lesions are found in patients with encephalopathy and myelopathy [62]. The pathological finding that correlates best with dementia is diffuse myelin pallor, which is characterized by hyperintensity of T2-weighted images in the deep white matter with magnetic resonance imaging and by reduced intensity of staining with Luxol fast blue. Immunocytochemical staining for myelin proteins does not show decrease staining intensities in areas of myelin pallor, and light and electron microscopic studies fail to show demyelinated axons or active demyelination [63]. These imaging and staining changes appear to be due to alterations in the blood-brain barrier. The second type of white matter lesions consists of small periventricular areas of demyelination that are found randomly through white matter; they bear a remarkable resemblance to the lesions described above in post-infectious encephalomyelitis. Whether these lesions evolve at the time of lymphocyte activation and autoimmune diseases early during HIV infections or whether they develop through some other mechanism is unknown, because there is no clinical correlate for these lesions. The third abnormality is vacuolar myelin damage found in hemispheric white matter, fiber tracts, and most strikingly in spinal cord primarily in the white matter tracts of the posterior and lateral columns. It is most prominent in the thoracic cord. The vacuoles may be very asymmetrical, few perivascular inflammatory cells or microglial nodules are found, and multinuclear cells are rare. Ultrastructurally, vacuolization represents intralaminar edema; the vacuoles are not intracytoplasmic. Macrophages are seen within these intralaminar gaps. Both demyelination and remyelination are found by electron microscopy [64].

The pathogenesis of these myelin changes associated with HIV infection are unknown. Virus is usually detectable by immunocytochemical staining for HIV antigens and consistently present by polymerase chain reactions in the brains of demented patients. Localization of virus is limited largely, if not exclusively, to cells of macrophage origin, i.e., microglia, macrophages, and perivascular macrophages. Limited defective infection of astrocytes may occur, but there is no convincing evidence of infection of neurons or oligodendrocytes despite the pathological changes in these cells or their membranes. The alterations in myelin membranes and neurons are thought to be mediated by secretory products of infected macrophages and microglia. Virus proteins, cytokines and neurotoxins have all been implicated either directly or via indirect effects on astrocytes or oligodendrocytes [65, 66].

In visna, another lentivirus infection, infected monocytes when they differentiate into tissue macrophages express surface viral proteins that, in turn, induce neighboring lymphocytes to release a lymphokine that induces class II antigen expression on endothelial and possibly glial cells [67]. Marked inflammation ensues. A similar cytokine-mediated disease has been postulated in HIV infection, and the correlation of tumor necrosis factor-α levels to the dementia and myelopathy [68, 69] would be consistent with such a speculation.

**Conclusion**

More than a century has past since Pierre Marie postulated an infectious agent in multiple sclerosis, and a number of virus isolations have been reported, but none have been convincingly linked to the disease (Table 4). Even those who hold to the idea of a viral etiology are undecided whether it may be many viruses
Table 4. Viruses Recovered from Multiple Sclerosis Patients

| Virus                               | Isolation Method                                      | Year |
|-------------------------------------|-------------------------------------------------------|------|
| Rabies virus                        | Encephalitis in mice inoculated with brain or blood    | 1946 [70] |
| Herpes simplex virus                | Cytopathic changes in cell culture inoculated with homogenate of brain | 1964 [71] |
| Scrapie agent                       | Scrapie developed in sheep 16–21 mo after inoculation with brain | 1965 [73] |
| Multiple sclerosis-associated agent | Decrease in polymorphonuclear cells in mice inoculated with MS tissue | 1972 [74] |
| Parainfluenza virus 1               | Cell cultures of brain tissue of 2 patients fused with other cells, and virus recovered | 1972 [75] |
| Measles virus                       | Cytopathic changes in monkey kidney cells inoculated with homogenate of brain biopsy | 1972 [76] |
| Simian virus 5                      | Syncytia formed in MRC5 cell cultures inoculated with patients' bone marrow cells | 1978 [77] |
| Chimpanzee cytomegalovirus          | Neonatal chimpanzee inoculated with brain cells of patient who developed paralysis 3 years later | 1979 [78] |
| Coronavirus                         | Fresh unfrozen brains inoculated into mice and grown in culture yielded virus | 1980 [79] |
| SMON-like virus                     | Cytopathic changes on MRC5 inoculated with CSF         | 1982 [80] |
| Tick-borne encephalitis flavivirus  | Blood from 2 patients inoculated i.c. into mice        | 1982 [81] |
| HTLV-1                              | RNA identified in T-cells of CSF                      | 1986 [82] |
| LM7 (retrovirus)                    | Found in leptomeningeal cell line from CSF             | 1989 [83] |
| HSV-1                               | Isolated from CSF during first attack                  | 1989 [84] |

*Modified from [85].

MS = multiple sclerosis; SMON = subacute myelooptic-neuropathy; CSF = cerebrospinal fluid; i.c. = intracerebrally; HTLV = human lymphotropic virus; HSV = herpes simplex virus.

or only one, whether a childhood viral infection is important for laying the ground work of the disease, the so-called common exposure factor, or whether one or many viruses may precipitate exacerbations.

What have we learned from other demyelinating diseases? We have learned that viruses can produce disease with long incubation periods, remitting and relapsing courses, and the loss of myelin with relative sparing of axons. In the case of progressive multifocal leukoencephalopathy, the most straightforward mechanism of demyelination proved operative, i.e., selective infection destroys oligodendrocytes. The identification of the infectious agent, however, required two steps. First, electron microscopic studies were necessary to know what kind of viruses to look for, and second, laboratory methods had to be developed to recover a new and previously unknown papovavirus. In postmeasles encephalomyelitis and in HIV infections, no infection of oligodendrocytes has been found to explain virus-induced demyelination. In postmeasles encephalomyelitis the etiologic agent has been identified only by the very characteristic manifestation of the systemic disease. At the time encephalitis develops, usually no intrathecal antibody synthesis is found and the virus is not recovered from the central nervous system. Indeed, our studies suggest that virus have never been in the central nervous system. In this disease an indirect mechanism may be operative, and if an analogous mechanism occurred in multiple sclerosis virus would need to be sought in lymphoid tissues prior to the clinical manifestations of the demyelinating disease.

Demyelination of the central nervous system in AIDS shows unique morphological changes in a new disease, due to a new virus. The virus is present in the central nervous system, but it is present in the "wrong" cells; a correlation between the amount of virus and the amount of disease is lacking, making it hard to fulfill even the most liberal modifications of Koch's postulates [86]. The obvious mediators of demyelination appear to be virally infected macrophages or microglia and current work focuses on the possible role of their soluble products in disruption of myelin sheaths.

In these studies the knowledge of what virus to look for, and when and where and how to search, is evident. That the virus has not been identified consistently in multiple sclerosis is certainly not evidence against the role of a virus. "Absence of evidence is not the same thing as evidence of absence" [87].

Supported by Po-1-NS 26643, from the National Institute of Neurological Diseases and Stroke, The National Institutes of Health.

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S60 Annals of Neurology Supplement to Volume 36, 1994