# Human Herpesvirus 6 Infection of the Central Nervous System

*Mary T. Caserta, MD*

**Address**
University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Rochester, NY 14642, USA.
E-mail: mary_caserta@urmc.rochester.edu

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Human herpesvirus (HHV) 6 infects all children, usually during the first year of life. High fever is the hallmark of primary infection, with febrile seizures the most common complication. After primary infection, HHV-6 remains latent or persistent at multiple sites, with intermittent reactivation. Many disorders of the central nervous system (CNS) have been linked to HHV-6 reactivation, including chronic seizure disorders, encephalitis, and demyelinating disorders including multiple sclerosis. Although multiple studies have pieced together an understanding of the molecular organization, viral characteristics, immunology, and epidemiology of HHV-6, the true role of this virus in diseases of the CNS is still unfolding.

## Introduction

All eight of the currently known human herpesviruses (HHVs) were identified in the 20th century. The first five were recognized before 1965, more than 20 years before the relatively recent discovery of the remaining three members, beginning with HHV-6. In 1986, Salahuddin *et al.* [1] were the first to identify HHV-6 in the peripheral blood mononuclear cells (PBMCs) of patients with AIDS or lymphoproliferative disorders. Two years later, HHV-6 was reported as the etiologic agent of the childhood illness exanthem subitum (roseola infantum) [2]. Although much has been learned about disease because of primary infection with HHV-6, and initial associations with diseases caused by reactivation have been reported, our knowledge of the role of HHV-6 in diseases of the central nervous system (CNS) is still being defined.

## Background

Human herpesvirus 6 causes widespread human infection, with numerous studies demonstrating seropositivity in 85% or more of healthy adults. Age-specific serosurveys initially suggested that primary infection occurred during early childhood, with a peak seroprevalence of 100% at 2 to 3 years of life. Subsequent studies using viral isolation and serology demonstrated that primary infection with HHV-6 occurred in a relatively narrow window of time, with the mean age of acquisition at 6 to 9 months and essentially all children infected by age 2 to 3 years [3]. The most characteristic clinical presentation of primary infection is that of an undifferentiated highly febrile illness that lasts 3 to 6 days, with some children exhibiting the classic syndrome of roseola.

Two variants of HHV-6 have been identified, HHV-6A and HHV-6B (Table 1). Both are lymphotropic viruses classified in the Betaherpesvirinae subfamily with HHV-7 and cytomegalovirus, the other known human β-herpesviruses [4]. The complete nucleotide sequences of HHV-6 variant A and HHV-6 variant B have been determined and found to be highly conserved, with an overall 90% sequence identity [5]. Despite this conservation, the two variants can be distinguished by restriction fragment length polymorphisms, reactivity with monoclonal antibodies, differential growth in established cell lines, and epidemiology. HHV-6B is the predominant strain identified in children with primary infection and in immunocompromised hosts; much less is known about the clinical and epidemiologic characteristics of HHV-6A. After primary infection, HHV-6 remains persistent or latent at several sites in the body, with reactivation and reinfection demonstrated in normal and immunocompromised hosts.

## Primary Infection of the Central Nervous System

In 1949, Berenberg *et al.* [6] reported that convulsions were the most common complication of roseola, occurring in up to one third of patients. More recent research has expanded the spectrum of neurologic complications of primary infection with HHV-6 (Table 2). Prospective studies of children with first-time febrile seizures have demonstrated that 20% to 30% had primary HHV-6 infection. Approaching this issue from a different perspective, Hall *et al.* [3] evaluated 160 children with culture-documented primary HHV-6 infection and found seizures to be the most common complication, occurring in 13% of children, with a peak age of 12 to 15 months. Although some reports have not found a significant difference in the duration or characteristics of seizures in children with primary

**Table 1. Characteristics of HHV-6**

| | |
|---|---|
| Classification | *Roseolavirus* genus of Betaherpesvirinae subfamily |
| Molecular characteristics | 159–162-kb double-stranded DNA genome with a unique central segment and two direct repeats containing approximately 97 unique genes |
| Variants | HHV-6A and HHV-6B |
| Tissue culture | All variants produce lytic infection in coculture with primary cord blood mononuclear cells |
| Cellular receptor | CD46 or membrane cofactor protein, present on all nucleated cells, unknown if other molecules are needed |
| Sites of latency or persistence | Salivary glands, peripheral blood mononuclear cells, CNS, female genital tract |

CNS—central nervous system; HHV—human herpesvirus.

