Human Herpesvirus 6 as a Viral Trigger in Mesial Temporal Lobe Epilepsy

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(See the major article by Kawamura et al on pages 1014–21.)

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Although the cause(s) of epilepsy remain largely unknown, a number of neurotropic viruses known to cause central nervous system (CNS) inflammation have been implicated in the development of seizures [1]. Herpesviruses are among these agents, and seizures are thought to result from either primary infection or reactivation of latent virus [1]. More recently, human herpesvirus 6 (HHV-6), particularly the HHV-6B species known to be acquired during early childhood, continues to be associated with epilepsy, in addition to several other CNS diseases. Importantly, this specific association between epilepsy and HHV-6B has been established based not on increased antibody responses in patients versus controls but rather on the detection of viral nucleic acids in viral proteins in resected epileptogenic tissue.

Though HHV-6 may be a commensal of the CNS, as suggested by the detection of low levels of viral nucleic acids in a subset of healthy control brains [2, 3], many studies have found significantly elevated HHV-6B viral DNA in epileptogenic brain tissue compared with control material. HHV-6 viral DNA has often been detected at higher levels in resected temporal lobe tissues than in nonepileptogenic control tissues, with the frequency ranging between approximately 30% and 70% [4–7]. This range of detection is probably due to varied tissue preservation and polymerase chain reaction (PCR) methods across laboratories. However, in our study using real-time PCR, 60%–70% HHV-6B positivity was observed in mesial temporal lobe epilepsy (MTLE) resections [8], and these findings have remained remarkably consistent across an expanded patient cohort using an entirely new PCR platform, digital droplet PCR (manuscript in preparation).

Not all studies, however, have observed an increased frequency of virus detection in epileptogenic brain tissue; Esposito and colleagues [9] recently reported similar frequencies of HHV-6B positivity (approximately 10%) in a temporal lobe epilepsy (TLE) cohort and autopsy controls, though significantly elevated levels of viral DNA were detected in the TLE patient material. The authors suggested that the increased presence of HHV-6B DNA in specific subgroups of patients with TLE might reflect a pathophysiologic role of HHV-6B in those patients.

The article by Kawamura and colleagues [10] in this issue of The Journal of Infectious Diseases further adds to the growing number of reports supporting an association between HHV-6 and epilepsy. This study compared resected brain material from 75 patients with intractable MTLE with or without hippocampal disease or mesial temporal sclerosis (MTS). Of the 9 herpesviruses analyzed (herpes simplex virus 1 and 2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, HHV-6A/6B, HHV-7, HHV-8), HHV-6 was the most frequently detected, which is consistent with findings of previous studies that have surveyed for multiple herpesviruses in epileptic tissue [4, 6, 9]. Kawamura et al [10] found HHV-6 DNA in approximately 22%–29% of the studied tissues (hippocampus, amygdala, and mixed amygdala/uncus). Interestingly, significantly greater levels of viral DNA were detected in MTS than in non-MTS patient material, and the incidence of febrile seizures was also significantly higher in the MTS group.

Observations stemming from the cohort studied by Kawamura et al [10] highlight a relationship between MTS, a history of childhood febrile seizures and HHV-6B positivity. Other studies have also correlated HHV-6B positivity with a history of febrile convulsions [6]. HHV-6B is the etiologic agent of roseola infantum, and
primary infection can result in fever in approximately 50% cases, and febrile seizures in a smaller subset. A 1994 study of infants and young children presenting to an emergency department with acute HHV-6 infections reported seizures in 13% [11].

Prolonged febrile seizures, or febrile status epilepticus (FSE), are associated with an increased risk of TLE [12]. The significance of these observations has given rise to an ongoing, prospective multicenter study, the Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study, the goal of which is to formally examine the relationship between prolonged childhood febrile seizures and the development of MTS and epilepsy, particularly TLE [13]. A major component of this study is to establish the frequency of HHV-6 infection as a cause of FSE, and in an article published in *Epilepsia* in 2012, HHV-6B viremia was reported in 54 of 169 subjects (32%) at the time of FSE presentation [14].

Given the link between HHV-6B primary infection and seizures—febrile and possibly also afebrile [15, 16]—and reports of HHV-6B in epileptogenic tissue, there is understandably substantial interest in the connections between this virus and epileptogenesis.

Kawamura and colleagues [10] extend these observational findings of an increased frequency of HHV-6 in MTLE to a functional analysis of host gene expression in the brain tissues of patients with MTS. They observed significantly increased expression of monocyte chemoattractant protein 1 (MCP-1) and glial fibrillary acidic protein (GFAP) in the HHV-6-positive versus HHV-6-negative amygdales tissues. Moreover, these expression levels positively correlated with HHV-6 viral load, suggesting a relationship—at least in the amygdala—between viral load and markers that directly (MCP-1) or indirectly (GFAP) reflect inflammatory or otherwise injurious processes.

