

Human Herpesvirus 6: an Evolving Story

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HUMAN HERPESVIRUS 6 (HHV-6) IS A β -HERPESVIRUS AND THE CAUSAL PATHOGEN OF EXANTHEM SUBITUM IN INFANTS. HHV-6 PERSISTS FOLLOWING PRIMARY INFECTION AND CAN REACTIVATE IN IMMUNOCOMPROMISED HOSTS WHERE IT HAS BEEN ASSOCIATED WITH MORBIDITY IN TRANSPLANT RECIPIENTS, MULTIPLE SCLEROSIS PATIENTS AND HIV-INFECTED INDIVIDUALS

KEY WORDS

■ HUMAN HERPESVIRUS 6 (HHV-6) ■ HERPESVIRUS ■ EXANTHEM SUBITUM ■ ROSEOLA INFANTUM ■ TRANSPLANTATION ■ AIDS ■ MULTIPLE SCLEROSIS (MS) ■ DRUG-INDUCED HYPERSENSITIVITY

SUMMARY

First isolated in 1986 from patients with lymphoproliferative disorders, human herpesvirus 6 (HHV-6) is a β -herpesvirus with two variants: HHV-6A and HHV-6B. HHV-6B is the major causal pathogen of exanthem subitum, a predominantly benign exanthematous disease of infants with occasional complications in the central nervous system. Infection with HHV-6 is common among the general population and the virus mainly seems to be transmitted from mother to infant via saliva. Following primary infection, HHV-6 persists latently and can reactivate in immunocompromised hosts, such as in individuals with AIDS or in transplant or multiple sclerosis patients where it possibly causes encephalitis and pneumonitis. Its precise role in these conditions is not well understood and further study is needed.

Introduction

HUMAN HERPESVIRUS 6 (HHV-6), initially named human B-lymphotropic virus (HBLV), was first isolated in 1986 from the peripheral blood mononuclear cells (PBMCs) of adults with lymphoproliferative disorders (Table 1).¹ Several reports followed that described the isolation of similar viruses, mainly from individuals with AIDS, that could infect B and T lymphocytes and other human cells, such as megakaryocytes and glioblastoma cells.² Ultimately, it was agreed that these were the same viral agent leading to the adoption, in 1987, of 'human herpesvirus 6' as the accepted epithet for the virus.³

Humans are the natural host of HHV-6 which is predominantly T-lymphotropic *in vitro*, replicating most efficiently in activated primary T cells and T-cell lines.² The virus is able to use the ubiquitous immunoregulatory receptor CD46 for entry into target cells and has a broader host tissue range *in vivo*.⁴

Nomenclature and taxonomy

Human herpesvirus 6 belongs to the genus *Roseolovirus* and is a member of the subfamily β -herpesviridae. It is closely related to both human herpesvirus 7 (HHV-7) and human cytomegalovirus (HCMV). Isolates of HHV-6 are classified into two distinct variants, HHV-6A and

HHV-6B. These two closely related variants show consistent differences in biological, immunological, epidemiological and molecular properties.⁵⁻⁸ HHV-6B is the primary causative agent of exanthem subitum,⁹ also known as roseola infantum or sixth disease, whereas no single disease has been definitively associated with HHV-6A.¹⁰

Ultrastructure

The virions of HHV-6, as with all herpesviruses, have four main structural elements (Figure 1): (i) an icosahedral nucleocapsid containing 162 capsomeres; surrounding (ii) an electron-dense core; enclosed in (iii) an envelope derived from cellular membrane and containing viral glycoproteins and embedded integral proteins; and (iv) a tegument between the nucleocapsid and the envelope.¹⁰ Within the core is a linear double-stranded DNA molecule of approximately 159–162 thousand base pairs comprising the viral genome. Complete genomic sequences for HHV-6A strain U1102⁷ and HHV-6B strains Z29⁶ and HST⁸ have been determined, and the HHV-6 genome is estimated to contain more than 100 protein-encoding genes.

