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HUMAN HERPESVIRUS 6 INFECTION: A REVIEW

Neha Rani[1], Rachita Mathur[2], Heena Singdia[3], Rohit Garg[4], Shivi Nijhawan[5], Deepika Kothari[6] Puneet Bhargava[7], Deepak K Mathur[8]
[1,3,6]Junior Residents, SMS medical college
[2,4,5]Senior Residents, SMS medical college
[7]Senior Professor, SMS medical college
[8]Senior Professor, HOD and additional principal, SMS medical college
Corresponding Author:
Dr. Puneet Bhargava
Senior Professor, SMS medical college

Abstract

Human herpesvirus 6 (HHV-6) is a widespread betaherpesvirus which is genetically related to human cytomegalovirus (HCMV) and now encompasses two different species: HHV-6A and HHV- 6B. HHV-6 infects a wide range of human cells in vitro, but preferentially replicates in activated CD4+ T lymphocytes. HHV-6 has been known to establish acute, incessant and permanent infection. Primary infection with HHV-6 causes roseolainfantum, pityriasisrosea. Persistent or reactivation of HHV-6 has been associated with multiple sclerosis, Guillain-Barre syndrome, chronic fatigue syndrome, lymphoproliferative disorders, connective tissue diseases and Kikuchi-Fujimoto disease. The formal demonstration of the causative role of HHV-6 in many acute and chronic human diseases is difficult due to the ubiquitous nature of the virus, chronicity of infection, existence of two distinct species, and limitations of current investigational tools. There are still numerous pending questions about HHV-6 which should stimulate future research works on the pathophysiology, diagnosis, and therapy of this remarkable human virus.

Introduction

The herpesvirus group consists of relatively large, DNA viruses that replicate within the nucleus and produce typical intranuclear inclusion bodies detectable in stained preparations. These are subgrouped according to their genome similarities into α,βand γherpesviruses. Eight members of this group are known to cause infection in humans. Herpes simplex virus type 1, herpes simplex virus type 2 and varicella- zoster virus belong to α subgroup; cytomegalovirus, human herpes virus type 6 and human herpes virus type 7 belong to subgroup β and Epstein-barr virus and human herpes virus type 8 belong to γ subgroup.α subgroup usually causes cutaneous diseases, viral exanthems are caused by β group and the γ herpes virus may cause cutaneous disease during reactivation or effects of latency. A common property shared by all herpesviruses is that they can remain latent within host.

Human herpesvirus 6 (HHV-6) is a widespread betaherpesvirus which is genetically related to human cytomegalovirus (HCMV) and now encompasses two different species: HHV-6A and HHV-6B and belong to genus roseolovirus[1]Human herpesvirus 6 (HHV-6) was initially discovered in 1986 from circulating blood lymphocytes of adults with lymphoproliferative diseases or AIDS and was labeled human B-lymphotropic virus[2]. As it was the sixth herpesvirus isolated, it was then subsequently renamed human herpesvirus 6. As for all herpesviruses, HHV-6 has been known to establish acute, incessant and permanent infection. Primary infection with HHV-6 causes roseolainfantum. Persistent or reactivation of HHV-6 has been associated with multiple sclerosis, Guillain-Barre syndrome, chronic fatigue syndrome, lymphoproliferative disorders, connective tissue diseases and Kikuchi- Fujimoto disease. Reactivation of HHV-6 may underlie the development of pityriasisrosea and two forms of drug rash: drug induced hypersensitivity syndrome and DRESS[1]. The formal demonstration of the causative role of HHV-6 in many acute and chronic human diseases is difficult due to the ubiquitous nature of the virus, chronicity of infection, existence of two distinct species, and limitations of current investigational tools. There are still numerous pending questions about HHV-6 which should stimulate future research works on the pathophysiology, diagnosis, and therapy of this remarkable human virus[1].

VIRUS PROPERTIES

Discovery and classification

Human herpesvirus 6 (HHV-6) was initially discovered in 1986 from circulating blood lymphocytes of adults with lymphoproliferative diseases or AIDS and was labeled human B-lymphotropic virus but soon appeared to infect essentially T-cells. In culture, infected cells B and specially T cells) are short-lived, large refractile cells and frequently contain intranuclear and/ or intracytoplasmic inclusion bodies. These cells were shown to be transmissible to novel cultures of phytohemagglutinin(PHA)- stimulated human leukocytes. Electron microscopy confirmed virus production and revealed a morphology similar to that of herpesvirusesi.e a capsid of icosahedral symmetry surrounded by a tegument within an enveloped particle of 200nm in diameter[3]. The genomic DNA did not cross-hybridize with the genomes of other known human herpesviruses therefore was considered different from them[4]. Finally based on both biological and genomic properties HHV-6 was officially classified as a member of order herpesvirales,family herpesviridae, subfamilybetaherpesvirinae and genus roseolovirus[5]. Two antigenetically distinct varities, HHV-6A and HHV-6B were identified later on and classified as two separate viruses[6].