HHV-6 infection compared with children with seizures not caused by primary HHV-6 infection, the results of other studies have been contradictory. Suga *et al*. [7] found that children with primary HHV-6 infection had higher frequencies of partial seizures, prolonged seizures, postictal paralysis, and repeated seizures, compared with children with febrile seizures not associated with HHV-6. In another study limited to children with primary HHV-6 infection and seizures, one third of patients had prolonged seizures, 29% had focal seizures, and 38% had repeated seizures, suggesting more severe CNS involvement [8].

Case reports and small patient studies have described other complications of the CNS in children with primary HHV-6 infection, including encephalitis, acute disseminated demyelination, afebrile neonatal seizures, and acute cerebellitis [9–12]. Various methods of investigation have been used to establish the association between HHV-6 and CNS disease, including polymerase chain reaction (PCR) or viral culture of PBMCs, serum, or cerebrospinal fluid (CSF), and immunohistochemistry or in situ hybridization of tissue. No consistent clinical or laboratory findings have been recognized among these patients, making it impossible to identify a unique clinical presentation. The outcomes reported also have been mixed and have included fatal cases of meningoencephalitis and complete recovery without sequelae. Based on the findings published to date, it is generally accepted that primary HHV-6 infection often is complicated by febrile seizures. However, the pathophysiology of seizures associated with primary HHV-6 infection is unknown and may be attributed to direct viral invasion of the CNS or undefined indirect effects of infection.

## Human Herpesvirus 6 DNA Persistence

As with the other known HHVs, several lines of evidence suggest that primary HHV-6 infection is followed by the lifelong presence of the virus in the host. Latent infection of numerous cell types is supported by the detection of HHV-6 DNA in the absence of viral replication. This is consistent with a report identifying CD46, a complement regulatory molecule present on the surface of all nucleated cells, as the first cellular receptor for HHV-6 [13]. Because of the ability to detect DNA by modern molecular methods in the absence of isolating actively replicating virus and the ubiquitous nature of infection, it is difficult to evaluate the clinical relevance of finding HHV-6 DNA in brain or CSF samples of various patient populations. Previous work has clearly demonstrated the neurotropic potential of HHV-6. Primary human astrocytes, oligodendrocytes, and microglia all have been shown to be susceptible to in vitro infection with HHV-6 [14,15]. Multiple studies have also documented the presence of HHV-6 DNA in brain tissue in most immunocompetent adults. Chan *et al*. [16] studied 10 regions of the CNS by PCR, including the cerebellum and frontal, temporal, parietal, and occipital lobes from the brains of 40 adult autopsy specimens; none of the patients had died from infection. Eighty-five percent of the specimens had detectable HHV-6 DNA in the CNS. More than one positive site was identified in 68% of the positive specimens, with an equal distribution in the left and right brain and in each region studied. HHV-6 variant A alone was found in 12% of specimens, whereas 21% had HHV-6 variant A and B detected in one or more tissue samples. This was a substantially higher frequency of HHV-6 variant A than noted in studies examining PBMC samples by PCR or in isolates obtained from children with primary infection, which are almost universally HHV-6 variant B. A greater incidence of HHV-6 variant A in the CNS also has been reported in brain tumor specimens [17].

