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Mechanisms of neuroinflammation in epilepsy linked to HHV-6 infection

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Over the past decade there has been growing interest in elucidating the role of neuroinflammation in seizure generation. Several preclinical studies have revealed that infection with neurotropic viruses such as HHV-6 can trigger an inflammatory cascade involving infected CNS cells. These findings are corroborated by clinical studies, that have shown an association with HHV-6 infection and different epilepsy syndromes and have detected HHV-6 viral DNA in saliva, blood, CSF and resected epileptogenic tissue from children and adults with seizures and chronic epilepsy.

In this focused review we will analyze main clinical associations that link HHV-6 infection with seizures and proposed pathogenic mechanisms by which infection with HHV-6 can lead to a proinflammatory milieu contributing to seizure generation and in some instances later development of epilepsy.

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Introduction

Several studies have linked infection with Human Herpesvirus 6 (HHV-6) to different epilepsy syndromes, including acute symptomatic seizures secondary to encephalitis [1], febrile seizures [2] and status epilepticus [3], and temporal lobe epilepsy [4•]. There is growing interest on defining the role of inflammatory mechanisms potentially triggered by primary infection with HHV-6, secondary reactivation and later development of epilepsy [5•].

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Patients who develop acute seizures in the context of viral encephalitis are considered at risk for later development of chronic epilepsy [6], although mechanisms of epileptogenesis involved are still unclear [7••].

After entering the CNS during initial viremia, HHV-6 can infect neurons, astrocytes and oligodendrocytes triggering cell death and release of proinflammatory mediators with activation of the innate and adaptive immune systems [7••].

Clinical manifestations of HHV-6 infection and its link with epilepsy syndromes

HHV-6 is an enveloped DNA virus that belongs to the β-herpesviridae family and was first isolated in 1986 [8]. Two viral species exist [9], HHV-6A and HHV-6B, which share 90% homology [10]. Primary infection occurs in almost 90% of children by age two years [11], with transmission through saliva. Acute primary infection typically manifests with nonspecific findings such as irritability, runny nose and fever [12•], or with the full-blown classic roseola (characterized by high fever and irritability followed by a distinctive rash right after the fever breaks) [13]. Encephalitis in the context of

secondary infection in immunocompromised adults is a rare occurrence [14].

Febrile seizures

Several studies have linked HHV-6 to febrile seizures and status epilepticus [3,15,16], with significant heterogeneity in terms of both prevalence and clinical course between Asian and North American studies [17]. Earlier studies primarily based on clinical observations have reported a high frequency of febrile seizures in association with full-blown roseola (which occurs in less than one third of children with primary HHV6 infection) [12•]. In a review of the literature between 1924 and 1964 among 581 children diagnosed with roseola, 22% were reported to have febrile seizures [18]. Similarly, more recent reviews of 416 cases of febrile seizures in children aged less than three years found primary HHV-6 infection in 24% [19•]. Recent population-based study that followed 277 infants from birth until age two years and analyzed serial saliva (and when available blood) samples by PCR, showed a cumulative incidence of HHV-6 infection of 77% by 24 months of age but none of these children had seizures [12•]. The consequences of prolonged febrile seizures in childhood study (FEBSTAT) was a multi-center prospective study that enrolled children aged one month through five years presenting with febrile status epilepticus [3]. Presence of HHV6A and HHV6B DNA and RNA was assessed using quantitative polymerase chain reaction (qPCR). Antibody titers were used in conjunction with PCR analysis to differentiate primary infection from reactivated or prior infection. HHV-6B viremia was found in 54 of 169 children (32%) vs. 9.7% of historical controls represented by children presenting with acute febrile illness without seizures [20].

Most recent studies report an association between acute seizures and HHV-6B infection [2,3,21–23], while the association with HHV-6A remains anecdotal [23].

HHV-6 encephalitis

HHV-6 encephalitis is infrequent and while primarily observed in immunocompromised patients during viral reactivation, anecdotal evidence exists of cases in immunocompetent hosts. HHV-6B DNA was detected in the CSF of nine of 138 patients (6%) presenting with focal encephalitis of unknown etiology [24]. Seizures are commonly observed at presentation. Reported incidence is 0–12% after bone marrow or peripheral blood stem cell transplantation and 5–21% after cord blood transplantation [25]. Interestingly, of 1000 patients enrolled in the California Encephalitis Project, only four immunocompetent children tested positive for HHV-6 by PCR [26]. This low detection rate may potentially be linked to many reasons, including for example the timing for sampling.

