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Human herpesvirus-6 infections

Human herpes virus-6 (HHV-6) was first discovered by Salahuddin and colleagues in 1986 after identifying herpes-like particles in the peripheral blood of patients with AIDS and lymphoproliferative disorders.[1] In the subsequent decade, it has been found to be clinically ubiquitous. However, although improved methods of diagnosis of HHV-6 infection have led to a better understanding of the spectrum of disease caused by the virus, there is still controversy about many of the associations.

Microbiology

Structurally, the double stranded DNA virus shares many characteristics of the other human herpes viruses, having the greatest homology with cytomegalovirus.[2] There are two distinct but closely related types: type A (characterised by the U1102 strain) and type B (characterised by the Z29 strain).[3 4] HHV-6, like HIV, shows tropism for CD4 cells,[5] and as with other herpes viruses, HHV-6 has been shown to cause persistent, asymptomatic infection.[6] The site(s) of latency have not been clearly established, but latent virus has been identified in kidneys, bronchial glands, monocytes and salivary glands.[6 7]

The virus can be isolated by tissue culture using continuous cell lines such as cord blood lymphocytes.[1 3] However, in the clinical setting, serodiagnosis and polymerase chain reaction (PCR) of blood, cerebrospinal fluid, or other sterile site are the most commonly utilised methods of diagnosis. Of the various serodiagnostic assays, the enzyme linked immunosorbent assay (ELISA) and neutralisation methods have been shown to be more sensitive than immunofluorescence.[7–10] No significant cross reactivity between HHV-6 and other human herpesviruses has been detected.[11] PCR, when available, provides a rapid method for determining the presence of HHV-6 DNA. However, as detailed below, a positive result may indicate either an acute infection, reactivation, or subclinical persistence of the virus.

Epidemiology

Horizontal person to person transmission is the most likely route of infection, although this is yet to be firmly established. Oral secretions appear to be the most probable source, as the virus has been detected in the saliva of a significant proportion of healthy adults.[6] Sexual transmission is thought not to be important.[7] The virus has been detected in donated organs,[12–14] and although transfusion associated infection is possible, it has not yet been reported. Vertical transmission (mother to fetus) and reactivation in pregnancy have been documented serologically but no syndrome of congenital infection has yet been described.[15] Breast milk does not appear to be an important source of infection.[16]

The virus has been identified in populations world wide. Estimates of seroprevalence, however, vary around the world, partly due to differences in the method of the assay.[1 7 8 17–21] Seroprevalence rates using immunofluorescence appear to be lower than those determined by neutralisation or ELISA, even in the same population.[22] At birth, most children are IgG antibody positive due to maternal immunoglobulin (approximately 70% by immunofluorescence, 95% by neutralisation).[20–22]

Antibody levels reach a nadir at 4–7 months, then increase throughout infancy so that by 12 months, two thirds have been infected, peak levels being reached at 2 to 3 years. Recent seroepidemiological studies of adult populations from the United States, Japan, and Europe report rates from 80% to almost 100%,[6 20–22] indicating that some waning of antibody may occur and that reinfection and reactivation may not occur frequently.

Disease associations

EXANTHEM SUBITUM

Of the many reported disease associations of HHV-6, exanthem subitum (or roseola infantum) is one of the few in which a causal link has been proved. Yamanishi *et al*, in 1988, were the first to make the association by isolating HHV-6 from the blood lymphocytes of four children with exanthem subitum and showing concurrent seroconversion to HHV-6.[21] Others have confirmed this finding.[8 16 23–25] Asano *et al*, in a study of 176 infants with confirmed HHV-6 infection, clarified the clinical features of exanthem subitum.[26] In addition to the well characterised rash, other features included erythematous papules on the mucosa of the soft palate called Nagayama's spots (in 65% of children), bulging fontanelle (26%), seizures (8%), diarrhoea (68%), cough

(50%), oedematous eyelids (30%), and cervical lymphadenopathy (31%).

Not every infant who acquires primary HHV-6 infection develops classical exanthem subitum. Estimates of the proportion of primary HHV-6 infected infants who do develop exanthem subitum range from 10% in the United States[25] to 98% in Japan.[26] This appears to be due to differences in study design (especially the definition of exanthem subitum), and possibly different strain characteristics: a greater proportion of the population show type A infection in Japan, whereas in the United States the majority of infections are with type B strains. The peak age of primary infection also appears to be earlier in Japan (4 to 7 months) versus the United States (9 months), but primary infection has been reported in an infant as young as 21 days.[27] Increased plasma viral load has been shown to correlate with more prolonged fever (greater than four days) but not with any other features of erythema subitum.[28]

FEBRILE CONVULSIONS/NEUROLOGICAL COMPLICATIONS

Neurological complications of HHV-6 infection have been described by a number of investigators. Asano *et al* found 8% of 176 children with exanthem subitum had febrile seizures.[26] A large prospective series by Breese-Hall *et al* of almost 1700 infants less than 3 years who presented to the emergency room with an acute febrile illness, found that almost 13% had primary HHV-6 infection, and 21 had febrile convulsions with HHV-6 infection.[29]

