Disease association and diagnosis of human herpesvirus 6

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HUMAN HERPESVIRUS 6 (HHV6) WAS FIRST REPORTED IN 1986 by Salahuddin et al (1) following the isolation of an agent from the peripheral blood mononuclear cells of a human immunodeficiency virus (HIV)-1-infected AIDS patient. The virus was initially termed human B lymphotropic virus, but the name was changed after it was shown to have a diverse cellular tropism with a predominant affinity for CD4-positive T lymphocytes (2). HHV6 is genetically most similar to human cytomegalovirus and possesses similar in vitro sensitivity to gancyclovir with some evidence of susceptibility to foscarnet (3).

Serological cross-reactivity of HHV6 with other human herpesviruses does not seem to be significant and is seldom a factor in primary HHV6 infections in young children (4). However, reactivation or co-infection of other herpesviruses with HHV6 in transplantation patients or others with immunological alterations may complicate serological interpretation in these cases.

There are two recognized HHV6 strain groups typified by prototype GS or U1102-like isolates designated as 'HHV6 variant A' and prototype Z29-like isolates as 'HHV6 variant B' (5). Viruses belonging to each can be identified on the basis of differential reactivity with monoclonal antibodies, in vitro cell tropism and genetically by polymerase chain reaction and restriction enzyme cleavage patterns (6,7). HHV6 is also distinguished from the recently described human herpesvirus 7 (HHV7) by a variety of serological and molecular techniques (8).

Infection with HHV6 is virtually universal in humans with serosurveys using sensitive methodologies in Canada (4) and other countries (9) indicating that antibody prevalence is close to 100% in individuals four years old to middle age. A small decline in prevalence and a more marked decrease in mean level of antibody may be seen with increasing age after 40 years. Virtually all newborns have antibody to HHV6 because of placental transfer of antibody, with antibody titre and prevalence declining towards six months of age. Although early HHV6 primary infections may occasionally occur in the presence of maternal antibody (10), the rate of infection rises rapidly up to one year of age, continues at a reduced rate into the second year and beyond with mean antibody levels peaking in this one- to four-year-old age group (4).

TABLE 1
Conditions in which human herpesvirus 6 (HHV6) may have a causative role or be a cofactor

HHV6 disease association	Causative/possible role
Exanthema subitum	Yes (sole?)
Nonspecific febrile illness – infants and young children	Significant
Heterophile-negative infectious mononucleosis-like illness (non-EBV, non-CMV)	5% (20%)
Viral hepatitis (non A,B,C)	Sometimes; may be fatal
Meningitis/encephalitis/ encephalopathy	Yes; rare
Bone marrow transplantation	Severe interstitial pneumonitis, poor graft function, suppression
Organ transplantation	Frequent reactivation or reinfection, uncertain impact
AIDS	Possible cofactor in disease progression
Hematopoietic malignancies (lymphoproliferative disorders)	Role in triggering lymphomas?
Chronic fatigue syndrome/ myalgic encephalitis	Questionable significance

CMV Cytomegalovirus; EBV Epstein-Barr virus

Previous research has indicated that HHV6 is the major, if not the only, cause of exanthema subitum or roseola infantum in infants and young children (11). The disease in young children typically has an abrupt onset with fever lasting for a few days and the appearance of a maculopapular rash coinciding with the decline in fever. Suboccipital lymphadenopathy is common, with one or more other symptoms such as diarrhea, vomiting, runny nose, cough and hepatomegaly less frequently observed. Hematologically, neutropenia is prominent with relative lymphocytosis during the exanthema phase. The most common complication is convulsive seizures, but even in these cases the prognosis is excellent. HHV6 isolates in exanthema subitum are mostly of the variant B type (12). HHV6 has also been identified as an important cause of acute nonspecific febrile illness in young children in whom the height

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of the fever and the presence of symptoms not usually associated with roseola, such as otitis and diarrhea, can result in varied, time consuming and expensive workup in the emergency department (10). In older children and adults, HHV6 has been investigated for either a causative role or as a cofactor in a variety of conditions (Table 1) including, but not limited to, heterophile-negative infectious mononucleosis-like illness (13), marrow suppression in bone marrow transplant recipients (14) and as a cofactor in the progression of AIDS (15). Hence, there is an obvious need for accurate, rapid laboratory diagnosis of HHV6 primary infection and infection/reactivation in adult or immunosuppressed patients.

The Surveillance, Influenza and Viral Exanthemata section of the Laboratory Centre for Disease Control (LCDC) provides investigational HHV6 diagnostic capabilities for a variety of specimen types. Sera provided with reasonable clinical documentation suggestive of HHV6 involvement, patient age and an indication of the time of sampling relative to disease onset may be forwarded for testing to LCDC via the provincial laboratories. In addition, specimens from specific collaborative studies may be accepted directly based on predetermined research objectives and agreements. Our current diagnostic methodologies for HHV6 include an enzyme-linked immunosorbent assay (ELISA) for serological identification of HHV6-specific immunoglobulin (Ig) G, or IgM antibodies after IgG removal (4) as well as the potential for viral isolation and molecular characterization of isolates through polymerase chain reaction-based assays. The ELISA is based on HHV6 antigen prepared from a continuous lymphocyte culture (HSB-2) infected with HHV6 variant A (GS) originally provided through a research agreement with the United States National Institutes of Health. HHV6 isolation can be attempted from appropriate specimens in either continuous HSB-2 lymphocytes or in primary cord blood lymphocytes.

During 1993 the LCDC analyzed sera from approximately 400 patients from across Canada and found that 54 (14%) demonstrated an IgG seroconversion and/or IgM. In addition, we analyzed serially collected sera from 22 transplantation patients and found that 36% of these patients had significant increases in either their IgG and/or IgM titres. Our studies have indicated that HHV6-specific IgM may not be present in primary HHV6 infection until as late as four to seven days post-onset of symptoms. This results in a low negative predictive value on HHV6 IgM-negative serum specimens collected within a day or two of disease onset. However, early acute and convalescent sera taken seven to 10 days apart may show seroconversions in both IgM and IgG antibody.

We continue to investigate the epidemiological significance and range of disease caused by HHV6 through collaborative clinical studies at a number of centres, and are continuing in the development and evaluation of additional diagnostic assays such as Western blot analysis. The combination of viral isolation and molecular characterization should provide definitive identification of infecting strains and could prove useful in distinguishing the nature of individual strains in different disease states. However, both require further study and refinement before the results obtained with either can be generally and reliably interpreted in the context of acute and/or chronic infection diagnosis.

There has been substantial progress in understanding the role of HHV6 infections in specific human diseases. Much remains to be determined, however, and the combination of careful clinical studies and innovative diagnostic techniques will be required to continue to evaluate the pathological significance and impact of this virus.

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