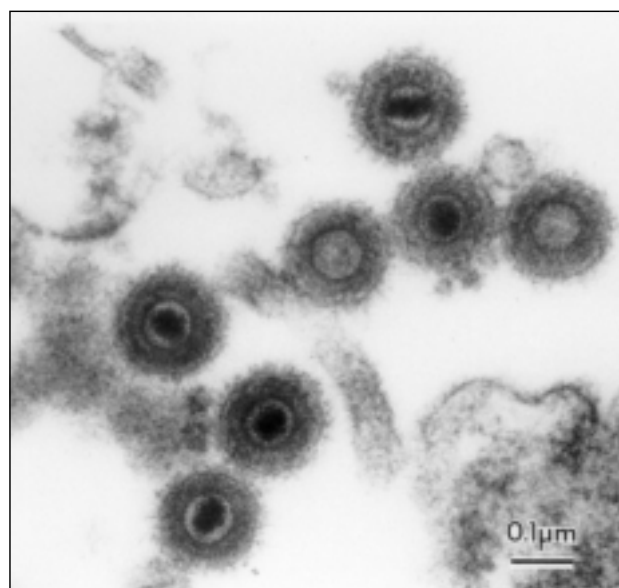


Figure 1: Electron micrograph of human herpesvirus 6 and infected cells.

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Table 1: Important dates in the history of human herpesvirus 6

Date	Event	Reference
1910	Definitive clinical description of exanthem subitum (roseola infantum)	Zahorsky ²²
1941	Prospective study of exanthem subitum leading to the hypothesis that a 'filterable virus' is the causative agent	Breese ¹⁹
1950–1951	Experimental inoculation of exanthem subitum demonstrated in humans	Kempe <i>et al.</i> ²⁰ Hellstrom and Vahlquist ²¹
1986	New virus, named human B-lymphotropic virus (HBLV), isolated from patients with AIDS and other lymphoproliferative disorders	Salahuddin <i>et al.</i> ¹
1987	HBLV renamed human herpesvirus 6 (HHV-6)	Ablashi <i>et al.</i> ³
1988	HHV-6 identified as causal agent in exanthem subitum	Yamanishi <i>et al.</i> ⁹
1990	Human herpesvirus 7 (HHV-7) isolated from CD4 ⁺ lymphocytes of healthy adult	Frenkel <i>et al.</i> ⁷⁹
	HHV-6 associated with infectious mononucleosis-like illness in adults	Steeper <i>et al.</i> ²⁵
1993	HHV-6 variants A (HHV-6A) and B (HHV-6B) formally recognized	Ablashi <i>et al.</i> ⁸⁰
1994	HHV-6 associated with febrile seizures	Hall <i>et al.</i> ²⁶
1995	Complete genomic sequence of HHV-6A determined	Gompels <i>et al.</i> ⁷
1999	Complete genomic sequence of HHV-6B determined	Dominguez <i>et al.</i> ⁶ Isegawa <i>et al.</i> ⁸

Detection and Serodiagnosis

Human herpesvirus 6 can be recovered easily from the PBMCs of exanthem subitum patients during the acute phase of disease.⁹ Lymphocyte activation with either phytohaemagglutinin or anti-CD3 antibody and maintenance in interleukin-2 are required.¹⁰ Cytopathic effects can be seen after 7–10 days' cultivation. The refractile giant cells usually contain one to two nuclei and, after the onset of cytopathic effects, lytic degeneration of the cells takes place. PBMC-associated HHV-6 viraemia has been detected in 66% of blood samples taken from children with exanthem subitum between days 0 and 7 of disease onset.¹¹ The rate of virus isolation from PBMCs is 100% within 2 days of the onset of clinical symptoms, gradually decreasing to 0% during the convalescent phase.

