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Review

The Significance of chromosomally integrated HHV-6 in cardiological diseases

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Abstract

Background: Human herpesvirus 6 (HHV-6) is a double-stranded DNA β-herpesvirus associated with sudden erythema and acute infections due to its cytopathic effects on host cells. It can integrate into the host genome and reactivate under conditions such as immunosuppression, leading to lifelong persistence. HHV-6 has been implicated in various diseases, including multiple sclerosis, Alzheimer's disease, ectodermal dysplasia, and myocarditis. Additionally, chromosomally integrated HHV-6 may negatively impact heart transplantation outcomes. This article emphasizes the importance of HHV-6 diagnostics and explores its role in disease pathogenesis.
Material and methods: The study utilized molecular techniques, including PCR and sequencing, to detect HHV-6 DNA in clinical samples. Cell culture assays were employed to assess cytopathic effects and viral reactivation. Statistical analyses, such as logistic regression and survival analysis, were performed to evaluate the association between HHV-6 integration and clinical outcomes, particularly in heart transplant recipients.
Results: HHV-6 was detected in patients with various diseases, with higher viral loads observed in immunosuppressed individuals. Chromosomally integrated HHV-6 was associated with poorer prognosis in heart transplant recipients. Reactivation of HHV-6 was linked to disease progression in multiple sclerosis and Alzheimer's disease.
Conclusion: HHV-6 plays a significant role in the pathogenesis of several diseases and may serve as a prognostic marker in transplant medicine. Accurate diagnostics and monitoring of HHV-6 are crucial for managing infections and improving patient outcomes.

Keywords: Chromosomal integration, Heart failure, HHV-6, Inflammatory dilated cardiomyopathy, Myocarditis

1. Introduction

Cardio-vascular diseases remain a prime factor of death in modern advanced society. The most significant cardiac condition is heart failure. Myocarditis is a severe cardiac disease characterized by an inflammatory response developing within the myocardium. The principal aetiological factors of myocarditis are autoimmune processes and viral infections. Moreover, chronic myocarditis might later result in the development of heart failure.

Human Herpes Virus-6 (HHV-6) is a β-herpesvirus responsible for inducing a sudden erythema in children. HHV-6 is a collective name for two species of double-stranded lymphotropic DNA viruses- HHV-6A and HHV-6B. The abovementioned subtypes can transition into symptoms-free latent forms, leading them to persist for the whole life of the infected cell. HHV-6B is a chief virus in primary infection. On the other hand, activation of HHV-6A occurs ordinarily in later phases during immunosuppression. HHV-6A subtype infects the cells exploiting the CD-46 receptor. It is habitually associated with neuroinflammatory diseases e.g. multiple sclerosis, and Alzheimer's disease. Furthermore, it might be correlated with non-neuronal diseases like AIDS as well. The HHV-6B subtype infects the cells with the CD-138 receptor. It is frequently an etiological factor of ectodermal dysplasia [1][2].

The virus in question is transmitted via contaminated saliva. The most recent estimations suggest that 90% of the adult population is seropositive for HHV-6. Typically, HHV-6 infection occurs between 6 and 15 months

of life. Moreover, the incubation period of the virus was evaluated for 1-2 months. As previously mentioned, classic HHV-6B infection in children correlates with a distinctive symptom- a sudden erythema, also known as a three-day fever. However, in the adult population, HHV-6B infection is an etiological factor of mononucleosis-like syndrome. Average symptoms of HHV-6 infection include mild and transient skin lesions (erythema), fever, febrile convulsions, neuroinfections, hepatitis and lymphadenopathy. Interestingly, the most common symptoms of HHV-6 infection are unrelated to the cardiovascular system. However, viral genes have been detected in myocarditis patients, suggesting that the reactivation of chromosomally integrated HHV-6 (ciHHV-6) might manage the persistence of heart failure.

