Manual of Childhood Infections: The Blue Book (4 edn)

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CHAPTER

107 Human herpesvirus 6 and 7

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Abstract

Human herpesvirus 6 (HHV-6) and 7 (HHV-7) constitute the *roseolavirus* group of β-herpesviruses. HHV-6 has two subtypes HHV-6A and HHV-6B. Both HHV-6 and HHV-7 tend to produce mild self-limiting illness in immunocompetent children that typically develops in late infancy and early childhood. HHV-6, in particular, is associated with a viral exanthem known as 'sixth disease' or roseola infantum (exanthema subitum), from which the *roseolavirus* group derives its name. HHV-6 is also the commonest single viral aetiology underlying febrile seizures in early childhood and has been associated with encephalitis of varying severity in immunocompetent children. Recent evidence links HHV-6 with the subsequent evolution of mesial temporal epilepsy. There is emerging evidence that HHV-6 can lead to complications in post-transplant patients, most notably post-transplant-associated limbic encephalitis. It may also contribute to, or serve as a marker for, an increased risk of graft-versus-host-disease and cytomegalovirus reactivation. Ganciclovir, foscarnet, and cidofovir have *in vitro* activity against HHV-6 and have been used to treat infections in severe illness and infection in immunocompromised patients.

Keywords: HHV-6, HHV-7, exanthem subitum, roseola infantum, sixth disease, febrile seizure, post-transplant acute limbic encephalitis

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See also Chapters 14, 20, 34.

Nature and name of organisms

- HHV-6 and 7 are closely related herpesviruses that cause a similar spectrum of disease. This chapter describes HHV-6 in detail and refers to HHV-7 when there are important differences.
- HHV-6 has a linear, double-stranded DNA of about 160kb. Two major variants A and B have been identified. Variant B is the type associated with the common clinical manifestations in childhood. The virus preferentially infects $CD4^+$ T lymphocytes but is also found in monocytes, macrophages, brain, and kidney cells.
- HHV-7 has a genome of ~145kb and has close homology to HHV-6, and both are more closely related to CMV than to other herpesviruses.

Epidemiology

- Infection is acquired in early childhood. 1° infection with HHV-6 typically occurs between 6 months and 3 years of age.
- At birth, up to 80% of infants have detectable maternal-derived antibody. In spite of this, neonatal infection has been reported, indicating that humoral immunity is not completely protective.
- Seropositivity rates for HHV-6 climb from a nadir of 5–10% at 6 months to a peak of 80–90% by the age of 2 years. The seroconversion rate is highest between 6 and 12 months of age. Antibody titres have been reported to fall in later life.
- Epidemiological studies around the world have shown similar rates of acquisition, apart from some isolated indigenous communities where rates of seropositivity may be ≤10%.
- HHV-7 tends to be acquired later than HHV-6. The median age of seroconversion is 2 years. HHV-7 shows a similar pattern of high titres in early childhood which declines in adult life.

Transmission

- Infection is transmitted by respiratory droplets from asymptomatic carriers, most likely family members, who carry latent virus in their saliva.
- ~1% of the population carries chromosomally integrated HHV-6 (CI-HHV-6). CI-HHV-6, transmitted through germ cells, accounts for the majority of congenital HHV-6 infection and is typically asymptomatic.
- Congenital HHV-7 has not been reported.
- HHV-6/7 has been isolated in cervical secretions and may lead to perinatal infection.
- HHV-7 may also be transmitted via breast milk.
- Transmission occurs all year-round.

Incubation period

- The mean incubation period for HHV-6 is 9–10 days.

Clinical features

Exanthem subitum/roseola infantum

- Exanthem subitum, also known as roseola infantum or sixth disease, is the classical clinical syndrome associated with HHV-6 and 7.
- Typically, a disease of infants and young children. There is abrupt onset of a high persistent fever, which may be complicated by seizures. The fever lasts 3–5 days, and a rash appears on defervescence. The rash is characterized by small, discrete blanching pink macules, predominantly on the trunk, with later extension to the limbs.
- The viral syndrome may be clinically indistinguishable from meningitis or bacterial sepsis.
- HHV-7 causes an identical clinical syndrome and has been shown to be the cause of a second episode in children with previous HHV-6 infection. Subclinical infection often occurs; T-cell clones against HHV-6 react with HHV-7, and this may protect children from clinical disease with a subsequent HHV-7 infection.

Non-specific febrile illness

- Most young children with acute HHV-6 infection do not present with classical exanthem subitum, but with a high fever (lasting 3–5 days), coryza, and signs of an URTI.
- Pharyngitis, inflammation of the tympanic membranes, puffy eyes, palpebral conjunctivitis, diarrhoea and vomiting, lymphadenopathy, and a maculopapular rash are all reported.
- In a survey of 1653 children <3 years presenting to an emergency department with acute febrile illness, 160 (9.7%) had evidence of 1° HHV-6 infection.