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Cell and tissue tropism in host

HHV-6 infects a wide range of human cells in vitro, but preferentially replicates in activated CD4+ T lymphocytes[7,8]. Atleast one component of cell surface receptor for virus anchorage to cell surface differs for HHV-6A and HHV-6B. HHV-6A uses CD46, a regulator of complement activation which is expressed on all nucleated cells, whereas HHV-6B uses CD134(OX40), a member of TNF- receptor superfamily which is present only on activated T-lymphocytes[9,10].CD46 also acts as a receptor for other human pathogens like vaccine strains of measles virus and Neisseria gonorrhoeae[11]. In addition to CD4+ T lymphocytes, HHV-6 can infect other cells like CD8+T lymphocytes(only HHV-6A), fibroblasts, NK cells, liver cells, epithelial cells, endothelial cells, astrocytes, oligodendrocytes and microglial cells. HHV-6A is more capable of infecting different cell lines than HHV-6B. The primary isolation of HHV-6 from a human specimen usually requires co-cultivation with primary highly susceptible cells consisting of peripheral blood mononuclear cells (PBMCs) or umbilical cord blood lymphocytes. HHV-6 can infect various kind of tissues including brain, tonsils, salivary glands, kidneys, liver, lymph-nodes, endothelial cells, and monocytes/macrophages[7,12-15]. Bone marrow progenitor cells and central nervous system cells are the sites for latency of HHV-6.

Latency and reactivation

Like other human herpesviruses, HHV-6 persists indefinitely in its host and capable of reactivation that is, the active production of detectable mature virions in some body compartments after a phase of apparently complete clearance. These properties attributes to the capacity of its genome to be maintained in nuclear latent form or to drive a low-level productive infection in some cells while inducing a fully lytic function in some cells. The viral gene U94, which is expressed during latent infection, is assumed to play a role in maintaining intracellular latency of the virus[16]. Reactivation occur through the transcription of IE genes in IE1 and IE2 regions following the likely transactivation effect of cellular and/or viral factors. Reactivation can be defined as reappearance of replicationcycle transctriptsand yield of infectious virus in peripheral blood or in a specific tissue or organ from an individual who has experienced a primary infection. Reactivation of a latent infection occurs more likely in people who are in immunosuppression. The effects are usually subclinical but in 1% of the population, HHV-6 reactivation is associated with fever, rash, hepatitis, gastroenteritis, encephalitis, pneumonitis and bone marrow suppression. In solid organ transplant patients, reactivation of HHV-6B is most common, while HHV-6A reactivation is most common in bone marrow transplantation. In otherwise healthy individuals, HHV-6 reactivation is associated with pityriasisrosea, drug-induced hypersensitivity syndrome and DRESS[1].

Chromosomal integration

HHV-6 DNA is covalently integrated into the subtelomeric region of cell chromosome(ciHHV-6), likely by a mechanism of homologus recombination between telomeric repeat sequences of viral and host cells. This phenomenon occurs in 0.2- 1% of general population in developed countries and is described for both HHV-6A and HHV-6B. This phenomenon may be considered a default pathway for HHV-6 latency and might directly lead to reactivation of virus. HHV-6 has the ability to infect sperm cells, thus individuals harboring the integrated virus in their germ line may transmit it to their offspring[17,18].

HUMAN INFECTION

Epidemiology

HHV-6 is a ubiquitous virus, detected in more than 90% of adult population in developed countries. HHV-6 infection usually acquired very early in life, between 6 months and 2 years of age, following the loss of protective maternal antibodies though it can also occur later in adults[19,20]. Congenital infections following intrauterine transmission has been reported in about 1% of children[1]. Some cases of perinatal transmission of virus has also been described. Saliva is assumed to be main vehicle for the virus transmission, infrequently transmission can also occur through organ transplantation[2].