The HHV-6B genome is around 160 thousand par basis long. It holds 119 open-reading frames encoded by 97 genes. The chief part of the described genes is in the Unique region, which contains two direct repeat sequences (DR-L and DR-R) on both extremities. The Unique regio holds genes common to all herpesviruses. Moreover, in both DR regions of the HHV-6 genome, there are telomeric repeats genes (TMR) like human telomeric sequences. One of the TMRs encodes perfect telomeric repeat (pTMR), representing a fully conserved telomere sequence. However, the other DR regio holds imperfect telomeric repeats (impTMR), containing telomeric repeats and telomer-like sequences. Moreover, the TMR sequences additionally contain Pac1 and Pac2 sequences, which are responsible for the cleavage and packaging of the HHV-6. The similarity between genomes of both subtypes of HHV-6 (HHV-6A and HHV-6B) was estimated to be 90-95%. However, the most significant differences in genomes of both subtypes are in immediate early 1 regio (IE1), where they are estimated to be about 30%. Thus, the described region might be valid to discriminate between HHV-6A and HHV-6B [3].

2. Materials and Methods

Authors searched four databases (Scopus, Web of Science, PubMed, and Embase) to identify the most relevant studies for this review. We included studies describing the characteristics of HHV-6 and its role in human diseases, particularly cardiovascular diseases. Additionally, studies investigating the correlation between HHV-6 and other viruses were included. However, studies that did not reference HHV-6 were excluded. Reviews and meta-analyses were also excluded.

3. Results

3.1 Mechanism of chromosomal integration of HHV-6

During the primal infection, HHV-6 genes are inserted into telomeric sequences [4]. The analysis of chromosomally integrated HHV-6 sequences revealed that the assimilation of a virus is only possible when pTMR in DR-R regio binds telomeric sequences adjacent to subtelomeres and impTMPR in DR-L regio attaches to telomeric sequences. Due to replication defects, the Pac1 sequence in DRL and Pac2 in DRR are being lost during the integration. The schematic structure of the HHV-6 virus genome is illustrated in Figure 1. The cell DNA reparation mechanisms are recruited after the HHV-6 penetration [5].

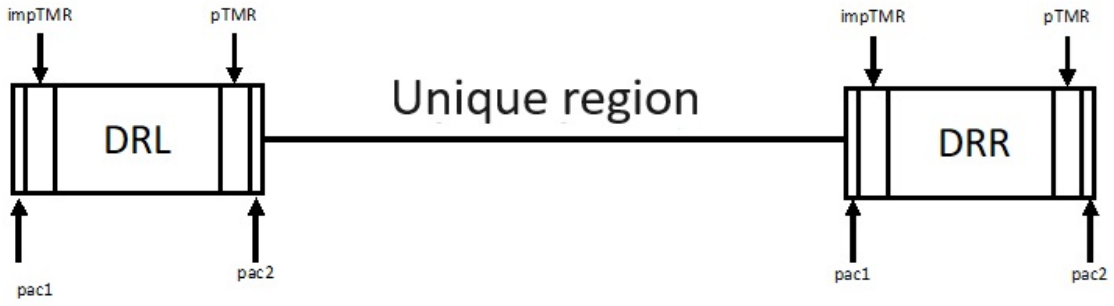

Figure 1. Schematic representation of the HHV-6 virus genome

Human telomeres, after the integration of HHV-6A/B genes, have significantly reduced stability and length compared to normal telomeres. The frequency of integration of both HHV-6 subtypes is estimated at 74% for HHV-6B and 26% for HHV-6A. As previously mentioned, the HHV-6 indicates the capability to remain in infected cells in latent form. Thus, it can persist for the whole life of a host and might reactivate in favourable conditions. Moreover, HHV-6 gene integration may also occur in germ cells. However, whether the integration occurs during the primal infection or reactivation is still unknown. It is believed that chromosomally integrated HHV-6 might be detected in 1% of the global population [4].

Moreover, the viral genome integrated into germ cells might be later inherited by the offspring. In favourable conditions like immunodeficiency in pregnancy viral genes might be reactivated. Moreover, the reactivation of the virus may also occur during hematopoietic stem cell transplantation, leading to graft versus host disease. For this reason, the differential diagnosis between active infection and the presence of chromosomally integrated HHV-6 is singularly crucial [6].

