On the possible viral aetiology of multiple sclerosis

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Introduction

Multiple sclerosis (MS) is the most important of the human demyelinating diseases, and is the commonest cause of neurological disability in young adults in Northern temperate regions.¹ It is usually characterized by multiple plaques of CNS demyelination, leading to a clinical pattern of acute relapses with varying periods of remission so that the disease is disseminated in both space and time.¹ The presence of inflammatory histological changes in the MS lesions such as perivenular lymphocytic infiltration, and the raised cerebrospinal fluid (CSF) immunoglobulins in an oligoclonal pattern detected in most MS patients are very suggestive of an immune basis for the disease,²³ one that may possibly be related to some kind of viral infection.

A viral aetiology of MS has been considered plausible for many years, but it is only relatively recently that this question has become amenable to investigation using modern molecular biological technology. Interest in this subject has therefore increased considerably over the last decade. Prior to this, the ‘viral hypothesis’ was invoked on the basis of evidence obtained from diverse sources, including epidemiological studies, classical virology and animal models of virus-induced demyelination. It should be appreciated that MS is a heterogeneous disorder with a variety of clinical patterns in terms of presentation, course and prognosis, and there are probably benign cases which are identified by chance only at post-mortem. This variability might suggest that there may be several possible aetiologies and pathogenetic mechanisms, and, therefore, that a viral aetiology might be relevant to some but not all cases. Other aetiologies, such as autoimmunity to myelin components and/or genetic predisposing factors, have been the focus of intensive study¹ and could be of great importance in producing the disease quite independently of a possible virus infection. In this context, it is relevant to make a distinction between the concepts of aetiology and pathogenesis, in that a virus may, for example, be the initiating cause of a disease (and therefore the aetiological agent), but the pathogenic mechanism may be quite different and operate through immune-mediated pathways. This issue is addressed further below. Even if a virus is indeed shown to be important in disease production, and not merely an epiphenomenon or irrelevent associated finding, the question as to whether such a virus operates via a direct or indirect mechanism would still need to be resolved. Our aim in this overview is to summarize the main evidence that has given some credibility to a possible viral cause of MS. We shall survey evidence obtained from (a) epidemiological studies, (b) laboratory studies of MS patients' body fluids and CNS tissues, and (c) animal models of virus-induced demyelination.

Epidemiological studies: evidence for an environmental factor(s) in MS

Epidemiological data accrued over the last 40 years has provided compelling evidence for the role of an environmental factor or factors in the aetiology
of MS. This has been reviewed in detail elsewhere, but essentially the evidence has been obtained from studies of the distribution of MS in patient populations in different geographical areas, and studies of the effects of migration of different populations to and from areas associated with high or low prevalences of MS. Examples of the former include a latitudinal gradient with a very high prevalence of MS in Northern temperate climates compared with the very low prevalence of the disease in equatorial zones, and also the rare documentation of possible ‘epidemics’ of MS in specific regions, mainly in certain North Atlantic islands. Particularly well-known is the very high incidence in the Faroe islands shortly after the end of the Second World War. The much-quoted migration studies have shown that individuals migrating from a high to a low-risk area for developing MS, e.g. Northern Europe to Israel or Africa, before the age of 15 years, have a reduced risk of subsequently developing MS. Individuals so migrating after this age, however, retain the high risk of MS of their initial area. This strongly suggests that an environmental factor, perhaps exposure to a virus before puberty, in some way influences the development of the disease in adulthood. Conversely, a form of reverse phenomenon appears to occur, in that the children born of individuals who had migrated from low to high MS risk areas acquired a higher risk of subsequently developing MS compared with that associated with the original countries of their parents.

