Human herpesvirus 6 in neurological diseases

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Human herpesvirus 6 (HHV-6) is a ß-herpesvirus first isolated in 1986 [1]. Two variants of HHV-6 have been identified, HHV-6A and HHV-6B [2]. HHV-6 shares DNA sequence homology and 66% amino acid similarity with cytomegalovirus (CMV) [3] and is closely related with the later identified human herpesvirus 7 (HHV-7) [4]. An increasing number of diseases are associated with HHV-6 infections [5-7]. HHV-6 variant B causes the common childhood disease exanthema subitum (ES) [3]. The clinical disease ES (roseola infantum, sixth disease) is known a hundred years already [8]. The pathologic characteristics for HHV-6 variant A are less well defined.

HHV-6 has the ability to infect a wide variety of blood, epithelial, and neural cells. It shares the tropism for CD4 T lymphocytes with human immunodeficiency virus (HIV) [9]. It also infects CD8 T lymphocytes, natural killer cells, macrophages, and megakaryocytes. It has potential ability to interact with other viruses and alter the natural history of infections. It may hide in salivary glands, neural cells, including oligogial cells, and even neurons [10-13]. In cell culture HHV-6 causes cell damage, the cells become swollen in a few days and lose their normal intercellular adherence (Fig 1). HHV-6 variants have different cell tropism. HHV-6A may induce latency in oligodendrocytes and, in contrast, HHV-6B infection seems abortive [14]. In an oligodendrocyte cell line HHV-6A infection induced significantly more cytopathic effect than infection with HHV-6B. In human astrocytes HHV-6A causes a lytic infection and HHV-6B has a tendency to latency [15]. HHV-6 uses human CD46 as a cellular receptor that may account for the wide range of host cells [16]. HHV-6 associated CNS diseases, due to virus reactivation, can occur in both immunocompromised and immunocompetent hosts [17].

Keywords HHV-6A, HHV-6B, neurological infection, encephalitis, serology, multiple sclerosis

1. Introduction

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2. Epidemiology and transmission
HHV-6 is ubiquitous and distributed worldwide. The HHV-6 prevalence varies between 70 and 100%. Some geographic variation might exist, although, differences in sensitivities and interpretations of serological assays are the primary reason for the variation [18]. The infection usually occurs before the age of 2 years. The peak age for virus isolation has been 6 to 9 months [19-21]. Even babies less than 3 months of age may have HHV-6 DNA in plasma and CSF in febrile conditions [22]. The virus is probably transmitted via saliva [18, 23]. Newborn babies have antibodies of maternal origin. These antibody levels decline in a few months at the same time when the babies start to acquire primary infection. HHV-6 variant A and variant B differ in their epidemiology and possibly in their transmission routes as well. HHV-6 may be transmitted congenitally and it may be chromosomally integrated [21, 24-27]. The neurovirulence of the variant A is thought to be more prominent. Both viruses can establish persistent infection in peripheral blood mononuclear cells (PBMCs).

3. Primary infection
Exanthema subitum, roseola infantum, is usually a benign disease. After a few days' high fever appear skin manifestations. Roseola resolves within few days, but may even be missing in a more than half of the cases. Additional features are gastroenteritis, cough, and lymphadenopathia [19, 21, 28]. The variant B is considered as the cause of the primary disease and the virus can be cultured from PBMCs. Seizures may appear and the children are often referred to a hospital outpatient department due to prolonged and complicated convulsions [21, 29, 30]. In a prospective study saliva was collected from babies and according to that study convulsions were not associated with the primary disease [31]. In most reports the role of convulsions is underlined as well as the role of HHV-6 leading to hospital due to significant neurological morbidity [30]. HHV-6 infection may account 25% of emergency department visits for children aged 6 to 12 months [32].

