



The Pathogenesis and Advances in Human Herpesvirus Associated Central Nervous System Diseases

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Abstract

Human Herpesvirus (HHV) is a large class of double stranded DNA virus that can cause a generalized rash after infection, mainly cause skin and mucous membrane damage, leading to the oral herpes, herpes dermatitis, genital herpes, et al. The virus will be long-standing with the host after infected, latent infection and cyclical recurrence are the pathogenic characteristics of HHV. Intermittent replication is one important reason that the virus cannot be completely eradicated by body immune system. HHV infection can stimulate the body's inherent and acquired immune response, including the inherent immune cells, cytokines and T lymphocytes. The host cells infected the virus can inhibit the replication and proliferation of HHV by inducing apoptosis. In recent decades, with the deepening research and understanding of HHV, the virus is associated with some Central Nervous System diseases (CNS), such as intracranial tumors, encephalitis and neurodegeneration diseases and so on. This paper will review the pathogenesis and advances of the CNS diseases caused by HHV for colleague's reference.

Keywords: Human herpesvirus; Central nervous system diseases; Pathogenesis

Introduction

Herpesvirus is a double stranded DNA virus that is susceptible to vertebrates, the viral plasmids ranged from about 120 nm to 260 nm [1]. At present, more than 100 species of herpesviruses have been found and some herpesviruses can cause some diseases in human, so we call these viruses as Human Herpesvirus (HHV). Based on their biological properties and genome sequences, the *Herpesviridae* divided into *Alphaherpesvirinae*, *Betaherpesvirinae* and *Gammaherpesvirinae* three subfamilies composed of nine human viruses [2,3]. The *Alphaherpesvirinae* subfamily is composed of Herpes Simplex Virus 1 and 2 (HSV-1 and HSV-2) and Varicella-Zoster Virus (VZV) with wide range of hosts, short replication cycle, fast breeding, is a kind of latent infectious virus within the sensory ganglion. Human Cytomegalovirus (HCMV) and Human Herpes Viruses 6A, 6B and 7 (HHV-6A, HHV-6B and HHV-7) belong to the *Betaherpesvirinae* subfamily, with narrow range of hosts, slow virus replication, long replication cycle, the infected cell's volume is increased and the virus can lurk in lymphocytes, endocrine glands, kidney and lymphoid follicles organizations; The *Gammaherpesvirinae* subfamily is composed of Epstein-Barr virus (EBV) and Human Herpes Virus 8 (HHV-8) main lurking in the T and B lymphocytes and cannot cause cytolytic changes of the host cell [3,4]. In addition, B-type herpes virus and simian herpesvirus also belong to the HHV, because of the latest research, people know little about them. In recent decades, some scholars has gradually found that HHV has the neuronophagia characteristics, it can infect nerve cells and persist for a long time [5-7]. When the body's immune system is low or suppressed, HHV lurking in nerve cells may be potential trigger for CNS diseases, but the exact pathogenesis remains unclear [7,8]. This passage will elaborate the pathogenicity and the research progress of HHV and its each subtype on CNS diseases separately as follows.

The Structure and Pathogenesis of HHV

HHV is a group of spherical double-stranded DNA viruses with an envelope; the average diameter is 150 nm [9]. The virus nucleocapsid is an icosahedral three-dimensional symmetrical structure, between the nucleocapsid and the capsule is the cortex of the matrix protein. The surface of the capsule has a spike that is composed of a virus-encoded glycoprotein [4]. In addition to Epstein-Barr virus (EBV), HHV-6 and HHV-7, HHV can replicate in human diploid nuclei, leading

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Received Date: 23 Dec 2020

Accepted Date: 22 Jan 2021

Published Date: 08 Feb 2021

Citation:

Dong L, Zhongjun L, Shuai Z. The Pathogenesis and Advances in Human Herpesvirus Associated Central Nervous System Diseases. *Clin Surg*. 2021; 6: 3054.

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to the lesion and the eosinophilic inclusion body appeared in the host cell nucleus [10]. HHV is widespread and mainly in the form of latent infection in the population. The pathogenicity of HHV is the viral envelope, which can fuse to the host cell membrane, the specific mechanisms is the viral envelope glycoproteins components can be combined with the corresponding receptors on the host cell membrane, inducing a fusion between the two membranes, the DNA in virus nuclear capsid released into the host cell nucleus, at last the host cell is infected by the virus. What's more, the infectious particles of HHV can through the way the membrane fused between host cell and adjacent uninfected cells or the intercellular bridge infects with other cells.