Several serological assays are available for investigating HHV-6, including immunofluorescence antibody assay, enzyme-linked immunosorbent assay, virus neutralization assay, radioimmunoprecipitation and Western blot analysis. Indirect immunofluorescence antibody assay is the most commonly used method for HHV-6 antigen and antibody detection, whereas the use of neutralization assays is less common.¹⁰

Hybridization and polymerase chain reaction (PCR) techniques can be used to detect HHV-6 DNA. Southern blotting is useful for rapidly screening large numbers of specimens, although it is generally less sensitive than PCR. Numerous HHV-6-specific PCR primer sets are available and some allow the discrimination of variants (Figure 2).^{10,12–14} A quantitative competitive PCR assay for HHV-6 has also been developed that demonstrates the persistence of a high HHV-6 viral load in the absence of apparent disease.¹⁵

Epidemiology

The early literature on HHV-6 seroprevalence contains several inconsistencies. These include estimates of the proportion of seropositive individuals in the general

population that vary from 3% to 90%, conflicting views on age-related changes in seropositivity, and on whether there is a correlation between HHV-6 antibody status and the progression of diseases associated with HIV.^{10,16} There have been few attempts to distinguish between HHV-6A and HHV-6B in serological studies. Differences in assessment criteria, experimental methods and significant cross-reactivity between HHV-6A, HHV-6B and HHV-7 may account for these inconsistencies.

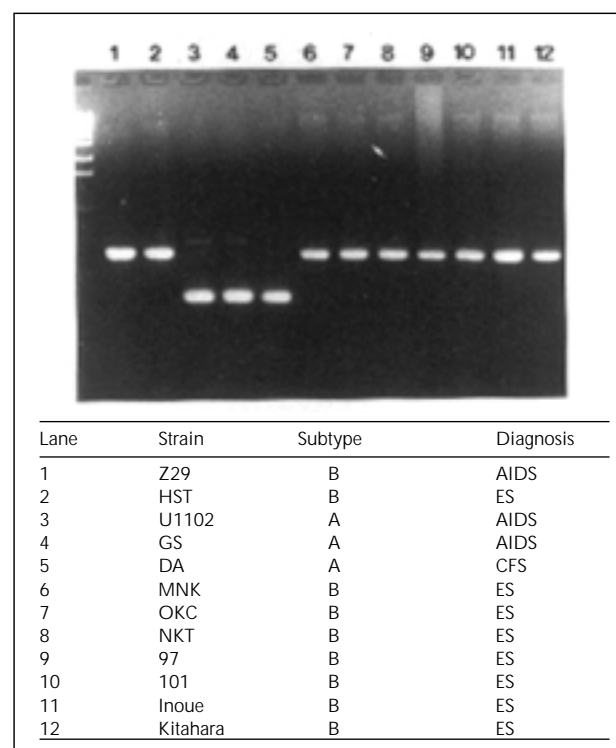


Figure 2: Polymerase chain reaction amplification of 12 laboratory strains and clinical isolates of human herpesvirus 6 DNA.¹⁴

Most recent studies suggest that the seroprevalence of HHV-6 is high and geographically widespread.¹⁰ Many reports indicate that almost all children are exposed to the virus by the time they are 6–12 months old and that about 90% of healthy individuals have HHV-6 DNA detectable in their saliva.^{17,18} About the same proportion of pregnant women have antibodies to HHV-6 and maternal antibody, transferred to the child through the placenta, is detectable in infants during the first few months after birth.¹⁰ As a result, it is believed that, in early life, infants may be protected against HHV-6 infection.

Primary HHV-6 Infection

AETIOLOGY

Prior to 1988, a viral aetiology had been postulated for exanthem subitum¹⁹ on the basis of indirect evidence, such as the long incubation time of the disease, frequent presence of leukopenia, lack of response to antimicrobial agents and the failure to detect bacteria in patients' body fluids. Efforts to isolate a virus were unsuccessful but, in the early 1950s, human transmission of the disease by experimental inoculation with blood of infants with exanthem subitum was demonstrated.^{20,21} Isolation of HHV-6B from the blood of infants in the acute phase of the disease was finally achieved nearly 40 years later.⁹ Exanthem subitum and other symptomatic primary HHV-6 infections appear to be caused exclusively by HHV-6B.

