REVIEW ARTICLE

Human herpesvirus 6-induced inflammatory cardiomyopathy in immunocompetent children

Surabhi Reddy, Eva Eliassen, Gerhard R Krueger[1], Bibhuti B Das[2]

HHV-6 Foundation, Santa Barbara, CA, [1]Department of Pathology & Laboratory Medicine, The University of Texas-Houston Medical School, Houston, TX, [2]Departement of Pediatrics, UTSW Medical Center, Dallas, TX, USA

ABSTRACT

Over the last decade, human herpesvirus 6 (HHV-6) has been implicated in the etiology of pediatric myocarditis and subsequent dilated cardiomyopathy (DCM). This review provides an overview of recent literature investigating the pathophysiological relevance of HHV-6 in inflammatory cardiomyopathy. We examined 11 cases of previously published pediatric myocarditis and/or DCM associated with HHV-6 and also our experience of detection of virus particles in vascular endothelium of HHV-6 positive endomyocardial biopsy tissue by electron microscopy. The exact role of the presence of HHV-6 and its load remains controversial as the virus is also found in the heart of healthy controls. Therefore, the question remains open whether and how cardiac HHV-6 may be of pathogenetic importance. Quantitative polymerase chain reaction or mRNA testing allows differentiation between low-level latent virus found in asymptomatic myocardium and active HHV-6 infection. Although only a small number of pediatric cases have been reported in literature, HHV-6 should be considered as a causative agent of inflammatory cardiomyopathy, especially in children under three who might be experiencing a primary infection. Future studies are needed to establish a threshold for determining active infection in biopsy samples and the role of coinfections other cardiotropic viruses.

Keywords: Human herpesvirus 6 cardiomyopathy, myocarditis in children, pediatric-dilated cardiomyopathy

INTRODUCTION

The current recommendations from an American College of Cardiology Foundation/American Heart Association/European Society of Cardiology scientific statement support a limited role for endomyocardial biopsy (EMB) in the evaluation of patients with dilated cardiomyopathy (DCM). The Class I indications are limited to patients with new-onset heart failure (<2 weeks) associated with a normal or dilated left ventricle with hemodynamic compromise and to patients with new-onset heart failure of 2 weeks to 3 months' duration with a dilated left ventricle, ventricular arrhythmia, or high degree atrioventricular blockade or to patients whose condition fails to respond to treatment in 1–2 weeks.[1] With the development of new molecular techniques such as electron microscopy, reverse transcriptase-polymerase chain reaction (RT-PCR) and *in situ* hybridization, the spectrum of most frequently detected viruses in EMB shifted from classic enteroviruses and adenovirus to the two most common pathogens found in EMB biopsies: parvovirus B19 (PVB19) and human herpesvirus 6 (HHV-6).[2,3] HHV-6 encompasses two closely related herpesviruses, HHV-6A and HHV-6B. Chromosomally integrated HHV-6 (ciHHV-6) is a rare inherited condition affecting 1% of the population, in which the complete genome of the virus is integrated into the chromosome and passed through the germline[4,5] HHV-6 as a cause of dilated cardiomyopathy has been well recognized in adults.[6] Depending on the localization of cardiotropic

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Address for correspondence: Dr. Bibhuti B Das, Department of Pediatrics, UTSW Medical Center, 1935 Medical District Dr, Dallas, TX 75235, USA.
E-mail: bdas99@hotmail.com

viruses in myocardial tissue, it causes different types of myocardial dysfunction, the pathophysiology is summarized in Figure 1. HHV-6A may cause direct infection of cardiomyocytes [Figure 2] whereas HHV-6B infects the vascular endothelium [Figure 3] and subsequently endothelial dysfunction and diastolic dysfunction.[7] We have previously described a practical approach to children presenting with acute systolic heart failure due to acute myocarditis or DCM.[8] This review will primarily focus on the issues specific to cardiac HHV-6 in immunocompetent children.

LITERATURE REVIEW OF HUMAN HERPESVIRUS-6 MYOCARDITIS AND DILATED CARDIOMYOPATHY IN IMMUNOCOMPETENT CHILDREN

A recent study by Simpson et al. showed 80% of 21 immunocompetent infants with myocarditis were positive for a cardiotropic virus from blood PCR tests, (of which 21 two were positive for HHV-6) compared to <4% of healthy 22 controls.[9] HHV-6 has been detected in 43% of patients from a review of archival tissue specimen from pediatric patients with idiopathic DCM or congenital heart diseases.[10] With these considerations in mind, we conducted this literature review with two specific aims (i) to summarize clinical profile of immunocompetent children with HHV-6 suspected myocarditis or DCM and (ii) to examine HHV-6 as a definite etiological agent for pediatric immunocompetent patients with myocarditis and DCM.