In addition, HHV-6 DNA has been detected in the CSF of children during and subsequent to primary infection [18]. In a study of 487 paired CSF and PBMC samples obtained from children with fever, signs of sepsis, or seizures, 42% of patients with evidence of current or past HHV-6 infection had detectable DNA in the CSF. In 29% of the patients with past infection, the CSF was the only site of DNA persistence. HHV-6 variant A was identified in 17% of CSF samples, significantly greater than the 2.5% detection rate of HHV-6 variant A in PBMC samples [19]. These data confirm the high prevalence of HHV-6 DNA in the CNS of adults and children and the suggestion of a greater neurotropism of HHV-6 variant A. The apparent augmented neurotropism of HHV-6 variant A is very relevant, especially in view of initial in vitro HHV-6 infection experiments of cultured human oligodendrocytes that have suggested that HHV-6 variant A is more virulent in the CNS [20]. Cultured supernatants from HHV-6A–infected cells consistently produced a greater degree of inhibition of proliferation and increased rates of cell death of oligodendrocytes compared with cells exposed to HHV-6 variant B. The importance of these findings will only become known once the true nature of HHV-6 infection of the CNS is

**Table 2. HHV-6–associated CNS disorders**

| | Normal host | Immunocompromised host |
|---|---|---|
| Primary infection | Febrile seizures<br>Acute cerebellitis<br>Encephalitis<br>Acute disseminated demyelination<br>Afebrile neonatal seizures | |
| Reactivated infection | Recurrent febrile seizures<br>Epilepsy<br>Encephalitis<br>MS | Encephalitis<br>PML |

CNS—central nervous system; HHV—human herpesvirus; MS—multiple sclerosis; PML—progressive multifocal leukoencephalopathy.

clarified. One major question to be definitively answered is whether HHV-6 plays an active role in the development of disease in the CNS beyond primary infection or if it is merely a passenger in normal or diseased cells.

## Human Herpesvirus 6 Reactivation

Reactivation of HHV-6 has been reported in many different patient populations by various methods. The best documentation of HHV-6 reactivation has been through viral culture in bone marrow transplant (BMT) patients [21•]. A low rate of reactivation has also been demonstrated recently in normal children by using a reverse transcription polymerase chain reaction (RT-PCR) assay, which was shown to be sensitive and specific for active viral replication when compared with culture [22,23].

Multiple diseases have been linked to HHV-6 reactivation; however, the data supporting these associations are variable in quality and need to be interpreted in view of the known persistence of HHV-6 DNA at different sites after primary infection. Early reports linked recurrent seizures and HHV-6 reactivation, based on the finding that children with multiple febrile seizures were significantly more likely to have HHV-6 DNA detected in their CSF by PCR than were children with a single febrile seizure [24]. In support of this finding, a trend was noted toward an increased frequency of seizures in children with past HHV-6 infection and HHV-6 DNA present in the CSF compared with children without detectable DNA in the CSF [18]. However, a significantly decreased incidence of recurrent seizures in children with a first-time febrile seizure associated with primary HHV-6 infection, compared with children with a seizure unassociated with primary HHV-6 infection, was reported by Jee *et al.* [25], casting doubt on this association. However, this report did not include any follow-up virologic analysis and did not select for patients with recurrent seizures. Two newer limited studies evaluating brain tissue specimens obtained at the time of epilepsy surgery from patients with temporal lobe epilepsy or mesial temporal lobe epilepsy have implicated HHV-6 in this specific clinical setting. Using PCR, HHV-6 DNA was detected in the lateral temporal lobe or hippocampus in 35% of patients undergoing temporal lobe epilepsy surgery at one center [26]. In a more recent report, Donati *et al.* [27•] found that four of eight patients with mesial temporal lobe epilepsy had HHV-6 DNA in the resected specimen; however, it was not found in patients with neocortical epilepsy. Additionally, the viral load of HHV-6 in the hippocampus from patients with mesial temporal lobe epilepsy was dramatically higher than that found in the temporal lobe specimens; active HHV-6 infection was confirmed in astrocytes in the hippocampus and lateral temporal lobe specimens by Western blot and immunohistochemistry. Taken together, these studies suggest an association between HHV-6 persistent or reactivated infection of the hippocampus and temporal lobe with the development of mesial temporal lobe epilepsy years after primary infection. These data are strengthened by the recognized association between complicated febrile seizures and damage to the hippocampus, and support the need for further study of the role of HHV-6 and recurrent seizure disorders.