According to HHV interaction with host cells, the form of viral infection can be divided into four ways, including proliferative infection, latent infection, integrated infection and congenital infection [11,12]. Proliferative infection is virus proliferates in the host cell and in the end causes host cell destroyed; about the latent infection, the virus can be stably present in the nucleus of the host cell without proliferating and the expression of viral genome is inhibited. When stimulated by external factors, the viral can be activated and transformed into proliferative infection; Integral infection refers to some DNA fragments of HHV can be integrated into the host cell chromosomal, changing the growth cycle and preventing apoptosis of the host cell, which is closely related to the occurrence of tumor; Congenital infection refers to certain HHV can infect fetus through the placenta, induced abortion, premature birth and congenital malformations [13,14]. In conclusion, understanding the structure and pathogenesis of HHV can help us prevent and control its infection and transmission and provide new ideas for the development of new drugs and vaccines for it.

The Subtype and Pathogenesis of HHV Subfamily

Herpes simplex virus (HSV)

Herpes Simplex Virus (HSV) is the most widespread causative agents of human viral infections affecting 60% to 95% of the adult population in the world wide [15]. It belongs to Alphaherpesvirinae subfamily, the genome is about 152k band the plasmid size is about 180 nm. According to the difference of antigenicity, HSV can be divided into HSV-1 and HSV-2. HSV-1 infection is wide spread, with the seroprevalence rate of 93% in the adult population [16] and mainly obtained from lip lesions can cause recurrent herpes lips and Herpes Simplex Encephalitis (HSE), with an incidence rate of 2 to 4 cases per million inhabitants per year [17,18]; around 500 million people are currently infected with HSV-2 worldwide and that approximately 20 million new cases occur each year [19]. HSV-2 is transmitted sexually, resulting in one of the most common genital diseases, affecting adolescents and adults and facilitating HIV transmission, which isolated from genital lesions, can cause genital herpes [20]. HSV-1 has strong pathogenicity, which can infect neurons, astrocytes and oligodendrocytes. How HSV-1 infects nerve cells, depends on its envelope protein glycoprotein D (gD), which binds several cell membrane receptors including Nectin-1, HVEM (herpesvirus entry mediator), and 3-O-sulfated heparan sulfate [21,22]. In recent years, more and more research found that there are kinds of CNS diseases have closely relationship with the reactivation of latent HSV in brain tissue, especially in immunocompromised hosts. About the mechanism of HSV-1 induced by HSE, studies have shown that the virus can retrograde along the trigeminal nerve branch

to the trigeminal ganglion or along the olfactory nerve into the brain, once HSV-1 invaded neurons, viral membrane proteins can bind to host cell components, then, virus-infected neurons either die by cell lysis or directly infect adjacent cells by non-pathogenic mechanisms [23]. In HSE patients, long-term intrathecal inflammation with increased proinflammatory factors in Cerebrospinal Fluid (CSF) has been observed; it suggested that a chronic, residual inflammation resulting in neurodegeneration might be part of the pathogenesis [24]. Non encoding Latency-Associated Transcripts (LATs) is the main gene express in HSV-1 infection, it not only plays an important role in setting up and maintaining the infection, but also necessary to reactive the latent state HSV-1 [25]. In addition to that, HSV-1 can also silence the expression of intracellular lytic enzymes in neurons, improve the anti apoptotic and survival characteristics of neurons, and delay the expression of host interferon [26,27]. CX3CR1 is an important chemokine receptor microglia and blood mononuclear cell surface expression, Menasria et al. [28] found that the CX3CR1 deficiency will increase the probability of occurrence of herpes simplex virus encephalitis. About neurodegenerative diseases, more and more studies have confirmed the association between Alzheimer's disease (AD) and HSV-1 infection. *APOEε4* gene mutations combined with HSV-1 infected, the incidence of AD is 12 times higher than that of individuals with such gene mutation or HSV-1 infected alone and *APOEε4* mutation makes people more susceptible infected to HSV-1 [29,30]. The reactivation of latent state HSV-1 can stimulate the body's inflammatory response and promote the deposition of Amyloid β-protein (Aβ), lead to intracellular calcium overload and induce glial cells to produce a large amounts of NO, result in neuronal loss and cognitive dysfunction, at last promote the development of AD [31]. About the cerebral vascular diseases caused by HSV, hemorrhagic stroke as a complication of HSE has mainly been reported in patients with HSV-1 encephalitis [32]. Although the reason of hemorrhage is unclear, according to the pathological changes of fibrinoid necrosis in hematoma cavity, inflammatory changes by HSV-1 infection lead to endothelial cell injury in small blood vessels inducing intracranial hemorrhage [33]; the other hypothesis includes immune inflammation in the brain tissue, increased intracranial pressure, virus-specific toxicity, hemorrhagic predisposing strains and high blood pressure [34,35]. About the ischemic stroke diseases, the vascular endothelial cell and vascular smooth muscle cell are the main part of the latent of HSV-2, when human immune function is suppressed, the latent herpes viruses can be activated and injury of vascular endothelial cells, change the phenotype of vascular endothelial cells, make a starting point from anticoagulation to coagulation, release of inflammatory cytokines and adhesion molecules, accelerate platelet aggregation and promote thrombosis [36]. In conclusion, there are many researches about CNS diseases caused by HSV, but the specific mechanism remains unclear and further study need to be carried out, only in this way to can we recognize the true face of the virus.

