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Herpes viral infection and the multiple sclerosis prodrome: is HHV-6A infection a second hit?

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Herpes viral infection and the multiple sclerosis prodrome: is HHV-6A infection a second hit?

This scientific commentary refers to 'Human herpesvirus 6A and axonal injury before the clinical onset of multiple sclerosis' by Grut *et al.* (https://doi.org/10.1093/brain/awad374).

Why multiple sclerosis occurs is not well understood, despite the identification of a number of genetic and environmental factors that contribute to disease risk.[1-3] Several recent studies underscored a strong association between Epstein-Barr virus (EBV) infection and the prodromal phase of multiple sclerosis.[4] EBV infection appears to occur a median of 7.5 years before symptom onset.[5] In addition, serum neurofilament light chain (sNfL) levels become elevated at least 2 years prior to symptom onset, supporting the notion that in many patients asymptomatic tissue injury precedes the first clinical relapse. However, the long duration of the multiple sclerosis prodrome is not well explained by current immunological concepts. If EBV were to trigger the disease through molecular mimicry, in analogy to *Campylobacter jejuni* infection and acute inflammatory demyelinating polyneuropathy,[6] one would expect symptom onset to occur in the weeks or months following EBV infection and not many years later. The multi-year prodrome strongly suggests that other factors operate following EBV exposure. Unlike many other autoimmune diseases of the CNS such as neuromyelitis optica and the autoimmune encephalitides, no specific CNS antigen associated with multiple sclerosis has ever been identified despite extensive efforts by numerous investigators. While such an antigen might exist, it is also possible that multiple sclerosis is not caused by a breach in immune self-tolerance to a single antigen. Other immune-related mechanisms, such as abnormal immune cell differentiation or migration, could contribute to disease pathogenesis without the need for a humoral, or cellular, antigen-specific immune response. Therefore, understanding the processes at play during the prodromal phase of multiple sclerosis is of critical importance for understanding how and why the disease occurs.

In this issue of *Brain*, Grut and colleagues[7] report an association between human herpesvirus 6A (HHV-6A) seropositivity and sNfL elevation in the multiple sclerosis prodrome. The authors developed a unique dataset by linking the Swedish multiple sclerosis registry to six microbiological serum or plasma biobanks. Serum or plasma samples were obtained from individuals who had subsequently been diagnosed with multiple sclerosis after the samples were acquired. All samples were obtained prior to the age of 40 and before the clinical onset of multiple sclerosis. Unaffected controls were matched to each case by biobank, sex, sample date and birth date resulting in 519 matched pairs. The median time of sample acquisition was 9.5 years prior to clinical onset, although the range was broad, from 33 years prior to onset to shortly before onset. The authors found that the proportion of HHV-6A seropositive samples was significantly higher among cases than controls (40% versus 25%), although unlike the EBV association, the HHV-6A association with multiple sclerosis was not invariant. Further, the authors found that sNfL levels were significantly higher in both HHV-6A seropositive and seronegative cases compared to controls, suggesting that tissue injury was already occurring in the individuals who would later be diagnosed with multiple sclerosis, regardless of their HHV-6A exposure. The authors additionally assessed EBV reactivity, and found that sNfL levels were higher in those samples that were seropositive for both EBV and HHV-6A, suggesting that perhaps the two viruses acted synergistically to effect CNS tissue injury. Interestingly, very few samples were HHV-6A seropositive and EBV seronegative, implying that EBV infection likely preceded HHV-6A exposure. HHV-6A seropositivity appeared to precede further increases in sNfL suggesting that HHV-6A infection might contribute to tissue injury in the prodromal phase.

This is not the first study to associate HHV-6 with multiple sclerosis. Many other studies have found evidence for serological activation of HHV-6 in affected individuals[8]; however, a causative role for HHV-6A in multiple sclerosis pathogenesis is not proven nor is the association generally accepted. HHV-6 has two distinct viral genomes: HHV-6A and HHV-6B. HHV-6B causes roseola infantum, whereas HHV-6A has not been shown directly to cause any human illness. Both viruses are gliatropic, meaning that they can infect microglia, oligodendroglia and astrocytes, and can therefore chronically infect CNS tissue, with the potential for viral reactivation many years after acute infection to cause encephalitis in immunocompromised hosts. Although several groups have found associations between serological responses against HHV-6 and multiple sclerosis, viral DNA has not been found consistently in the tissues or fluids of patients, leading to scepticism over whether these ubiquitous viruses do in fact have a role in disease pathogenesis.[9] Distinguishing HHV-6A from HHV-6B serologically has also been challenging until recently. The data presented by Grut and colleagues[7] add weight to the argument in favour of HHV-6A contributing to multiple sclerosis pathogenesis by showing that exposure to HHV-6A—as revealed by seropositivity

