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Review article

Infection with HHV-6 and its role in epilepsy

Luca Bartolini[a,b,*], William H. Theodore[a], Steven Jacobson[b], William D. Gaillard[c]

[a] Clinical Epilepsy Section, National Institute of Neurological Disorders and Stroke, NIH, 10 Center Drive, Bethesda, MD 20892, USA
[b] Division of Neuroimmunology and Neurovirology, National Institute of Neurological Disorders and Stroke, NIH, 10 Center Drive, Bethesda, MD 20892, USA
[c] Center for Neuroscience, Children's National Medical Center, George Washington University, 111 Michigan Ave NW, Washington, DC 20010, USA

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ABSTRACT

Infection with Human Herpesvirus-6 (HHV-6) has been associated with different epilepsy syndromes, including febrile seizures and status epilepticus, acute symptomatic seizures secondary to encephalitis and temporal lobe epilepsy.

This neurotropic DNA virus is ubiquitous and primary infection occurs in up to 80% of children by age two years. While two viral variants have been identified, HHV-6B is the one that has been primarily linked to disease in humans, including epilepsy. After initial viremia, the virus can establish chronic latency in brain tissue, peripherally in tonsils and salivary glands and infect several different cell lines by binding to the complement regulator CD-46.

In this review we will focus on discussing the evidence linking HHV-6 infection to different epilepsy syndromes and analyzing proposed pathogenic mechanisms.

1. Introduction

Viral infections with neurotropic viruses such HHV-6 have been linked to acute seizures and epilepsy in children (Bartolini et al., 2019; Theodore et al., 2008). Syndromes described in the context of both primary infection and reactivation include febrile seizures (Laina et al., 2010), acute symptomatic seizures secondary to encephalitis (Theodore, 2014), status epilepticus (Epstein et al., 2012) and TLE (Fotheringham et al., 2007). While other pathogens, such as for example Arboviruses (Solomon and Vaughn, 2002), Dengue virus (Murthy, 2010) and influenza virus (Ekstrand et al., 2010) have been linked to acute seizures in the context of systemic infections, this review will focus on the role of HHV-6.

HHV-6, first isolated in 1986 (Salahuddin et al., 1986), is an enveloped DNA virus that belongs to the β-herpesviridae family. Primary infection, practically ubiquitous, occurs in up to 90% of children by age two years (Okuno et al., 1989). Transmission occurs through saliva. Acute primary infection can lead to a broad range of symptoms, including nonspecific findings such as fussiness, rhinorrhea and fever (Zerr et al., 2005), or classic roseola (high fever and fussiness followed by a distinctive rash right after the fever breaks) (Asano et al., 1994). Conversely, development of encephalitis generally occurs via reactivation or secondary infection in immunocompromised adults (Gewurz et al., 2008). The two viral species HHV-6A and B, share 90% homology (Braun et al., 1997), and in 2014 they were classified as two distinct species (Ablashi et al., 2014). Both viruses are neurotropic and have been associated with neurological diseases in humans. HHV-6B has been previously linked to different types of seizures, epilepsy and encephalitis. HHV-6A has been detected in serum and urine (Akhyani et al., 2000), and CSF (Alenda et al., 2014) from patients with multiple sclerosis and, anecdotally, in saliva from a child with acute seizures (Bartolini et al., 2018).

HHV-6A and HHV-6B can infect several cell lines by binding to the ubiquitous complement regulator CD46 (Santoro et al., 1999; De Bolle et al., 2005). It has been suggested that specific isoforms of CD46 allow binding of HHV-6A and HHV-6B to CD46 (Hansen et al., 2017). Certain strains of HHV-6B use a separate receptor, CD134 (Tang et al., 2013). The virus can enter the CNS during initial viremia or retrograde

