Human Herpesvirus 6

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Human herpesvirus 6 (HHV-6) is a member of the family Herpesviridae. This family of eight viruses includes four Alphaherpesvirinae (herpes simplex virus type 1 [HSV-1], herpes simplex virus type 2 [HSV-2], human herpesvirus 8 [HHV-8], and varicella-zoster virus [VZV]); one Gammaherpesvirinae (Epstein–Barr virus [EBV]); and three Betaherpesvirinae (cytomegalovirus [CMV], HHV-6, and human herpesvirus 7 [HHV-7]) [1]. Common physical traits of these clinically important DNA viruses include large size (150–200 nm), an icosahedral nucleocapsid encased in an envelope that has multiple surface projections, and a large number of structural proteins. Their genomes are linear and double-stranded, varying in size from 120 to 230 kb and specifying a large number of enzymes involved in nucleic acid metabolism. The intranuclear replication of herpesviruses is complex and destruction of the infected cells accompanies the production of progeny. A state of viral latency follows primary infection; the site of latency is different for each of the viruses. For example, HSV-1, HSV-2, and VZV establish latency in neuronal cells, HSV-1 favoring the trigeminal ganglia, HSV-2 the sacral ganglia, and VZV the posterior root ganglia. In contrast, CMV maintains latency in monocytes and macrophages, EBV in B lymphocytes, and HHV-6 and HHV-7 in T lymphocytes. Viral persistence in infected hosts is lifelong. Periodic reactivation can occur with each of the herpesviruses, thus they are "incurable."

The seroprevalence of each of the herpesviruses varies according to a number of demographic factors including age, race, socioeconomic status, and country of residence. Among healthy young adults in the United States, the seroprevalence of herpesviruses ranges from <10% for HHV-8 to almost 100% for VZV, HHV-6, and HHV-7 [2]. The seroprevalence for EBV, CMV, and HSV-1 range from 50 to 75% and the seroprevalence of HSV-2 is about 25%. Spread of infection usually occurs as a result of contact with body secretions containing virus. Infectious virus may be present in skin or mucosal lesions (e.g., HSV-1, HSV-2, and VZV); in blood and transplanted organs from previously infected donors (e.g., CMV and EBV);

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or in genital (e.g., HSV-2) or oral (e.g., HSV-1, EBV, CMV, HHV-6, and HHV-7) secretions from previously infected but asymptomatic individuals. Thus, susceptible contacts are at risk of contracting infection from persons who have acquired an herpesvirus, in the recent or distant past. Indeed, the majority of herpesvirus infections result from contact with asymptomatic individuals shedding virus as a result of viral reactivation of a distant infection.

The clinical manifestations of herpesvirus infections depend upon the specific virus, whether the infection is primary or reactivated, and the immunologic status of the host. In general, the severity of symptoms is greater with primary vs. reactivated infections and among those with compromised immune systems.

HHV-6 is genetically most closely related to the other Betaherpesvirinae, CMV and HHV-7. HHV-6 was originally named human B-lymphotrophic herpesvirus because it was first isolated from peripheral blood lymphocytes of patients with HIV and lymphoproliferative diseases in 1986 [3]. It subsequently was recognized as an herpesvirus and was named HHV-6 because it was the sixth member of the herpesvirus family. In 1988 the virus was isolated from the lymphocytes of infants with roseola [4] and it is now recognized as the prime cause of this common childhood infection.

HHV-6 infection is ubiquitous and the major mode of transmission appears to be respiratory and oral secretions. Primary infection is common during infancy and about 50% of all children have been infected by 15 months of age [5]. The peak incidence of infection occurs during the second 6 months of life, corresponding to the time of waning transplacental, neutralizing IgG antibodies [6]. Most children have been infected by 2 years of age. Following initial infection with HHV-6, active viral shedding persists for long periods of time; in many infants high copies of viral DNA are detectable in oral secretions for more than a year [5]. Following primary infection, HHV-6 becomes latent in the salivary glands, brain, and mononuclear cells or macrophages.

