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REVIEW



Prevention and treatment of temporal lobe epilepsy: lessons from hepatitis B story!

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ABSTRACT

Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy and hippocampal sclerosis (HS) is the most common pathological substrate of TLE. Considering the significant consequences of uncontrolled seizures (e.g. increased morbidity and mortality), epilepsy prevention remains a necessity that potentially could save many lives. Human herpes virus-6 (HHV-6) has been linked to TLE in humans. The relationship between HHV-6 and HS-TLE could be attributed to a neuro-inflammatory cascade triggered by the infection, involving direct neuronal damage and production of several pro-inflammatory cytokines under certain conditions that are still incompletely understood. Hepatitis B virus (HBV) infection is another chronic viral infection with a life-long latency. HBV infection is linked to various clinical conditions, including liver cirrhosis. There are currently three ways to fight HBV infection and its consequences; primary prevention (by vaccination), secondary prevention (by drug therapy), and tertiary prevention (by liver transplantation). Considering the similarities between the natural histories of HHV-6 and HBV infections, and also the successful strategies which are currently available to fight HBV infection and its long-term consequences, here, we propose three strategies to fight HHV-6 and its possible long-term consequence (i.e. HS-TLE): Primary prevention: by developing vaccines to prevent HHV-6 infection; Secondary prevention: by considering trials of antiviral drugs to treat HHV-6 infection, when it happens in the childhood to hopefully prevent its long-term consequences; and, Tertiary prevention: by stem cell therapy for drug-resistant epilepsy.

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Introduction

Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy [1] and hippocampal sclerosis (HS), also known as mesial temporal sclerosis (MTS), is the most common pathological substrate of TLE [2]; more than two-thirds of patients with drug-resistant TLE have signs of HS on their brain MRIs [1]. It is estimated that in the USA [3], from a drug resistant HS-TLE prevalence population of about 200,000 patients, as many as 143,000 to 191,000 patients still suffer from drug-resistant seizures and are in need of treatment, and the patient numbers continue to grow (incidence of 3.1 – 3.4 cases per 100,000 people per year) [3]. Unfortunately, history has shown us that while epilepsy surgery is a valuable option for many patients with drug-resistant HS-TLE, it does not work well for all [4]. Therefore, considering the significant consequences of uncontrolled seizures (e.g. increased morbidity and mortality) [5,6], epilepsy prevention

remains a necessity that potentially could save many lives, improve quality of life for many patients and reduce the costs associated with pharmaco-resistant epilepsy for healthcare systems.

The aim of the current narrative review is to study the link between human herpes virus-6 (HHV-6) and TLE in humans and to propose hypothetical strategies for prevention and treatment of TLE. Considering the similarities between the natural histories of HHV-6 and hepatitis B virus (HBV) infections, in order to make the proposed hypotheses more understandable, we have used the successful models that have been achieved for HBV infection in the scientific history (i.e. primary, secondary, and tertiary prevention strategies) as comparable examples.

Human herpes virus-6 and epilepsy

Human herpes virus-6 (HHV-6) has been linked to TLE in humans [7,8]. There are two viral species HHV-6A

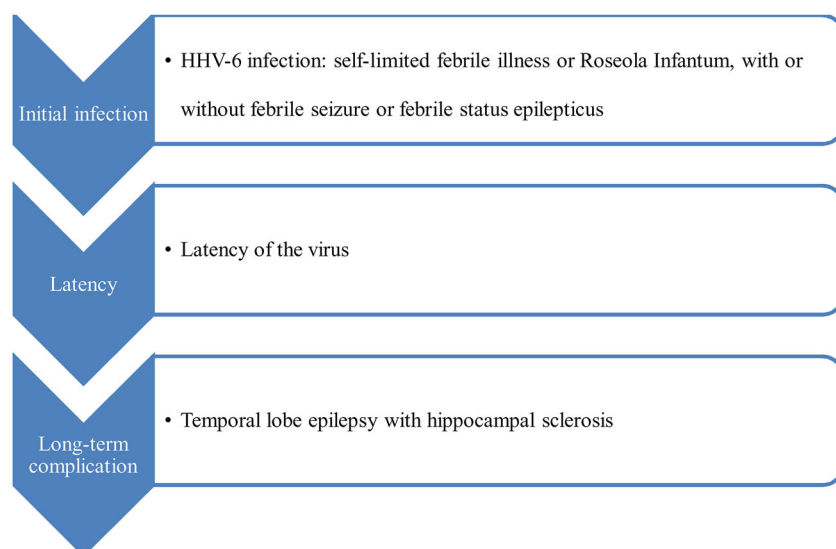


Figure 1. Natural history of human herpes virus-6 (HHV-6) infection to hippocampal sclerosis.