Abbreviations: CNS, central nervous system; ddPCR, droplet digital polymerase chain reaction; DRESS, drug reaction with eosinophilia and systemic symptoms; EAAT2, excitatory amino acid transporter 2; EBV, Epstein-Barr virus; FSE, febrile status epilepticus; GFAP, glial fibrillary acidic protein; HHV-6, Human Herpesvirus-6; HHV-7, Human Herpesvirus-7; HS, hippocampal sclerosis; IFN, interferon; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; MTLE, mesial temporal lobe epilepsy; NF, nuclear factor; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcription polymerase chain reaction; TLE, temporal lobe epilepsy; TNF, tumor necrosis factor

* Correspondence author at: National Institute of Neurological Disorders and Stroke, Clinical Epilepsy Section, Building 10, room 7-5680, 1 Center Drive, Bethesda, MD 20814, USA.
E-mail address: luca.bartolini@nih.gov (L. Bartolini).

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neuronal spread (Harberts et al., 2011) and establish chronic latency in brain tissue and peripherally in tonsils/salivary glands (Donati et al., 2003). A third disease stage, infection reactivation (Campadelli-Fiume et al., 1999), usually is observed in the context of immunosuppression and documented by viremia (Yalcin et al., 1994). HHV-6 can also integrate near telomeres of infected cells, a mechanism known as chromosomal integration; up to 1% of infected individuals have the entire HHV-6 genome in every cell of their body and transmitting the virus vertically in Mendelian fashion (Morissette and Flamand, 2010).

Different mechanisms have been implicated in seizure generation. Herpesviruses can cause direct neuronal damage and death, especially in immunocompromised hosts, resulting in robust release of cytokines and activation of innate and adaptive immune system (Vezzani et al., 2016). Alterations in blood brain barrier permeability leading to neuronal hyperexcitability are also seen and result in profound alteration of neuronal circuits with modification at the level of receptors, ligands and channels, eventually contributing to epileptogenesis (Löscher and Brandt, 2010).

While other recent reviews conducted an in-depth analysis of a specific aspect of the relationship between HHV-6 infection and epilepsy, such as febrile seizures (Mohammadpour Touserkani et al., 2017) or MTLE (Wipfler et al., 2018), with this focused review, we provide a concise update encompassing all major clinical manifestations related to seizures and epilepsy of primary and secondary infection with HHV-6. We also discuss basic pathophysiological mechanisms that have been described with HHV-6 infection.

2. Febrile seizures/febrile status epilepticus

Febrile seizure prevalence is estimated at one in 30 children, increasing to one in five if one sibling is affected and one in three if both parents and a previous child have had febrile seizures (Berg, 1993), clearly indicating a multifactorial etiology with possible genetic influence increasing susceptibility (Audenaert et al., 2006).

Several studies have linked HHV-6 to febrile seizures and status epilepticus (Kondo et al., 1993; Suga et al., 2000; Epstein et al., 2012).

The average incidence of febrile seizures in a review of the literature from 1924 to 1964 among 581 children diagnosed with roseola was 22% (Millichap, 1968). More recently a review of 416 cases of febrile seizures, with no specific distinction in terms of type or duration, in children aged less than three years found primary HHV-6 infection in 24% (Millichap and Millichap, 2006). As a comparison, a prospective observational study (Hall et al., 1994) that enrolled children under three years of age presenting to the emergency department with acute febrile illness, found primary HHV-6 infection (documented by qPCR and seroconversion) in 160/1653 (9.7%) children and 21/160 (13%) of them had seizures, although duration and type of seizures were not specified. Peak age of infection was six to nine months.

With a different, population-based study design, other investigators (Zerr et al., 2005) showed a cumulative incidence of primary HHV-6 infection of 77% by 24 months of age in 277 infants that were followed from birth until age two years, and whose saliva (and when available blood) was analyzed weekly by PCR. None of these children had seizures.