4. Neurological disorders associated with HHV-6
HHV-6 is associated with many brain and spinal cord diseases. It has been identified in encephalitis, myelitis, in multiple sclerosis, and in epilepsy [33, 34]. Reports on encephalitis both in children and adults have been published [35-38]. Primary infection by HHV-6 variant A was reported to be associated with encephalomyelitis [39]. We have identified HHV-6 DNA in neurons in fatal encephalitis by in situ hybridisation [40]. Myelitis has been identified after cord blood transplantation [41]. Infarction of basal nuclei was shown in a 6 years old child [42], and acute disseminated demyelination (ADEM) in a 19 months old child [43]. HHV-6 specific DNA was observed in cerebrospinal fluid (CSF), and in MRI.
scan alterations mimicked that of acute disseminated encephalomyelitis (ADEM). Specific DNA is also detected in hippocampal and temporal lobe tissue in patients with temporal lobe epilepsy [44]. In mesial temporal lobe epilepsy HHV-6B DNA was detected in 15 of 24 patients compared to zero of 14 with other syndromes, and HHV-6 protein could be detected in cultured primary astrocytes from 7 of 7 patients [45]. According many reports HHV-6 may play role in multiple sclerosis (MS). It may have the potential to trigger tissue damage associated with MS lesion by inducing autoimmunity. HHV-6 may have the potential to activate latent HIV [46], latent Epstein-Barr virus (EBV) [47] and latent human papilloma virus (HPV) [48].

In chronic neurological diseases, especially in MS, the specific antigen has been identified in plaques, and viral DNA in neurons and oligodendrocytes [49-52]. Akhyani et al. [53] reported increased prevalence of HHV-6A in MS. We have observed serological response to HHV-6 variant A in all patients with MS, and in a subpopulation low avidity antibodies, indicating acute primary infection [54]. Using mRNA as a marker of active HHV-6 infection, variant A has been detected in blood of patients with relapsing and remitting MS (RRMS) [52, 55], as well as in CSF cells [56]. Soldan et al. [57] showed a similar lymphoproliferative response to HHV-6B in MS patients and controls, but response to HHV-6A was increased only in MS patients. HHV-6 has the intriguing property to modulate the immune response because it infects immune cells [58]. MS is regarded as an autoimmune disease in which infections may induce exacerbations [59, 60]. We together with others [52, 54, 55, 56, 61] have suggested that there is a subpopulation of MS patients that have an active HHV-6 infection, caused by variant A. The HHV-6A active infection in CNS might increase the risk of exacerbations in patients with RRMS. The proportion of active infection seems to be higher in early disease (54, 55). Derfuss and co-workers [61] reported intrathecal HHV-6 antibody production in 21% of MS patients when using an antibody index (AbI). In our series the frequency of intrathecal antibody production to HHV-6A was nearby the same, 11% in clinically definite MS (CDMS) and 21% in clinically possible MS (CPMS) [54]. As criteria, we used the S/CSF antibody ratio [62], and HHV-6 specific AbI [63]. We emphasize the presence of intrathecal HHV-6 variant A antibody production in MS.

Chronic fatigue syndrome (CFS) is associated with HHV-6 infection especially if fever, muscle pain, sleeping disorders or depression are present [64]. Dr. Anthony Komaroff [65] concluded in his extensive review article that active infection with HHV-6 might trigger CFS in a subset of patients. Due to the transforming capability of the virus, it may be the cause, at least partly, in neoplastic diseases [13]. In a diffuse leptomeningeal oligodendroglialomatosis HHV-6 variant A has been identified [66].

Both variants HHV-6A and HHV-6B are widely distributed in brain [67, 68]. However, variant A may be more predominant [69]. In the CSF HHV-6 variant A has been identified more frequently than HHV-6 variant B. The specificity of infection caused by variant A or variant B is difficult to establish. By variant-specific PCR HHV-6 variants A and B could both be identified, even in mixed infections in biological samples. Boutolleau et al. [70] could highlight the potential greater neuropathogenic role of HHV-6A in immunocompromised patients and young infants.

5. Dual and sequential infections

The occurrence of acute primary HHV-6 infection in a patient with confirmed previous infection, usually ES, presents an interesting new aspect of HHV-6 infections. We have identified children with antibodies to both HHV-6 variants. Serological response to the other variant presents past infection with high avidity, and to the other variant primary infection with low avidity. In some cases the interval between infections seems to be a few weeks, and both antibody responses show low avidity and sequential maturation (own unpublished data). Borghi et al. [71] reported subacute cerebellitis and myoclonic dystonia in a 3 years old girl, probably associated with variant A infection. The child had had roseola infantum 1 year earlier, and one month after chickenpox she developed acute neurological symptoms. HHV-6B was identified in peripheral blood and HHV-6 variant A in the CSF.
6. Diagnostic methods

Culture. HHV-6 can be cultured from peripheral blood mononuclear cells, but needs to be cocultivated. The method is time consuming and suites seldom for routine clinical practice.

