A Practitioner’s Guide to Human Herpesvirus-6 (HHV-6) and Human Herpesvirus-7 (HHV-7)

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ABSTRACT

Human herpesvirus-6 (HHV-6) and HHV-7 are newly recognized ubiquitous human viruses first discovered in patients with AIDS or lymphoproliferative disorders. Much more information is available about the clinical characteristics of infection with HHV-6 than HHV-7. Primary infection with HHV-6 occurs in early childhood and is most commonly manifested as an undifferentiated highly febrile illness, with seizures noted to be the most common complication. A subset of children develop the classic manifestations of roseola infantum or exanthem subitum. Other neurologic diseases in adults such as encephalitis and multiple sclerosis also have been linked to HHV-6; however, the role of HHV-6 in these clinical entities has not been fully elucidated. Although HHV-6 and HIV are both tropic for CD4+ lymphocytes and interact in vitro, there is no evidence at present that HHV-6 plays a role in HIV disease. HHV-7 is similar to HHV-6 in genetic organization and structure. Little is known of the clinical characteristics of infection with HHV-7 or its ability to cause disease in children or reactivation in adults.

INTRODUCTION

Human herpesvirus-6 (HHV-6) is a lymphotropic herpesvirus that causes universal human infection. Although initially isolated in 1986 from six adults with lymphoproliferative disorders, including two with HIV-related malignancy, it is now accepted that primary infection in early childhood is the rule.¹ Over the past dozen years, many human diseases have been associated with HHV-6 in both adults and children. However, its role in many of these disorders remains unclear. Although the characteristics of primary infection in the young child have been well described, the bridge between the illness of acute infection in childhood and the varied clinical syndromes reported in adults has yet to be properly constructed.

HHV-7 is a genetically similar lymphotropic herpesvirus that also causes ubiquitous human infection. Much less is known about HHV-7 and its ability to cause disease in adults or children. Despite these uncertainties, new information about these two new members of the human herpesvirus family is accumulating rapidly. This review will focus on the most well established clinical aspects of infection with HHV-6 and HHV-7 (Table 1).
HUMAN HERPESVIRUS-6:
CASE ILLUSTRATION

A 10-month-old white female infant was brought to the emergency department because of fever for 24 hours. The mother described a fever of 105°F rectally, with loose stools and irritability. The patient was seen by her private pediatrician 1 day prior to the visit and diagnosed with a viral syndrome. The pediatrician prescribed acetaminophen, but the fever was poorly responsive to antipyretics. The patient was afebrile the following morning, but in mid-afternoon her temperature was again found to be 105°F, and her parents then brought her to the emergency department. Her past medical history was unremarkable except for neonatal jaundice. She had no hospitalizations and no ill contacts and her immunizations were up to date.

Physical examination in the emergency department yielded the following information: temperature 40.2°C, heart rate 177 beats/min, respiratory rate 32 breaths/min and blood pressure 106/76 mmHg. She was an awake and alert infant with intermittent irritability. The examination of her ears was notable for gray tympanic membranes bilaterally with normal mobility and landmarks. Her neck was supple without adenopathy. Results of chest, cardio-vascular, and abdominal examinations were benign. Examination of her extremities and skin uncovered no abnormalities. The white blood cell count in the emergency department was $3.8 \times 10^9/L$, with a differential of 69% neutrophils, 26% lymphocytes, and 5% monocytes. A blood culture and urine culture were obtained and subsequently found to be negative. The patient was discharged with a diagnosis of viral syndrome with possible acute gastroenteritis. HHV-6 was recovered from the peripheral blood mononuclear cells after 13 days in coculture with cord blood mononuclear cells. A portion of the patient’s mononuclear cell sample was also positive for HHV-6 by nested polymerase chain reaction (PCR). Seroconversion to HHV-6 was demonstrated by indirect immunofluorescence assay (IFA).

