Human Herpesvirus 6

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The development of techniques for the culture of lymphoid cells and the isolation of viruses that infect these cells led to the discovery of human herpesvirus (HHV) 6 in 1986. At the time, HHV-6 was the first new human herpesvirus to be discovered in roughly a quarter of a century, and its isolation marked the beginning of an era of discovery in herpesvirology, with the identification of HHV-7 and HHV-8 (Kaposi’s sarcoma–associated herpesvirus) during the following decade. Like most human herpesviruses, HHV-6 is ubiquitous and capable of establishing a lifelong, latent infection of its host. HHV-6 is particularly efficient at infecting infants and young children, and primary infection with the virus is associated with roseola infantum (exanthem subitum) and, most commonly, an undifferentiated febrile illness. Viral reactivation in the immunocompromised host has been linked to a variety of diseases, including encephalitis, and HHV-6 has been tentatively associated with multiple sclerosis. This article discusses the major properties of HHV-6, its association with human disease, and the pathobiological significance of viral reactivation.

Human B-lymphotropic virus was first isolated in 1986 from the peripheral blood mononuclear cells (PBMC) of persons with HIV infection or lymphoproliferative disorders. The virus was subsequently determined to have a broad host-cell tropism, including T cells, and the virus was designated “human herpesvirus 6 (HHV-6).”

HHV-6 was etiologically linked to a human disease in 1988, when Yamanishi et al. [1] described the association of the virus with exanthem subitum (roseola infantum). HHV-6 was subsequently found to be a ubiquitous agent that infects almost all individuals in early childhood and is capable of becoming reactivated in both normal and immunocompromised persons. The scope and nature of disease caused by HHV-6 has yet to be fully defined, particularly in persons with reactivated infection. The aim of this review is to focus on the biology of HHV-6 as it pertains to an understanding of potential pathogenic mechanisms of HHV-6, and to review the information on disease associations, with a special emphasis on those conditions that may be associated with viral reactivation.

BASICS

Epidemiology and primary infection. Primary infection with HHV-6 occurs within the first 2 years of life and is usually associated with an undifferentiated febrile illness, although a subset of children exhibit the classic manifestations of roseola infantum (exanthem subitum; reviewed in [2, 3]). In a large prospective study of North American children, the peak age of acquisition of HHV-6 was 6–9 months; the most consistent clinical presentation of infection was abrupt onset of high fever (mean temperature, 39.6°C) [4]. Other common manifestations of infection included inflammation of tympanic membranes and irritability [5]. Notably, the rash characteristic of roseola was detected either during the illness or following defervescence in only ~20% of the patients with primary HHV-6 infection [5]. The mean duration of illness was 6 days, and the most common complication of primary HHV-6 infection was febrile seizures; these occurred in 13% of the children studied [4].

Overall, primary HHV-6 infection is a major cause of acute febrile illness in young children. It is also a major cause of visits to the emergency department, hospitalizations, and febrile seizures. Acute HHV-6 infection accounted for 20% of visits to the emergency department for febrile illnesses among children 6–8 months of age; 13% of these children were hospitalized [4]. These findings point to the economic significance of HHV-6 infection, and they underscore the importance of making the correct differential diagnosis, to avoid unnecessary use of antibiotics. However, the relatively nonspecific nature of
HHV-6–associated disease symptoms and the infrequent occurrence of the classic rash associated with roseola make it difficult to definitively diagnose primary HHV-6 infection. Therefore, there may be value to the development of a rapid test for this infection, such that ineffective treatments and/or expensive laboratory tests are not applied to this common, self-resolving illness.

After primary infection with HHV-6, the viral genome persists in peripheral blood mononuclear cells (PBMC), possibly in cells of myeloid lineage. The virus also appears to persist in the salivary glands, and viral DNA can be routinely detected in saliva by use of PCR [2]. HHV-6 DNA has also been identified in the CSF of children, both during and subsequent to primary infection, and in brain tissue from immunocompetent adults, at autopsy, which implicates the CNS as an additional site of either viral latency or persistence [6].

**Virology.** Much information about the basic virology and genetics of HHV-6 has been published; this has been reviewed elsewhere [2, 3] and is briefly summarized in table 1. HHV-6 is a β-herpesivirus, mostly closely related to HHV-7 and somewhat more distantly related to human cytomegalovirus (CMV).

