Arch Public Health
1997, 55, 273-278

Novel human herpesviruses

by

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Abstract

During the last decade, the Herpesviridae *family has been enlarged by three novel human herpesviruses: H.H.V.-6 in 1986, H.H.V.-7 in 1990 and H.H.V.-8 in 1994. H.H.V.-6 and H.H.V.-7 cause exanthema subitum and/or febrile seizures on primary infection. H.H.V.-6 is also proposed as an etiological factor in multiple sclerosis. H.H.V.-8 causes Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. Recently, the presence of H.H.V.-8 D.N.A. has been associated with multiple myeloma (Morbus Kahler) and sarcoidosis.*

Key-words

Herpesviridae-classification, Herpesvirus-6, Herpesvirus-7, Herpesvirus-8, Multiple-Myeloma-virology, Multiple-Sclerosis-virology.

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Introduction

The five "classic" human herpesviruses have been known and characterized for a number of decades: Herpes Simplex viruses types 1 and 2 (H.S.V.-1; H.S.V.-2), Varicella-Zoster virus (V.Z.V.), Epstein-Barr virus (E.B.V.) and human cytomegalovirus (H.C.M.V.). Recently, three novel lymphotropic human herpesviruses have been characterized: H.H.V.-6 (1), H.H.V.-7 (2), and H.H.V.-8 (3). In this short overview, H.H.V.-6 and 7 will be treated together because of their numerous similarities in structure, epidemiology and clinical potential.

Human herpesviruses 6 and 7

H.H.V.-6 and H.H.V.-7 belong to the *Betaherpesvirinae* (cytomegalovirus-like) subfamily, and mainly infect CD4-positive T-lymphocytes. Upon primary infection, the H.H.V.-6B subtype and H.H.V.-7 can cause exanthema subitum (roseola infantum, sixth disease) and febrile seizures. More than 90% of children are latently or chronically infected with H.H.V.-6 and/or H.H.V.-7 by the time they enter kindergarten. This suggests a principally maternal close-contact route (e.g. saliva) as a likely mode of horizontal virus transmission to the infant. Upon H.H.V.-6/7 reactivation (or perhaps re-infection) in adults, a wide variety of anecdotal clinical syndromes have surfaced in the literature, including fulminant hepatitis, interstitial pneumonitis, abortion, inhibition of bone marrow engraftment, chronic fatigue syndrome, and multiple sclerosis. A definitive causative role for the novel herpesviruses has not yet been established in most of these conditions (with the exception of exanthema subitum and febrile seizures), but features such as reactivation under immune suppression, tropism for lymphoid cells and ability to transform certain cell types in vitro make H.H.V.-6 a likely pathogen in transplant patients and a potential etiologic (co)factor in malignancies.

The often mild character of H.H.V.-6 and H.H.V.-7 primary infections implies that most cases either remain unnoticed or are diagnosed solely on clinical grounds. Most of the epidemiological data have been gathered using commercially available specific antibody tests (ELISA, IFA). The polymerase chain reaction (P.C.R.) is a highly sensitive and specific technique to detect the presence of H.H.V.-6/7 D.N.A. in lesions or body fluids. This technique has provided strong evidence that H.H.V.-6 has an etiologic role in the initiation and/or exacerbation

of graft-versus-host disease following allogeneic bone marrow transplantation (4).

Viruses have long been suggested to be among the etiological factors that cause multiple sclerosis (M.S.). Recently, H.H.V.-6 D.N.A. has been reported to be present in active M.S. plaques. An increased IgM serum antibody response to the p41/38 H.H.V.-6 early antigen was found in patients with the relapsing-remitting form of M.S., when compared with patients with chronic progressive M.S., patients with other neurologic diseases, patients with other autoimmune diseases, and normal controls. These antibody studies have been supported by the detection of H.H.V.-6 D.N.A. in 15 out of 50 sera of M.S. patients and in none of the controls (5).

No specific treatments are currently used for infections caused by H.H.V.-6 or H.H.V.-7 and most cases recover spontaneously and uneventfully. Foscarnet and angiclovir have been used with some success against H.H.V.-6 infections in the immunocompromised host.