Varicella-zoster virus (VZV)

Varicella-Zoster Virus (VZV) is an exclusively human virus primarily causing chickenpox, belonging to the subfamily of *Alphaherpesvirinae*. The virus genome is about 172 kb, 71 genes including 70 kinds of open reading frame (Open Reading Frame, OFR) and can encode 67 different proteins, including 6 glycoproteins (GP I ~ GP VI), named gE, gB, gH, gI, gC and gL. The gE, gB and gH glycoproteins were found in the infected cells and viral bodies [37,38]. At present, the research on the envelope glycoprotein gE

is more in-depth. It is encoded by OFR68, mediating cell adhesion, penetration, fusion and transmission between virus and host cells. gE also contains an epitope associated with neutralization, which is the primary candidate antigen for the preparation of virus subunit vaccines and DNA vaccines [1,39,40]. VZV has only one serotype and human is the only known host. Initial infection with VZV results in chickenpox (PVA), which is typically seen in children aged 1 to 9 years. In most temperate climates, more than 90% of people are infected before adolescence [41]. The CNS diseases caused by VZV infection are rare; the mean annual incidence of VZV CNS infection was 3.0 cases per 100,000 inhabitants [42]. The most frequent diagnosis of patients with VZV CNS infection was encephalitis (83.3%), followed by meningitis (13.3%) and cerebellitis (3.3%). VZV has neurotrophic characteristics, if it infects human body, the virus can lurk in the ganglia nerve cell. After the initial infection or latent infection, VZV may lurk in cranial nerve, spinal nerve and autonomic nerve. For example, if activated again, the virus lurking in the dorsal root ganglion can cause herpes zoster and the clinical manifestations are herpes zoster neuralgia (PHN), viral vascular lesions, viral spinal cord lesions and viral retinal necrosis, among them PHN is common [43,44]. The activated VEV reaches the innervated region along the nerve axons, causing multiple cranial nerve damage, so we call it multiple cranial neuritis syndromes (RHS). The common CNS disease caused by VZV infection is stroke and the main pathological changes are vascular stenosis, vasodilation, aneurysm, vasculitis and so on [45,46]. When the latent VZV is activated in the ganglion, on the one hand it can along the nerve fibers retrograde into the brain and pass through the vascular wall into the blood and spread along the blood flow, on the other hand it has a direct injury of the blood vessel wall and a large number of inflammatory cells infiltration cause the intravascular elastic membrane rupture, cerebral vascular thrombosis and fibrous tissue hyperplasia and other pathological changes, leading to granulomatous vasculitis and necrotizing vasculitis and other pathological changes [47-49]. At the same time, VZV infection can also lead to the inflammatory cytokines increased, promote vascular endothelial cells express tissue agents, increase blood agglutination, inhibit the tissue Plasminogen Activator (tPA) production, eventually leads to formation of thrombus [48]. In conclusion, limited to the low incidence of CNS disease caused by VZV, the research about its mechanism is still in the initial stage. However, for some unknown causes of diseases in clinical practice, we still cannot ignore its possibility.