Two strain groups of HHV-6 have been recognized: variant A and variant B. These viruses are ~88% identical at the nucleotide level, and the complete sequences of representative isolates are available via GenBank (http://www.ncbi.nlm.nih.gov:80/cgi-bin/Entrez/framik?db=Genome&gi=10586; http://www.ncbi.nlm.nih.gov/cgi-bin/Entrez/framik?db=Genome&gi=15112). In almost all studies, HHV-6B has emerged as the predominant strain found in both normal and immunocompromised hosts. It is not clear whether the differences in the detection of HHV-6A and HHV-6B relate to different tissue tropism, differences in mode or age of acquisition, differences in the ability to reactivate and cause human disease, or the geographical distribution of these viruses [2, 3].

**Immunology.** CD46 is an essential component of the membrane receptor for HHV-6 [7]. It is also the receptor for the Edmonston strain of measles virus, and it functions as a complement regulatory protein present on the surface of all nucleated cells; this is consistent with the broad cell tropism of HHV-6 (table 1).

The principle target cell for HHV-6 is the mature CD4+ T cell, and the virus has pleiotropic effects on cells of the immune system, which include the ability to dis regulate cellular cytokine production, to modulate natural killer cell function, and to modify the expression of key cell surface receptors, including CD3, CD4, and CXCR4 [8–10]. Some of these properties may be related to virally encoded immunoregulatory molecules, which include 2 chemokine receptor homologs (U12, U51), a functional chemokine (U83), and an OX-2 homolog (U85) [11–14].

**HHV-6 in the Immunocompromised Host**

**Bone marrow transplantation.** HHV-6 can be cultured from the PBMC of bone marrow transplant (BMT) recipients, but the virus cannot be cultured from the blood of healthy normal adults. Thus, it has been suggested that HHV-6 reactivation may contribute to disease in the immunocompromised host (table 2). Although the exact frequency of reactivation is difficult to determine, ~30%–45% of BMT recipients develop HHV-6 viremia within the first several weeks following transplantation.

Multiple complications have been linked with HHV-6 in the bone marrow transplantation setting; however, it is difficult to make definitive associations between virus infection and disease, because of the ubiquity and persistence of the virus in almost all adults. One association that has been identified in most studies is the development of fever and rash associated

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**Table 1. Biology of human herpesvirus 6 (HHV-6).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
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<tbody>
<tr>
<td>Tropism</td>
<td>T lymphotropic. HHV-6 infects a broad range of cells in vitro, including primary T cells, monocytes, natural killer cells, dendritic cells, astrocytes, and cell lines of T cell, B cell, megakaryocyte, glial, and epithelial origins.</td>
</tr>
<tr>
<td>Variants</td>
<td>HHV-6 A and HHV-6 B. The 2 virus groups differ in their in vitro cell tropism, reactivity with monoclonal antibodies, and restriction fragment length polymorphisms. The 2 groups exhibit ~12% overall divergence at the nucleotide level.</td>
</tr>
<tr>
<td>Receptor</td>
<td>CD46 is one essential component of the membrane receptor for HHV-6. The role of coreceptors or ancillary molecules is uncertain.</td>
</tr>
<tr>
<td>Genome size</td>
<td>The viral genome is double-stranded DNA, of ~160,000 bp in length. It has a central unique region of ~144,000 bp, flanked on each end by direct-repeat elements of variable length (~13,000 bp, prior to virus being cultured).</td>
</tr>
<tr>
<td>Replication</td>
<td>In peripheral blood mononuclear cells, viral replication is slow and lytic; syncytia are induced.</td>
</tr>
<tr>
<td>Herpesviridae family</td>
<td>Subfamily: Betaherpesvirinae (along with cytomegalovirus and HHV-7); genus: Roseolovirus (with HHV-7).</td>
</tr>
<tr>
<td>Transmission</td>
<td>The virus is believed to be transmitted via oral secretions from adults to infants. In utero transmission has also been suggested. May be transmitted by blood, bone marrow, or transplanted organs.</td>
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</table>
with HHV-6 viremia after transplantation. A low incidence of other disease manifestations previously associated with HHV-6 has also been reported, including bone marrow suppression, pneumonitis, and encephalitis (reviewed in [15]), and graft-versus-host disease in some individuals has been reported (reviewed in [16]). However, it appears that asymptomatic HHV-6 reactivations predominate in the post-BMT setting [17]. Therefore, the pathogenic significance of HHV-6 reactivation in BMT recipients remains uncertain.