EPIDEMIOLOGY

Human herpesvirus-6 was first identified as the etiologic agent of the common childhood illness roseola infantum or exanthem subitum in 1988 by Yaminishi and others. They were able to propagate HHV-6 from the peripheral blood mononuclear cells of four infants with fever and subsequently showed seroconversion in all four patients. Serologic studies per-
formed since that time have demonstrated widespread human infection with HHV-6. Large studies from the United States and Sweden using enzyme-linked immunosorbent assay and IFA initially reported HHV-6 seroprevalence rates of 80% to 95% in healthy adolescents and adults. Further detailed age-specific data revealed seropositive rates as low as 6% in infants 4 to 5 months of age, followed by a dramatic increase in both seropositivity and geometric mean titers in children 1 to 2 years of age. Approximately 100% of children 2 to 3 years of age are seropositive for HHV-6, as are newborns. Cumulative data support the concept of universal human infection with HHV-6, with acquisition of the virus in early childhood following the predictable decrease in transplacental antibody. Although the precise modes of transmission have not been definitely established, spread via oral secretions from adults to infants is supported by the demonstration of HHV-6 DNA in both saliva and the majority of salivary gland biopsy specimens studied to date. These data also support the concept of lifelong persistence or latency of HHV-6 in the human host following primary infection. The possibility of horizontal sexual spread or perinatal acquisition by the newborn is suggested by the demonstration of HHV-6 DNA in the cervixes of 20% of pregnant women and in 10% of women attending an STD clinic.

Two strain groups of HHV-6 have been recognized: HHV-6 variant A and variant B. The viruses can be distinguished based on their in vitro cellular tropism, reactivity with monoclonal antibodies, restriction fragment length polymorphisms, and nucleotide sequence composition. Although the frequency of detection of HHV-6 variant A differs between studies, variant B generally is the predominant strain found in both normal and immunocompromised hosts. HHV-6 variant A has been detected with a higher prevalence in patients with chronic fatigue syndrome and in biopsy samples of Kaposi’s sarcoma lesions. A recent study also has shown a high prevalence of HHV-6 variant A infection in infants with fever in Zambia, whereas variant A and B coinfection has been described in both normal and diseased lung tissue in 65% of samples examined. It is not clear whether the differences in the detection of HHV-6 variant A and variant B 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 location of the population studied.

The early serologic surveys of HHV-6 antibody prevalence were completed prior to the recognition of the two distinct variants; therefore, these initial reports do not distinguish between infection with HHV-6 variant A and B. Many of the questions regarding the epidemiology of variant A and B will hopefully be answered by more specific serologic techniques. Serologic studies are also limited by the fact that in vitro HHV-7 shares antigenic cross-reactivity with HHV-6. Additionally, cross-reactive antibodies have been identified in children with either HHV-6 or HHV-7 primary infection, and in vitro HHV-7 reactivates HHV-6. Studies aimed at diagnosing HHV-6 primary infection or reactivation using IgM detection are flawed by the reports of the lack of uniform production of IgM in children with primary HHV-6 infection and the recognition that 5% of adults may have detectable IgM. Taken together, these data point to the hazards of using serologic studies alone in the investigation of HHV-6 infections.

**CLINICAL MANIFESTATIONS**

**Primary infection**

The clinical features of primary infection with HHV-6 have been well described and generally consist of an undifferentiated febrile illness of infancy. In a prospective study of HHV-6 infection by Hall and colleagues in Rochester, NY, 160 children with acute HHV-6 infection were identified by isolation of the virus and seroconversion. Peak age of primary HHV-6 infection was 9.4 months, with only one child over 25 months of age. All children were febrile, with 87% of patients exhibiting fever of 39°C or greater. In a study of 176 children in Japan with exanthem subitum, the average length of fever was 4.1 days. The study conducted in Rochester found that 15% of children
with primary HHV-6 infection had fever for 6 or more days. Additional symptoms included irritability, inflamed tympanic membranes, upper respiratory tract signs, and gastrointestinal complaints. Rash has been variably reported to occur with primary HHV-6 infection. In prospective studies in the United States, only 17% to 36% of children developed a rash concurrent with or subsequent to fever. Conversely, rash is noted in 98% or more of children with primary HHV-6 infection reported from Japan. Methodologic differences in patient recruitment may account for these discrepancies. Laboratory characteristics noted in children with primary HHV-6 infection include lower mean numbers of total white blood cells, lymphocytes, and neutrophils compared with febrile children without primary HHV-6 infection.