PCR. Detection of specific viral DNA from serum, plasma, CSF or saliva may confirm the diagnosis. In neurological symptoms, CSF sample is optimal. Serum is better than cellcontaining specimens for PCR test, although it cannot confirm primary infection, because specific DNA can also be detected in reactivations and positive CSF-PCR may be insignificant [72-76], and chromosomally integrated HHV-6 may interfere diagnostic considerations [77, 78]. Quantitative PCR would be beneficial for monitoring the response to therapy [79, 80]. The PCR test should be performed for several viruses at the same time, because the sample may contain several herpes group viruses [81-83]. We have shown a short and transient appearance of specific DNA in the CSF in children with serologically confirmed primary HHV-6 infection, thus highlighting the diagnostic difficulties in HHV-6 [84].

Serological tests. HHV-6 specific IgG antibodies may show immunity, and avidity of IgG antibodies the timing of the infection (85, 86). In young children antibodies may be transferred from the mother [87]. By avidity testing, primary HHV-6 infection can be confirmed from a single serum specimen when antibodies are present. In seronegative cases a follow-up serum sample is needed, however, with a concomitant positive nucleic acid finding, it may indicate acute primary infection. Recent emphasis is directed to identifying the two types of HHV-6, variants A and B [30]. Specific HHV-6 IgM may present in patients with reactivation and be absent in some patients with primary infection, and thus should be interpreted with caution. In our series with primary HHV-6 infection, confirmed by HHV-6 IgG seroconversion, IgM turned out to be nonspecific (own unpublished data).

Intrathecal antibody production can be measured by comparing serum and CSF antibody levels. The antibody ratio ≤20 indicates CNS antibody production with the presumption that no other antibodies are present in the CSF. IgG index [(CSF IgG/Serum IgG) x (Serum albumin/CSF albumin)] measures general IgG production in the CNS [88]. Oligoclonal bands (IgG band not detectable in serum) indicate CNS antibody production more specifically, although the viral specificity cannot be confirmed at the moment [89].

Immunohistochemistry. HHV-6 antigen can be detected from tissue sections [51]. The specificity is low because the virus may hide latently in many cells. The same regards viral DNA detection using in situ hybridization [40].

7. Therapy

Therapy is usually unnecessary in uncomplicated primary HHV-6 infections. In vitro, many antivirals show activity against HHV-6 infection. Akhyani and colleagues [90] reported that only foscarnet and cidofovir exhibited antiviral activity in HHV-6A infected human astrocytes, whereas in HHV-6A and HHV-6B infected T cells acyclovir, ganciclovir, foscarnet and cidofovir exhibited antiviral activity. Pöhlmann et al. [91] treated a neutropenic patient with encephalitis succesfully with cidofovir and foscarnet. Ljungman et al. [92] showed a decrease in viral load in saliva by treating patients with ganciclovir. In MS, interferon is the drug of choice, but specific antiviral compounds have been administered with the presumption that a virus may be associated. Friedman et al. [93] used in their clinical trial valacyclovir to treat MS patients. A positive effect was suggested in clinical picture, but not in MRI. Komaroff [65] refers to an open-label study of valganciclovir in patients with CFS and evidence of active HHV-6 infection, demonstrating an impressive reduction in both viral load and symptoms. Prerequisite in all trials would be defined serological or DNA finding, and double blind therapy regimens, before conclusions of effect can be drawn.

8. Conclusions

The disease associations of HHV-6 are increasing and problems associated with HHV-6 infections extend from simple infections to neurological and neuropsychiatric complications, and from congenital
disorders to malignancies. HHV-6 presents diagnostic challenges and therapeutic demands. Exanthema subitum is the starting point of recognizing HHV-6 infections. Molecular approach will improve future prospects. Variant A appears to be more prevalent than variant B in patients with neurological symptoms. By using the IgG avidity test, the two variants can probably be separated and the roles of the variant A and variant B will be learned more about.

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References