CLINICAL SIGNS AND SYMPTOMS

Exanthem subitum was first described in 1910 by Zahorsky²² and has long been recognized as a common disease of infants (Table 1). The course of the disease usually starts with a sudden and acute fever that lasts for about 3–6 days. As the fever subsides, a rash may appear on the trunk and face, spreading to the lower extremities (Figure 3). The severity of febrile symptoms has been correlated with the magnitude of viral replication.²³ In most cases exanthem subitum is benign and may be associated with other signs and symptoms including diarrhoea, cough, lymphadenopathy and bulging fontanelles. In immunocompetent adults, primary infection can cause mononucleosis-like symptoms, haemophagocytic syndrome and hepatitis.^{24,25}

COMPLICATIONS

In infants, most major complications of primary infection occur in the central nervous system (CNS).²⁶ Febrile convulsions or seizures are most commonly reported and HHV-6-associated seizures account for one-third of all febrile seizures in children under 2 years of age. Seizures often appear late in the clinical course of primary infection and may be prolonged or recurrent.

Human herpesvirus 6 DNA has been detected in cerebrospinal fluid (CSF) both during and after primary infection, suggesting that the virus persists within the CNS.²⁶ The presence of viral DNA in the CSF has been linked to an increase in the recurrence of febrile convulsions. The prognosis in these cases is generally good and seizures are usually self-limiting and benign. Meningitis, encephalitis and residual CNS deficits, however, have been associated with HHV-6 infection.¹⁰

Human herpesvirus 6 may be the causative agent of childhood transient erythroblastopenia²⁷ and certain types of liver dysfunction.^{28,29} Hepatic dysfunction associated with HHV-6 is usually uncommon, short-lived and mild, but fatal and chronic hepatitis has been reported. Idiopathic thrombocytopenic purpura induced by primary HHV-6 infection has also been described.³⁰

Transmission of HHV-6

The mode of transmission of HHV-6 between individuals has not been fully elucidated. Although local and seasonal



Figure 3: Infant presenting with the rash typically associated with exanthem subitum.

outbreaks of exanthem subitum have been observed in children's institutions,³¹ infant–infant horizontal transmission is probably not of major significance.

Human herpesvirus 6 DNA has been detected by PCR in the female genital tract,³² including the cervical secretions of women in late pregnancy.³³ These findings suggest that infectious viral particles may be transmissible perinatally to newborn infants transvaginally. Intrauterine transmission has been postulated as viral DNA has been detected in fetuses and in the blood of newborn babies.^{26,34} Dahl *et al.*,³⁵ for example, detected HHV-6 DNA in 41–44% of samples taken during months 3–8 of pregnancy and this was significantly higher than age-matched controls (24%). In addition, HHV-6 DNA has also been detected in 1–1.6% of cord blood samples taken from babies born to ostensibly healthy mothers.³⁶ Thus, HHV-6 reactivation seems common during pregnancy, when transfer to the fetus may occur. More interestingly, the HHV-6 genome has been found integrated within the chromosomes of PBMCs,^{37,38} suggesting a possible transplacental route of transmission.

The majority of epidemiological data indicate that transmission occurs after birth and that the role of intrauterine and perinatal transmission is minor. HHV-6 DNA has been detected by PCR in the saliva¹⁸ and on throat swabs¹⁶ from children and healthy adults, including mothers. Although it is difficult to isolate HHV-6, identical viral DNA restriction fragment length polymorphisms and PCR products have been found in separate specimens from mother–infant pairs.³⁹ These findings support the hypothesis that the most common mode of HHV-6 transmission is horizontal, from mother to infant, via the saliva.