An Australian observational study (Francis et al., 2016) (Table 1) enrolled 151 children (median age 1.7 years) presenting to the Emergency Room with febrile seizures. The investigators obtained pernasal samples and 143 of them were examined by RT-PCR for viral genetic material. HHV-6 was detected in 17/143 (12%) samples vs. 31/143 (22%) rhinoviruses, 30/143 (21%) adenoviruses, 28/143 (20%) enteroviruses and 19/143 (13%) influenza. Overall, co-detection of two or more viruses occurred in 48/143 (34%) cases. These data highlight the potential role of other viruses both singularly and during co-infection with HHV-6. Ninety eight of 150 cases (65%) had simple and 50/151 (33%) complex febrile seizures; 17/151 (11%) had seizures lasting 18–60 min, 38/151 (25%) had multiple seizures and 12/151 (8%) had

Table 1
Selected cross-sectional studies analyzing cohorts of children presenting with febrile seizures (FS)/febrile status epilepticus (FSE).

First author, year	Material; technique	*N* (cases)	%HHV-6B pos cases	Age (cases)	*N* (controls)	%HHV-6B pos controls	Age (controls)	Remarks
Hukin J, 1998	Blood, saliva; Ab, nested PCR	35 FS	15/35 (43%)	Mean 16 mo	33 febrile	15/33 (45%)	Mean 12 mo	
Suga S, 2000	Blood; culture, Ab	105 FS	21/105 (20%)	Median 20 mo	N/A	N/A	N/A	Sz clustering and long sz higher in HHV6 pos group
Laina I, 2010	Plasma; Ab, qPCR	65 FS	8/65 (12%)	Mean 21 mo	85 febrile	0	N/A	2/65 (3%) were HHV-6A positive
Epstein L, 2012	Blood; Ab, qPCR	169 FSE	54/169 (32%)	Median 16 mo	N/A	N/A	N/A	0/75 CSF samples pos for HHV-6B
Farshadmoghadam et al. (2014)	Blood; qPCR	78 FS	44/78 (57%)	N/A	72 febrile	31/72 (43%)	N/A	Combined cases + controls Mean age = 9.11 mo
Francis JR, 2016	Nasal aspirate; qPCR	134 FS 17 FSE	17/143 (12%) total	Median 1.7 years	N/A	N/A	N/A	31/143 (22%) rhinovirus + 30/143 (21%) adeno + 28/143 (20%) entero + 19/143 flu +
Tembo J, 2018	Plasma; qPCR	97 FS 5 FSE	4/97 (4%) FS 2/5 (40%) FSE	Median 26.5 mo	95 febrile	10/95 (10.5%)	Median 20.0 mo	
Bartolini L, 2019	Saliva; ddPCR	30 FS 3 FSE	15/30 (50)% FS 1/3 (33%) FSE	Mean 2.1 years	51 febrile 46 healthy	19/51 (37%) 16/46 (35%)	Mean 5.9 years (febrile) 14.1 years (healthy)	Study also included (*n*, % HHV-6B pos): 24/57 (42%) acute sz in chronic epilepsy 4/12 (33%) new onset sz 2/13 (15%) new onset epilepsy

ddPCR = droplet digital PCR; qPCR = quantitative PCR; Ab = antibody testing; FS = febrile seizures; FSE = febrile status epilepticus; mo = months;N/A = not available; pos = positive; sz = seizures.

focal seizures. The proportion of cases presenting with complex febrile seizures was highest in the cohorts with influenza (8/19, 42%) and HHV-6 (7/17, 41%). No controls were enrolled, limiting interpretation of these data.

A Greek study (Laina et al., 2010) (Table 1) analyzed 65 children presenting with febrile seizures (duration and type were not specified) with a mean age of 21 months and identified primary HHV-6 infection in 10/65 (15%) of them by means of RT-PCR in plasma and antibody titers vs. 0/85 control children. Six of 10 (60%) had classic roseola. Eight of 10 (80%) were identified as HHV-6B and 2/10 (20%) as HHV-6A. Two of 10 (20%) children with primary HHV-6 infection vs. 8/52 (15%) without the infection had complex febrile seizures. This difference was not significant. The age of the control population was not clearly stated and overall 41/85 (49%) had positive HHV-6 IgG antibodies, indicating prior exposure to HHV-6.

