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Guest Editorial

Association of human herpesvirus-6 and multiple sclerosis: here we go again?

For over 50 years, viruses have been implicated in the eitology of multiple sclerosis (MS) (Johnson, 1994). This is based on a number of epidemiological, genetic and virological studies. The epidemiology of MS supports a geographic association with evidence of MS clustering (Martin and Gale, 1997). There is an increased incidence of MS in temperate climates (less in the tropics) and migration to and from high prevalence areas of the disease influences the likelihood of developing MS. An increased risk of MS has also been suggested in children exposed to infectious agents while in adults, MS disease exacerbations increase with viral infection (Johnson, 1994). A variety of animal models have been developed in which viruses can cause diseases with long incubation periods, a relapsing remitting course, and demyelination (Johnson, 1994; Dalgleish, 1997).

Importantly, many of these viral-associated models have been demonstrated to be immune mediated. In MS patients, similar immune abnormalities have been reported to a number of viruses. Many of these studies involve the demonstration of increased antibody titers to a particular virus while in some studies virus was isolated from MS CNS material. A partial list of the many viruses that have been associated with MS is shown in Table 1. However, no virus to date has been definitively associated with this disease. This serves as an important reminder that issues of MS pathogenesis are complex and multifactorial. Genetic influences as well as environmental factors are associated with this disorder. Which (if any) of these environmental agents plays a role in the MS disease process remains to be determined. This editorial will discuss aspects of human herpesvirus 6 (HHV-6) which has gained renewed attention as a possible factor in patients with chronic, progressive neurologic disease (Challoner *et al*, 1995; Soldan *et al*, 1997; Ablashi *et al*, 1998) highlighted by three papers that appear in this months issue of *NeuroVirology* (Albright *et al*, 1998; Kimberlin and Whitley, 1998; McCarthy *et al*, 1998).

Kimberlin and Whitley (1998) have written a detailed and comprehensive review on HHV-6 and its association with neurologic disease. They succinctly discuss the virology, epidemiology, and biologic properties of the virus. While HHV-6 has been shown to be clinically associated in a variety of neurologic disorders, the authors appropriately emphasize that many of these studies were based on small case reports and retrospective studies. In particular, the role of HHV-6 in the pathogenesis of MS is discussed. As outlined above, is this yet one more virus on a long list of possible agents associated with this disease, or will HHV-6 be shown to be clinically relevant in the MS disease process? Kimberlin and Whitley comment that even though preliminary findings correlating HHV-6 and MS are intriguing, these results must be approached with caution. This has a familiar ring for those of us who have been investigating the possibility of a viral etiology in the pathogenesis of MS. A more detailed analysis of how such a newly described beta-herpes virus has been implicated in MS can serve to highlight how an environmental agent is linked with a neurologic disease and what lessons can be learned through such a process.

The list of viruses associated with MS in Table 1 suggest a number of interpretations. Clearly, a search for a single virus causal agent has failed to definitively associate any of these candidate viruses with MS (Johnson, 1994; Martin and Gale, 1997; Dalgleish, 1997). Simplistically, this could mean viruses are not associated with MS or that no one viral agent causes disease, i.e., infection with a putative 'MS virus' results in MS; no evidence of this agent would be found in disease free individuals. An example of such causality is HIV-I and AIDS. However, there are a number of examples in which infection with a single viral agent leads to disease only in subset of patients as in HTLV-I associated myelopathy/tropical spastic paraperesis (HAM/TSP). While over 20 million people worldwide are infected with HTLV-I, less than 5% will develop the associated neurologic disorder. This is in part due to genetic influences and host virus-specific cellular immune responses (Jacobson, 1995). Interestingly, both genetics and immune abnormalities have also been associated with MS. Alternatively, the list of viruses in Table 1 may suggest that multiple agents may be related to the MS disease process and is consistent with the clinical heterogeneity of this disorder. Viruses may act as environmental 'triggers' in genetically susceptible individuals in which potentially virus-specific immune responses may be immunopathogenic. Lastly, Table 1 may be an incomplete list in which an MS associated agent has yet to be discovered.

How then has HHV-6 been linked to MS? As with the majority of viruses associated with MS, serological studies have demonstrated increased HHV-6 titres (Sola *et al*, 1993; Wilborn *et al*, 1994; Soldan *et*

Table 1 A partial list of viruses that have been associated with the pathogenesis of multiple sclerosis and the year(s) that these reports appeared in the literature. (Adapted from Johnson RT (1994)