and B; they share 90% homology [7]. It is an enveloped DNA virus that belongs to the β -herpesviridae family [7]. HHV-6 has both neuro-invasive and pro-inflammatory properties, with the ability to infect astrocytes and oligodendrocytes leading to increased production of various inflammatory mediators, such as IFN- α and TNF- α [7]. There are several studies confirming the detection of HHV-6 DNA in hippocampal brain tissue of patients with HS-TLE [7–9]. The primary viral infection often occurs in early life and results in a self-limited febrile illness; in a portion of children Roseola Infantum (Exanthema Subitum or Sixth Disease) develops [10]. This is followed by life-long latency of the virus in various cell lines, including neural cells [11]. The mechanisms by which latent HHV-6 infection reactivates or causes damage from persistent subclinical active infection are not completely understood [7]. The relationship between HHV-6 and HS-TLE could be attributed to the epigenetic modifications and integration of the virus in the chromosome that might cause dysregulation of neuronal cells that reduces their capacity to regulate neurotransmitters [8,12]. Alterations in blood brain barrier permeability and also direct neuronal damage and death are other possible mechanisms by which HHV-6 may cause epilepsy [7,13].

The significance of initial precipitating events among patients with HS-TLE has long been recognized [14]; febrile seizures have been associated with later development of HS-TLE. On the other hand, detection of HHV-6 viral DNA in blood, saliva and CSF of children with febrile seizures has ranged from 8 to 40% in various studies [14,15]. In a prospective study [16], the authors concluded that HHV-6B infection is commonly associated with febrile status epilepticus, a condition

associated with an increased risk of hippocampal injury and subsequent HS-TLE. Although, the relations between HHV-6, febrile seizure and HS-TLE is still controversial and not confirmed yet [14,17], **Figure 1** shows a plausible schematic course of the initial HHV-6 infection and febrile seizure potentially leading to HS-TLE.

Lessons to learn from hepatitis B virus

Hepatitis B virus (HBV) infection is another chronic viral infection with a life-long latency. HBV infection is linked to various clinical conditions, including acute or fulminant hepatitis, various forms of chronic infection, cirrhosis, and hepatocellular carcinoma [18]. In occult HBV infection, HBV DNA may persist in two forms: episomal free cccDNA or integration into the DNAs of hepatocytes. The mechanism of liver damage due to occult HBV infection is still not well elucidated; some data imply the persistence and transcription of HBV cccDNA in hepatocytes and subsequently, production of cytokines, such as TNF- α and interferon- γ , that may result in damage to hepatocytes [18]. **Figure 2** shows a schematic course of the initial HBV infection to the end result of liver cirrhosis and hepatocellular carcinoma. Therefore, while there exist some differences, there are significant similarities between the natural history of HBV infection resulting in liver cirrhosis and that of HHV-6 potentially leading to HS-TLE.

There are currently three ways to fight HBV infection and its consequences; primary prevention (by vaccination), secondary prevention (by drug therapy), and tertiary prevention (by liver transplantation) [19]. Vaccines against HBV infection are highly effective