Human cytomegalovirus (CMV)

Human Cytomegalovirus (CMV) is a double-stranded DNA virus belongs to the *Betaherpesvirinae*. It is the largest herpes virus with the DNA length more than 240 kb. Together with animal cytomegalovirus, Human Cytomegalovirus (HCMV), also referred to in recent literature as Human Herpesvirus 5 (HHV-5), which can lead to human congenital and acquired infection [1,50]. The incidence of congenital HCMV infections is between 0.3 and 1.2%, which is usually caused by a primary infection of the mother during pregnancy with an intrauterine transmission rate of 40% to 50% [51]. Children especially the infant are the susceptible population [52]. Congenital HCMV infection refers to the fetus infected the virus through the placenta, which can cause multisystem and multiorgan damage [52,53]. In the CNS, neural stem cells, neurons and glial cells are generally susceptible to HCMV. About 5% to 17% of children with congenital infections with HCMV showed different levels of neurological sequelae after birth, including sensory neurological

deafness, mental retardation, movement disorder, epilepsy, retinal choroid infection and so on [53]. At present, the mechanism of HCMV latent infection is mainly focused on the silence of the early immediate early promoter (MIEP), virus interference causes host cell death, virus escapes from the body immune cell attacking and non-coding RNA regulation and so on, among them silence virus MIEP prevents the virus from being activated is the main mechanism [54]. Recently, studies have shown that the expression of the MIEP gene is dependent on cell differentiation. In some undifferentiated cells, MIEP remains silent, so HCMV is in a latent infection state; however, in differentiated cells, MIEP is activated and the virus in a proliferation state in host cells. Some other study found that UL138 can up regulate the expression of TNF- α receptor on the surface of HCMV infected cells and activate the activity of TNF- α -mediated NF-KB signaling pathway, suggesting that it can activate MIEP, changing HCMV from latent infection into proliferative infection status [55]. In recent years, about the CNS disease caused by HCMV, there are some research reports. Some scholars have reported that HCMV is closely related to the occurrence of Glioblastoma (GBM). Rahbard et al. [56] found in GBM patients HCMV activity is higher than in healthy controls from analyzing GBM patients' blood samples HCMV DNA by Polymerase Chain Reaction (PCR). Liliana et al. [57] found that HCMV Immediate Early (IE) proteins are a negative regulator of GBM Sox2 protein expression, which can control the growth of GBM. Zhang et al. used the technology of immunohistochemistry and in situ hybridization evaluated the expression of HCMV pp65 antigen in brain sections from 26 Rasmussen Encephalitis (RE) patients found that elevated expression of HCMV pp65 was observed in RE brain tissue and was correlated with the clinical features, suggesting that HCMV infection may be involved in the occurrence and progression of RE [58]. When infected the HCMV, the fat in human body is increase specially the oxidized low-density lipoproteins, leads to the formation of foam cells and destruction of vascular endothelial cells [59]. Chen et al. [60] found HCMV-DNA was detected in 35 cases of the ischemic stroke patients; the detection rate of early gene/protein in HCMV group was significantly higher than that in control group, so they thought HCMV infection might relate to the pathogenesis of atherosclerosis. In short, the research about HCMV has become the focus of the HHV, understand and grasp its pathogenicity and pathogenic mechanism will help us have a better knowledge to prevent and treat diseases in CNS.

Human herpesvirus 6 (HHV-6)

Human Herpesvirus 6 (HHV-6) was first described in 1986 from peripheral blood lymphocytes of AIDS patients with various lymphoproliferative diseases [61]. Due to the virus is addicted to B lymphocyte, is also named as "human B lymphocyte virus". HHV-6 belonging to the *Betaherpesvirinae* subfamily is a linear double-stranded DNA with a length of 162 kb to 170 kb. The virus genome contains a 145 kb unique sequence of U and around U, there are the same direction repeat sequence DRR and DRL and located at both ends of DR have a six nucleotide repeat sequence (GGGTTA)_n, which plays an important role in the long-term latency of HHV-6 [62]. It is however just recently, in 2014, that converging results of phenotypic and genetic studies led to the classification of HHV-6A and HHV-6B as two distinct species among viruses defined as HHV-6 [63]. HHV-6A infection is acquired later in life and that primary infection is typically without clinical symptoms and the prevalence of HHV-6B infections is very high, above 90% in the general adult population [64,65]. About the exact transmission and latency of