**Laboratory studies in MS patients**

**Serological studies in MS patients**

An obvious indirect way of providing evidence for a viral cause of a disease is to demonstrate significantly raised serum or CSF antibody titres to particular viruses in affected individuals, and to analyse the patterns of infections with common (especially childhood) viruses in these patients. There are, however, many potential problems in interpreting viral antibody titres, such as the occurrence of non-specific antibody responses due to polyclonal stimulation of the immune system with activation of memory B cells, antibody cross-reactivities, differences in assay techniques, and long-term persistence of raised antibody levels from a previous causally irrelevant infection. Numerous studies, however, have documented significantly raised serum antibody levels to measles virus in patients with MS, although the actual significance of these findings is still unclear. Insight into this question was provided by the study of Compston et al., who found that patients with MS had rubella and measles at a later age and reported mumps infection more frequently than controls. However, in view of the known association of MS with particular Major Histocompatibility Complex (MHC) haplotypes, e.g. HLA-DR2, the question arose as to whether such serological abnormalities are primarily a consequence of the DR type per se. Using the current HLA nomenclature the phenotypic association with MS is designated DRw15, DQw6). Therefore, DR2+ MS patients were compared with normal DR2+ controls, with the finding that the various serological abnormalities such as raised measles and rubella antibody titres detected in MS patients could not be explained by an effect of DR type alone. A subsequent analysis of this population revealed that there was a statistically significant association between the occurrence of MS and patients’ recall of glandular fever or infectious mononucleosis in individuals seropositive for Epstein-Barr virus (EBV) compared with seronegative controls. The association was strongest where the EBV infection had occurred at or before the age of 17 years. Taken together, these findings may be interpreted as suggesting that the aetiology of MS may be linked with a delayed infection with EBV. Further clarification of the significance of this interesting data is awaited and will require analysis of large groups of patients.

It should be mentioned that serum antibody levels to the Human Lymphotrophic Virus Type-1 (HTLV-1) were reported in one study to be significantly raised in different populations of MS patients compared with controls. However, these findings have not been confirmed by others, and the raised levels may reflect non-specific polyclonal activation of the immune system in the disease. Clearly, an association of MS with the retrovirus HTLV-1 would be of particular interest in view of the unequivocal association of this virus with tropical spastic paraparesis (TSP) which is an inflammatory demyelinating myelopathy endemic in Japan and the Caribbean. The question of retroviral involvement in MS is also addressed below.

**Viral isolation in MS tissues**

Isolation of infectious virus from, or demonstration of viral particles by electron microscopy in, CNS tissues obtained from MS patients would clearly provide strong evidence for the viral hypothesis. Although the history of MS research has been characterized by the apparent isolation of a variety of different viruses, none of these findings has subsequently been confirmed by other groups. Johnson has listed the following viruses in this category: rabies virus; herpes simplex virus (HSV); scrapie agent; parainfluenza virus 1; measles virus; ‘MS-associated agent’ (‘Carp agent’); ‘bone marrow’
agent; chimpanzee cytomegalovirus (CMV); and coronavirus. There are, moreover, intrinsic problems with the interpretation of such viral isolations, such as the possibility of accidental contamination of the tissues and/or instruments at the time of collection or isolation, coexisting virus infection irrelevant to MS, and difficulties and variables in the method of isolation itself.

A somewhat more convincing story has recently emerged from the laboratory of Perron and colleagues. This group was able to isolate a leptomeningeal cell line (LM7) from the CSF of a patient with clinically definite MS. LM7 was found to produce specific viral reverse transcriptase activity, and viral particles were detected by electron microscopy. Although this indicated the presence of a retrovirus in this patient, it was not HTLV-1, Human Immunodeficiency Virus Type-1 (HIV-1), or HIV-2 on the basis of serological studies. Also, the retrovirus was isolated from the sera of 54% of clinically definite MS patients, especially in those at the beginning of a relapse. LM7 retrovirus could also be transmitted \textit{in vitro} to a normal human leptomingeal cell culture, and specific antibody against this retrovirus could be detected in MS patients. Also, HSV immediate-early trans-activating proteins strongly enhanced the expression of the latent retrovirus present in LM7 cells, suggesting that perhaps HSV could act as a co-factor with a retrovirus in triggering MS. Although the significance of these intriguing findings is difficult to assess at present, further analysis of this interesting cell line, together with confirmatory data from more than one laboratory, is eagerly awaited.

**Detection of viral nucleic acids by molecular hybridization and PCR**

In recent years molecular techniques have been increasingly brought to bear on the question of viruses and MS. For example, a careful study from Belfast used ISH to detect measles N genomic sequences in the brains of 2/8 cases of MS, and in 1/56 controls. This is clearly of some interest in view of the established measles serological abnormalities in MS already mentioned, but the true significance, if any, of this observation remains unclear. Although one study reported the use of ISH to demonstrate HTLV-1 RNA in cultures derived from the CSF of four MS patients, these results have not been confirmed by others. Interest in the possible role of a retrovirus was again generated three years later, when some members of the same group and others reported the use of PCR to detect HTLV-1 DNA sequences in the peripheral blood mononuclear cells in a high percentage of MS cases. The amplified sequences appeared to be related to the HTLV-1 proviral genome. However, subsequent studies (e.g. those described in references 23,24) failed to confirm such findings. Whether the positive results were due to contamination during the PCR procedure or some other cause is unknown. PCR was also used recently to search for HSV DNA sequences in formalin-fixed brain tissues obtained from MS patients, but these results were also negative.

