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ANNOTATION

DO HUMAN T-LYMPHOTROPHIC VIRUSES (HTLVs) AND OTHER ENVELOPED VIRUSES INDUCE AUTOIMMUNITY IN MULTIPLE SCLEROSIS?

A. G. DALGLEISH*, J. K. FAZAKERLEY† AND H. E. WEBB†

**CRC, Northwick Park Hospital, Harrow, HA1 3UJ; †Rayne Institute, St Thomas' Hospital London SE1 7EH, UK*

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Do human T-lymphotrophic viruses (HTLV's) and other enveloped viruses induce autoimmunity in multiple sclerosis?

A virally induced autoimmune reaction may be important in the pathogenesis of multiple sclerosis. The role that glycolipids and myelin basic protein presented to the virus may play in this process is considered. The most likely cells to be the source of autoantigens are neurons, myelin and oligodendrocytes. Viral infection of class II-expressing cells and association of the viral envelope autoantigens and the class II molecules could trigger an autoimmune reaction. It is suggested that for MS to develop following a virus infection the virus will need to cause expression of class II antigens on brain cells as well as fulfill the same role as an antigen presenting cell. The part which T-lymphotrophic viruses (HTLVs) and other enveloped viruses may play in this phenomenon is discussed.

Introduction

The recent paper from Koprowski and Gallo's laboratories (Koprowski *et al.* 1985) linking the human T-cell leukaemia–lymphoma virus (HTLV-I) with multiple sclerosis (MS) is yet another reminder that we know very little about the cause or causes of MS and that this is but one of the numerous viruses that have been linked, either epidemiologically, serologically or by isolation to this disease. Indeed, there are those who do not see a causal role for viruses at all, and regard MS as being an autoimmune disease, with antibodies and sensitized T-cells raised against a component of the myelin

sheath, for example, myelin basic protein (MBP) or a component of its supporting cells, the oligodendrocytes (Waksman, 1985).

If a viral cause for MS is to be entertained then one might expect clear epidemiological evidence of an infective agent. However, a low association between infection and clinical manifestation of neurological disease is common after virus infections, for example, subacute sclerosing panencephalitis (SSPE) and measles or rubella, and encephalitis following infection with mumps or other common viruses such as, varicella, herpes, or EB virus. Furthermore, other well recognized causal agents induce disease in only a small percentage of cases, e.g. Coxackie B3 and polymyositis, Epstein-Barr virus and Burkitt's lymphoma. Of the large number of insect-borne encephalitides, only a small percentage of those infected get any symptoms of neurological involvement, although headache and abnormal CSFs without clinical neurological signs is likely to be more frequent (Varma & Webb, 1985).

If a virus has a role in MS, then even allowing for low infectivity and possible low clinical expression, one would expect to see some supporting epidemiological data. There are two main pieces of evidence. Firstly the well known association with latitude. Not only do people living between latitudes 45° and 65° develop MS more frequently than people in more tropical climes but this risk appears to be acquired before the age of 15 years. People who emigrate from a low to a high risk area or *vice versa* after the age of 15 years take with them the risk of developing MS associated with the country where they spent their childhood (Kurtzke, 1980; Dean & Kurtzke, 1971; Alter, Kahana & Loewenson, 1978). This data suggests that the disease develops a long time after the 'risk' is acquired. The mean age of infection has been given as 10 years and that of disease onset as 30 years (Kurtzke, 1980; Alter *et al.*, 1978). Secondly, outbreaks or clusters of MS have been reported. The most famous of these occurred in the Faroe Islands (Kurtzke & Hyllested, 1979), no cases of the disease were recorded there before 1939. Between 1943 and 1960, 24 cases were reported amongst the native Faroese. The Islands were occupied by British troops between 1940 and 1945 and it can be argued that they introduced the putative MS agent into a susceptible community, i.e. a point source epidemic. A similar but less dramatic increase in MS in Iceland has been reported (Kurtzke, Gudmundsson & Bergmann, 1980).

More recently an unusual prevalence of MS has been recognized in a previous low risk area in Key West Florida (Sheremata *et al.*, 1985). Key West is a small island with a population of 26 000, 4000 of whom are native born. Although MS was first recognized 58 years ago it was only in 1981 that a real increase in incidence was noted. Of 37 patients with MS, 34 began their illness whilst living in Key West and therefore did not migrate to the island because of their illness. Further epidemiological evidence suggests a susceptibility in whites from upper socio-economic groups (a characteristic shown with Hodgkin's disease and paralytic poliomyelitis) as well as an association with dairy farming (Acheson, 1977; Agranoff & Goldberg, 1974; Kaplan, 1980). Moreover, an increase in MS in countries that are familiar with the disease and without a large shifting population such as described in Norway (Larsen *et al.*, 1984) and Sweden (Kinnunen, 1984) and also noted in Britain and some parts of Australasia, may also suggest the presence of a causative agent in these communities.