## Human Herpesvirus 6–associated Encephalitis

Encephalitis has been associated with HHV-6 reactivation in normal and immunocompromised hosts. Most evidence for HHV-6 as a cause of encephalitis in normal hosts is based on a small number of case reports in adults and children. Although the data reported are not standardized, most patients had nonspecific findings such as fever and mental status changes with mild pleocytosis and elevated CSF total protein concentrations. Electroencephalography results were normal or with diffuse slowing. Imaging studies primarily revealed normal computed tomography scans. McCullers *et al.* [28] reported the largest study of normal patients with encephalitis associated with HHV-6. In their retrospective evaluation of patients with undefined encephalitis and focal neurologic findings, nine of 138 patients had HHV-6 DNA present in the CSF. Most of these patients had a decreased level of consciousness with seizures and abnormal electroencephalography findings. Four patients underwent neuroimaging, with two showing areas of decreased density in the parietal lobe or contrast enhancement in the frontotemporal lobe. After evaluating all of these reports, the etiologic link between HHV-6 and the clinical syndromes identified in these patients has depended on the detection of HHV-6 DNA in the CSF, making the findings difficult to interpret.

As noted earlier, HHV-6 reactivation in peripheral blood samples has been well-documented in immunocompromised hosts, especially in patients who have undergone bone marrow transplantation. Many of the complications seen in

this patient population have been associated with HHV-6 reactivation, including fever, rash, interstitial pneumonitis, delayed engraftment or myelosuppression, graft versus host disease, and encephalitis. The data supporting HHV-6 as an etiologic agent in these disorders are variable in quality, with many positive and negative studies published to date. In addition, very few large studies of immunocompromised patients with encephalitis associated with HHV-6 have been reported, making the exact magnitude of the problem difficult to determine. Case reports of patients with encephalitis associated with HHV-6 after solid organ transplantation have not provided a reliable estimate of the incidence of this disorder. Among BMT patients, the published incidence of encephalitis associated with HHV-6 ranges from 0% to 16% [21•,29–32]. Because the most data regarding HHV-6–associated encephalitis are from BMT patients, the remainder of this discussion will focus on this population.

Similar to the case reports from normal hosts, HHV-6–associated encephalitis in immunocompromised hosts tends to present with nonspecific findings of altered mental status and fever, with or without accompanying seizures or focal findings. CSF and neuroimaging studies are normal or with mild abnormalities. Most patients present with symptoms 2 to 5 weeks post-transplant, coincident with the peak time of HHV-6 reactivation in the peripheral blood. However, HHV-6 has also been implicated in cases of encephalitis several months after transplant [29]. Insomnia and amnesia have been noted in several patients in different studies, with the largest group reported by Wainwright *et al*. [33•], who described five patients with limbic encephalitis after cord blood stem cell transplantation characterized by short-term memory dysfunction, confusion, and insomnia. All of the patients had temporal lobe seizures on prolonged electroencephalography monitoring, with magnetic resonance imaging showing increased T2 signal changes in the hippocampus, and increased metabolism of the hippocampus on positron emission tomography scanning. Of the three patients that had CSF analysis, only two had slightly elevated total protein concentrations, but all had HHV-6 DNA variant B detected by PCR. Additionally, HHV-6 proteins were identified by immunohistochemistry in astrocytes of the hippocampus in one postmortem specimen, supporting the conclusion that this patient had active HHV-6 infection at the time of death. Most other reports have relied solely on the detection of HHV-6 DNA in CSF or peripheral blood as a means of establishing an etiologic link between the clinical symptoms of encephalitis and HHV-6. Because of the variability in sensitivity of published PCR methods and the high prevalence of HHV-6 DNA detection in multiple body sites after primary infection, it is very difficult to evaluate the validity of these reports. Additionally, the proper selection of control samples is critical. In a retrospective study of BMT patients with CNS disorders, HHV-6 DNA was identified in the CSF of five of 11 BMT patients with symptoms of unknown etiology, compared with zero of 11 patients with known causes [31]. Only 1% of more than 100 control patients had HHV-6 DNA in the CSF. Although at first glance these data appear very convincing, the number of patients with encephalitis was very small, and the control patients were pediatric patients with hematologic malignancies not matched to the BMT patients by age or degree of immunosuppression, diminishing the strength of these results. In studies using quantitative PCR for HHV-6 DNA in blood and CSF after BMT, increased viral loads have been documented in patients with encephalitis; however, the results were neither statistically significant nor associated with mortality [29,30].