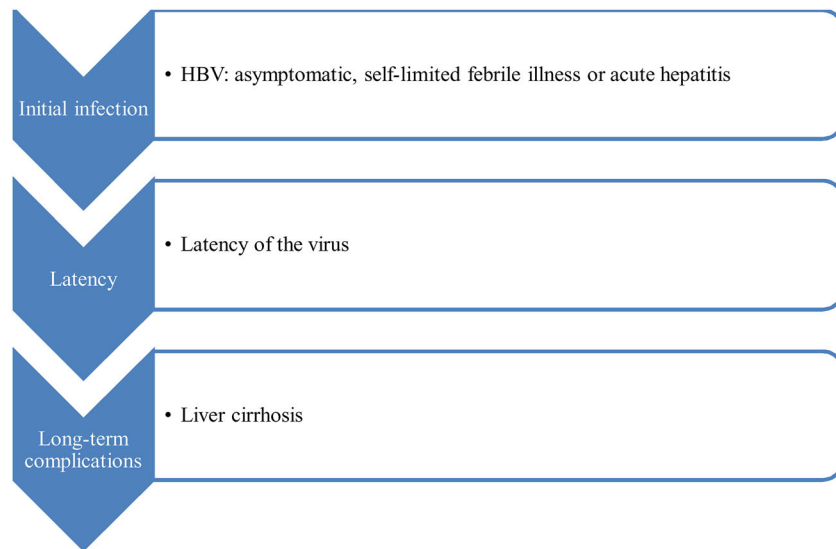


Figure 2. Natural history of hepatitis B virus (HBV) infection to liver cirrhosis.

[20]. There are reports showing a decline in the prevalence of HBV infection following the implementation of infant vaccination programs, and also demonstrating a decline in the incidence of long-term complications of chronic HBV infection in children and young adults [20]. In addition, two types of treatment have currently been approved for HBV infection: pegylated interferons or nucleos(t)ide analogues (lamivudine, adefovir, entecavir, tenofovir disoproxil, or tenofovir alafenamide) [21]. These treatments are effective in suppressing HBV replication and in decreasing the risk of developing cirrhosis and hepatocellular carcinoma [22]. Finally, liver transplantation is a successful strategy to help patients affected with chronic and long-term consequences of HBV infection [23,24].

Considering the similarities between the natural histories of HHV-6 and HBV infections, and also the successful strategies which are currently available to fight HBV infection and its long-term consequences, here, we propose the following strategies to fight HHV-6 and its possible long-term consequence (i.e. HS-TLE). These proposals gain more significance when we look at the burden of HS-TLE and the current available therapeutic options for the affected patients [3,4].

1. Primary prevention: it is helpful to think about developing vaccines to prevent HHV-6 infection. Currently, there is no vaccine available against this virus and as a matter of fact, when we searched the PubMed on April 10, 2019, with key words of “HHV-6” or “human herpesvirus 6” and “vaccine”, it yielded no relevant papers. However, a recent paper [25] identified HHV-6B epitopes (CD4⁺ and H-2K^d-restricted CD8⁺ T-cell epitopes

on the glycoprotein Q1) that are recognizable by T-cells and could contribute to the development of potential vaccines in the future [25].

2. Secondary prevention: it is helpful to think about using antiviral drugs to treat HHV-6 infection when it happens in the childhood to hopefully prevent its long-term consequences (i.e., HS-TLE). The antiviral compounds ganciclovir, foscarnet, artesunate, and cidofovir may be effective against HHV-6 infection, but these are not formally approved therapies and the indications for treatment are not clear yet [26,27]. Designing future studies to investigate and clarify the indications for treatment of HHV-6 and usefulness of this strategy to prevent the possible long-term consequences of this infection (i.e., HS-TLE) is a difficult task that is worthy of consideration by the scientific community. A potential cohort of patients in which such a trial might be considered is children presenting with febrile status epilepticus. Potential challenges in designing such a trial are: 1. enrollment, which would likely require a multi-center approach and substantial funding to reach to a sufficient number of participants; 2. definition of study outcomes: HS-TLE may develop years after the initial insult and it may prove to be very difficult to follow enrolled children for such a long time to define the impact of the investigational drug; and finally 3. ethical implications of utilizing a treatment that has no clear immediate benefit for the child.
3. Tertiary prevention: it is helpful to think about this strategy with the hope to help those who have already been affected by drug-resistant HS-

TLE. Despite the fact that there is nothing immediate in the pipeline, neural stem cell transplantation into the hippocampus might offer an alternative therapy to hippocampal resection in patients with drug-resistant HS-TLE in the future [28]. Application of stem cell therapy for drug-resistant epilepsy is currently under investigation and preliminary, but promising results have been obtained [29].