We made a comprehensive literature reviews in the PubMed and Ovid Medline. Standard search terms such as HHV-6 myocarditis and HHV-6 cardiomyopathy were used and references were reviewed to identify additional cases, and they were manually filtered to identify pediatric case studies that fulfilled the criteria of our review [Figure 4]. Our results are summarized in Tables 1 and 2.

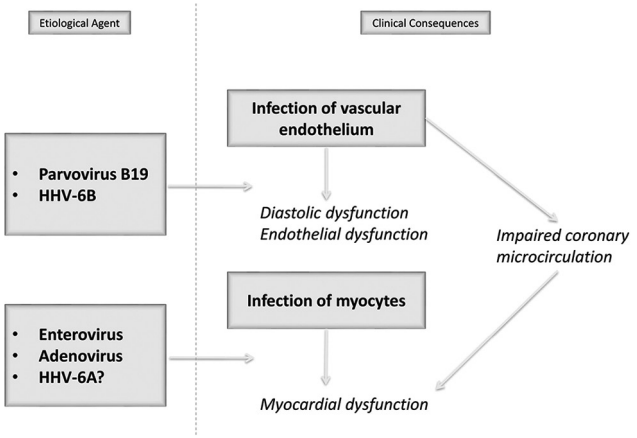

Figure 1: Possible mechanism of viral myocarditis

PATIENT-SPECIFIC OBSERVATIONS OF HUMAN HERPESVIRUS-6 INFLAMMATORY CARDIOMYOPATHY

Spotnitz and Lesch describe three distinct pathological stages of viral myocarditis: (1) acute myocarditis with myocyte damage/necrosis and intramyocardial inflammation from active viral infection, (2) subacute/chronic myocarditis with myocyte damage from protracted viral infection and immune-mediated response, and (3) DCM from chronic myocarditis involving scarring/fibrosis of cardiac tissue.[11]

From Tables 1 and 2, 6/11 (55%) cases in our review fall within the first category (acute myocarditis), evidenced by acute systolic heart failure and histopathological evidence of myocardial inflammation and damage. These patients presented with the classic symptoms of HHV-6 primary infection: febrile illness and exanthem. Other noted symptoms within this group were tachycardia, respiratory distress, convulsions, and lymphadenopathy. Laboratory investigations revealed markers for inflammation (i.e., leukocytosis, leukocytopenia, elevated C-reactive protein) and markers for cardiac damage (i.e., elevated troponin and/or creatine kinase myocardial bound). Due to the acute, fulminant presentation of myocarditis in these cases, acute systolic heart failure typically precluded a full diagnostic workup including cardiac catheterization and EMB. Myocarditis was confirmed at autopsy.

Furthermore, our analysis shows 2/11 (18%) of the cases fell within the second category (subacute/chronic myocarditis), with involvement of mononuclear cell infiltration and a small amount of fibrosis.[12] One patient eventually recovered after left ventricular assist device (LVAD) support and antiviral treatment.

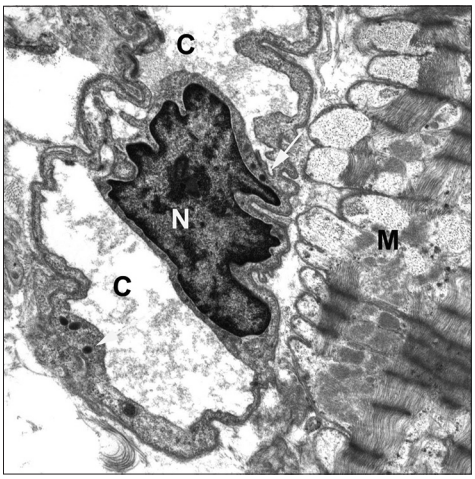

Figure 2: Endomyocardial biopsy showing a capillary (C: Capillary lumen; N: Nucleus of endothelial cell) with adjacent myocardium (M). Arrows show herpesvirus particles. Note the myocardial hypoperfusion damage, (×12,000)

Coincidentally, the patient demonstrated symptoms of exanthem subitum. In the rest, 3/11 (27%) of cases describe DCM, confirmed by echocardiograph findings of ventricular dilatation and/or histopathological evidence of endomyocardial fibrosis. This subset primarily presented with respiratory distress and arrhythmia, with no remarkable evidence of cardiac inflammation (burnt-out myocarditis) suggestive of DCM.