A recent US study (Bartolini et al., 2018) (Table 1) enrolled 115 patients (mean age 6.3 years) all within 24 h of a single or multiple seizures, 51 age-matched controls (mean age 5.9 years) presenting with a febrile illness without seizures and 46 older healthy controls (mean age 14.1 years), whose samples were previously collected. Cases included 30 children with febrile seizures (simple and complex, mean age 2.1 years), three with FSE (mean age 8.6 years), 57 with breakthrough seizures in the context of epilepsy (mean age 8.5 years), 13 with new onset epilepsy (mean age 5.9 years), and 12 with first unprovoked seizure (mean age 7.9 years). Saliva was analyzed with ddPCR for HHV-6 A and B and EBV viral DNA and for a panel of neuroinflammatory cytokines with a bead-based assay. HHV-6B DNA was found in 46/115 (40%) of cases vs. 19/51 (37%) fever controls and 16/46 (35%) healthy controls, with no differences. When analyzing only the population of children presenting with febrile seizures, HHV-6B DNA was found in 15/30 (50%), a similar detection rate to that of fever controls aged less than four years (8/24, 33%). HHV-6A DNA was found in only 1/53 (2%) case of breakthrough seizure in the context of epilepsy. EBV DNA was also detected with no differences in 20/115 (17%) cases, 8/51 (16%) fever controls, and 13/46 (28%) healthy controls. IL-8 and IL-1β were increased in saliva of 32 random samples from cases compared with 30 fever controls: IL-8 cases mean (SD): 1158.07 pg/mL (1427.41); controls: 604.92 (754.04); $p = 0.02$. IL-1β 185.76 (230.57); controls 86.99 (187.39); $p = 0.0002$. IL-1β level correlated with HHV6 viral load ($p = 0.007$).

Similar results regarding viral data in a population of young children (mean age 15.9 months) with febrile seizures were described in an older Canadian study (Hukin et al., 1998) (Table 1). The investigators determined HHV-6 infection status in blood and saliva by means of nested PCR and antibody testing in 35 children aged six months–two years presenting with febrile seizures (18 simple and 17 complex, with no difference in incidence of acute or past HHV-6 infection) and 33 controls with a febrile illness. Acute HHV-6 infection was identified with no differences in 15/35 cases (43%) and 15/33 controls (45%). Evidence of past HHV-6 infection was demonstrated in 13/35 (37%) febrile seizure patients and in 8/33 (24%) controls.

Status epilepticus in the context of a febrile illness is also a topic of particular interest in consideration of possible involvement of neurotropic viruses such as HHV-6. The Consequences of Prolonged Febrile Seizures in Childhood (FEBSTAT) study (Epstein et al., 2012) (Table 1) utilized qPCR analysis of blood from children aged one month–five years presenting with FSE. No HHV-6A infections were identified. HHV-6B viremia was found in 54/169 children (32%), including 38 with primary infection and 16 with reactivated infection. Twelve of 169 (7%) children had HHV-7 viremia, including eight with primary and four with reactivated infection. The investigators concluded that HHV-6 infection is commonly associated with febrile status epilepticus, based on a comparison with historical controls represented by young children with acute febrile illness, in which HHV-6 DNA detection rate was 160/1653 (9.7%) (Hall et al., 1994). These results in blood are different than recently reported in saliva (Bartolini et al., 2018), where HHV-6 DNA detection in children with acute febrile illness but no seizures was higher (19/51, 37%), and comparable to FEBSTAT observations in blood from children with status epilepticus. While saliva and blood represent different biological compartments, it is interesting to note that prior studies showed similar results when comparing HHV-6 DNA detection in saliva and blood from febrile infants (Clark et al., 1997), healthy adults (Jarrett et al., 1990; Cone et al., 1993) and patients with DRESS (Descamps et al., 2013). This discrepancy in detection rates highlights the need for further studies analyzing blood and saliva from simultaneous cases and controls.