Pathophysiology

Following the entry of virus into the body by oral route, it replicates in salivary gland and satellite lymphoid tissues of oropharynx probably tonsils and cervical lymph nodes. Systemic diffusion of virus occurs mainly by blood route attributes to tropism of virus for peripheral blood mononuclear cells and vascular endothelial cells, as reflected by isolation of infectious virus from blood during acute phase of infection. Lymphatic spread of virus is also possible. This spreading of virus leads to the active, abortive or latentinfection of susceptible cells in other organs including T-lymphocytes and monocytic cells in lymphoid tissue, liver, kidney and skin epithelial cells; hematopoietic stem cells in bone marrow and neuroglial cells in CNS. Entry of virus into CNS might occur by crossing of the blood brainbarrier through olfactory pathway[21].

Effects on immune system

A specific immune response to HHV-6 was recognized very soon after its discovery. In patients with primary infection, serological studies have shown the appearance of IgM antibodies during the first week and their subsequent disappearance after 1 month, while IgG antibodies are detected alter than IgM but persists indefinitely. Some of these antibodies have virus neutralizing properties, but their role in control of active infection is not well understood. Cellular immunity is believed to play a major role in control of active infection as reflected by deleterious effects of T-cell immune response suppression. CD4+ and CD8+ T cells proliferate in response to HHV-6A and HHV-6B antigen[22,23].

HHV-6 can stimulate the effectors of innate immunity: an increased secretion of proinflammatory cytokines such as interleukin-1β, TNF-α, and α- interferon, is observed in peripheral blood mononuclear cells while NK- cell activity associated with IL-15 synthesis is elevated in HHV-6A infection[24,25]. Like other herpesviruses, HHV-6 has ability to both stimulate and modulate immune responses[7,26,27]. This modulation permits evasion of the HHV-6 specific immune response and improve the microenvironmental conditions for promoting virus persistence. For example, the upregulation of proinflammatory cytokines in PBMCs is associated with downregulation of IL-2 synthesis and a subsequent decrease of T- cell activation. HHV-6 has also been shown to promote the shift of T-helper cell profile from Th1 to Th2 by upregulating IL-10 and downregulationg Il-12. It also downregulate the expression of HLA class 1 expression on dendritic cells and also has strong suppressor effects on the growth and differentiation of bone marrow progenitors which may affect the differentiation of macrophages and population of thymocyte precursors. Many of these effects are specifically mediated by HHV-6-encoded proteins those act as analogues of cell chemokines and are believed to promote viral growth, viral dissemination, and/or escape from the immune response.The U21 protein has been shown to reduce the expression of HLA class I expression; the U83 gene encodes a chemotactic protein which is an agonist for several human CC chemokine receptors (CCRs) and the U12 and U51 genes encode chemokine receptors which presumably activate and recruit host cells. The U24 gene product induces the internalization of the T cell receptor/CD3 complex, which may alter the patterns of T cell activation. HHV-6 has the capacity to perform a fine tuning regulation of cell functions which can cause modulation of other viral infections affecting the same target cell and organ. For example, HHV-6 can act as a cofactor for HIV in AIDS because of the common tropism of HHV-6 and HIV for CD4+ T- cells; transactivation of the HIV-1 LTR by HHV-6 proteins, and induction of CD4 expression on CD8+T cells and NK cells by HHV-6 making these cells susceptible to HIV infection[28].

CLINICAL FEATURES

Primary infection

Cutaneous effects: HHV-6 primary infection cause acute febrile disease in children of 6 months to 3 years of age, most emblematic of which is exanthema subitum also known as roseolainfantum or sixth disease[29,30]. It is an acute febrile illness with a maculopapular eruption and is the most common exanthematic fever in children under the age of 2 years, reported to account for 24% of acute febrile illness presenting at paediatric emergency department. Peak incidence of disease is between 6 and 9 months. It has the incubation period of 10-15 days. The first sign of illness is abrupt onset of fever which persists for 3-5 days and initially is usually accompanied by few or no symptoms. Irritability, inflamed tympanic membranes, ulcers at posterior palate and uvula and occasionally, periorbitaloedema and haematuriaare the early manifestations. As the fever subsides, discrete rose-pink maculopapules erupt on neck and trunk, later may spread to arms, face and legs and are usually accompanied by cervical and occipital lymphadenopathy. After 1 or 2 days the rash fades without leaving any pigmentation or scaling. It can be followed by complications like febrile convulsions, encephalitis, thrombocytopenia, purpurafulminans, and haemophagocytic syndrome[1]. Other cutaneous manifestations associated with primary HHV-6 infection are papularpurpuric gloves and socks syndrome, Gianotti-Crosti syndrome, stevens-johnson syndrome and pityriasisrosea[1].