Human herpesvirus 8

H.H.V.-8 (previously called Kaposi's sarcoma-associated herpesvirus, K.S.H.V.) is a member of the *Gammaherpesvirinae* (E.B.V.- and herpesvirus saimiri-like) subfamily, and infects CD19-positive B-lymphocytes (3). H.H.V.-8 D.N.A. footprints were identified in Kaposi's sarcoma lesions, and in certain types of multicentric Castleman's disease, primary effusion lymphoma (body-cavity-based non-Hodgkin B-cell lymphomas), angiosarcoma, and recently also in bone marrow dendritic cells from patients with multiple myeloma (Morbus Kahler) and monoclonal gammopathy of undetermined significance (M.G.U.S.) (5). In the latter two conditions, H.H.V.-8 probably resides in dendritic cells rather than in the plasma cells themselves. In those cells, H.H.V.-8 produces a virally encoded interleukin 6 (vIL-6) homologue that stimulates polyclonal myeloma cell proliferation. Genetic accidents (e.g. translocations) are more prone to happen in such a rapidly proliferating population, and may give rise tot the monoclonal malignant clone. If confirmed that the dendritic cells stimulate the plasmocyte proliferation, this forms a novel and interesting "remote control" mechanism for virally induced malignacies (7). H.H.V.-8 does not seem to be ubiquitous in most populations and is thought to be primarily sexually transmitted (in the same way as H.S.V.-2). This

mode of transmission probably accounts for the difference in epidemiology between H.H.V.-8 and most other herpesviruses. However, sexual transmission of H.H.V.-8 does not sufficiently explain the remarkable male predominance of classic and AIDS-related Kaposi's sarcoma.

For H.H.V.-8, no routine diagnostic assays are used at present (although serology and P.C.R. reagents are available for research purposes). No specific treatment is available, but cidofovir, angiclovir, adefovir, and foscarnet have marked anti-HHV-8 activity (9).

Significance of novel human herpesviruses in human diseases

H.H.V.-6, H.H.V.-7 and H.H.V.-8 are considered novel, only because of their recent discovery as human pathogens. Therefore, they should not be catalogued as "emerging" viruses. These herpesviruses, as well as the diseases that they are associated with, have most probably been co-evolving with us since ancient times. Based on their virological and pathological charachteristics, H.H.V.-6, H.H.V.-7 and H.H.V.-8 are true members of the herpesviridae family, causing latent infection which probably persists lifelong.

H.H.V.-6 and H.H.V.-7 infect a large proportion of the population, in analogy to H.S.V., C.M.V., E.B.V. and V.Z.V., but only cause serious morbidity and mortality in a minority of cases, mainly in patients with impaired host defence mechanisms. The putative relationship of H.H.V.-6 with multiple sclerosis is both exciting and puzzling and will be the topic of much debate in the coming decade.

H.H.V.-8 is likely to gain recognition as an important pathogen because of its association with several diseases for which the etiology is presently unknown, e.g. Kaposi's sarcoma, Morbus Kahler and sarcoidosis. The exact contribution of H.H.V.-8 to the pathogenesis of these diseases remains to be elucidated; it is highly probable that other factors (genetic factors, other (co-)pathogens) will also play a role in the progression from infection to disease.

The discovery of novel viruses has always depended on the development of novel techniques. Given the current level of molecular biological sophistication, the discovery of human herpesvirus type 9 (H.H.V.-9) might be only just around the corner.

Résumé

Au cours des 10 dernières années, la famille des *Herpesviridae* s'est vue élargie par la détection de 3 nouveaux types de virus d'herpès humains : H.H.V.-6 en 1986, H.H.V.-7 en 1991 et H.H.V.-8 en 1995.

H.H.V.-6 et H.H.V.-7 sont, lors d'une infection primaire, les causes principales d'exanthème ainsi que de convulsions fébriles. On propose également H.H.V.-6 comme facteur étiologique dans la sclérose en plaques. H.H.V.-8 cause le sarcome de Kaposi, la maladie de Castleman multicentrique et certains lymphomes des cavités. Récemment, la présence de l'A.D.N. du H.H.V.-8 a été associée au myélome multiple (maladie de Kahler) et à la sarcoïdose.

Samenvatting

In het voorbije decennium breidde de *Herpesviridae*-familie uit met drie nieuwe humane herpesvirussen, nl. H.H.V.-6 in 1986, H.H.V.-7 in 1990 en H.H.V.-8 in 1994.

H.H.V.-6 en H.H.V.-7 zijn de belangrijkste oorzaken van exanthema subitum en/of febriele convulsies. H.H.V.-6 wordt ook genoemd als een etiologische factor in multiple sclerosis. H.H.V.-8 veroorzaakt. Kaposi's sarcoma, de multicentrische ziekte van Castleman en primair effusie lymphoma. Recent werd de aanwezigheid van H.H.V.-8 D.N.A. ook in verband gebracht met het multiple myeloma (ziekte van Kahler) en sarcoidosis.

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