3.2 Detection of chromosomally integrated HHV-6

The most standard diagnostic technique used for detecting HHV-6 is PCR of blood samples. However, there is no possibility of differentiation between HHV-6A and HHV-6B infection by applying commonly used primers. A single high viral load (105 copies/ml) does not allow us to decide whether the infection is initiated by acute HHV-6 infection or the presence of ciHHV-6 [6]. However, according to scientific data, the decreasing level of viral gene copies over time is a confirmation of acute infection. On the other hand, stable levels of viral genes over time indicate ciHHV-6 presence [7].

Moreover, it was revealed that in the case of ciHHV-6, viral DNA will be present in all clinical samples, including cell-free samples. In the serum or plasma of patients with ciHHV-6, the level of detected DNA varies and depends on the time of separation from whole blood. However, usually it is 10-100 times lower than in blood. Dwindling the number of viral gene copies in the blood is an exclusion criterion of chromosomally integrated HHV-6 diagnosis [8].

On the other hand, ddPCR is currently applied as a diagnostic approach for the latent forms of HHV-6. It is possible to compare the level of viral gene copies to number of cells in the sample using ddPCR. It is believed that a ratio close to one virus copy per human cell is assumed to suggest the presence of ciHHV-6 [8]. Interestingly, because the HHV-6 infection of nails and hair follicle cells is remarkably unlikely, every presence of viral genes in the mentioned structures confirms ciHHV-6 presence [9]. Thus, nails and hair follicles are valuable sources of samples for viral diagnostics. A 0.5-1 cm long hair or a nail fragment removed from the bulb is subjected to DNA extraction. Then, the extracted DNA is used for PCR to detect HHV-6 genes [10][11]. The differences between active infection and chromosomally integrated form diagnostic are summarized in Table 1.

	Levels of HHV-6 DNA in blood	DNA HHV-6 in serum/plasma	HHV-6 genes copies to human cell ratio (in ddPCR)	HHV-6 DNA presence in hair follicles and nails
Active HHV-6 infection	Present and decreasing over time	-	-	-
Presence of ciHHV-6	Present and relatively stable	+	about 1	+

Table 1. The diagnostic difference between the active infection and chromosomally integrated HHV-6

3.3 A significance of HHV-6 in cardiac diseases

The detection of HHV-6 is frequent in myocarditis and inflammatory dilated cardiomyopathy biopsy samples. Symptoms of the patient and the progress of the disease are related to the type of the virus and the course of the infection. If the virus levels are reduced by the inflammatory response or antiviral treatment, the ejection fraction of the patient might be improved [12]. Chromosomally integrated HHV-6 might affect every nucleated cell in the organism. Thus, it might be detected in 1% of HHV-6-infected patients [13]. Moreover, the positive correlation between the surface expression of receptors and virus reactivation and replication has been proven. Moreover, the inflammatory response strengthens with every replication cycle, increasing damage to the host's tissues [14].

HHV-6 infects endothelial cells of various blood vessels and capillaries, resulting in endothelial cell dysfunction. Thus, HHV-6 might induce thrombotic microangiopathy or vasculitis. Moreover, there are reports that HHV-6 infection might be correlated with various vascular pathologies, including leukocytoclastic vasculitis, "coronary vasculitis" in transplant recipients, and Kawasaki disease. Furthermore, the HHV-6 and HHV-8 genetic materials have been detected in patients with atherosclerosis of coronary arteries. The endothelium dysfunction might also result in heart ischemic symptoms. The genetic material of HHV-6 has been revealed in coronary arteries of post-heart graft patients from healthy donors. Thus, it is believed that the virus might be reactivating in cardiomyocytes.

Moreover, the presence of chromosomally integrated HHV-6 has been diagnosed in cardiomyopathy and heart failure patients [15]. The HHV-6 infection may also induce cytopathic effects and indicate inflammation; thus, it may trigger chronic myocardial damage. Secreted cytokines during the inflammation may even influence the extracellular matrix, resulting in cardiac remodelling. Moreover, during immunosuppression, chromosomally integrated HHV-6 might induce reactivation of other latent viruses, like parvovirus B19, Epstein-Barr virus, and cytomegalovirus [16].

