

# Learning More About HHV-6 Encephalitis

Joseph R. Berger, MD

*Neurol Neuroimmunol Neuroinflamm* 2021;8:e948. doi:10.1212/NXI.0000000000000948

## Correspondence

Dr. Berger  
joseph.berger@  
pennmedicine.upenn.edu

In this issue of *Neurology*<sup>®</sup> *Neuroimmunology & Neuroinflammation*, a retrospective study using an institutional virology database addresses the clinical nature, radiologic findings, and biological underpinnings of human herpesvirus 6 (HHV-6) encephalitis. The data had been accumulated systematically over a decade and included all individuals from whom blood or CSF had tested positive for HHV-6 DNA. From a cohort of 926 individuals tested for HHV-6, 45 individuals met the criteria of HHV-6 febrile seizures or encephalitis. This population comprised 30 children or adolescents and 15 adults (older than 18 years old); 28 (62%) were immunocompromised and 17 (38%) were immunocompetent. Efforts were made to identify individuals with chromosomally integrated HHV-6 DNA (ciHHV-6) by testing hair follicles for the presence of HHV-6 DNA in those with exceedingly high copy numbers of HHV-6 DNA in blood and CSF.

HHV-6 was first recognized to be associated with human disease in 1988 when it was isolated from the peripheral blood mononuclear cells of children with exanthem subitum (roseola infantum).<sup>1</sup> As with herpesviruses, HHV-6 is an enveloped, double-stranded DNA virus that has an electron-dense core surrounded by an icosahedral nucleocapsid. There are 2 variants of HHV-6, variant A and variant B, distinguished by nucleotide sequences, cellular tropism, and antibody reactivity. HHV-6 is a member of the beta human herpes virus family and establishes latency in a broad range of tissues including salivary glands, tonsils, kidneys, liver, and lymph nodes.<sup>2</sup> Saliva is believed to be the major vector of transmission.<sup>3</sup> HHV-6 is ubiquitous; more than 80% of the adult population<sup>4</sup> has serologic evidence of previous infection. Unlike other herpesviruses, HHV-6 may chromosomally integrate and ciHHV-6 is found in approximately 1% of the population.<sup>5</sup> As noted by the authors, the presence of ciHHV-6 may distort the numbers of patients labeled with febrile seizures or encephalitis attributed to HHV-6.

Primary infection with HHV-6 results in roseola, a self-limited disease in infants and children characterized by fever, rash, pharyngitis, and usually mild systemic symptoms lasting 3 days on average. Neurologic complications of primary HHV-6 infection include febrile seizures, a complication observed in 13% of infected children.<sup>6</sup> These seizures may differ from febrile seizures accompanying other infections because they are more often partial or prolonged or associated with postictal paralysis.<sup>7</sup> Occasionally, encephalitis, including cerebellitis<sup>8</sup> and rhombencephalitis<sup>9</sup> may accompany roseola.

The prototypical HHV-6 encephalitis in adults is a limbic encephalitis that follows hematopoietic stem cell transplantation (HSCT). This entity has been referred to as *post-transplantation acute limbic encephalitis* (PALE). PALE is characterized by fever, behavioral changes, and seizures with medial temporal lobe abnormalities typically seen on brain MRI. As the authors of this study demonstrate, the limbic abnormalities on MRI are not universally present; only 2-thirds of their patients had brain MRI abnormalities, and their appearance may require several days from symptom onset to develop. Quite reasonably, the authors recommend that all HSCT recipients with altered mental status or seizures have CSF HHV-6 studies. They emphasize the value of detecting HHV-6 in the blood in suspected cases because not all the patients with unexplained neurologic symptoms attributed to HHV-6 after HSCT demonstrated viral DNA in their CSF.

