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Review

The natural history and laboratory diagnosis of human herpesviruses-6 and -7 infections in the immunocompetent

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Abstract

Background: Human herpesviruses-6 and -7 (HHV-6/7) are widespread in all populations. In some individuals HHV-6 is found integrated into human chromosomes, which results in a high viral load in blood. HHV-6 variant B (HHV-6B) and HHV-7 primary infections, although usually silent, not infrequently cause the childhood exanthem *roseola infantum* and are sometimes accompanied by neurological illness. HHV-6 variant A (HHV-6A) is not associated with any disease.
Objectives: The present review focuses on the immunocompetent individual and considers the epidemiology of the two viruses and their role as human pathogens. It discusses the importance of satisfactory diagnostic tests to distinguish them, compares those currently available, and recommends how best to differentiate primary from persistent infection in each case.
Results: It is explained that at the present time antibody avidity immunofluorescence tests are the most reliable discriminators of the two types of infection. In primary infection these tests can be supplemented by PCR for viral DNA in blood but careful interpretation is required for HHV-6 in view of the high persistent viral DNA load seen with chromosomal integration.

Since the contribution of primary HHV-6 and -7 infections to the burden of severe neurological illness in young children is only now emerging as significant, the need to test for these viruses in such cases is stressed.
Conclusions:

1. Primary HHV-6/7 infections must be distinguished from persistent infections.
2. Chromosomal integration of HHV-6 requires urgent study.
3. HHV-6A/B must be distinguished in clinical situations.
4. Where serious neurological disease/encephalitis is temporally related to immunisation it is particularly important to test for HHV-6/7 primary infection since otherwise the condition might wrongly be diagnosed as a vaccine reaction.
5. Because less is currently known about HHV-7 and HHV-6A than HHV-6B, future studies should concentrate on the former two.
6. Improvements in diagnostic tests are required for each virus.

Keywords: HHV-6 variant A; HHV-6 variant B; HHV-7; Congenital infection; Antibody avidity

Abbreviations: CMV, cytomegalovirus; CSF, cerebrospinal fluid; EBV, Epstein Barr virus; EIA, enzyme immunoassay; HHV-6, human herpesvirus-6; HHV-6A, human herpesvirus-6 variant A; HHV-6B, human herpesvirus-6 variant B; HHV-7, human herpesvirus-7; RT-PCR, reverse transcription PCR

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Contents

1. Introduction

Human herpesviruses-6 and -7 (HHV-6 and -7) are closely related viruses that are the sole members of the *Roseolovirus* genus of the β-herpesviruses. These two viruses are characteristically T-lymphotropic (although they can infect other cell types), highly prevalent and associated with a rash, *roseola infantum* (*exanthem subitum* or 6th disease). HHV-6 and -7 share some common antigenic epitopes and nucleic acid sequence identity ranges from 20.7% to 75.7% in various genes; they also share several properties with the other human β-herpesvirus, cytomegalovirus (CMV) (Black and Pellett, 1999). As with all herpesviruses, HHV-6 and -7 persist for life after primary infection and it has been proposed that HHV-6 is latent in monocytes and bone marrow progenitor cells (Kondo et al., 1991; Luppi et al., 1999) and HHV-7 in T-lymphocytes (Frenkel et al., 1990). After first infection both HHV-6 and -7 are shed in saliva chronically (Jarrett et al., 1990; Kido et al., 1990; Wyatt and Frenkel, 1992; Hidaka et al., 1993).