Persistence and *In Vivo* Distribution

The site of latent infection with HHV-6 has not been conclusively identified. The reliability of PCR-detected HHV-6 DNA, as an indirect indicator of *in vivo* distribution, depends on the sensitivity of the

techniques being used. Evidence supporting the persistence of HHV-6 in host tissues includes the presence of HHV-6 DNA in the monocytes,⁴⁰ saliva, salivary glands and CNS.⁴¹ The HHV-6 virus has also been shown to infect early bone marrow progenitor cells, *in vivo*, where it persists latently.⁴²

Reactivation

Herpesviruses persist in the host following primary infection and are important pathogens in the immunocompromised. Reactivation of HHV-6 has been reported following organ transplantation, in individuals with AIDS and is associated with multiple sclerosis (MS), chronic fatigue syndrome and drug hypersensitivity. Latent HHV-6B has been recovered from cells infected with HHV-7^{43,44} and the measles virus.⁴⁵ There may be a role, therefore, for HHV-7-mediated and/or measles virus-mediated HHV-6 reactivation. Clinical manifestations in patients with neoplastic disorders and collagen vascular disease have also been described.¹⁰

BONE MARROW TRANSPLANTATION

Asymptomatic HHV-6 reactivation appears to be common following allogeneic bone marrow transplantation (allo-BMT).⁴⁶ Reactivation with symptoms, such as bone marrow suppression,⁴⁷ encephalitis,⁴⁸ pneumonitis^{49,50} and acute graft-versus-host disease⁵¹ in bone marrow transplant recipients has also been recognized.

Studies have shown that immune reconstitution is more rapid after allogeneic peripheral blood stem cell transplantation (allo-PBSCT) than allo-BMT.⁵² The DNA of HHV-6 is most frequently detected at 3 weeks post-transplantation. Detection rates for HHV-6 DNA at 3 and 4 weeks after allo-BMT were significantly higher than after allo-PBSCT. Detection of HHV-6 DNA is associated with delayed platelet engraftment within the first 4 weeks after both allo-BMT and allo-PBSCT. These results suggest that there are fewer HHV-6 reactivations and related complications after allo-PBSCT than allo BMT.

SOLID ORGAN TRANSPLANTATION

In a study of 21 kidney transplants, HHV-6 was shown to infect renal tissue and correlate with rejection or immunosuppressive therapy.⁵³ In many cases, reactivation occurred in the early post-transplant period and HHV-6 established *in vivo* latency within the kidney.

A prospective study by Osman *et al.*⁵⁴ on kidney transplant patients indicated that HHV-7 may be a cofactor in 'CMV disease'. An association between HCMV and HHV-6 was inconclusive in this study, although it has been reported elsewhere.⁵⁵ Furthermore, Griffiths *et al.*⁵⁶ have reported that HHV-6 and -7 may be responsible for some episodes of hepatitis and pyrexia following liver transplantation.

AIDS AND HIV INFECTION

Reactivation of HHV-6 in people with AIDS may be associated with interstitial pneumonia, encephalitis and retinal disorders, and necropsies carried out on AIDS patients have shown the presence of HHV-6 across a wide range of host tissues, including those of the lung, lymph node, spleen, liver and kidney.⁵⁷ This appears to support the suggestion of Lusso and Gallo,⁵⁸ that HHV-6-related disease in HIV-seropositive individuals is a function of its cofactor role in contributing to immune deficiency, rather than a direct effect on specific target organs.

In vitro, HHV-6 has been shown both to inhibit and stimulate HIV replication.⁵⁹ Further studies using organs collected at autopsy from people with AIDS have shown that the presence of HHV-6 is significantly associated with

an elevated HIV-1 proviral load *in vivo*.⁶⁰

In a study of 22 infants with vertical HIV-1 infection, 10 were found to have concurrent HHV-6 infection at the start of the study.³⁴ In five of the HHV-6-negative children, HIV disease had not progressed by 1 year of age, whereas it had progressed in all 10 children with HHV-6 infection. The findings suggest an association between HHV-6 infection and the progression of HIV.

In an *in vitro* study, two CD34⁺ human haematopoietic progenitor cell lines became susceptible to HIV-1 infection when infected concurrently by HHV-6.⁶¹ Further examination of the underlying mechanism of this phenomenon ruled out the possibility that HHV-6 modifies the cell surface availability of HIV-1-specific high-affinity receptors, such as the members of the chemokine receptor family.