Pityriasisrosea is an acute self-limiting disease, probably infective in origin and mostly occur between the ages of 10 and 35 years but is also reported in infancy, childhood or old age and slightly more common in females. Many infectious agents have been suspected as causative agent for pityriasisrosea including HHV-6 and HHV-7, later is detected more frequently in individuals with acute pityriasisrosea from peripheral blood mononuclear cells and unaffected skin. Other viruses may act as a trigger for pityriasisrosea are HHV-8, herpes simplex virus 2, hepatitis C and H1N1 influenza. Individuals who are in immunosuppression with oral corticosteroid and after bone marrow transplantation are predisposed to develop eruptions. Several drugs have been reported to cause pityriasisrosea like-drug reaction including ACE inhibitors, beta blockers, aspirin, barbiturates, adalimumab etc. First manifestation of the disease is usually the appearance of herald patch, which is larger and more conspicuous than the lesions of later eruption and is usually situated on the thigh, upper arm, trunk or neck. It may rarely appear on face, scalp, penis, palm or sole. It is a sharply defined, erythematous, round or oval plaque covered by a fine scale and usually of size 2-5cm in diameter. After an interval of usually 5-15 days(may be short as few hours or as long as 2 months) general eruption begin to appear in crops at 2-3 days interval over a week or 10 days. In its classical form the eruption consists of discrete oval lesions, dull pink in color and covered by fine dry silvery-grey scales. Their centre tend to clear and assume a wrinkled, atrophic appearance and a tawny color with marginal collarette of scale attached peripherally and free edge internally. The long axis of lesions characteristically follow the Christmas tree pattern on the upper chest and back. The lesions are usually confined to the trunk, base of neck and upper third of arms and legs but may involve face, scalp and palms. Pityriasisrosea may be atypical in the appearance or distribution of lesion or its course. The herald patch is undetected in about 20% of cases. In children, the lesions may be predominantly papular or urticarial in early stages.Papular variant may be more common in pregnant women. Others forms may occur rarely including papulovesicular, vesicular, purpuric, erythema multiforme like lesions, follicular and pustular lesions[1].

Non-cutaneous effects: HHV-6 infection is also associated with less typical combination of fever, seizures, skin rash, and gastrointestinal and respiratory tract symptoms. Infrequently, primary infection is associated with a more severe disease such as hepatitis, thrombocytopenia, infectious- mononucleosis like syndrome, hemophagocytic syndrome, gastroenteritis, colitis or myocarditis[7]. It may also involve CNS and causes meningoencephalitis and encephalitis[19]. HHV-6B variant is more likely to cause primary infection than HHV-6A. Congenital HHV-6 infection following primary infection of fetus or embryo during pregnancy has been found to occur in about 1% of children and associated with abnormalities at birth and during immediate postnatal period and CNS developmental defects[2].

Reinfection and reactivation

HHV-6 reactivation occurs in patients with immunosuppression.

Clinical symptoms associated with HHV-6 reactivation in transplant recipients are fever, rash and transiently decreased numbers of circulating blood cells belonging to granulocyte/macrophage, erythroid and megakaryocytic lineages. In hematopoietic stem cell transplant patient, reactivation of HHV-6 may lead to opportunistic diseases like subacute limbic encephalitis and delayed engraftment[2]. The risk of reactivation is high within first 4 weeks of allogenic transplant recipients which subsequently leads to life threatening illness involving the CNS and bone marrow. CNS dysfuntion leads to delirium and neurocognitive decline in transplant patients and bone marrow suppression any cause secondary graft failure. HHV-6 reactivation has also been reported in solid organ transplant patients and is associated with concomitant febrile episodes, leukopenia, thrombocytopenia, hepatitis, pneumonitis, bone marrow suppression and encephalitis. The majority of cases of reactivation in transplant patients are attributed to HHV-6B. Reactivation has also been reported to cause graft rejection, facilitation of superinfection with fungus and opportunistic pathogens[2]. It may also accelerate the progression of HIV infection to AIDS and can act as opportunistic infection in AIDS patients causing encephalitis, pneumonitis and retinitis[2]. Drug induced hypersensitivity syndrome appears to be associated with HHV-6 infection and is characterized by severe adverse drug reactions associated with skin rash, fever, lymphadenopathy, liver dysfunction and blood leukocyte abnormalities[2]. The proposed mechanism for this event is that the drug trigger the viral multiplication thus resulting in immune activation by viral antigens and extensive antiviral T cell response at origin of disease. Amoxicillin and sodium valproate are capable of directly stimulating HHV-6 multiplication[2].