## Demyelinating Disorders

Human herpesvirus 6 has also been implicated in demyelinating disorders of the CNS, including fulminant demyelinating encephalomyelitis, progressive multifocal leukoencephalopathy, and multiple sclerosis (MS) [33•,34–36]. The association between MS and HHV-6 was initially suggested by the identification of an HHV-6 DNA fragment in MS brain samples by representational difference analysis [37]. In addition, HHV-6 proteins were detected in the oligodendrocytes of MS plaques significantly more often than in normal-appearing white matter. Active HHV-6 infection was also found in control brain sections in astrocytes and macrophages but not in oligodendrocytes. Since these findings, numerous studies have examined the relationship between MS and HHV-6, using various methodologies. Most reports found a significant increase in the frequency detection of HHV-6 DNA in serum or PBMC samples of MS patients and elevated concentrations of antibodies to HHV-6, compared with controls [38–42]. Chapenko *et al*. [43] recently described an increased rate of detection of HHV-6 DNA in PBMCs and plasma samples of patients with MS compared with controls; this study also documented an association between the presence of viral RNA in PBMC samples and DNA in plasma with disease activity in patients with the relapsing and remitting form of MS. In spite of these positive findings, many negative PCR-based studies have also been published [44–46]. It is clear that much more work is needed to determine whether HHV-6 plays an etiologic role in the development or progression of MS.

## Diagnosis

The isolation of HHV-6 in culture remains the gold standard for the confirmation of active viral replication. This method is expensive and time-consuming, and requires up to 14 days to finalize. Two other methods have been shown to correlate with viral culture in the detection of active HHV-6 replication—plasma or serum DNA PCR and RT-PCR. Secchiero *et al*. [47] were the first to report the detection of HHV-6 DNA in the serum of six of seven children with exanthem subitum. Although not replicated in all subsequent studies, most reports have confirmed the utility

of this method for the accurate detection of viral replication in primary and reactivated HHV-6 infection [48,49]. In addition, Norton *et al*. [23] developed an RT-PCR assay on PBMC samples for HHV-6 RNA that was 95% sensitive and 99% specific for identifying active viral replication, compared with culture.

Although many authors have reported the results of quantitative PCR for HHV-6 genome copy numbers on various body fluids from normal and immunocompromised populations, the role of this methodology is unclear. In a prospective study of 26 BMT patients, quantitative DNA PCR of PBMC samples, viral culture, and plasma PCR were compared [48]. Similar to other reports, approximately 50% of the patients had HHV-6 viremia at 2 weeks post-transplant. The plasma PCR assay was 92% sensitive and 97% specific, compared with viral culture. The patients with viremia had a significantly increased concentration of HHV-6 DNA in PBMC samples, compared with culture-negative patients. No specific value of DNA could perfectly discriminate between the patients with viremia and the patients who remained culture-negative.

Several serologic methods, including indirect immunofluorescence assays, neutralization assays, and enzyme-linked immunosorbent assays, have been described for the measurement of antibody concentrations to HHV-6 in serum or plasma. These assays have the greatest utility when combined with a measure of viral replication to discriminate between primary and reactivated HHV-6 infection in individual patients or when used to determine the prevalence of previous HHV-6 infection in large population groups. Serologic assays have not been found to be reliable in the detection of HHV-6 reactivation.

## Conclusions

Human herpesvirus 6 causes ubiquitous infection in the human population. Febrile seizures are the most common complication of HHV-6 primary infection and occur in 10% to 20% of patients, accounting for up to one third of febrile seizures in childhood. Recent evidence suggests that HHV-6 might also play a role in temporal lobe epilepsy and MS. Many reports also describe encephalitis associated with primary or reactivated infection with HHV-6. Because HHV-6 is a DNA-containing virus that remains latent or persistent after primary infection, the viral genome can be detected at numerous sites in adults and children. This characteristic of HHV-6 makes it difficult to determine when HHV-6 is playing an active role in CNS disorders. Laboratory methods that can accurately distinguish between latent and active virus will be helpful in determining the etiologic role of HHV-6 in these clinical settings.

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