The role of the HHV-6 virus in myocardial diseases was possible to determine by the recent clinical data analysis. In a study on 71 patients with non-ischemic cardiomyopathy, the coronary microcirculation dysfunction in connection with viral infection and myocarditis was assessed. The PCR revealed that 41 patients had been infected with the virus; 41% were positive for parvovirus B19, and 17% with HHV-6. The endothelial dysfunction in viral-infected patients occurred regardless of myocarditis and endothelial activation. However, it was more noticeable in patients with concomitant myocarditis [12].

Moreover, by using hybridization in situ and electron microscopy, Krueger et al. have found viral particles in cardiomyocytes, proving the presence of HHV-6 antigens in degenerating cardiomyocytes. Furthermore, viral antigens have been also observed in endothelial cells [12].

In another study, 37 of 70 patients diagnosed with shortness of breath on exertion and/or reduced exercise tolerance were confirmed by echocardiography for isolated left ventricular dysfunction during the diastole. The HHV-6 genes have been detected in endomyocardial biopsy of 35 of them. Moreover, ten patients were diagnosed with reduced function of coronary endothelium and left ventricular failure. These patients were seropositive for Parvovirus B19. However, three of them were co-infected with another virus. The abovementioned data reveals that the endothelial and microcirculation dysfunction might be induced by Parvovirus B19, supported by co-infection with other cardiopathic viruses, e.g. HHV-6, and as such, may constitute a possible pathogenetic mechanism underlying diastolic dysfunction [12]. The possible pathological effects of HHV-6 infection have been summarized in Figure 2