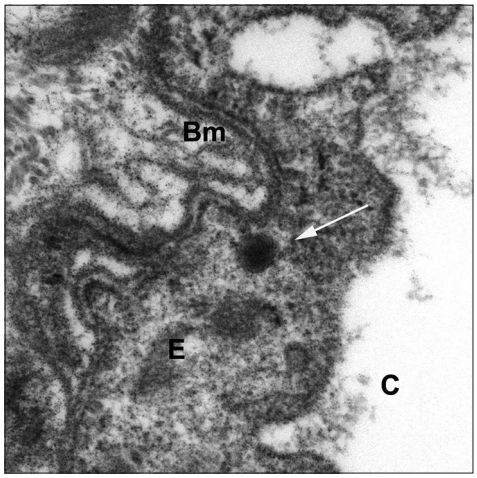

Figure 3: Endomyocardial biopsy, higher magnification showing typical human herpesvirus-6A particle (arrow) in an endothelial cell, Bm: Basement membrane, E: Endothelial cells, C: Capillary (×80,000)

It is estimated that one-third of patients with viral myocarditis experience complete recovery, one-third show residual cardiac dysfunction, and one-third experience cardiac failure resulting in death or transplantation.[13] This review demonstrates that most HHV-6-associated cases of myocarditis and DCM have a severe clinical course and fall within the latter category. Seven out of 11 (64%) cases resulted in sudden death, frequently within a week of initial symptoms. This confirms a previous study conducted by Mahrholdt *et al*. of 31 adult patients with HHV-6-associated myocarditis.[14] Compared to patients with Coxsackie B, PVB19, and EBV infection, patients with HHV-6 more frequently presented with new-onset acute systolic heart failure and subsequently progressed toward chronic heart failure.[14]