The most widely recognized clinical manifestation of infection with HHV-6 in normal infants is roseola (exanthema subitum). The first isolation of HHV-6 was from the blood of four Japanese infants with this exanthematous infection [4]. Although HHV-6 is the primary cause of roseola, it is estimated that only 10–30% of infants infected with this virus will exhibit the classic clinical manifestations of this illness [6]. These manifestations include the abrupt onset of high fever ($\geq$40°C), irritability, and a diffuse "rash of roses" eruption spreading from the trunk to the face and extremities. Typically, body temperature begins to normalize at the time of rash appearance. In addition to some combination of fever, irritability, and rash, HHV-6 infection in infants may be associated with other common signs and symptoms, including, in decreasing order of frequency, occipital cervical lymphadenopathy, inflamed tympanic membranes, signs of upper respiratory tract infection, cough, gastrointestinal complaints (especially diarrhea), and seizures [7]. HHV-6 infection is considered to be one of the most important etiologies of febrile seizures in infancy.

Uncommon but reported manifestations of primary HHV-6 infection in normal infants and children include a prolonged febrile illness; elevated liver function tests;

arthritis; peripheral blood abnormalities, including low platelet count and low total white blood cell count; hemophagocytosis; Gianotti–Crosti syndrome; large vessel arteritis; and encephalitis. HHV-6 DNA was isolated from the cerebrospinal fluid of 14 of 35 adults referred to the National Institutes of Health with encephalitis of undetermined etiology [8]. Other recent possible associations with HHV-6 infection in children include acute appendicitis [9]; respiratory failure [10]; and cardiomyopathy [11]. An association between infection with HHV-6 in adults and brain tumors has been proposed [12].

Although most reactivated HHV-6 infections are asymptomatic, in some immunosuppressed hosts, reactivated infection can be associated with a febrile illness associated with rash and bone marrow suppression; precipitation of graft-vs.-host disease (GVHD); and disseminated infection involving the lungs, liver, and CNS. The likelihood of clinical manifestations is greatest in the presence of substantial immunosuppression, including the use of anti-CD3 antibodies; solid organ transplant recipients; and co-infection with CMV or HHV-7. Overall, it is estimated that between 30 and 50% of bone marrow and solid organ transplant recipients experience reactivated HHV-6 infections, although most of these episodes of reactivation are asymptomatic. In one recent study of hematopoietic stem cell transplant recipients, the occurrence of HHV-6 infection increased the likelihood of acute GVHD and non-relapse-related mortality [13].

Diagnosis of HHV-6 infection, especially in normal infants, usually is based on clinical findings. Isolation of infectious virus (research settings) or the presence of HHV-6 antigens, nucleic acids, and antibodies may be detected but generally such testing is not necessary [14]. Furthermore, even when these tests are used, it may not be possible to distinguish recurrent from primary infection. Definitive diagnosis of primary infection requires both the isolation of the virus and the occurrence of seroconversion. HHV-6 DNA has been detected in the cerebrospinal fluid of children with primary infection, especially in the presence of seizures [15]. Persistence of HHV-6 DNA in the CSF of healthy children and adults also has been reported and its role in subsequent neurologic consequences, if any, debated [16].

The management of HHV-6 infections is supportive; the role of specific antiviral therapy is not well established. Agents that have been used on occasion based upon good in vitro activity against HHV-6 include, in order of decreasing in vitro activity, cidofovir, ganciclovir, and foscarnet [13].

In summary, the sixth member of the herpesvirus family is ubiquitous, infecting most children by 2 years of age. The most distinctive feature of early childhood infection is roseola and the virus is responsible for a substantial proportion of febrile illnesses early in life, including those that precipitate febrile seizures. Severe primary infections are uncommon among the immunocompetent, and reactivated infections are usually not associated with symptoms. However, among the immunosuppressed, reactivated infections can be severe and life threatening. Therapy is symptomatic and supportive. Although some antiviral agents have good in vitro activity against HHV-6, their therapeutic role is not yet established.

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