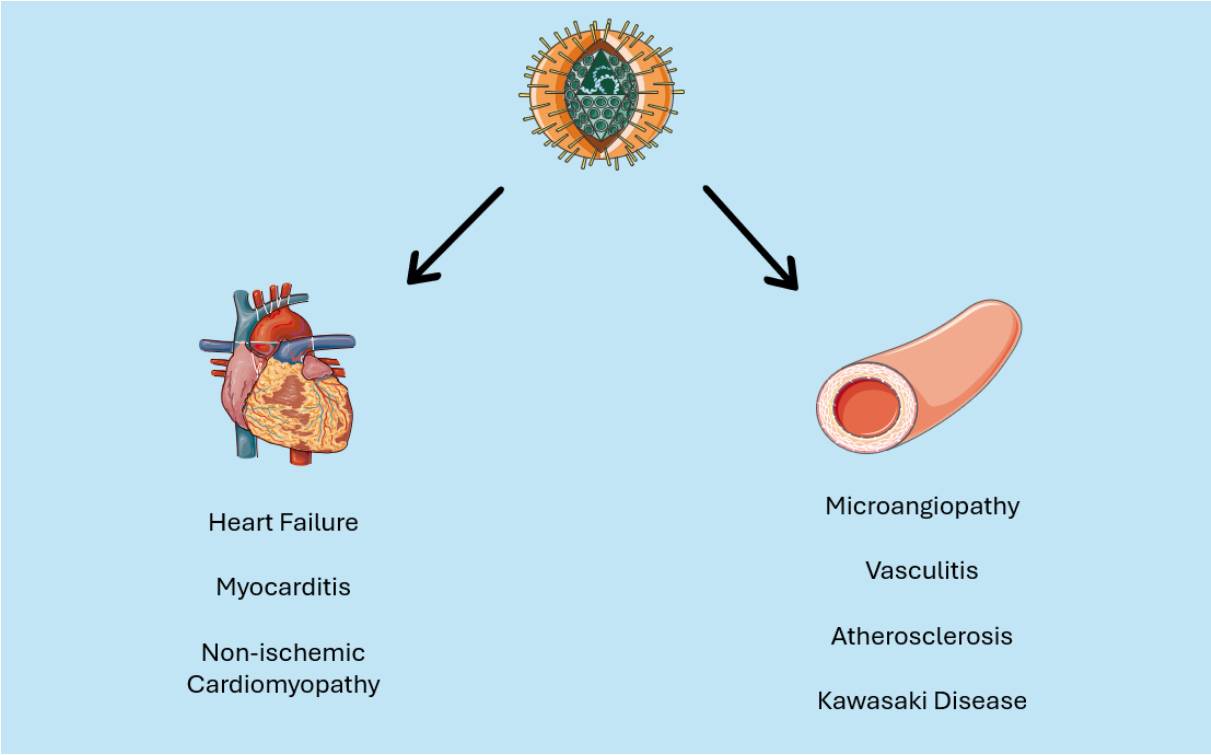

Figure 2 The pathological effects of HHV-6 infection. Figure was created using Servier Medical Art under CC BY 4.0 licence

3.4 Influence of HHV-6 infection for the therapies

There is too little data in the literature to predict whether the heart graft in a newborn with ciHHV-6 will be successful. In a series of 21 transplant recipients with ciHHV-6, 13 patients (61,9%) suffered from graft versus host disease or transplant rejection. Moreover, in another study after a parenchymal organ graft, the reported frequency of HHV-6 infection was estimated from 66% to 91%, inducing symptoms-free infection. A patient diagnosed with ciHHV-6 with severe neonatal dilated cardiomyopathy with decompensated heart failure (after

consultation with multiple paediatric heart transplant centres), was not considered a candidate for transplantation due to the elevated risk of rejection and HHV-6 reactivation in the setting of immunosuppression [12].

Anti-HHV-6 therapy only suppresses the viral gene expression. However, it cannot delete the viral genes from the cardiomyocytes. The application of immunosuppressive treatment in combination with antiviral drugs such as ganciclovir, acyclovir, or valacyclovir for acute HHV-6-related myocarditis and severe heart inflammation is habitually recommended by experienced centres. Moreover, the inflammation related to HHV-6 is an unfavourable prognostic factor for heart transplantation. The case of a 14-month-old child with primary HHV-6B myocarditis, successfully treated with artesunate, a semi-synthetic derivative of artemisin is known. Moreover, there is evidence that interferon-β therapy reduces viral myocardial damage induced by enteroviruses. Thus, implementing interferon-β improves the long-term survival of patients chronically infected by enteroviruses [16].

The endomyocardial biopsy of patients with myocarditis revealed that the incidence of HHV-6 is notably higher compared to parvovirus B19. The patient might be considered ciHHV-6 positive if the level of antibodies in the serum is permanently increased. Moreover, it was proven that there is a positive correlation between the level of viral mRNA and progressive heart failure. Thus, it might be crucial to control the level of mRNA during the infection. However, it is essential to understand that elevated levels of antibodies in symptoms-free patients are not required to be treated if mRNA levels do not indicate active infection. Eventually, ciHHV-6 reactivation is more frequent in patients with weakened immune systems, and it is these patients who require more extensive periods of treatment and close monitoring to detect the recurrence of symptoms [17].

3.5 Importance of Chromosomal integration of HHV-6

Like other herpes viruses, HHV-6 can persist in infected cells in latent form and might reactivate in specific conditions, like immunosuppression. The reactivation results in the development of symptoms of sub-acute infection, especially in patients with impaired immunity and autoimmune diseases. However, there are hypotheses that the clinical significance of HHV-6 may lie more in the intensification of other viral infections than in its direct effect. Moreover, HHV-6 might activate other viral infections (e.g. EBV, B19V). Thus, it is believed that co-infection may increase the pathogenicity of different viruses.

For this reason, even a transient viral infection may be sufficient to cause chronic disease through direct cytopathic effects or the induction of low-grade inflammation with cytokine release. Secreted cytokines affect signalization paths and extracellular matrix components. The abovementioned mechanisms might have a pivotal role in HHV-6-induced heart diseases. Moreover, there are reports that despite frequent detection of the virus in dilated cardiomyopathy patients, HHV-6-induced myocarditis is quite rare. Specific conditions might promote the development of HHV-6-induced heart diseases e.g. immunosuppression or co-infection with Parvovirus B19. It is believed that HHV-6 should be looked for in cases of isolated dilated cardiomyopathy of unknown aetiology. However, there is a need for further studies on the role of HHV-6 in cardiovascular diseases.