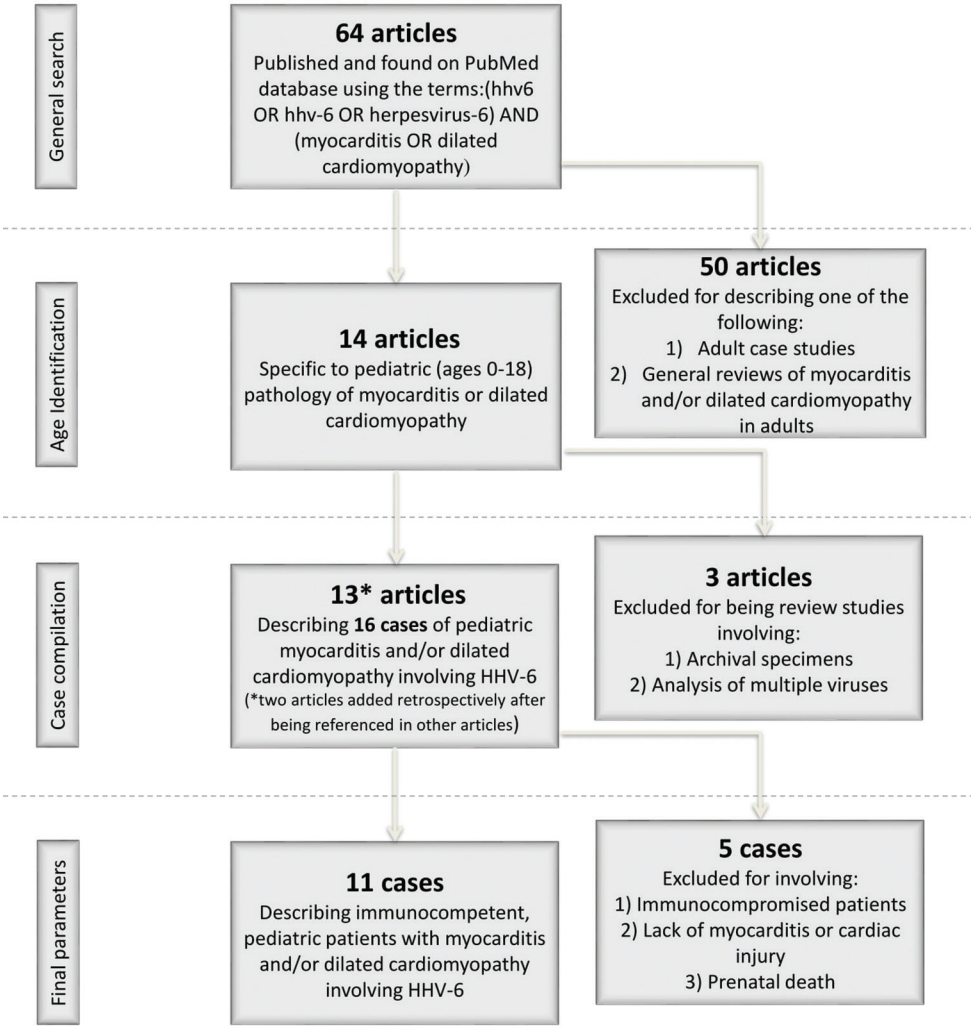

Figure 4: PubMed and Ovid Medline review process and outcome summary

Table 1: Clinical profile of immunocompetent patients with suspected myocarditis and dilated cardiomyopathy

Age, sex	Clinical presentation	Physical examination	Lab findings	EKG	Echo	Gross and histopathology	Treatment	Final diagnosis	Outcome	References
Fetus (22 weeks gestation), male	N/A		N/A	N/A	Enlargement of right atrium, LV, and RV, reduced contractility in RV and absent in the LV, mitral and aortic stenosis	Dilation of ventricles/ tricuspid valve, thickened septal cusp, commissural fusion/thickened cusps/cords in mitral valve, mononuclear cell infiltrates, myocytolysis, disorganization of myocytes, fibrosis, foci of calcification, and necrosis (autopsy)	None	Myocarditis	Termination of the pregancy	Ramalho *et al.*, 2011[35]
1 months, female	Fatigue, poor feeding, respiratory distress	Muffled cardiac tones, hepatomegaly	Elevated AST, LDH, cardiac troponin	ST-T wave changes, PVCs	LV dilatation, low LVEF (36%)	Hypertrophy of myocardiocytes, perivascular fibrosis (RV biopsy)	Inotropes, antiarrhythmics, levosimendan	DCM	Chronic heart failure	Papadopoulou-Legbelou *et al.*, 2016[24]
5 months, female	5-day history of fever, rash, lethargy, poor feeding, convulsions	Hypotonia, tachycardia	Lymphocytosis; Elevated AST, LDH, CK-MB	Vent. arrhythmia	N/A	Mononuclear cell infiltrates, edema and necrosis of myocytes (autopsy)	Antiarrhythmic	Acute myocarditis	Sudden cardiac arrest and death	Yoshikawa *et al.*, 2001[36]
13 months, female	Fever, poor feeding	Bilateral otitis media, erythematous mucous membrane, cervical lymphadenopathy, edema of hands and feet	Elevated AST, ALT; leukopenia, thrombocytopenia	N/A	No abnormal findings	Atypical lymphoid cells with viral inclusions (autopsy)	Antibiotics, IVIG	Acute myocarditis	Congestive heart failure and death on day 5	Prezioso *et al.*, 1992[37]
14 months, NA	Acute heart failure one week after primary HHV-6 infection	Pallor, tachycardia, tachypnea, dyspnea	Elevated troponin-T, CK-MB, AST, ALT, pro-BNP	ST-T wave changes	Low LVEF (10%), mitral and tricuspid regurgitation	Mononuclear cell infiltrates, activated macrophages, small amount of fibrosis (EMB)	Inotropes, diuretics, IVIG, ganciclovir; artesunate after suspected ganciclovir resistance	Chronic lymphocytic myocarditis	LVAD support followed by full recovery	Spotnitz and Lesch, 2006[11]
14 months, female	3-day history of fever, hypotonia	Diffuse rash, tachycardia, gallop rhythm, tachypnea, status epilepticus	Elevated CRP; thrombocytopenia	N/A	Enlarged LV, low LVEF, mitral and tricuspid regurgitation	N/A	Steroids, antibiotics, anticonvulsants	Myocarditis	Myocardial recovery but seizures continued	Rantala *et al.*, 2000[38]
2 years, female	Fever, rash	Ecchymoses and petechiae of lower extremities	Pancytopenia	N/A	N/A	Confirmed myocarditis (autopsy)	Prednisone	Acute lymphocytic myocarditis	Cardiogenic shock and death on day 6	Stefanski 2016[39]

Contd...