FEBSTAT investigators also analyzed MRI findings both acutely and at one-year follow-up and showed a direct correlation at one year between febrile status epilepticus and development of HS. Interestingly, on multivariate analysis and after adjusting for age, cases where HHV-6/HHV-7 viremia was detected showed more hippocampal growth bilaterally (Lewis et al., 2014), perhaps indicating a “protective” effect of the infection. Considering that the effects of chronic HHV-6 infections may take years to develop, a longer follow-up would probably shed more light on these preliminary findings and possibly clarify the role of HHV-6 infection in the development of HS further.

A recent case–control study conducted in Zambia (Tembo et al., 2018) (Table 1) enrolled 102 children with first febrile seizure of any kind (median age 26 months) and 95 controls with a febrile illness without seizures (median age 20 months) and analyzed plasma by RT-PCR. Six of 102 (6%) cases tested positive for HHV-6B, vs. 10/95 (10.5%) controls, with no differences. No specimens were positive for HHV-6A. Within the children with FS the investigators found HHV-6B infection to be associated with FSE (OR, 15; 95% CI, [1.99–120]; $p = 0.009$). This result needs to be interpreted with caution, considering that only five cases of FSE were enrolled and two of them were HHV-6B positive.

In summary, the literature reports mixed results regarding frequency of HHV-6B infection in children presenting with febrile seizures, possibly due to different biological compartments analyzed (saliva vs. blood), and different detection techniques. The majority of studies that utilized a simultaneous control population (often consisting of age-balanced children with a febrile illness and no seizures) did not find significant differences. Febrile status epilepticus may represent a specific population of interest where HHV-6B infection could play a role, but additional large studies collecting blood and saliva from cases and simultaneous controls that are balanced for age are needed to test this association, and potentially reach stronger conclusions.

3. Temporal lobe epilepsy

Mesial temporal lobe epilepsy, a common epilepsy syndrome, often is associated with HS, with pathological features of neuronal cell loss and gliosis (Engel, 2001). A study using RT-PCR (Donati et al., 2003) detected HHV-6B in brain specimens of 4/8 (50%) patients with MTLE and 0/7 patients with neocortical epilepsy. The authors detected viral antigen in GFAP–positive glia in the same specimens of patients with MTLE. In a subsequent study (Fotheringham et al., 2007), HHV-6B viral DNA was detected by TaqMan PCR in brain specimens from 11/16 (68%) additional patients with MTLE and 0/7 additional patients without MTLE. A larger study (Kawamura et al., 2015) enrolled 75 patients with MTLE (52 with HS and 23 without) and examined resected amygdala, hippocampus and uncus by real-time PCR for viral DNA, reverse-transcriptase PCR for viral mRNA and TaqMan Gene Expression Assay. HHV-6 DNA was detected in 15/66 (23%) of hippocampi specimens and detection rate was higher in HS patients (14/15, 93%) than non-HS, so was viral load. mRNA expression was not detected in any specimen which tested positive for HHV-6 DNA, suggesting that no reactivation had occurred in HS patients and that latent infection may play a pathogenic role. No HHV-6A positive sample was identified. Host gene expression levels in amygdala of patients with HS revealed higher expression of MCP-1 and GFAP in HHV-6 positive

samples and a positive correlation between viral load and protein expression. Overexpression of these proteins results in neuronal loss and gliosis and has been previously described in resected epileptogenic tissue from the hippocampus (Xu et al., 2011). MCP-1 is a chemokine that participates in regulation of migration and infiltration of monocytes and macrophages, cells in which HHV-6 can establish latent infection; overexpression of MCP-1 can increase migration of infected cells into the amygdala and facilitate chronic changes.