A study of 21 infants with exanthem subitum, seizures and other central nervous system complications found that the central nervous system became involved in the pre-eruptive phase of the infection.[30] Four of the 21 children had encephalitis, diagnosed on the basis of the severity of central nervous system involvement, abnormal electroencephalograms, abnormal cerebrospinal fluid analysis, and neurological sequelae.[30]

PCR has been used to define the neuroinvasiveness of HHV-6, in acute infection, but the reported incidence of children with primary HHV-6 infection who have viral DNA detected in their cerebrospinal fluid varies from 10% to 90%, once again due to differences in study design.[31–33] HHV-6 DNA has been shown to persist in the cerebrospinal fluid after primary infection,[32–34] particularly those with recurrent febrile convulsions.[33] It is likely, but not proved, that HHV-6 can invade the brain and establish latency during a primary infection, and cause seizures upon reactivation.

There are studies that associate serological evidence of HHV-6 infection with a range of neurological disorders,[35–39] for example, Guillain-Barré syndrome, multiple sclerosis, Parkinson's disease. However, in all of these studies, the evidence is circumstantial and a causal link has not been proved.

OTHER REPORTED CLINICAL ASSOCIATIONS IN THE NORMAL HOST

The following diseases have at some point been attributed to HHV-6 infection through case reports and small case series: infectious mononucleosis-like syndrome/hepatitis,[37–39] chronic fatigue syndrome,[40 41] chronic marrow suppression in a normal adult,[42] haemophagocytic syndrome,[43] intussusception,[44 45] and pneumonitis.[46] The major piece of evidence used in linking these phenomena has been a rise in antibody titre to HHV-6 and on occasion, positive viral culture. In each of these diseases, however, an aetiological association remains to be proved given the following: the ubiquitous nature of HHV-6 in the community demanding large numbers in any study to prove an association, the fact that HHV-6 can establish latency and reactive during times of stress like other herpesviruses, and possible serological cross reactivity between the herpes viruses.

MANIFESTATIONS IN THE IMMUNOCOMPROMISED HOST

Much of the recent literature surrounding HHV-6 has concentrated on the clinical spectrum in the immunocompromised host. Reactivation of the recipient's strain, exogenous infection with the donor's strain, or reinfection with a new strain may all occur. In the bone marrow transplant population, small series of patients have been reported with interstitial pneumonitis in the presence of HHV-6,[47] often in association with graft-versus-host-disease (GVHD).[48] The relative contribution of the HHV-6 and the GVHD to the pneumonitis is unclear. Reactivation of HHV-6 occurred in almost 50% of 25 children during the first two months after bone marrow transplant in a series reported by Yoshikawa *et al*.[48] Thirty per cent had skin rashes that resembled GVHD. Severe bone marrow suppression after bone marrow transplant has also been described in patients with HHV-6 reactivation (or infection), with a suggestion that strain A may be more suppressive than strain B.[49]

Reactivation has also been shown in up to 80% of patients one to two months after renal transplant.[50] A possible correlation between renal graft rejection and the reactivation of HHV-6, similar to the situation with cytomegalovirus, has been proposed,[12] but is controversial.[50]

Studies using DNA hybridisation, PCR on tissue samples, and serological assays have examined the role of HHV-6 infection in the development of lymphoproliferative disease, and although some studies suggest a possible role in a small number of B cell lymphomas, causality remains unproved.[51 52]

The role of HHV-6 in HIV infection has been studied as both viruses share a tropism for CD4 positive lymphocytes. It has been proposed that HHV-6 may function as a cofactor in the progression of HIV infection, but seroprevalence studies have been equivocal,[6 7 18] while studies of HHV-6 antigen and DNA detection have given conflicting results.

Treatment

HHV-6 shows a sensitivity pattern to antiviral agents similar to cytomegalovirus in that both foscarnet and ganciclovir appear to be effective in inhibiting viral cytopathic effects in vitro, and that the virus appears relatively resistant to acyclovir at non-toxic doses.[53] Some work suggests that strain B may be more sensitive to ganciclovir than strain A.[54] Clinical trials of these agents have not been performed for this virus and in the majority of circumstances an antiviral agent is not indicated.

Summary

HHV-6 is ubiquitous in the community, appears to be acquired early in life, and has been proved to cause the clinical syndrome of exanthem subitum, and rarely to cause encephalitis. Like other herpesviruses, HHV-6 is capable of establishing latent infection and reactivating under a variety of stimuli. Improved diagnostic techniques have led to increased recognition of HHV-6 in the presence of many diseases, but much of the evidence for an aetiological role is inconclusive. There is accruing evidence for possible pathological roles in the immunocompromised host, but the evidence is less convincing for the range of

associations otherwise listed for the normal host at the present time.

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