Several well described and studied animal models of MS associated with viruses exist. Neurological diseases pro-

duced by viruses in animals include meningitis, encephalitis, spongiform encephalopathies and peripheral neuropathy. Some of these are associated with lesions of demyelination. Animal models of virally induced neurological disease such as Theiler's virus (Lipton, 1975), Semliki Forest Virus (SFV) (Webb *et al.*, 1979), mouse hepatitis virus (MHV) (Beushawson & Dales, 1985) and lactic dehydrogenase virus (LDV) of mice (Pease & Murphy, 1980) demonstrate markedly different pathologies.

Each of the above models results in CNS inflammation and demyelination and each of these models has various other different features in addition to demyelination which resemble those of MS. In all cases the strain of virus, and the status of the mice used (age, strain) are important. In addition to a role for an infectious agent in MS there seems to be a genetically determined susceptibility to the disease. For example, encephalitis and demyelination following infection of mice with MHV has been shown to be dependent upon the genetic type of the mouse (Stohlman & Frelinger, 1978). The strain specificity for LDV has been shown to correlate with the presence of endogenous retroviruses (Pease & Murphy, 1980). If MS is considered to have an immunopathology in which demyelination results directly from the immune response, then this is paralleled by both Theiler's (Lipton & Dal Canto, 1975) virus and SFV (Fazakerley, Amor & Webb, 1983). Certain strains of MHV destroy oligodendrocytes directly leading to demyelination (Weiner, 1973) and a similar direct viral destruction of these myelin supporting cells cannot yet be ruled out in MS. Lymphocyte reactivity to MBP has been demonstrated in both MS patients and rats infected with mouse hepatitis virus (Sheremata, Cosgrove & Eylar, 1975; Watanabe, Wege & ter Meulen, 1983). Antibodies and T-cell reactivity to glycolipids have been demonstrated in MS patients (Arnon *et al.*, 1980; Offner, Konat & Sela, 1981) and polyclonal antiglycolipid sera and monoclonal antibodies raised to a glycolipid component of myelin have been shown to cross-react with Semliki Forest virus (Khalili-Shirazi, Gregson & Webb, 1986) as have anti-galactocerebroside, glucocerebroside and ganglioside sera (Webb *et al.*, 1984). By immunoelectronmicroscopy using protein A gold these same sera also labelled virus budding from CNS cell membranes (Evans & Webb, 1986). Given the epidemiological evidence, any virus involved in MS would be likely to be able to persist for long periods in nervous tissue, and each of the above experimental virus infections have also been shown to persist in the brain for long periods (Verelizier, Verelizier & Allison, 1975; Brahic & Stroop, 1981; Atkinson *et al.*, 1986; Rowson & Mahy, 1975). The clinical course of MS is often one of relapse and remittance and this can also be produced in mice infected with Theiler's virus (Lipton & Dal Canto, 1979).

Whereas the collective mouse models provide many tantalizing clues as to the possible nature of a human MS agent, it is the lentiviruses such as the visna/maedi viruses of sheep and goats which may be the closest model yet for human MS. Lentiviruses are non-transforming retroviruses which produce demyelinating diseases in sheep and goats. The incubation time is very long, hence lenti (slow) -viruses, and the persistence of the virus in the host is thought to be due to its ability to infect and 'lie low' in macrophages (Peluso *et al.*, 1985). These viruses are of particular interest as they have been shown to be similar to HTLV-III/LAV (HIV), the causal agent of the acquired immune deficiency syndrome (AIDS) in both structure and function (Soningo *et al.*, 1985). The recent recognition that HTLV-III is clinically neurotropic and

that many cells in the brain have been shown by in-situ hybridization to harbour the virus (Shaw *et al.*, 1985) makes the possibility that a similar agent could be involved in MS attractive.