Central nervous system complications

Numerous complications of primary HHV-6 infection have been described in isolated case reports, including fulminant hepatitis, hemophagocytic syndrome, intussusception, pneumonitis, and fatal multi-system disease in both normal and immunocompromised children. The etiologic role of HHV-6 in most of these reports was not definitively established and requires further study. Seizures have been identified as a common complication of primary HHV-6 infection with a rate of approximately 10% to 15% in unselected patients. In studies of children presenting to hospitals because of first-time febrile seizures, primary infection with HHV-6 has been identified in 20% to 35% of patients. The clinical characteristics of 21 children with central nervous system complications of roseola were described by Suga and colleagues. Generalized seizures were noted in 71% of the children, with prolonged convulsions in one third. In a small series of children in Japan, reactivation of HHV-6 was suggested as a cause of recurrent febrile seizures based on finding HHV-6 DNA in CSF of all eight children with three or more febrile seizures. However, a recent case control study of 36 children with a first-time febrile seizure associated with primary HHV-6 infection found a decreased risk of recurrent seizures compared with a matched control group of children with first-time febrile seizures not associated with primary HHV-6 infection. Further studies are needed to clarify the exact pathogenic role of HHV-6 infection in first-time and recurrent febrile seizures.

Several case reports and small patient series have identified HHV-6 as the cause of acute encephalitis in both immunocompetent adults and children. Although a clear clinical presentation has not emerged, the majority of the patients described have had depressed levels of consciousness with seizures or focal neurologic findings and a mild to moderate mononuclear cell pleocytosis. Variable recovery has been reported for these patients. Encephalitis also has been described in a small number of immunocompromised patients following bone marrow transplantation or secondary to HIV infection. Using immunohistochemical staining, active HHV-6 infection has been detected in astrocytes and neurons, with demyelination and reactive astrogliosis identified as the major pathologic findings. Reports of this type must be tempered with data demonstrating the presence of HHV-6 DNA in the cerebrospinal fluid (CSF) of normal children and in brain tissue from adults dying from non-neurologic diseases. Whether the presence of HHV-6 DNA or proteins in the central nervous system of patients with neuropathologic lesions represents merely passenger virus in cells destroyed by other unseen enemies or whether HHV-6 is the direct cause of the disease is unclear.

Early serologic surveys of patients with neurologic disease identified increased titers to HHV-6 in patients with multiple sclerosis (MS). Challoner and colleagues extended this association by demonstrating HHV-6 DNA in the brains of MS patients by representational difference analysis and showed that active HHV-6 infection was localized to the cells surrounding demyelinated plaques. Two recent case reports have also demonstrated HHV-6 antigens associated with areas of demyelination in brain tissue from patients with rapidly progressive variants of MS. Soldan and colleagues described a significantly increased immunoglobulin M response to an HHV-6 early antigen in patients with relapsing and remitting MS compared with patients with other
neurologic or inflammatory diseases. HHV-6 DNA also was detected in the serum of relapsing and remitting MS patients, suggesting active viral replication. These data contrast with two PCR-based studies of brain tissue and CSF from patients with MS that failed to show an association with HHV-6. The lack of detailed descriptions of the patients included in these reports makes comparison between them difficult.