Conclusion

Temporal lobe epilepsy is the most common type of drug-resistant epilepsy and considering the significant consequences of uncontrolled seizures, epilepsy prevention remains a necessity that potentially could save many lives, improve quality of life of many patients, and reduce the costs associated with pharmaco-resistant epilepsy for healthcare systems. Human herpes virus-6 has been linked to TLE. The relationship between HHV-6 and HS-TLE could be attributed to alterations of host gene expression leading to direct neuronal damage and production of pro-inflammatory mediators. In addition, HHV-6 may not be completely benign in immunocompetent people. It can be associated with encephalitis and poor prognosis [30]. HBV infection is another chronic viral infection with a life-long latency. HBV infection is linked to various clinical conditions, including liver cirrhosis. There are currently three ways to fight HBV and its consequences; primary prevention (by vaccination), secondary prevention (by drug therapy), and tertiary prevention (by liver transplantation). Considering the similarities between the natural histories of HHV-6 and HBV infections, it is reasonable to design future studies to develop vaccines to prevent HHV-6 infection or antiviral drugs to treat HHV-6 infection. These strategies may also potentially prevent other consequences of HHV-6 [31,32]. Finally, stem cell transplantation into the hippocampus may help patients with drug-resistant HS-TLE in the future. For all these hypotheses to be more plausible and appealing to the scientific community, first we should clarify the exact link between HHV-6 and TLE and its natural history in humans by performing well-designed large scale longitudinal studies. In spite of some contradictory studies [15,33], the spectrum of HHV-6 related neurological diseases has considerably expanded over the past few years and many studies and a recent meta-analysis suggest a pathogenic role of HHV-6B infection in the development of TLE, especially when associated with HS, and with a history of febrile seizure(s) [7].

Disclosure statement

No potential conflict of interest was reported by the author(s).

References

- [1] Engel J, Jr, McDermott MP, Wiebe S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA*. 2012;307(9):922–930.
- [2] Wiebe S. Epidemiology of temporal lobe epilepsy. *Can J Neurol Sci*. 2000; 27(01):S6–S10.
- [3] Asadi-Pooya AA, Stewart GR, Abrams DJ, et al. Prevalence and incidence of drug-resistant mesial temporal lobe epilepsy in the United States. *World Neurosurg*. 2017; 99:662–666.
- [4] Asadi-Pooya AA, Rostami C. History of surgery for temporal lobe epilepsy. *Epilepsy Behav*. 2017; 70:57–60.
- [5] Asadi-Pooya AA, Nikseresht AR, Yaghoobi E, et al. Physical injuries in patients with epilepsy and their associated risk factors. *Seizure*. 2012;21(3):165–168.
- [6] Sperling MR, Barshow S, Nei M, et al. A reappraisal of mortality after epilepsy surgery. *Neurology*. 2016; 86(21):1938–1944.
- [7] Bartolini L, Theodore WH, Jacobson S, et al. Infection with HHV-6 and its role in epilepsy. *Epilepsy Res*. 2019; 153:34–39.
- [8] Wipfler P, Dunn N, Beiki O, et al. The viral hypothesis of mesial temporal lobe epilepsy - is human herpes virus-6 the missing link? A systematic review and meta-analysis. *Seizure*. 2018; 54:33–40.
- [9] Ablashi D, Agut H, Alvarez-Lafuente R, et al. Classification of HHV-6A and HHV-6B as distinct viruses. *Arch Virol*. 2014;159(5):863–870.
- [10] Zerr DM, Meier AS, Selke SS, et al. A population-based study of primary human herpesvirus 6 infection. *N Engl J Med*. 2005;352(8):768–776.
- [11] Yao K, Crawford JR, Komaroff AL, et al. Review part 2: human herpesvirus-6 in central nervous system diseases. *J Med Virol*. 2010;82(10):1669–1678.
- [12] Engdahl E, Dunn N, Niehusmann P, et al. Human herpesvirus 6 B induces hypomethylation on chromosome 17p13.3, correlating with increased gene expression and virus integration. *J Virol*. 2017; 91:e02105–16.
- [13] Bartolini L, Libbey JE, Ravizza T, et al. Viral triggers and inflammatory mechanisms in pediatric epilepsy. *Mol Neurobiol*. 2019;56(3):1897–1907.
- [14] Shukla G, Prasad AN. Natural history of temporal lobe epilepsy: antecedents and progression. *Epilepsy Res Treat*. 2012; 2012:195073.
- [15] Bartolini L, Piras E, Sullivan K, et al. Detection of HHV-6 and EBV and cytokine levels in saliva from children with seizures: results of a multi-center cross-sectional study. *Front Neurol*. 2018; 9:834.
- [16] Epstein LG, Shinnar S, Hesdorffer DC, et al. Human herpesvirus 6 and 7 in febrile status epilepticus: the FEBSTAT study. *Epilepsia*. 2012;53(9):1481–1488.
- [17] Asadi-Pooya AA, Nei M, Rostami C, Sperling MR. Mesial temporal lobe epilepsy with childhood febrile seizure. *Acta Neurol Scand*. 2017;135(1):88–91.
- [18] Makvandi M. Update on occult hepatitis B virus infection. *World J Gastroenterol*. 2016;22(39):8720–8734.