**Solid-organ transplantation.** A variable proportion of renal transplant patients (up to 66% in some studies) undergo HHV-6 reactivation or reinfection, as measured by viral isolation or PCR analysis. Reactivation occurs most commonly following treatment for organ rejection with OKT3 or antithymocyte globulin and is probably related to the significant degree of immunosuppression associated with these 2 products. Some reports have suggested an association between HHV-6 reactivation and graft rejection, but this remains uncertain. HHV-6 reactivation does, however, lead to subsequent reactivation of CMV [18], although a recent prospective study of 52 renal transplant patients concluded that there was no evidence that HHV-6 had a negative impact on clinical outcome [18]. HHV-6 reactivation has also been described as occurring in liver transplant patients. In this setting, high DNA loads of CMV and for HHV-6 have been independently associated with biopsy-proven graft rejection (reviewed in [16]).

**HIV type 1 (HIV-1) infection.** Persons with HIV-1 infection exhibit frequent reactivation of HHV-6, as evidenced by the isolation of HHV-6A from a number of HIV-1–positive individuals in the late 1980s. Several cases of HHV-6–associated disease in HIV-1–positive persons (including pneumonitis and encephalitis) have been described [19]. However, in most HIV-1–positive adults, HHV-6 reactivation is thought to have a minimal effect on disease progression [20]. In contrast, in infants with vertically acquired HIV-1 infection, primary HHV-6 infection has been associated with more rapid progression of disease during the first year of life [21]. More research is necessary in order to fully understand what role HHV-6 infection may play in the progression of HIV-1 infection.

**Chronic fatigue syndrome.** Persons with chronic fatigue syndrome exhibit a number of immunologic abnormalities suggestive of immunosuppression, including, in some studies, the reactivation of latent herpesviruses, such as HHV-6. It has been suggested in the popular media and elsewhere that HHV-6 reactivation may be causally involved in the pathogenesis of chronic fatigue syndrome, but similar claims have also been made for a variety of infectious and noninfectious causes. There is no compelling evidence that HHV-6 plays a role in chronic fatigue syndrome, although more studies of this debilitating disorder are needed.

### HHV-6 AND THE CNS

**Febrile seizures.** Primary HHV-6 infection has been associated with febrile seizures in infants and young children [4]. This association has been particularly pronounced in children 12–15 months of age; in this age group, 36% of children with primary HHV-6 infection had convulsions, versus only 13% of children with non-HHV-6–related febrile illnesses [4]. A parallel PCR-based study found persistence of the virus after primary infection in both PBMC and CSF [6]. HHV-6A, although rare overall, was more frequently detected in CSF than it was in PBMC. However, HHV-6A was still detected much less frequently than HHV-6B, even in CSF samples (HHV-6A was detected alone or in combination with HHV-6B in only 17% of positive CSF specimens, whereas HHV-6B alone was detected in 83% of such samples) [6].

In a follow-up prospective study, among children whose first
febrile seizures were caused by HHV-6, the incidence of recurrent febrile seizures was significantly less than that among matched controls whose original febrile seizures were due to other causes (20% vs. 40%; P < .04) [22]. However, Suga et al. [23] found that the frequency of more severe forms of convulsions and postictal paralysis was significantly higher among children with primary HHV-6 infection than it was among those without such infection. Clearly, additional studies are needed in order to resolve these findings and to elucidate the long-term neurological significance of HHV-6–associated febrile seizures.

**HHV-6 as a cause of meningitis or encephalitis.** As noted above, HHV-6 has been implicated as a cause of encephalitis in transplantation recipients (reviewed in [15]). The virus has also been implicated as a cause of meningitis and encephalitis in immunocompetent individuals. In a retrospective study of 138 well-studied patients with focal encephalitis of unknown etiology, 9 were found to have HHV-6 DNA in their CSF, whereas the results of PCR and serological assays for other herpesviruses were negative [24]. Clinical outcomes in these putative cases of HHV-6–associated focal encephalitis were variable, ranging from complete recovery (in 4 cases) to moderate impairment and death (in 1 case) [24].