3.6 Impact of chromosomally integrated HHV-6 for immune response

As previously mentioned IE1 regio indicated the most colossal discrepancies between the two subtypes of HHV-6 (HHV-6a and HHV-6B). Thus, the products of both IR1 regions - protein U90 varies the most [18]. The study designed by Peddu et al. revealed that specific genes like U90 might be preferentially expressed relative to others. Moreover, patients positive for ciHHV-6 indicated statistically significant elevated levels of antibodies against U90 in serum than control. Of interest, the same study reported that CMV seropositive patients with ciHHV-6 contain more increased levels of antibodies than ciHHV-6 negative. These results indicated that spontaneous gene expression from integrated HHV-6 leads to an increase in antigenic burden. Thus, the antibody response is much more significant [19].

3.7 HHV-6 infection in other diseases

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe cutaneous condition indicated by T-cells end eosinophiles hyperreaction induced by the drug. It is characterized by fever, morbilliform rash and various systemic sequelae, including hepatitis, interstitial nephritis, and myocarditis [20]. Hyperactivation of the eosinophils might result in heart infiltration, resulting in the development of eosinophilic myocarditis. However, it is a rare complication [21]. There is known a case of a 60-year-old woman admitted to the hospital due to DRESS-like symptoms, however without a convincing drug indicator. Further examination revealed that the patient was HHV-6 positive. Thus, it is believed the reactivation of HHV-6 was the trigger of eosinophile activation, resulting in heart infiltration, rush, and other patient DRESS symptoms [22].

As previously mentioned HHV-6 might persist in the cells in latent forms. Recent studies indicated that the HHV-6B subtype might establish chronic latency in brain tissue. Moreover, there is evidence that the reactivation of HHV-6B might be responsible for triggering epilepsy syndromes, including febrile seizures and status epilepticus, acute symptomatic seizures secondary to encephalitis, and temporal lobe epilepsy [23].

On the other hand, there is a report of a 44-year-old heart transplant recipient patient, who developed gastroduodenitis, pancreatitis, and hepatitis. On histopathologic examination, the gastric, duodenal, and bile ductular epithelium showed a multinucleate giant cell transformation. Furthermore, the electron microscopy revealed the herpes particles with a thick tegument layer in the duodenum. Further PCR and serological examination confirmed HHV-6 infection. Thus, there are clues that HHV-6 might be an aetiological factor of gastroduodenitis and pancreatitis in immunosuppressed individuals [24].

4. Discussion

The discovery of the HHV-6 virus's ability to insert into the patient's genome undoubtedly contributed to a better understanding of the pathomechanisms of viral infections and their effects on the human organism. Current knowledge allows us to explain plural mechanisms leading to the integration of the viral genome in chromosome telomeres. Modern diagnostic approaches make it possible to differentiate acute infection and chromosomal integration. It is noteworthy the presence of ciHHV-6 is a negative prognostic factor for heart transplantation. Thus, the ability to differentiate acute infection and chromosomal integration is crucial to determine whether the transplantation will be successful or not. HHV-6 might also be an aetiological factor of endothelial dysfunction, resulting in ischemic complications. Moreover, the described virus might also damage the cells by inducing an inflammatory response. Thus, it is not surprising that available clinical data indicate that ciHHV-6 might have a significant impact on the development of cardiovascular diseases. Because these kinds of diseases remain a prime death factor in modern society, it is especially essential to extend the studies of HHV-6. Moreover, recent studies and reports suggest that HHV-6 might infect other non-cardiac tissues like the liver or pancreas. Particularly interesting might be the ability of HHV-6 to infect brain tissue. Moreover, encephalitis might later have consequences in the development of epilepsy. Thus, the HHV-6 infection remains a valuable topic for further studies.

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