Mesial temporal lobe epilepsy (MTLE)

Several studies analyzing resected temporal and hippocampal epileptogenic tissue from temporal lobe epilepsy cases associated with mesial temporal sclerosis (MTS), observed a high frequency of HHV-6B detection by PCR compared with adjacent brain tissue or epileptogenic tissue from neocortical cases [4•,27,28,29].

A meta-analysis [30] that included 10 studies with a total of 645 MTLE cases (456/645, 71% with associated hippocampal sclerosis (HS)) and 136 controls, showed a higher pooled HHV-6 DNA detection rate in pathological specimens from patients with MTLE (126/645, 19.5%) than controls (14/136, 10.3%) ($p < 0.05$). Within the MTLE group, the cohort of patients with associated HS had a higher detection rate (101/456, 22.1%), while the one without HS had similar detection rate compared to controls (22/189, 11.8%), possibly indicating that HHV-6 infection may be associated with HS more than broadly with MTLE. Forty five of 126 (36%) of MTLE patients with positive HHV-6 DNA had a history of febrile seizures compared with 94/519 (18%) MTLE patients without detectable HHV-6 DNA, possibly suggesting that febrile seizures associated with HHV-6 infection may trigger chronic pathogenic mechanisms contributing to the development of MTLE.

Mechanisms of neuroinflammation in HHV6 infection

While both viruses are thought to be neurotropic and have been associated with neurological diseases in humans, HHV-6B is the species that has been primarily linked to different epilepsy syndromes [31•]. HHV-6A has been described in association with a febrile illness in immunocompromised infants in Sub-Saharan Africa [32] and has detected in serum and urine [33], and CSF [34] from patients with multiple sclerosis.

After entering the CNS during initial viremia or retrograde neuronal spread [35], HHV6 can establish chronic latency in brain tissue and peripherally in the salivary glands [27]. Specialized olfactory-ensheathing glial cells located in the nasal cavity were demonstrated to support HHV-6 replication *in vitro* [35]. This finding supports the notion that the olfactory pathway may represent a port of entry for HHV-6 to the CNS, similarly to what is seen in case of infection with several other neurotropic viruses, including herpes simplex viruses, borna disease virus, rabies virus [36]. Infection reactivation [37] may occur at a later stage in the context of immunosuppression [38]. A peculiar aspect of HHV-6 is that it can also integrate near telomeres of infected cells. This mechanism is known as chromosomal integration and results in up to 1% of infected individuals to have the entire HHV-6 genome in every cell and transmitting the virus vertically [39].

HHV-6 can modulate adaptive immune response by binding to the ubiquitous complement regulator CD46 [40,41]. This mechanism leads to T cell induction of interleukin

(IL)-17 [42], and inhibition of IL-10 production [43]. While certain strains of HHV-6B use CD134 as cell receptor [44•], specific isoforms of CD46 allow binding of HHV-6A and HHV-6B to CD46 [45]. Complement activation has been suggested to play an important role in neuroinflammation triggered by HHV-6 infection, similarly to what has been described in infected patients affected by multiple sclerosis [46].

HHV-6 can infect astrocytes and oligodendrocytes [47] *in vivo* leading to increased production of several cytokines, including IL-1β, interferon (IFN)-α and tumor necrosis factor (TNF)-α. Transcriptional microarray analysis on infected astrocytes showed that HHV-6A infection augmented the expression of several proinflammatory cytokines after stimulation with TNF-α, IL-1β, and IFNγ, including chemokines such as chemokine ligand (CCL)-2, CCL-5, and C-X-C motif chemokine (CXCL)-2 [48]. HHV-6 can also infect T cells, favoring a T helper 1 proinflammatory response [49] with reduced IL-10 and IL-14 gene expression. While mechanisms leading to epileptogenesis after HHV-6 infection are incompletely understood, *in vitro* studies of HHV-6-infected astrocyte cultures showed decrease in glutamate transporter Excitatory amino acid transporter (EAAT)2 expression [4•]. Furthermore, gene expression studies revealed upregulation of Glial fibrillary acidic protein (GFAP) and CCL-2 — also known as Monocyte Chemoattractant Protein-1 (MCP-1) in amygdala of MTLE patients with HHV-6 infection with a positive correlation with viral load [28] and in resected epileptogenic tissue from the hippocampus [50]. The the upregulation of GFAP and CCL-2 is consistent with astrogliosis and neuronal cell death, which may contribute to development of MTLE [51,52]. CCL-2 is a protein that participates in regulation of migration and infiltration of macrophages and monocytes. HHV-6 can establish latent infection in these cells and by upregulating CCL-2 can facilitate migration of infected cells into the amygdala and induce chronic changes seen in MTLE.