In a multicentre, longitudinal study of individuals with a documented date of HIV seroconversion, sera were tested for anti-HHV-6 immunoglobulin G, but no association between antibody status and HIV disease progression was found.⁶² The presence of even high levels of HHV-6 antibodies did not seem to predict the clinical or immunological progression of HIV disease in this study.

Based on the findings thus far, the role of HHV-6 as a cofactor in HIV infection clearly requires further investigation.

MULTIPLE SCLEROSIS

As reviewed recently by Clark,⁶³ several studies have suggested an association between HHV-6 and MS, and HHV-6 DNA has been detected by PCR in the brain, CSF, PBMCs and serum of MS patients. Challoner *et al.*⁶⁴ for example, using representational difference analysis, found a DNA fragment identified as the major DNA binding protein gene of HHV-6 in the brain tissue of MS patients. Overall, the serological, molecular and virus-isolation findings of these studies suggest that active HHV-6 infection may be a factor in at least a subset of MS patients.

The more recent literature on the involvement of HHV-6 in MS remains ambiguous. Some studies have found no association between MS and levels of HHV-6 antibodies or DNA in CSF,⁶⁵ PBMCs^{65,66} and serum of MS patients.⁶⁷ One study suggests that intrathecal chronic active or primary HHV-6B infection contributes to MS progression while the local effects of HHV-6A are less important.⁶⁸ Another study, however, found that seven of 34 MS patients had HHV-6A DNA detectable in their PBMCs as opposed to none in controls, implicating latent HHV-6A, and not HHV-6B, in the pathogenesis of MS.⁶⁹ The studies by Ablashi *et al.*,⁷⁰ Soldan *et al.*,⁷¹ Friedman *et al.*,⁷² and Blumberg *et al.*⁷³ all support a positive correlation between HHV-6 and MS pathogenesis.

Several alternative theories exist for the aetiology of MS⁶³ and further experiments will need to look at the potential involvement of HHV-6 and the role of other infectious agents and environmental stimuli. If HHV-6 plays a role as an initiator or amplifier of inflammatory lesions in some MS patients, these individuals might benefit from antiviral therapy.

DRUG HYPERSENSITIVITY

Drug-induced hypersensitivity syndrome is characterized by a severe, potentially fatal, multi-organ reaction that usually appears after prolonged exposure to certain drugs. Clinical signs include a maculopapular rash progressing to exfoliate erythroderma, fever and lymphadenopathy. Leukocytosis, atypical lymphocytes, liver dysfunction and renal disturbance are also observed. Its delayed onset and clinical resemblance to infectious mononucleosis suggest that underlying viral infections may trigger and activate the disease in drug-sensitive individuals. Reactivation of HHV-6B, possibly in concert with HHV-7, has been shown to contribute to the development of a severe drug-induced hypersensitivity syndrome.^{74,75}

Treatment

There have been no major controlled clinical trials, and few *in vitro* studies, of antiviral agents for the treatment of HHV-6 infection. A new susceptibility assay using flow cytometry has recently been developed and pyrophosphate analogues, β -guanine analogues, nucleoside phosphonates and benzimidazole ribonucleosides have all been assessed for anti-HHV-6 and anti-HHV-7 activity.⁷⁶ The sensitivity of HHV-6 is similar to HCMV and its sensitivity to guanine analogues differs from that of HHV-7, suggesting a difference in the specificity of viral enzymes.⁷⁷

There has been a controlled clinical trial of aciclovir in MS patients.⁷⁸ This study indicates that aciclovir inhibits MS exacerbations, suggesting that an aciclovir-susceptible virus might be involved in the pathogenesis.

Conclusions

The history of HHV-6 is a short one, illuminated predominantly by techniques developed as a result of

HIV research. The role of HHV-6 in exanthem subitum is well understood and most children recover completely with only symptomatic treatment. More research on the role of HHV-6 in immunocompromised hosts and MS is warranted. Despite obvious difficulties, clinical trials should be conducted that are aimed at directly assessing the effect of agents on HHV-6, particularly in MS and organ transplant patients.

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