**Possible mechanisms of virus-induced demyelination**

In general terms, a virus could be involved in the aetiology of MS in at least three different ways: (i) It could produce a single initial infection following which it is cleared from the CNS, but thereby initiates a series of chronic inflammatory changes, probably immune-mediated; (ii) a virus could cause recurrent infections resulting in frequent attacks of MS: or different viruses might cause the same CNS damage via similar mechanisms; and (iii) MS attacks could result from reactivation of a virus which is latent or persistent within the CNS, e.g. a retrovirus, measles or HSV. More than one of these mechanisms might be used by a particular virus, but in each case it is highly likely that the virus interacts in some manner with the immune system in finally producing neurological disease.

Although a wide range of viruses are capable of producing demyelination \textit{in vitro} and/or \textit{in vivo} (reviewed in reference 15), it seems reasonable to assume that in MS a virus which is known to infect humans may be involved in such a process. Direct infection of oligodendrocytes (which make CNS myelin) is produced by JC virus in progressive multifocal leukoencephalopathy (PML), a human demyelinating disease. However, there is as yet no convincing evidence of such a direct mechanisms leading to oligodendrocyte dysfunction in MS.

In view of the indirect evidence for viral involvement already mentioned, and the documented abnormalities of humoral and cell-mediated immunity in MS patients, which will not be considered here (see reference 27), the concept of virus-induced immune-mediated demyelination in MS is very plausible. Johnson has reviewed in detail the various possible mechanisms of such a process. These include sensitization of the host to myelin antigens such as MBP by, for example, incorporation of myelin antigens into the virus envelope, or actual modification of the antigenic structure of myelin membranes by the virus. Further, in the case of infection of oligodendrocytes by an enveloped virus which contains host cell glycolipids, it is conceivable that self-reactive antibodies directed against host cell glycolipids may be induced.
In this context, it is relevant to mention important work on T-cell responses to measles virus in MS patients, which also suggest a possible role for measles virus in the disease. Jacobson et al. showed that there exists a measles-specific cellular immune abnormality associated with MS, in that most MS patients failed to generate measles-specific cytotoxic T cells (CTL) or had significantly lower CTL responses than normal controls or patients with other diseases. The actual significance of these findings in relation to the pathogenesis of MS is still unclear, but they indicate that if measles virus infection is indeed involved at some stage of the disease, then an ongoing immune dysfunction, presumably related to the initial viral infection, is maintained long term.

The concept of virus-induced autoimmunity due to cross-reacting viral and myelin antigens is attractive. As Hughes has pointed out, virus infections can induce MS relapses, and also increase the number of circulating activated T cells which cross the blood-brain barrier into the CNS. Conceivably, a virus such as measles, acquired in childhood, may predispose susceptible individuals to react abnormally to subsequent intercurrent infections, with the result that, for example, autoimmune T-cell responses are generated against epitopes shared between myelin antigens and a particular virus. Although the antigenic specificity, if it exists, of such an abnormal response is not known at present, the MHC specificity known to occur in MS may become significant in that the viral/myelin epitope(s) may be presented successfully by CNS macrophages or microglia to T helper cells in association with the appropriate MHC molecules. There is also some evidence for specificity of the T-cell receptor (TCR) in MS patients with restricted use of the TCR repertoire in patients' peripheral T cells and also within brain lesions. Thus all three components of the trimolecular complex may interact, resulting in activation of T helper cells, the latter then leading to cytokine release with the generation of an inflammatory reaction and demyelination. It should be emphasized, however, that the generation of such autoimmune T-cell responses in MS patients does not necessarily have to follow exposure to a viral autoantigen, although clearly the latter would be a plausible candidate.