**HIV infection**

Many studies have explored the possible in vitro interactions of HIV-1 and HHV-6 with conflicting results. Dual infection of CD4+ lymphocytes by HHV-6 and HIV-1 has been observed. Additionally, HHV-6 infection induces de novo expression of CD4 molecules on the surface of CD8+ and natural killer cells, suggesting that HHV-6 could enhance the virulence of HIV by converting normally resistant cells to potential targets for HIV infection. Experiments using molecular biologic techniques have demonstrated transactivation of the HIV promoter by HHV-6. Negative studies have noted the inhibition of HIV replication in cultured lymphocytes by the addition of HHV-6. A serologic study by Fox and colleagues did not detect a difference in either the prevalence or titer of antibody to HHV-6 between a group of HIV-positive and HIV-negative homosexual men and normal blood donors. Similarly, PCR-based studies have not shown a difference between normal adults and HIV-infected individuals in the rate of HHV-6 DNA detection in saliva or peripheral blood mononuclear cells. In a study by Fairfax and colleagues, the ability to detect HHV-6 was directly correlated with patients' CD4 cell counts and was not different between normal controls and HIV-infected patients with CD4 counts greater than 400 cells/mL. Reactivation of HHV-6 in HIV disease has been suggested by finding HHV-6 DNA in the plasma or serum of HIV-seropositive patients. Active HHV-6 infection also has been demonstrated by immunocytochemistry in multiple tissue specimens from a small number of AIDS patients at autopsy and in a significantly greater proportion of lymph node biopsy samples from patients with HIV compared with non-HIV-infected controls. HHV-6 antigens have been detected in the retinas of patients with HIV-related retinitis. The clinical significance of these findings is unclear.

**Immunocompromised hosts**

HHV-6 has been associated with a number of diseases in non-HIV-infected immunocompromised hosts. Case reports and small patient series have suggested an etiologic role for HHV-6 in Hodgkin's disease, renal allograft rejection, and fever following liver transplantation. In bone marrow transplant patients, HHV-6 has been linked to pneumonitis, skin rashes, and bone marrow suppression. A single case report also documented the occurrence of rash in a patient with leukemia, with demonstration of HHV-6 antigen in the skin and improvement with ganciclovir. A recent comprehensive review of HHV-6 concluded that no proof existed for an etiologic role of HHV-6 in non-Hodgkin's lymphoma, cervical carcinoma, Kaposi's sarcoma, or collagen vascular disease. The exact role, if any, that HHV-6 plays in the other diseases listed above awaits further study.

**DIAGNOSIS AND TREATMENT**

Unfortunately, a reliable method for the diagnosis of acute or reactivated HHV-6 infection is not readily available outside of research laboratories. The limitations of serologic testing have been outlined above. Isolation of the virus in culture is technically challenging, requiring co-cultivation of the peripheral blood lymphocytes with stimulated cord blood mononuclear cells. Results are not routinely available for 2 to 3 weeks. The detection of HHV-6 DNA in peripheral blood mononuclear cells or saliva by PCR cannot distinguish between acute, latent, or reactivated infection. The presence of HHV-6 DNA in plasma or serum has been shown in one study to correlate with acute infection. No further verification of this method, however, has been published.

The treatment of HHV-6 infections with antiviral agents has not been systematically stud-
ied. HHV-6, like cytomegalovirus (CMV), does not possess a thymidine kinase enzyme and, therefore, is not inhibited readily by acyclovir in vitro.\textsuperscript{51} Ganciclovir and foscarnet have shown reasonable activity against HHV-6 in vitro, with a subset of studies demonstrating variable resistance of HHV-6 variant A strains to ganciclovir.\textsuperscript{23,82}

### HUMAN HERPESVIRUS-7: CASE ILLUSTRATION

A 34-month-old white male toddler was brought to the emergency department because of a 1-day history of fever and the onset of a generalized seizure. He had no respiratory symptoms, vomiting, diarrhea, rash, or exposure to toxins. The child had a history of frequent otitis media, which had been treated with myringotomy tubes 2 years prior to this illness.