Virus	*Year*
Rabies virus	1946, 1964
Herpes simplex virus	1964
Scrapie agent	1965
Multiple sclerosis associated agent	1962
Parainfluenza virus 1	1972
Measles virus	1972
Simian virus 5	1978
Canine distemper virus	1978
Chimpanzee cytomegalovirus	1979
Coronovirus	1980
SMON-like virus	1982
Tick borne encephalitis	1982
HTLV-I	1986
LM7, MSRV (retrovirus)	1989, 1997
HSV-I	1989
MS1533 (retrovirus)	1994
HHV-6	1993, 1995

al, 1997; Ablashi *et al*, 1998). Since it has been well established that patients with MS often display increased antibody titers (particularly IgG) to many viruses, serological reports alone are not compelling proof of virus/disease associations. However, the report by Challoner and colleagues in 1995 for the first time, used an unbiased search for an MS-associated pathogen using the technique of representational difference analysis (RDA). In this manner, PCR amplification enriched for DNA sequences in MS disease tissue relative to control DNA (PBL of healthy donors). More than 70 DNA fragments were analyzed. One fragment from one MS case was 99.4% homologous to the MDBP gene of HHV-6B variant Z29 strain (Challoner *et al*, 1995). The authors exploited this observation by immunohistochemically localizing HHV-6 antigens to regions of MS plaques and demonstrating expression of HHV-6 reactive oligodendrocytes in MS cases but not in controls. In a true sense this was a landmark report in our understanding of MS pathogenesis in that an unprejudicial molecular probing of disease tissue from an MS brain suggested a virus association.

This 1995 Challoner report has spawned renewed interest in a viral etiology of MS but, as the authors discuss, their studies are insufficient to establish a virus/disease causal link. Other investigators must confirm these findings. Recent reports using a variety of immunological and molecular techniques have supported an association of HHV-6 and MS in a subset of patients (Sola *et al*, 1993; Wilborn *et al*, 1994; Soldan *et al*, 1997; Ablashi *et al*, 1998). Other reports have not (Liedtke *et al*, 1995; Nielsen *et al*, 1997). The capacity of this virus to infect the CNS and establish latency is an area of intense investigation and two reports in this months *NeuroVirology* address these issues. The excellent study by Albright *et al* (1998) clearly demonstrate that HHV-6 can infect cultured adult oligodendroglia as well as microglia. Infection of oligodendrocytes resulted in the release of low or undetectable levels of virus. Could similar mechanisms be operative in the MS lesion? The authors suggest the possibility that oligodendrocytes surrounding the MS plaque may be induced to replicate a latent virus. However, they appropriately caution an HHV-6/MS link and even suggest that HHV-6 may be just a 'passenger' virus with no relationship to the pathogenesis of MS.

The work by McCarthy *et al* (1998) demonstrate that HHV-6 infection of nonimmortalized human fetal astrocytes can trans-activate the HIV-I promoter. While this study focused on the astrocyte as a 'reservoir' for HIV latency and how HHV-6 (or CMV) may act as a co-factor in AIDS associated neurological disease, could similar mechanisms be operative in MS? HHV-6 has been shown to infect both primary human fetal astrocytes *in vitro* (He *et al*, 1996) and adult astrocytes *in situ* (Mackenzie *et al*, 1995). This latter report demonstrated HHV-6 antigens predominantly in astrocytes in a case of chronic progressive myelopathy associated with demyelination, axonal loss, chronic inflammation, and gliosis. Could latent HHV-6 in the CNS of MS patients transactivate other viruses (potentially retroviruses) that may also be associated with MS pathogenesis? Perron *et al* (1997) have recently characterized an apparently novel human retrovirus with homology to but distinct from the endogenous retroviral sequences ERV9. This virus has been isolated from MS patient cell lines (designated MS associated retrovirus [MSRV]) and circulating virion associated MSRV-RNA was found in 53% of MS sera (9/17) compared to 7% of controls (3/44) (Garson *et al*, 1998). Similar to work of McCarthy *et al* (1998), Perron *et al* (1997) have demonstrated that proteins from another herpesvirus member (HSV-1) can transactivate MSRV *in vitro*.

The search for a viral etiology in MS has led investigators in many directions for so many years. As presented in this editorial, extreme caution must be exercised in the interpretations of virus-associations and neurologic disease. Will a single viral agent ever be shown to be involved in MS or will multiple viral 'triggers' be associated with disease? If a virus is known to be ubiquitous, how can definitive proof of cause and the effect be established? In the absence of such proof, can anti-viral therapeutic strategies be rationally applied in MS clinical trials? Would the failure of such a trial rule out a virus association? Would its success prove causation? These and many other questions remain unanswered. Investigations to confirm or refute

virus associations in MS undoubtedly will lead us into new areas of neurovirological research where information is being acquired at an expanding rate. For example, Kimberlin and Whitley's review in this months NeuroVirology discuss that no findings of HHV-6 infection of primary oligodendrocytes have been reported in the literature yet in this same issue Albright *et al* (1998) have shown that these cells can be infected. As our understanding of virus-host interactions increases, we can seek to apply this information to clinically relevant questions of neurologic disease etiology, mechanisms of disease pathogenesis, and clinical intervention and therapy. We must keep an open and cautious mind as to the role, if any, viruses may play in chronic progressive neurologic disease such as MS.

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