## RELATED ARTICLE

Human Herpesvirus  
6 Encephalitis in  
Immunocompetent and  
Immunocompromised  
Hosts

Page e942

From the Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Go to [Neurology.org/NN](https://www.neurology.org/NN) for full disclosures. Funding information is provided at the end of the article.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License 4.0 (CC BY-NC-ND), which permits downloading and sharing the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Although individual case reports of meningoencephalitis<sup>10</sup> and focal encephalitis<sup>11</sup> attributed to HHV-6 have been reported in immunocompetent persons, the immunocompetent subjects with HHV-6 encephalitis in this study were all were infants younger than 2 years with primary infection. The authors propose that high viral copy numbers in the blood and CSF of immunocompetent with encephalitis most likely represents the presence of ciHHV-6, leading to misdiagnosis and a delay in establishing and treating the correct diagnosis. They recommend that testing for HHV-6 in immunocompetent individuals be limited to infants younger than 3 years of age developing seizures or encephalopathy in association with a fever who have suspected primary HHV-6 infection. Although some of the previous reports of HHV-6 encephalitis in immunocompetent individuals may have been the consequence of ciHHV-6, it is unlikely to account for all reported cases. For instance, in one elderly immunocompetent man with meningoencephalitis attributed to HHV-6, viral DNA was not only amplified from brain sections at the time of autopsy, but HHV-6 gp 102 protein was also demonstrated by immunohistochemical studies of neurons and glial cells,<sup>12</sup> an observation that would seem to refute that possibility that all HHV-6 encephalitis cases in immunocompetent subjects are due entirely to ciHHV-6. Therefore, additional confirmatory studies will be needed before the adoption of such a broad policy.

## Study Funding

No targeted funding reported.

## Disclosure

Disclosures available: [Neurology.org/NN](https://www.neurology.org/NN).

## References

1. Yamanishi K, Okuno T, Shiraki K, et al. Identification of human herpesvirus-6 as a causal agent for exanthem subitum. *Lancet* 1988;1:1065–1067.
2. Agut H, Bonnafous P, Gautheret-Dejean A. Laboratory and clinical aspects of human herpesvirus 6 infections. *Clin Microbiol Rev* 2015;28:313–335.
3. Rhoads MP, Magaret AS, Zerr DM. Family saliva sharing behaviors and age of human herpesvirus-6B infection. *J Infect* 2007;54:623–626.
4. Saxinger C, Polesky H, Eby N, et al. Antibody reactivity with HBLV (HHV-6) in U.S. populations. *J Virol Methods* 1988;21:199–208.
5. Pellett PE, Ablashi DV, Ambros PF, et al. Chromosomally integrated human herpesvirus 6: questions and answers. *Rev Med Virol* 2012;22:144–155.
6. Hall CB, Long CE, Schnabel KC, et al. Human herpesvirus-6 infection in children. A prospective study of complications and reactivation. *N Engl J Med* 1994;331:432–438.
7. Suga S, Suzuki K, Ihira M, et al. Clinical characteristics of febrile convulsions during primary HHV-6 infection. *Arch Dis Child* 2000;82:62–66.
8. Abu Sitta E, Khazan A, Luttmann K, Hanrahan J. HHV-6: an unusual cause of cerebellar ataxia. *BMJ Case Rep* 2020;13:e234303.
9. Crawford JR, Kadom N, Santi MR, Mariani B, Lavenstein BL. Human herpesvirus 6 rhombencephalitis in immunocompetent children. *J Child Neurol* 2007;22:1260–1268.
10. Birnbaum T, Padovan CS, Sporer B, et al. Severe meningoencephalitis caused by human herpesvirus 6 type B in an immunocompetent woman treated with ganciclovir. *Clin Infect Dis* 2005;40:887–889.
11. McCullers JA, Lakeman FD, Whitley RJ. Human herpesvirus 6 is associated with focal encephalitis. *Clin Infect Dis* 1995;21:571–576.
12. Portolani M, Tamassia MG, Gennari W, et al. Post-mortem diagnosis of encephalitis in a 75-year-old man associated with human herpesvirus-6 variant A. *J Med Virol* 2005;77:244–248.