Other investigators have suggested a possible contribution of the transcription factor NF-κB in patients with HHV-6 infection who develop MTLE [29]. Dysregulation of this protein complex has been observed in cancer, inflammatory diseases and viral infections [53].

Lastly, HHV-6 virokines modulating leukocyte migration may play a key role in neuroinflammatory activation leading to epileptogenesis. Specifically, the U83 gene encodes a specific agonist of the chemokine receptor CCR-2 which is expressed on monocytes and macrophages. U83 is one of the few genes that are not present in the genome of Human Herpesvirus 7 (HHV-7), the closest homologue of HHV-6A and -6B. Interestingly, this other roseolovirus has not yet been associated with neuroinflammatory diseases [54•].

Disease models for the study of HHV-6

A small animal model for HHV-6B has been very challenging to design, because HHV-6B utilizes mainly the CD134 receptor [44] that appears only on activated T cells. A few studies have used pig tailed macaques [55], marmosets [56], cynomolgus macaques, and African green moneys [57], which are susceptible to human roseolovirus strains [58,59••], but the natural history of these infections in their natural hosts and how well they mimic HHV-6 in humans is still incompletely understood.

A marmoset (Callithrix jacchus) model was developed to study HHV-6A and HHV-6B infections [56]. Marmosets that received multiple intravenous injections of HHV-6A developed neurological symptoms, while those infected with HHV-6B remained asymptomatic, despite HHV-6 DNA was found in the brain of infected animals with both strains.

The pig-tailed macaque model showed highly efficient sustained replication of HHV-6A both *in vitro* and *in vivo* [55]. After initial inoculation, with appearance of plasma viremia and clinical symptoms such as fever and lymphadenopathy, the virus entered a clinically latent state, similarly to what has been described in healthy children for HHV-6B infection. These findings suggest the potential utility of this experimental model to study HHV-6 infection in humans.

The CD46 transgenic mouse model demonstrated long-term persistence of viral DNA in the brain of infected animals after intracranial and intraperitoneal infection with HHV-6A. Activation of the toll-like receptor 9 (TLR9) pathway, in the absence of clinically apparent signs of disease was also demonstrated [60]. Infection with HHV-6B did not yield any signs of viral replication in transgenic murine CD46 cells either *in vitro* or *in vivo*, probably due to the main utilization of CD134 receptor.

Wang and Colleagues [61] have recently created the first humanized mouse model mimicking HHV-6B pathogenesis. The researchers injected stimulated human cord blood mononuclear cells (CBMCs) into the peritoneum of immunodeficient humanized mice. This resulted in a high ratio of activated T-cells expressing CD134, creating ideal conditions for HHV-6B infection. Clinically, they observed a condition similar to acute graft-versus host disease (GVHD), with viral replication observed in all main organs, but especially high in the spleen and lungs (~10,000 copies/ng of total DNA 8 days postinfection). A significant increase in levels of IL-6, IL-8, CCL2 and CCL8 in the early phase of infection was also documented, similarly to what has been described during primary infection in humans.

At present, no disease model specific for HHV-6 and epilepsy exists.

Conclusions

HHV-6 infection has been linked with different types of acute seizures and epilepsy syndromes in children. Mechanisms of

epileptogenesis correlated with viral infection are incompletely understood, but growing evidence suggests that dysregulation of innate and adaptive immunity may play a key role in the cascade of neuroinflammatory events leading to epilepsy, especially MTLE [31•]. These observations are also the basis for novel potential therapeutic targets such as antiviral or immunomodulatory treatments. Recent advances in small animal models of HHV-6 infection will also likely expand the knowledge on pathogenic mechanisms and contribute to the development of such novel preventive and therapeutic strategies [59••].

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ddmod.2020.04.001.

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

• important, original research or focused review on the topic
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