HHV-6, it's not yet clear. HHV-6A and HHV-6B can infect many cells in vivo: T cells, especially CD4+ T cells, but also CD8+ T cells, monocytes-macrophages, hematopoietic cells of the bone marrow, epithelial cells of the kidney and salivary glands, endothelial cells, microglial cells, oligodendrocytes, and astrocytes [66]. The current research on the mechanism of HHV-6A and HHV-6B suggests that the virus epitopes may be observed and are able to modulate the inflammatory response and the specific immune response by: Stimulating the synthesis of proinflammatory cytokines; reducing the expression of HLA class I antigens at the surface of infected cells; producing analogues of chemokines and chemokine receptors. These phenomena are believed to help the virus actively replicate by escaping from the immune response [65,66]. HHV-6 can infect and keep latency status in the CNS for a long time and predominantly infects astrocytes, oligodendrocytes and microglia, can damage the CNS vascular endothelium [67]. About the CNS diseases, there is a link between Multiple Sclerosis (MS) and HHV-6, in the axonal demyelination site and oligodendrocytes of MS patients' brain tissue, the detection rate of HHV-6B antigen in MS patients are higher than normal control group, the reason may be that there is a cross-antigen between HHV-6B and the MS patient's CNS myelin proteins or oligodendrocytes. When human body is infected with HHV-6, T cells are activated and trigger a series of autoimmune inflammatory responses, which cause the neuro to have a demyelinating lesion [68]. Some scholars found HHV-6B DNA in resected brain tissue from Mesial Temporal Lobe Epilepsy (MTLE) patients, localized viral antigen to Glial Fibrillary Acidic Protein (GFAP) positive glia in the same brain sections, so they thought HHV-6B had an association with mesial temporal lobe epilepsy [69]. In a word, although there are not many CNS associated with HHV-6, more and more evidence will help us uncover its mystery as research goes deeper.

Human herpesvirus 7 (HHV-7)

Human Herpesvirus 7 (HHV-7) was first isolated from activated CD4+ peripheral blood T cells of a healthy individual by Frenkel et al. in 1990 [70]. It is currently known to belong to the *Betaherpesvirinae* subfamily [71]. HHV-7 is a 150 bp linear double-stranded DNA, including a single unique U area (133 kb) and a sequence of direct repeats on the left and right sides with a 109 Open Read Frame (ORF). Epidemiological surveys around the world found HHV-7 is a ubiquitous virus with a seroprevalence exceeding 90% in the adult population [72] and virus often exists in CD4+ T and salivary cells with the latent and low levels of replication status. Primary infections often occur in infancy and the clinical manifestations are infant acute rash and roseola infantum. After the initial infection, HHV-7 often exists in the human body followed by a lifelong latent state with possible reactivation in case of immunodeficiency. About the pathogenesis of HHV-7, the virus and the Human Immunodeficiency Virus (HIV) both use CD4 molecule as receptor. When binding to CD4+ T cells receptors, HHV-7 can reduce the CD4 expression and cause CTL cell immune function abnormalities [10,73]. Clear HHV-7 primary infections are poorly documented, except for a few potential cases of exanthema subitum. Viral-like syndrome with mononuclear cells in blood, seizures, or other neurological impairments have also been associated with HHV-7 in studies lacking statistical power, while the association with pityriasis rosea is still being questioned [74]. About the CNS disease, there are not researches associated with HHV-7; most of them are case reports. In particular, little is known about its pathogenic role in CNS disease in non immunosuppressed adults. Fay et al. [75] reported a previously healthy child with

acute hemorrhagic brainstem encephalitis associated with HHV-7 infection. Li et al. [76] detected HHV-7 protein KR4 and inflammatory molecules of Tumor Necrosis Factor-Alpha (TNF- α), Transforming Growth Factor-Beta (TGF- β), Interleukin-1 (IL-1) and Interleukin-6 (IL-6) by Immunohistochemistry (IHC) and real-time PCR (rt-PCR) from 305 patients with drug-resistant epilepsy and the HHV-7 DNA was detected by nested PCR in 63 Hippocampal Sclerosis (HS) samples suggesting a possible association between HHV-7 positivity, activation of TGF- β and drug-resistant epilepsy, especially HS. So, the above cases remind us HHV-7 may be a pathological factor and that a timely diagnosis is crucial for the early administration of specific treatment.