There are already links between malignancy (particularly leukaemia) and neurological disease. Visna virus causes lung tumours (maedi) in some sheep and a demyelinating encephalomyelitis (visna) in others, or sometimes both together. Another retrovirus, the feline leukaemia virus (FeLV) causes leukaemia/sarcoma in some cats, and acquired immunodeficiency in others and neurological involvement has been reported in others, although the causal relationship to neurological disease has not in this case been indisputably proved (Hardy *et al.*, 1985). Infection of mice with LDV and endogenous C-type viruses is associated with the development of leukaemia (Pease & Murphy, 1980). The viral association between leukaemic and neurological disease is not confined to the retroviruses. Epstein-Barr virus can produce encephalitis, or peripheral neuritis in some, lymphoma in others (Grose *et al.*, 1975). In Marek's disease of birds, another herpes virus, produces both neuritis and lymphoma (Payne, Frazier & Powel, 1976). Progressive multifocal leucoencephalopathy (PML) is associated most commonly with lymphoma, but also with other carcinomas (Johnson, 1982) and the virus producing PML (JC virus) produces gliomas in young Syrian hamsters (Walker *et al.*, 1973). Hodgkin's lymphoma and MS in the same patient are not commonly recognized, however, both have a socio-economic association with higher social class, and family clusters of MS and HD have been recognized to occur in different generations (Cartwright, Leeds Lymphoma Registry, personal communication). HTLV-I is accepted as the causal agent of adult T-cell leukaemia-lymphoma (ATLL) which is endemic in Japan and the Caribbean and which is being increasingly recognized in the United Kingdom (Greaves *et al.*, 1984). Although causal, only about 1% of infected persons develop disease and this may take 10–30 years to manifest. HTLV-I has already been associated with neurological disease. Tropical spastic paresis and tropical axial neuropathy have both been reported as having a strong association with HTLV-I in the absence of HTLV-I leukaemic disease (Gessain *et al.*, 1985). Furthermore, HTLV-I associated myelopathy found in areas of Japan where HTLV-I leukaemias are prevalent, is a disease clinically distinguishable from MS only by its non-remitting nature (Osame *et al.*, 1986). There is, therefore, considerable evidence to suggest that the same agent can cause leukaemic syndromes in some people and neurological disease in others.

Patients with MS have activated T-cells in both the CSF and peripheral blood (Bellamy *et al.*, 1985; Hafler *et al.*, 1985). Activation is usually recognized by an increased expression of the 'Tac' or interleukin-2 (IL-2) receptor and increased expression of major histocompatibility (MHC) class II human leukocyte antigen (HLA). It is interesting to note that HTLV-I also 'activates' T-cells, and that recently it has been shown that HTLV-I can turn on not only the IL-2 gene but also the gene for its receptor (Greene *et al.*, 1986). More recently Greene and his colleagues have demonstrated that HTLV-I can transactivate or 'turn on' class II major histocompatibility antigens (MHC or Ia), (Greene, personal communication). Furthermore, lentiviruses e.g. Visna, are very similar to HIV, also infect cells of the monocyte–macrophage lineage persistently, and induce expression of class II antigens, although this is probably due to virus induced interferon (Kennedy *et al.*, 1986). The propensity of MS CSF cultures to grow

immortal T-cell lines has been observed independently by both ourselves and other workers. Recently one of us (AGD) has observed an immortal T-cell line, with no similarity to any cell line carried in the laboratory at the time, from a case of MS, which persistently produced low levels of reverse transcriptase which is the hallmark of retroviral replication and a further 'primary' culture produced continuous reverse transcriptase levels for at least 4 weeks. However, no virus was seen on electron microscopy. Moreover, many other viruses have also been associated with MS. High antibody titres against the measles virus were reported from many laboratories in the 1960s and subsequent reports have described high titres of antibody both in the serum and the CSF to a wide variety of other viruses, which include many common viruses such as rubella, mumps, influenza, parainfluenza, herpes, varicella and Epstein-Barr (ter Meulen & Stephenson, 1983).

How may these observations be reconciled?

If demyelination in MS results eventually from a virally induced response by the immune system, then is this an immune response to viral antigens on the surface of the myelin or supporting glial cells, or has an autoimmune response been generated? One possibility is that viruses induce an autoimmune reaction to myelin basic protein (MBP) by structural homology with this protein. Three independent computer searches (Jahnke *et al.*, 1985; Fujinami & Oldstone, 1985; Waksman, 1985) have indicated the possible chemical basis for such a cross sensitization by demonstrating the presence of homologous peptide sequences in encephalitogenic regions of MBP and in antigens of measles, influenza Epstein-Barr virus and several papova and adenoviruses. Viruses such as measles, rubella and varicella have been shown to sensitize T-lymphocytes to MBP in cases of post infectious encephalomyelitis. In a study of such encephalomyelitis associated with rubella, multiple T-cell clones obtained from the CSF showed equal reactivity to the virus and MBP (Zamvil *et al.*, 1985).