Chronic infection

HHV-6 appears to be act like an infectious trigger for the development of multiple sclerosis and hashimoto's thyroiditis[2]. HHV-6 infected thyroid cells are susceptible to NK-cell mediated cell killing, suggesting apossible mechanism for autoimmunity induction. It has also been known to cause myocarditis and cardiomayopathy. HHV-6 is capable of infecting vascular endothelial cells and may affect coronary and peripheral arteries. Its role has also been supported in chronic fatigue syndrome and angioimmunoblastic T-cell lymphoma.

HHV-6 IN PREGNANCY

Pityriasisrosea may be associated with an active HHV-6 infection. In pregnancy it may lead to premature delivery with neonatal hypotonia and fetal death especially if it develops within 15 weeks of gestation[1].

DIAGNOSIS[2]

Diagnostic methods for HHV-6 include indirect and direct approach. Indirect method assess the level of antibodies in blood and direct methods are used to detect virus in blood or tissues.

Diagnostic Approach	Method	Advantages	Disadvantages
Indirect (serology)	Assay for IgG and IgM detection by IFA, ELISA	Easy collection and storage of serum samples, readily accessible techniques, diagnosis of primary infection, studies	Lack of interpretation for diagnosis of reactivations, no differentiation between HHV-6A and HHV-B, delayed/altered response if immune deficiency is present, cross-reactivity with other betaherpes viruses
Direct	Virus isolation in cell culture	Reference method in virology, evidence of infectious virus, precise investigations of virus strains	Labor-intensive method, high cost, limited Sensitivity
	Antigen detection	Uses conventional equipment, gives evidence of virus gene expression, discrimination between HHV-6A and HHV-6B	Need for standardization, limited sensitivity with current reagents, difficulties of readout in some cases
	Qualitative viral DNA PCR	High sensitivity and specificity, discrimination between HHV-6A and HHV-6B	No distinction between active infection, latency, and ciHHV-6
	Quantitative viral DNA realtime PCR	High sensitivity and specificity, discrimination between HHV-6A and HHV-6B, longitudinal follow-up studies, comparison of viral loads in blood versus organs	Need for international standardization, need for specific thresholds for active infections and ciHHV-6
	Detection of viral transcripts by RT-PCR	Distinction between active and latent infections, recognition of active infection in ciHHV-6 subjects	Limited sensitivity (to be evaluated), need for standardization
	Droplet digital PCR	Precise method for measuring nucleic acid amounts, identification of ciHHV-6	Limited sensitivity (to be evaluated), adaptation to clinical specimen diversity

TREATMENT

Antiviral drugs

Three drugs initially developed to target HCMV infection have been shown to be efficient against HHV-6 infection both in vitro and in vivo: ganciclovir, foscarnet and cidofovir[2,7]. None of these drugs is officially approved for HHV-6. All of these drugs exhibit same inhibition activity against both HHV-6A and HHV-6B in vitro.

Ganciclovir: it is a nucleoside analogue. It acts by inhibiting viral DNA polymerase enzyme by its triphosphorylated form. The first phosphorylation of ganciclovir is catalyzed by a protein kinase encoded by HHV-6 U69 gene, while further phosphorylation steps are dependent upon the activation of cellular kinases. Acquired resistance to ganciclovir occurs due to mutation of target viral gene like protein kinase and DNA polymerase gene[2]. Recommended induction dose is 5mg/kg b.i.d. It can cause bone marrow toxicity as an adverse event.

Foscarnet: it is a pyrophosphate analogue. It acts by inhibiting viral DNA polymerase enzyme by its dephosphorylated form. Acquired resistance to foscarnet occurs due to mutation in viral DNA polymerase gene[2].

Cidofovir: it is a nucleotide analogue. It acts by inhibiting viral DNA polymerase enzyme by its dephosphorylated form. Its Phosphorylation depends upon the activity of cellular kinases. Acquired resistance to cidofovir occurs due to mutation in viral DNA polymerase gene[2]. Acyclovir has been found to be effective in HHV-6 infection but very high dose is required.

Other drugs reported to be effective against HHV-6 includes brincidofovir, artesunate, valomaciclovir, S2242, cyclopropavir, CMV423, A5021, 3-deaza-HPMPA and H2G. Brincidofovir is an orally administerd nucleotide analogue, a lipid-ester derivative of cidofovir, acts against viral DNA polymerase and is less nephrotoxic than cidofovir. Artesunate is a semisynthetic derivative of artemisinin, acts by modulation of cellular activation pathway involving Sp1 and NF-kB. Valomaciclovir is a nucleoside analogue targets viral DNA polymerase enzyme. Recently the complementary use of immunotherapy in

hematopoietic stem cell transplant patients has been considered through the generation of polyclonal cytotoxic T lymphocytes targeted to several opportunistic viral infections including HHV-6.

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