A recent meta-analysis (Wipfler et al., 2018) included 10 studies with a total cohort of 645 MTLE cases (456/645, 71% with associated HS) and 136 controls. The pooled analysis showed higher HHV-6 DNA detection rate in pathological specimens from patients with MTLE (126/645, 19.5%) than controls (14/136, 10.3%) ($p < 0.05$). Interestingly, 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 detectable HHV-6 DNA had a history of febrile seizures (no distinction was made in terms of features or duration, for example febrile status epilepticus vs. simple or complex febrile seizures) compared with 94/519 (18%) MTLE patients without detectable HHV-6 DNA, suggesting that febrile seizures due to HHV-6 infection may trigger a chronic insidious pathogenic mechanism contributing to the development of MTLE.

In summary, several studies and a recent meta-analysis suggest a pathogenic role of HHV-6B infection in the development of MTLE, especially when associated with HS, and with a history of febrile seizures.

4. HHV-6 encephalitis

Seizures and, less frequently, status epilepticus (Chordia and Chandrasekar, 2014; Shahani, 2014) have been described during the course of HHV-6 encephalitis, which is a rare disorder, especially in the immunocompetent host. Its reported incidence is 0–12% after bone marrow or peripheral blood stem cell transplantation and 5–21% after cord blood transplant (Ogata et al., 2015; Wainwright et al., 2001). In the California Encephalitis Project, only four immunocompetent children of 1000 patients enrolled tested positive for HHV-6 by means of PCR (Isaacson et al., 2005). Other studies have reported HHV-6 encephalitis in immunocompetent children during the course of roseola (Asano et al., 1992; Kawamura et al., 2011; de Ory et al., 2013). A Japanese nationwide survey (Yoshikawa et al., 2009) from 2293 hospitals between 2003 and 2004 reported 86 cases of roseola-associated encephalitis, identified by serology (53 patients) and PCR (33 patients), mostly in children younger than two years. Forty-three of 60 patients (72%) had seizures and altered mental status and 17/60 (28%) had isolated seizures. HHV-6 DNA was found in 21/39 (54%) of patients whose cerebrospinal fluid was tested.

HHV-6 encephalitis is rare, and usually seen in the immunocompromised adult during reactivation or secondary infection. There have been several reports of roseola-associated encephalitis in young children and, like in other forms of encephalitis, seizures are often part of the clinical presentation.

5. Proposed mechanisms associated with epileptogenesis following HHV-6 infection

While classic inflammatory changes are lacking from TLE surgical specimens, pathological analyses revealed that HHV-6 has both neuroinvasive and proinflammatory properties, with ability to infect astrocytes (Fig. 1) and oligodendrocytes (Opsahl and Kennedy, 2005) leading to increased production of different inflammatory mediators, including IL-1β, IFN-α and TNF-α. HHV-6 can also infect T cells, with the result of reduced IL-10 and IL-14 gene expression, suggesting that