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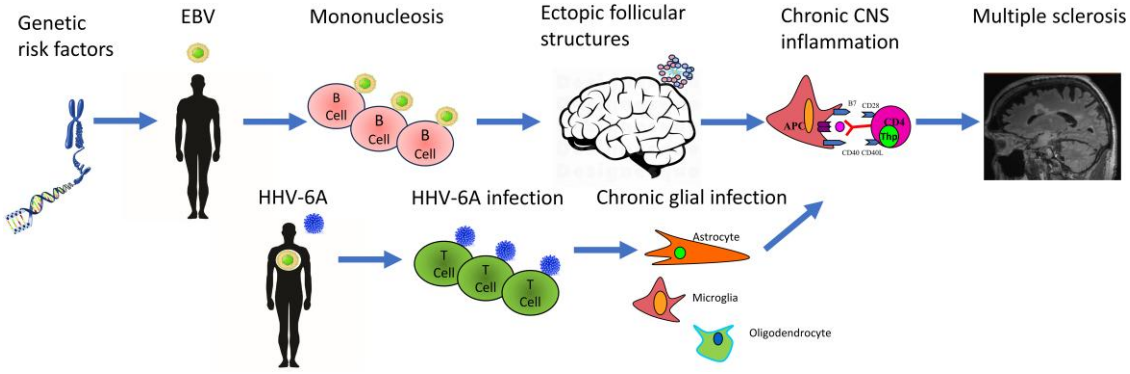

Figure 1 Model for how chronic viral infections might contribute to multiple sclerosis. In genetically susceptible hosts, EBV infection causes infectious mononucleosis with high viral load. Unidentified alterations in B-cell function occur that result in a propensity for B cells to enter the CNS and form ectopic follicular like structures along with other cells including dendritic cells and plasma cells. These structures could cause demyelination and tissue injury through secretion of toxic factors. HHV-6A infection, occurring sometime after EBV infection, could spread from T cells to glial cells in the CNS. HHV-6A infection could contribute to chronic CNS inflammation that, along with EBV infection, results in demyelination and axonopathy. EBV = Epstein-Barr virus; HHV-6A = human herpesvirus 6A.

in pre-symptomatically acquired samples—is significantly associated with the multiple sclerosis prodrome.

Although the long-reported association between EBV and multiple sclerosis has gradually gained increasing acceptance among specialists, proof that EBV triggers multiple sclerosis remains elusive, largely because there are no animal models with which to directly test the hypothesis that EBV triggers abnormal immune responses leading to the disease. Sceptics of the EBV hypothesis point out that the EBV association is exactly that, an association which could be a proxy for another, as yet unidentified, trigger. The same concerns apply, perhaps even more so, to the HHV-6A association. Although Grut and colleagues[7] present a reasonable argument, the study has several methodological issues that must be considered when interpreting the results. First, serial samples for study participants were not available. Temporal inferences made with respect to causation are therefore based on cross-sectional data and remain unproven. Second, the methods for determination of HHV-6A seropositivity are not as well established as those for EBV, a limitation that the authors acknowledge. Third, sNfL Z-scores in the matched controls were higher than expected suggesting that at least some of the controls may have experienced some sort of CNS injury at the time of sample acquisition. Unfortunately, medically relevant data for the control samples is not available to help interpret this observation.

Chronic, active viral infection within the CNS could contribute to multiple sclerosis, but the presence of either EBV or HHV-6A viral genomes in CSF samples from patients has not been conclusively established. Nonetheless, it remains possible that chronic infection with one or more viruses could contribute to disease activity and progression. If HHV-6A CNS infection is directly implicated in multiple sclerosis pathogenesis, then therapeutic strategies targeting this virus could potentially have a role in treatment.

The results from the present study do not show that HHV-6A causes multiple sclerosis; rather, they suggest that HHV-6A infection may be a contributing factor in some patients following EBV infection. In addition to the potential for direct CNS infection, HHV-6A could cause chronic CNS inflammation and HHV-6A infected cells could become targets for immune-mediated injury by CD8+ effector cells, microglia and macrophages. It is possible that the viral connection to multiple sclerosis risk involves a 'two-hit' process in which HHV-6A infection following an EBV infection adds to risk (Fig. 1).

Establishing whether this two-step process occurs will require acquisition of serial serum samples from a large group of pre-symptomatic individuals. The Department of Defense Serum Repository, which was used to identify EBV as a risk factor, could also potentially be used to understand and confirm the role of HHV-6A. Using this repository, an auto-antibody motif common in human peptides that is also present in viral pathogens was recently identified from samples obtained during the multiple sclerosis prodrome and was also detected in a cohort of participants with relapsing multiple sclerosis within 90 days of symptom onset.[10] That two EBV proteins—BRRF2 and envelope glycoprotein M—share homology with this motif suggests that reactivity against these viral epitopes could trigger autoreactivity against human peptides with similar sequences.

Identification of CSF antibodies that recognize HHV-6A peptides and cross react with human CNS peptides would add credence to a potential role for HHV-6A in molecular mimicry. PCR studies are needed to determine whether HHV-6A DNA can be detected in the saliva, peripheral blood mononuclear cells or CSF of newly diagnosed patients relative to well matched unaffected controls to provide evidence for a role of active HHV-6A infection in multiple sclerosis. At present, vaccinations against EBV and HHV-6A are not commercially available. However, should such vaccines become available, individuals who are at high risk for developing multiple sclerosis could become early beneficiaries of a primary prevention strategy.

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