Results of the child’s physical examination were normal except for a temperature of 103°F. A complete blood count revealed a white blood cell count of 5.7 x 10\textsuperscript{9} cells/L with 74% neutrophils and 26% lymphocytes. Blood and urine cultures were subsequently found to be negative. The child was discharged with a diagnosis of a simple febrile seizure. HHV-7 was isolated from his peripheral blood mononuclear cells at the time of the acute visit, and seroconversion to HHV-7 was demonstrated on paired acute and convalescent sera.

### EPIDEMIOLOGY

The first isolation of HHV-7 was reported by Frenkel and colleagues in 1990.\textsuperscript{83} Since this initial report, HHV-6 and HHV-7 have been demonstrated to be closely related members of the human herpesvirus family.\textsuperscript{84} Both share nucleotide sequence similarity and have antigenic cross-reactivity.\textsuperscript{20} HHV-7 primarily infects CD\textsuperscript{4+} lymphocytes and can be recovered from the peripheral blood mononuclear cells and saliva of both healthy and ill adults and children.\textsuperscript{85,86} As with HHV-6, serologic surveys have demonstrated universal human infection with HHV-7, with a seroprevalence of greater than 75% at 3 to 6 years of age.\textsuperscript{87,88} In a small study of children with primary HHV-7 infection documented by viral isolation and seroconversion, the mean age of the patients was 22.4 months, significantly older than children with acute HHV-6 infection.\textsuperscript{21} Persistence or latency of HHV-7 in both the peripheral blood mononuclear cells and saliva has been documented by PCR.\textsuperscript{89,90} Although the exact mode of transmission or spread of HHV-7 has not been determined to be via oral secretions, it is suggested by the frequent isolation of HHV-7 from saliva samples of adults and children. HHV-7 DNA also has been detected in 3% of cervical specimens from pregnant women, making sexual transmission a possibility.\textsuperscript{10}

### CLINICAL MANIFESTATIONS

Much less is known about the clinical characteristics of infection with HHV-7 compared with HHV-6. Tanaka and colleagues were the first to associate primary HHV-7 infection with clinical symptoms by their report of two children with roseola concomitant with the isolation of HHV-7 from the peripheral blood mononuclear cells.\textsuperscript{91} Since then, case reports and small patient series have described both roseola, second episodes of roseola, and hepatitis in Japanese children with serologic evidence of primary HHV-7 infection.\textsuperscript{92-95} Fever, irritability, and febrile seizures were the most common manifestations of primary HHV-7 infection in U.S. children.\textsuperscript{21} Seizures and acute hemiplegia of childhood also were reported in two children from Japan.\textsuperscript{96} Care must be taken in the interpretation of these studies because the total number of patients studied was very small. Additionally, cross-reactive antibodies between HHV-6 and HHV-7 have been documented in patients with both primary HHV-6 infection and primary HHV-7 infection, suggesting that the use of serology alone for the diagnosis of HHV-6 or HHV-7 infection is unreliable.\textsuperscript{21} Reactivation of HHV-6 by HHV-7 also may play a role in the clinical characteristics ascribed to HHV-7 infection, further confounding the role of each of these viruses in disease manifestations.

Reactivation of HHV-7 has been associated
with the development of CMV disease following renal transplantation and the dermatologic disorder pityriasis rosea. The significance of these findings is unclear.

**DIAGNOSIS AND TREATMENT**

No method is available presently for the diagnosis of HHV-7 infection outside of research laboratories. In vitro studies of the activity of various antiviral compounds against HHV-7 are also lacking.

**SUMMARY**

HHV-6 and HHV-7 are closely related lymphotropic herpesviruses. Both cause ubiquitous infections of early childhood followed by lifelong persistence or latency. Several clinical syndromes have been associated with HHV-6 primary infection and reactivation in both normal and immunocompromised hosts. The exact role that HHV-6 plays in these diseases has yet to be elucidated fully. The range of clinical manifestations and importance of infection with HHV-7 is even less well defined, requiring further study.

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