Is this then the answer to MS: molecular cross-reactivity between viruses and MBP which generates an autoimmune response to MBP. Unfortunately it seems not to be so simple. Firstly, many tests demonstrate no reactivity of MS patients to MBP, and in those tests that do demonstrate some activity not all the patients are positive, and reactivity is not specific to this disease, being found in addition in other non-demyelination neurological diseases (Leibowitz, 1983). Secondly, immune reactivity to MBP has been investigated extensively in several species in the most studied non-viral model of MS experimental allergic encephalitis (EAE), but with few exceptions encephalitis induced by MBP produces no demyelination. Demyelination in EAE results only from immunization with whole white matter, whole myelin, oligodendrocytes or various glycolipids and appears to be a function of an immune response to the latter (Paterson, 1977; Raine *et al.*, 1977; Konat *et al.*, 1982). Antibodies to glycolipids demyelinate cerebellar tissue cultures, those to MBP do not (Saida *et al.*, 1977). Anti-glycolipid antibodies (Arnon *et al.*, 1980) and T-cell reactivity (Offner *et al.*, 1981) have been demonstrated in MS patients, and the latter are more specific to this disease than is reactivity to MBP. Furthermore, ganglioside specific T-cell lines have been isolated from the CSF of MS patients (Belamy, Davison & Feldman, 1986). It seems that immune sensitivity to glycolipids may be more important in MS than reactivity to MBP (Ilyas & Davison, 1983).

Webb & Fazakerley (1984) and Fazakerley & Webb (1986) gave their reasons for hypothesizing that viral envelope glycolipids might produce autoimmunity, with reference to the CNS and MS.

Whatever the antigens involved in MS, they must be 'presented' to T-lymphocytes in conjunction with the class II MHC antigens (Ia). Class II antigens have now been found on endothelial cells, astrocytes and macrophages within and surrounding MS lesions (Suzumura *et al.*, 1986) and furthermore, brain vascular endothelial cells can be stimulated *in vitro* by activated T-cell supernatants or purified interferon to express Ia, and to present antigens such as MBP to T-cells (Massa, Dornes & ter Meulen, 1986).

Nearly all the viruses described in animal models of MS and all the viruses implicated in the human disease are enveloped viruses. Enveloped viruses incorporate components of the membrane of their host cell into the viral envelope when they bud. The host cell components could include proteins such as MBP, and glycolipids such as galactocerebrosides. In the case of proteins, feline leukaemia virus (FELV) is an enveloped retrovirus which incorporates class II MHC antigens in its envelope, dependent on the density of expression of the MHC antigens on the virus producer cell lines (Azocar, Essex & Yunis, 1983). Similarly we have recently shown that HTLV-I, HIV and vesicular stomatitis virus all incorporate class II MHC antigens into their envelopes when grown in cells expressing this antigen (Clapham, Dalgleish, Weiss, in preparation). In the case of glycolipids, all budding enveloped viruses incorporate host cell glycolipids into the viral envelope.

Hypothesis

A virally induced autoimmune reaction seems to be the most likely explanation for MS, but induced by which virus? We have previously proposed (Webb & Fazakerley, 1984) that the disease could be initiated by one or more of several enveloped viruses (measles, mumps, parainfluenza etc.) budding through CNS cells and incorporating the same host cell glycolipid autoantigen into these viral envelopes. In the case of larger budding viruses incorporation of host cell proteins such as MBP is, as discussed above, also possible.

Viral infection of class II expressing cells and association of the viral envelope autoantigens and the class II molecules, could trigger an autoimmune reaction. The most likely autoantigens are those on the neurons, the myelin and its supporting oligodendrocytes. Infection of these cells with viruses capable of transactivating class II antigen expression such as HTLV-I and II (and possibly others), or with viruses capable of inducing class II antigens by the induction of interferon such as visna, could allow an enveloped virus to pick up both neuronal and class II antigens which might mimic an antigen presenting cell, so that host antigens are presented as 'foreign', in association with class II antigens. Such an event may well depend upon the spatial association of the antigens on the surface of the viral envelope. Furthermore, the type of class II antigen may also be important. Class II molecules, however, have not been found on the surface of neurons, myelin or oligodendrocytes. In the CNS only astrocytes and endothelial cells (Fontana & Fierz, 1986) have been demonstrated to be class II inducible cells. There thus seems to be a discontinuity between those cells that are likely to express autoantigens and those that are capable of inducing a demyelinating autoimmune reaction. Whereas it is possible that an enveloped virus could 'pick up' a class II antigen

from one cell and then infect a neural cell and 'pick up' a neural antigen as well, this is unlikely as 'collected' antigens are probably shed and may not survive a further cycle of infection. However, a virus may translocate host proteins from one cell to another upon fusion with the cell membrane. The expression of class II antigens on brain cells, particularly astrocytes, oligodendrocytes and myelin, may allow an enveloped virus to mimic an antigen presenting cell.

It is of interest that the HTLVs appear to be in a relatively unique position to fulfil both steps, i.e. transactivate class II antigens and pick up class II antigens in their envelopes (Clapham *et al.*, in preparation).

It is possible that other common enveloped viruses may in time be shown to have similar capabilities. However, in some instances one virus may induce class II antigen expression and another virus fulfil the role of an antigen presenting cell.

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