Neuroinflammation is increasingly recognized as a key component underlying epileptic disease pathogenesis [17]. Several studies have demonstrated increased inflammatory pathway expression in HHV-6B-positive patients with MTLE. For instance, Li and colleagues [6] demonstrated unregulated NFKB in the glial cells of HHV-6B-positive patients with MTLE. Others have examined levels of inflammatory cytokines in the periphery of patients. In a 2013 study, Mao and colleagues [18] reported significantly increased interleukin 17A levels in serum samples from epileptic patients during interictal periods, compared with healthy controls. In this cohort, serum interleukin 17A levels correlated with seizure severity and frequency. Observations from these translational studies corroborate findings from animal models of seizure induction, specifically that proinflammatory cytokines, such as interleukin 1β, contribute to seizure duration and recurrence and blood-brain barrier damage, which may then perpetuate brain inflammation [19].

In addition to MCP-1, Kawamura et al [10] detected elevated GFAP in the HHV-6-positive amygdales samples from patients with MTS. GFAP is an astrocyte-specific marker, associated with reactive gliosis during epilepsy [20]. In vitro, HHV-6 infects primary human fetal astrocytes [21] and human progenitor-derived astrocytes [22]. Fotheringham and colleagues [8] cultured primary astrocytes from an HHV-6B-positive MTLE brain resection and by immunofluorescence demonstrated co-staining of viral antigens and GFAP. Similar results have been reported using immunohistochemistry to analyze paraffin-embedded MTLE resections, particularly in hippocampal regions [5, 6]. The colocalization of HHV-6 antigen with astrocytes has also been reported in conditions of CNS/immune dysregulation, such as limbic encephalitis (after stem cell transplantation) [23], AIDS encephalopathy [24], and multiple sclerosis [25].

How might these observations in MTS/MTLE of increased HHV-6 viral detection and increased markers of neuroinflammation and astrocyte activation be mechanistically associated with epilepsy? Inflammation and HHV-6 infection have each been demonstrated to induce dysregulation of glutamate homeostasis in astrocytes, which is hypothesized to play a central role in the pathogenesis of epilepsy. Excess glutamate may be excitotoxic, and contribute to neuronal depolarization. Furthermore, glutamate receptor antagonists have demonstrated anticonvulsant properties [26].

In vitro, HHV-6 infection of primary astrocytes has been shown to down-regulate levels of glutamate transporter expression, which supports the concomitant observation of decreased glutamate uptake in infected versus uninfected astrocytes [27]. Inflammatory cytokines, such as interleukin 1β, can also inhibit astrocyte reuptake of glutamate [17]. Because HHV-6–infected astrocytes have been demonstrated in CNS disorders, including MTLE, and because the virus can induce a metabolic dysregulation that is considered to contribute to epileptogenesis, this mechanism is biologically plausible. Importantly, the role that HHV-6 (or other viruses) may play in the pathogenesis of epilepsy suggests new clinical interventional approaches that target virus infection in the CNS.

Primary infection with HHV-6B occurs by the age of 2 years, and, as with other herpesviruses, latency persists for the life of the host. The CNS, in addition to mononuclear peripheral blood cells, may be a site of viral latency; 1 study demonstrated that the virus may enter the CNS via the olfactory pathway [28]. Despite undetectable viral messenger RNA (3 transcripts were probed) in the resected tissue, Kawamura and colleagues [10] observed a positive correlation between MCP-1 and GFAP expression and HHV-6 viral DNA loads, suggestive of a latent infection. If the virus persistently infects resident glial cells, disrupting astrocyte homeostasis and triggering CNS immune responses toward (latent) antigens, this may be one mechanism by which the seizure threshold is lowered. Resultant inflammation from seizures may then contribute to the reactivation of HHV-6 from latency in glial or other CNS resident cells.
Although additional studies are needed to more firmly refine the mechanisms underlying the association between HHV-6 and epilepsy, the work by Kawamura and colleagues [10] underscores the relationship between HHV-6B, childhood febrile seizures, MTS, and ultimately MTLE. This work and that of others probe at the very cause(s) of epilepsy, and may lead to the identification of effective therapeutic targets. If HHV-6–related febrile seizures are, in fact, involved in the etiology of temporal sclerosis and TLE, then it is highly plausible that efficacious, CNS-penetrable antivirals administered to patients at a young age could mitigate the developing disease.

Note

Potential conflict of interest. Both authors: No potential conflicts of interest.

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References