- [19] Whitford K, Liu B, Micallef J, et al. Long-term impact of infant immunization on hepatitis B prevalence: a systematic review and meta-analysis. *Bull World Health Org.* 2018;96(7):484–497.
- [20] Leoni MC, Ustianowski A, Farooq H, et al. HIV, HCV and HBV: a review of parallels and differences. *Infect Dis Ther.* 2018;7(4):407–419.
- [21] Tang LSY, Covert E, Wilson E, et al. Chronic hepatitis B infection: a review. *JAMA.* 2018;319(17):1802–1813.
- [22] Suk-Fong Lok A. Hepatitis B treatment: what we know now and what remains to be researched. *Hepatol Commun.* 2019;3(1):8–19.
- [23] Li W, Li L, Han J, et al. Liver transplantation vs liver resection in patients with HBV-related hepatocellular carcinoma beyond Milan criterion: a meta-analysis. *Clin Transplant.* 2018;32(3):e13193.
- [24] Ferrarese A, Zanetto A, Russo FP. Hepatitis B and liver transplantation. *Minerva Gastroenterol Dietol.* 2018; 64(2):147–157.
- [25] Nagamata S, Aoshi T, Kawabata A, et al. Identification of CD4 and H-2K(d)-restricted cytotoxic T lymphocyte epitopes on the human herpesvirus 6B glycoprotein Q1 protein. *Sci Rep.* 2019;9(1):3911.
- [26] Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev.* 2015;28(2):313–335.
- [27] Milbradt J, Auerochs S, Korn K, et al. Sensitivity of human herpesvirus 6 and other human herpesviruses to the broad-spectrum anti-infective drug artesunate. *J Clin Virol.* 2009;46(1):24–28.
- [28] Hattiangady B, Shetty AK. Neural stem cell grafting in an animal model of chronic temporal lobe epilepsy. *Curr Protoc Stem Cell Biol.* 2011; 2: 2D.7.
- [29] Hlebokazov F, Dakukina T, Ihnatsenko S, et al. Treatment of refractory epilepsy patients with autologous mesenchymal stem cells reduces seizure frequency: an open label study. *Adv Med Sci.* 2017;62(2): 273–279.
- [30] You SJ. Human herpesvirus-6 may be neurologically injurious in some immunocompetent children. *J Child Neurol.* 2020;35:132–136. Oct 21. [Epub ahead of print].
- [31] Stevanović V, Barušić Z, Višković K, et al. Acute necrotizing encephalopathy of childhood associated with human herpes virus 6 in Croatia. *Neurol Sci.* 2019;40(3):639–641.
- [32] Tsukahara A, Nakajima H, Hosokawa T, et al. Human herpes virus 6 brainstem encephalitis in a patient with primary macroglobulinemia. *Neurol Sci.* 2017; 38(3):507–508.
- [33] Esposito L, Drexler JF, Braganza O, et al. Large-scale analysis of viral nucleic acid spectrum in temporal lobe epilepsy biopsies. *Epilepsia.* 2015;56(2):234–243.