The search for a direct role for HHV-6 in the development of encephalitis in patients with AIDS has produced divergent results. HHV-6 was found in a 14-month-old HIV-1–positive child who had a brief history of fever, lethargy, and seizures at presentation and who developed a fulminant encephalitis that led to death 5 days after admission. At autopsy, HHV-6–infected cells were found in involved gray matter by means of immunohistochemistry [25]. Evidence of active HHV-6 infection, as detected by immunohistochemical localization of viral proteins in areas of demyelination, was also found in 4 of 6 unselected adult AIDS patients [26]. However, in other studies, HHV-6 antigens could not be detected within brain tissue from children or adults with AIDS, even though HHV-6 DNA could be readily visualized by in situ hybridization in white-matter oligodendrocytes and in other cell types [27, 28].

The question of how frequently HHV-6 DNA can be found in normal brain tissue has been addressed in several studies; most recently, a survey of 31 normal brain tissues, examined by use of solution PCR, found HHV-6 DNA to be present in approximately one-third of specimens [29]. Taken together, these findings suggest that HHV-6 is, in general, a nonpathogenic, resident virus of the human brain with a potential for neurovirulence. This conclusion is supported by in vitro studies demonstrating the ability of HHV-6 to cause a restricted or minimally productive infection of human microglia, astrocytes, and oligodendrocytes.

**HHV-6 infection of CNS white matter.** The role of HHV-6 as a potential agent of demyelination of white matter has generated considerable interest in recent years. An association between HHV-6 and multiple sclerosis (MS), the most common demyelinating disease of the human CNS, was reported by Challoner et al. [30] in 1995. HHV-6 protein expression was detected in perilesional oligodendrocytes in the brains of 12 of 15 patients with MS but not in those of 41 control individuals. Similar results have been reported more recently by 2 other groups [31, 32]; however, Coates and Bell were unable to replicate these results in their series of 23 MS brain tissues with use of the same serological reagents employed by Challoner et al. [33].

The results of both PCR-based and serological studies are equally controversial. Soldan et al. [34] detected HHV-6 DNA in cell-free serum of 30% of relapsing/remitting patients with MS (suggesting the presence of active HHV-6 replication) versus 0 (0%) of 47 control individuals without MS. Elevated IgM responses to the virus were also found in 73% of the patients with MS, versus only 18% of the subjects without MS [34]. In contrast, several other studies have failed to detect cell-free HHV-6 DNA in serum and CSF samples obtained from patients with MS [35–37]. Therefore, although the potential association of HHV-6 with MS is provocative, it is very much unproven. Furthermore, it is notable that many viruses have been previously implicated in the etiology of MS, but none has been causally linked to the disease.

Recent findings suggest that HHV-6 may play a role in the pathogenesis of another demyelinating disorder: progressive multifocal leukoencephalopathy (PML). PML is a primary demyelinating disease of the CNS occurring almost exclusively in individuals with severely impaired cell-mediated immunity; the JC polyoma virus is generally accepted as the etiologic agent of this disease. In a combined study that employed both in situ PCR and immunocytochemistry, high frequencies of oligodendrocytes co-infected with HHV-6 and expressing JC virus proteins were found within the demyelinating lesions of PML [28]. No HHV-6 proteins were found in control brains, including those of 18 patients with AIDS but without PML. The relevance of these neuropathological studies to the pathogenesis of PML and the role of HHV-6 as a potential cofactor in demyelination remain to be determined.

**CONCLUSIONS**

HHV-6 is an ubiquitous parasite that has effectively colonized the vast majority of the human population. It is spread with great efficiency during early childhood and establishes a persistent lifelong relationship with its host. Primary virus infection is frequently accompanied by febrile illness, which may or may not be manifest as classical roseola (exanthem subitum). In adults, viral reactivation can occur, most notably in the context of immunosuppressive therapy or disease. Outcomes
of such reactivations may include rare cases of encephalitis, pneumonitis, graft rejection, and asymptomatic infections (which appear to predominate).

It has recently been proposed that the virus plays a role in MS, although the data remain incomplete and inconclusive. There has also been long-standing interest in the possible involvement of HHV-6 in chronic fatigue syndrome, but there are no compelling data to support this proposed association. Overall, the biological properties and pathogenic potential of HHV-6 remain incompletely described and warrant further investigation.

References