Febrile seizures

- 1° infection with HHV-6 in young children is estimated to carry a risk of febrile seizure in the region of 30%.
- HHV-6 has been identified in one-third of children <2 years presenting with a first febrile convulsion.

Encephalitis

- HHV-6 has been associated with encephalitis of varying severity in otherwise healthy patients, in some cases mimicking HSV infection.
- Case series of adult and paediatric patients with encephalitis show a prevalence of HHV-6 in the CSF of 1–3% of patients.
- HHV-6 infection has been linked to subsequent mesial temporal lobe epilepsy.
- Isolated cases of HHV-7-associated encephalitis have been reported.

Infection of immunocompromised hosts

- HHV-6 was first isolated from immunocompromised patients with lymphoproliferative disorders.
- It infects a variety of immune cells, having a particular tropism for $CD4^+$ T cells. Evidence suggests that infection impairs the immune response, in particular inhibiting IL-12 production and consequently inhibiting antiviral activity.
- HHV-6/7 have not been clearly associated with severe disease in children living with HIV.
- Among children with haematological malignancy, HHV-6 viraemia is common and is a marker for impaired cellular immunity. In this population, co-infection with HHV-6 and CMV has been associated with lymphopenia, anaemia, and more frequent episodes of febrile neutropenia.
- HHV-6 reactivation post-HSCT has been documented in 30–70% of cases and typically occurs within 2–4 weeks of transplant. It has been associated with CMV reactivation, an increased incidence of acute GVHD, and increased non-relapse mortality. HHV-6/CMV co-infection post-HSCT increases the risk of CMV-related disease.
- HHV-6 reactivation also occurs post-solid organ transplant and has been associated with fever, elevated transaminases, and bone marrow suppression in liver transplant patients.
- Post-transplant acute limbic encephalitis (PALE) is a clinical syndrome seen in patients after either HSCT or solid organ transplantation. It is characterized by neuropsychiatric symptoms, in particular anterograde amnesia, personality change, and irritability. The CSF may be normal or demonstrate mild pleocytosis and elevated protein. There is a strong association with HHV-6 in the CSF. Treatment with ganciclovir/foscarnet has been associated with a decrease in the CSF viral load and clinical improvement. The prognosis is variable. Some patients with PALE are left with permanent neurological deficit.

Other associations

- HHV-6 has been reported as a rare cause of fulminant hepatitis. Other associations include pneumonitis, myocarditis, and haemophagocytic syndrome. However, as this virus may reactivate during acute illness, its role in the pathogenesis of these condition remains uncertain. Previously suggested associations with Kawasaki disease and with multiple sclerosis have been discounted.

Diagnosis

- In most cases, no laboratory diagnosis is made, or the child has recovered by the time a diagnosis is made.
- Leucopenia with relative lymphocytosis is common.
- Acute and convalescent serology will show a rising antibody titre.
- In the acute phase, HHV-6/7 DNA can be detected in peripheral blood mononuclear cells by PCR and culture. The viruses can also be detected in throat swabs and the CSF.
- HHV-6 is kept latent by cell-mediated immunity but can reactivate intermittently, usually asymptomatically.
- Discriminating 1° HHV-6 infection from CI-HHV-6 can be difficult and requires examination of serial viral PCR titres and their interpretation in light of the clinical context. CI-HHV-6 is expressed in all cells in the body and can be detected in the patient's hair follicles.

Treatment

- In most cases, only symptomatic treatment is needed.
- In immunocompromised patients who have co-infection with CMV and HHV-6, treatment of CMV infection with foscarnet or ganciclovir appears to also suppress the HHV-6 viral load.
- Aciclovir has no activity against HHV-6/7.
- There is no trial evidence of benefit from these drugs in generalized or limbic encephalitis, but, in view of the potential severity of the illness, antiviral treatment should be given when HHV-6 encephalitis is suspected.

Prevention

- There is no vaccine against HHV-6/7. As in most cases, the viruses cause mild illness, and it is unlikely that mass immunization would be considered, even if an effective vaccine were produced.
- Some transplant units routinely monitor patients post-transplantation for HHV-6, along with CMV and EBV. Treatment is not given routinely to asymptomatic or mildly symptomatic patients with a detectable HHV-6 viral load, but, where a rising viral load is associated with a significant clinical problem, antiviral treatment might be considered.

Future research

Future research will help to clarify the importance of HHV-6/7 in the immunocompromised host and may identify further clinical syndromes that can be attributed to these pathogens.

Further reading

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