Epstein-Barr virus (EBV)

Epstein-Barr Virus (EBV) known as human herpes virus 4, belonging to the *Gammaherpesvirinae* subfamily that infects the majority of the world's population and 90% to 95% of the adult human population carries EBV as a chronic latent infection [77]. It was first discovered in children's lymphoma by Epstein in Africa in 1964 and can be transmitted through the saliva and blood transfusion [78]. It is a double-stranded DNA virus and the genome is about 172000 bp. The cellular immunity plays a major role in the control of EBV infection. In most cases, the host immune system maintains a balance with the virus, and the virus lurks in memory B lymphocytes without causing significant clinical symptoms. In some cases, this balance is broken, EBV-infected cells undergo clonal proliferation, causing a corresponding lymphoproliferative disease [79-81]. The specific pathogenic mechanism is as follows: When EBV is initially infected with the human body; Toll-Like Receptor 9 (TLR9) of B lymphocyte can identify the virus and then activate the NF-KB cell pathway to inhibit its replication, so the virus can keep a lifelong latent infection within B lymphocytes. When the body resistance is low, the virus become reactive, the host initiates the adaptive immune response, producing EBV-specific T lymphocytes (mainly CD4+ T lymphocytes and CD8+ T lymphocytes) to control and eradicate EBV. CNS involvement by EBV is rare and may be in the form of acute disseminated encephalomyelitis or demyelination most of the infections are asymptomatic; however, EBV sometimes causes a systemic infection or reactivation that may directly involve the CNS. Up to 7% of EBV-infected patients develop neurological symptoms and the most common CNS complications of EBV infection include encephalitis, cerebellitis, meningitis, cranial nerve palsies/neuritis and myelitis [82]. More than 90 percent of the CNS lymphoma is associated with an EBV infection; Walter et al. [83] found 2 cases of RE brain tissue have the EBV fragments amplified by PCR, so they thought the disease may be associated with Epstein-Barr virus infection. Shyam et al. [84] presented a rare case of EBV encephalitis in a young patient with meningitis-like symptoms and cerebellar hemorrhage on MRI, with the diagnosis confirmed on Cerebrospinal Fluid (CSF) analysis by positive PCR. Fonseca et al. [85] found the specific EBV DNA sequences and confirmation by direct sequencing by PCR in 11 primary glioma patients, so they infected EBV infection may be associated with the glioma. Parisi et al. [86] reported a case of fatal EBV-associated Hemophagocytic Lymphohistiocytosis (HLH) with severe involvement of the CNS showing florid hemophagocytosis in the choroid plexus, with extensive neuron loss and gliosis in the cerebrum, cerebellum and brainstem. In a word, EBV infection may be related to the occurrence of some CNS diseases, but the pathogenesis is still unclear, still need to be further studied.

Human herpesvirus 8 (HHV-8)

Human Herpesvirus 8 (HHV-8) belonging to *Gammaherpesvirinae* subfamily was first discovered by Chang and Moore in 1994. It has been associated with Kaposi's sarcoma (KS), multifocal castleman's disease and primary effusion lymphoma [87,88]. In the viral capsid, the shape of DNA is linear and double stranded, while in the infected host cell and released from the viral capsid, the shape of the DNA is circular [87]. Reports about the length of the HHV-8 genome have been complicated by its numerous, hard-to-sequence, terminal repeats. Renne et al. [89] reported a length of 170 Kilo bases (Kb) but Moore et al. [90] suggested a length of 270 Kb after analysis with Clamped Homogeneous Electric Field (CHEF) gel electrophoresis. About the route of transmission, the virus firstly thought to be transmitted only sexually, but now is also considered to be infected through low risk or more casual behaviors [91]. In recent years, some scholars found the occurrence of some CNS diseases have related to HHV-8. Karatas et al. [92] used the real-time polymerase chain reaction method to analysis the specimens of 33 patients with Mesial Temporal Lobe Epilepsy (MTLE) undergone temporal lobectomy with amygdalohippocampectomy due to intractable seizures and firstly found the presence of HHV-8 viral genome in the brain tissue of 1 patient with MTLE. Hannachi et al. [93] enrolled 108 patients, who meet the fourth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria of schizophrenia and found the prevalence of HHV-8 in schizophrenic patients was significantly higher than that in healthy controls by an indirect immunofluorescence assay. Although the prevalence of HHV-8 is not as ubiquitous as other HHV, there is strong evidence that it is required and quite possibly is the primary etiological agent for the formation of several life threatening neoplasms, including KS. Therefore, the development and optimization of improved diagnostic assays is critical for the identification, diagnosis, and monitoring of HHV-8 infection.

In a word, with the deepening research of HHV, more and more studies have found that HHV is associated with the occurrence of some CNS diseases in recent years, but the pathogenic mechanism is not very clear and the overall research level is still in the preliminary stage. To further understand its latent mechanism is conducive to prevent and control of HHV infection and transmission, what's more it also can provide new ideas for the development of new drugs and vaccines.

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