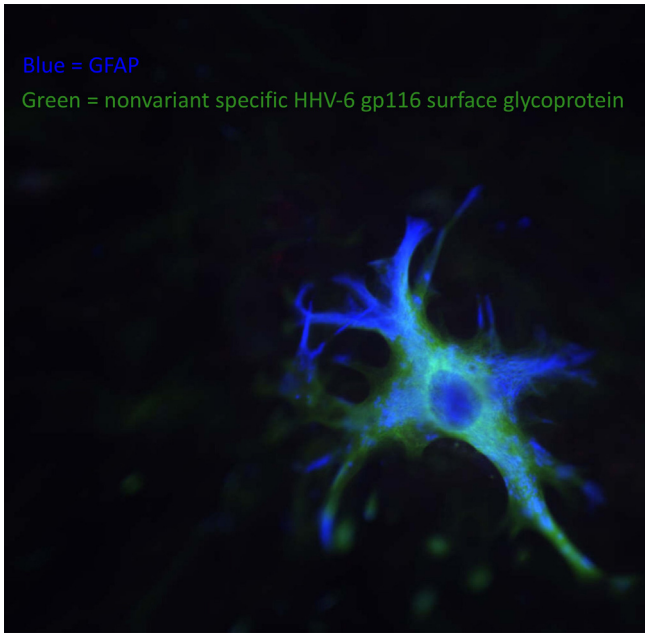

Fig. 1. HHV-6 isolated and cultured primary astrocyte from HHV-6B positive mesial temporal lobe epilepsy resected tissue. Cells were stained for the nonvariant specific HHV-6 gp116 surface glycoprotein (green) and glial fibrillary acidic protein (GFAP, blue) as a marker for astrocytes.
Modified from Fotheringham et al., 2007. Association of human herpesvirus-6B with mesial temporal lobe epilepsy. PLoS Med. 4(5):e180 (Original figure under Creative Commons Attribution license).

HHV-6 infection favors a T helper 1 proinflammatory response (Mayne et al., 2001). Another key aspect of HHV-6B adaptive immune response modulation, is binding to CD46 leading to T cell induction of IL-17 (Yao et al., 2010), and inhibition of IL-10 production (Astier et al., 2006) (Fig. 2). This mechanism involving complement activation may contribute to neuroinflammation as described for example in infected patients affected by multiple sclerosis (Alvarez-Lafuente et al., 2009).

The mechanisms by which latent HHV-6B infection reactivates following primary infection or causes direct damage from persistent subclinical active infection are incompletely understood (Campadelli-Fiume et al., 1999). In vitro infection with HHV-6 of astrocyte cultures showed a significant decrease in glutamate transporter EAAT2 expression (Fotheringham et al., 2007). Classic inflammatory changes such as cellular infiltrates are lacking in resected epileptogenic tissue where HHV-6 is detected, and evidence points to other mechanisms mediated by inflammatory mediators such as chemokines/cytokines. Gene expression studies showed upregulation of GFAP and MCP-1 in amygdala of MTLE patients with HHV-6 infection and a positive correlation between expression level and viral load (Kawamura et al., 2015) and in resected epileptogenic tissue from the hippocampus (Xu et al., 2011). Higher expression of these proteins results in inflammatory changes including gliosis and neuronal loss, which may contribute to development of MTLE (Ortinski et al., 2010; Robel et al., 2015). MCP-1 regulates migration and infiltration of macrophages and monocytes. HHV-6 can establish latent infection in these cells; therefore, increased expression of MCP-1 can facilitate migration of infected cells into the amygdala and induce chronic changes seen in MTLE. Similarly, leukocyte chemoattraction mediated by U83, a chemokine-like protein encoded by the virus that promotes monocyte and macrophage infiltration was observed (Reynaud and Horvat, 2013). Other studies suggest a possible role of the transcription factor NF-κB in patients with HHV-6 infection who develop MTLE (Li et al., 2011).