In view of the ability of retroviruses to produce chronic neurological disease in man and animals (see below), the findings of Perron et al., and the other indirect evidence for viral involvement in MS, the question arises as to how infection with a retrovirus might lead to the development of the disease. Certainly immune mechanisms are very likely to be involved, but precisely how they might interact with viral factors is unclear. Rudge has postulated an ingenious possible mechanism, namely that a retrovirus is involved in the pathogenesis of MS, but acts through its ability to encode a superantigen. The essence of his argument is that such a superantigen is a retrovirally-encoded Vb selective element which non-specifically stimulates T-cell clones. Among the many antigens against which the T-cell clones might be directed are myelin antigens such as myelin basic protein (MBP) which is able to induce encephalitis. The attachment of the superantigen to the beta chain of the TCR is largely independent of MHC control, and this reaction is conceptualized as triggering the cascade of immune responses that lead to demyelination. This hypothesis could explain many of the features of MS, and is well worth investigating, but its plausibility will rely heavily on the unequivocal confirmation by more than one group of the presence of a consistently identifiable retrovirus in MS cases, even if indirect methods have to be used.

Animal models of virus-induced demyelination

Although by their very nature animal models of virus-induced demyelination only produce a form of indirect evidence for the viral aetiology of MS, nevertheless they can reveal important insights into the possible mechanisms by which a virus can initiate a pathogenetic cascade leading to CNS myelin destruction. Such mechanisms are to be distinguished from those operating in the very useful model experimental allergic encephalomyelitis (EAE), the chronic relapsing form of which displays many similarities to MS itself.

Two models which have been particularly useful and interesting in this context are visna-maedi of sheep and Theiler's murine encephalomyelitis virus (TMEV). The visna-maedi disease complex is the prototype 'slow virus' disease, described by Sigurdsson in the 1950s. The visna retrovirus (a lentivirus) produces a chronic progressive illness with persistent inflammation characterized by arthritis, pneumonitis and encephalitis. The CNS lesions are usually found in periventricular locations where perivascular cuffing with lymphocytes and macrophages is abundant, and are often associated with demyelination, especially in Icelandic sheep. In British sheep, repeated episodes of focal encephalitis occur with resultant gliosis and scar formation, where as the brain disease in Icelandic sheep is more rapidly progressive. The pathogenetic events leading to lymphoproliferation and tissue destruction have now been elucidated, and are probably initiated by the production of an unique lentivirus-induced interferon which increases Class II antigen expression within the inflammatory lesions while restricting viral
replication, the latter possibly accounting for the slow pace of the disease. In the brains, only a small percentage of the oligodendrocytes are infected with the virus, so the main mechanism of demyelination is almost certainly indirect, presumably via the generation of Class II antigen-induced T cell responses and release of cytokines and/or toxic viral proteins. The insights gained from studies of TMEV have been somewhat different from, although no less useful than, those of visna. TMEV is a single-stranded RNA murine picornovirus. In the early phase of the disease, it infects grey matter neurons, and may produce an acute poliomyelitis in affected mice. After a few weeks, it infects oligodendrocytes in spinal cord white matter, producing chronic inflammation and primary demyelination. A variety of determinants of disease production and demyelination have now been investigated. For example, Brahic and his colleagues have demonstrated the existence of MHC Class I restricted cytolytic T lymphocytes in certain groups of susceptible mice, and that in conjunction with antibodies they are determinants of resistance to infection but not demyelination. This group has also used a variety of mouse techniques to establish the genetic determinants of susceptibility to the disease. Myelin gene expression in mice infected with TMEV can also be investigated in this model system.

**Conclusion**

From this brief survey, it is clear that there is no hard evidence for direct involvement of a virus in the aetiology of MS. There is, however, serological and immunological data to implicate some kind of indirect viral involvement, possibly as a triggering event leading to an abnormal delayed immune response to a common viral infection, such as measles or EBV, acquired in childhood or adolescence. In some way, particular MHC genes may exert an influence on the immune response to a virus or to an epitope shared between a virus and a myelin antigen such as MBP. The identity of such a putative virus is unknown, but a retrovirus or a paramyxovirus are as likely candidates as any other. Yet even if a virus were to be regularly identifiable in the tissues of most MS patients, the questions of its actual pathogenetic significance and the mechanisms of demyelination would still have to be resolved. There certainly exist good animal models of virus-induced demyelination, but the relevance of these to the pathogenesis of MS remains to be determined. We are sceptical of the viral hypothesis of MS, but recognise that failure to demonstrate a virus in the disease does not mean that it is not actually present, i.e. 'absence of evidence is not evidence of absence.  

**Acknowledgements**

We thank Professor D.A.S. Compston for advice, and Dr Henry McFarland for helpful review of the manuscript. This paper was written while P.G.E. Kennedy was a Scholar-in-Residence at the Fogarty International Center for Advanced Study in the Health Sciences, National Institutes of Health, Bethesda, Maryland, USA.

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