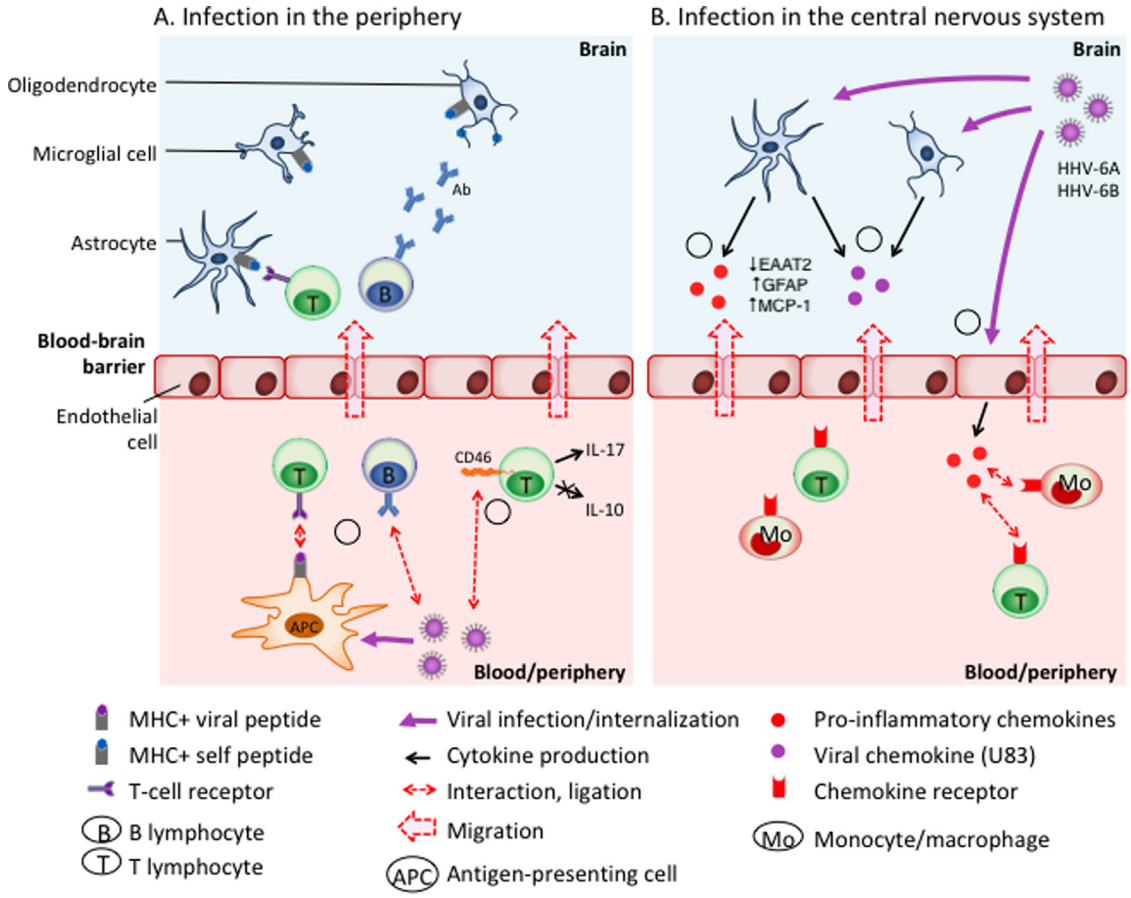

Fig. 2. Potential pathways for neuroinflammation triggered by HHV-6 infection in the periphery (left) and CNS (right). (a) Molecular mimicry between viral proteins and brain proteins: HHV-6A or -6B infection in the periphery may activate cross-reactive T and B cells, promoting lymphocyte infiltration in the CNS, resulting in cytotoxic effects against resident cells, particularly those that express myelin antigens such as oligodendrocytes (1). Through CD46 binding, peripheral infection could induce IL-17 and inhibit IL-10 production by T cells (2). (b) Infection of astrocytes with release of several neuroinflammatory mediators, promoting leukocytes infiltration (3). Production of the viral chemokine U83 by infected CNS cells, also promoting leukocyte infiltration (4). Infection of endothelial cells with production of chemokines, facilitating the passage of leukocytes through the blood-brain barrier (5).
Modified from Reynaud and Horvat, 2013. Human Herpesvirus 6 and Neuroinflammation. ISRN Virology, vol. 2013, Article ID 834890, 11 pages. https://doi.org/10.5402/2013/834890 (Original figure under Creative Commons Attribution license).

6. Conclusions

The spectrum of HHV-6 related neurological diseases has considerably expanded over the past decade and several studies have confirmed a link between infection with this neurotropic virus and acute seizures in children and in some cases with later development of epilepsy. Growing data from specimens, including blood, saliva and resected epileptogenic tissue, have revealed a complex interplay of inflammatory mechanisms that may be trigger by HHV-6 infection and may play an important role in epileptogenesis and acute seizure generation, potentially representing an early therapeutic target.

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