Table 1: Contd...

Age, sex	Clinical presentation	Physical examination	Lab findings	EKG	Echo	Gross and histopathology	Treatment	Final diagnosis	Outcome	References
6 years, male	Upper respiratory infection	Maculopapular rash, dyspnea	N/A	N/A	Enlarged LV, low LVEF, mitral regurgitation pericardial effusion	Diffuse myocarditis with granulomas, dilatation of all chambers (autopsy)	Inotropes	Chronic myocarditis	Chronic heart failure, death following mitral valve surgery	Bourgeois *et al*., 2012[20]
11 years, male	3-day history of fever, acute respiratory distress	Rash of upper extremities, tachycardia, hypotension, cyanosis, tachypnea, cervical lymphadenopathy	Elevated CRP, troponin-T; thrombocytopenia, lymphocytopenia	N/A	N/A	Mononuclear cell infiltrates, pericardial and subpleural petechial hemorrhage (autopsy)	Inotropes	Acute interstitial myocarditis	Acute systolic heart failure and sudden death	Sergi *et al*., 2007[25]
11 years, female	Diarrhea, respiratory distress	N/A	N/A	N/A	N/A	Mononuclear infiltrates in myocardium (autopsy)	N/A	Acute myocarditis	Sudden death	Bourgeois *et al*., 2012[20]
1-19 years, male/ female	N/A	N/A	N/A	N/A	N/A	Inflammatory and myocyte necrosis pattern as described for the Dallas criteria of myocarditis	N/A	End-stage DCM	Heart transplantation	Comar *et al*., 2008[10]
At birth male	Respiratory distress acute heart failure	Hypotension, systolic murmur, gallop rhythm	Elevated pro-BNP	Tachycardia, prolonged QTc, low voltages	LV dilatation, low LVEF, mitral regurgitation	Endocardial fibroelastosis, interstitial edema, no infiltrates or myocyte damage	Inotropes, ganciclovir	DCM with endocardial fibroelastosis	Sepsis and death on Day 16	Das *et al*., 2016[23]
4 years, female	Fever, general fatigue	Arrhythmia, hypotension	N/A	N/A	Enlarged LV and LA, low LV EF, mitral regurgitation	N/A	Diuretics, inotropes, antiarrhythmics, IVIG, ganciclovir, foscarnet	DCM	Chronic heart failure	Strenger *et al*. 2010[40]

ALT: Alanine transaminase, AST: Aspartate transaminase, BNP: B-type natriuretic peptide, CK-MB: Creatine kinase-MB, CRP: C-reactive protein, DCM: Dilated cardiomyopathy, EMB: Endomyocardial biopsy, EM: Electron microscopy, IVIG: Intravenous immunoglobulin G, LA: Left atrium, LDH: Lactate dehydrogenase, LV: Left ventricle, LVAD: Left ventricular assist device, LVEF: Left ventricular ejection fraction, N/A: Not applicable, PVCs: Premature ventricular contractions, RV: Right ventricle, EKG: Electrocardiogram, EF: Ejection fraction

Table 2: Examining human herpes virus 6 as an etiological agent for myocarditis and dilated cardiomyopathy in immunocompetent patients

Age, sex	PCR DNA serum	PCR DNA heart tissue	+ PCR DNA other organs	Serology HHV-6 IgG/IgM	Staining	ciHHV-6 testing	HHV-6 variant	Physical signs of HHV-6 infection	Other noncardiac features	References
Fetus (22 weeks gestation), male	ND	+	ND	ND	ND	ND	ND	N/A	N/A	Ramalho *et al.*,2011[35]
5 months, female	ND	+	Liver, kidneys, spleen, lymph nodes	-/+	-- (ABC method)	ND	B	Exanthem subitum	N/A	Yoshikawa *et al.*, 2001[36]
13 months, female	ND	ND	ND	ND	+ (EM, ISH)	ND	ND	Erythema, fever	Liver disease	Prezioso *et al.*, 1992[37]
14 months, NA	+ (2800 copies/mL)	+	ND	+/+	+ (ISH)	-- (via fingernails)	B	Exanthem subitum	N/A	Hakacova *et al.*, 2013[12]
14 months, female	ND	ND	CSF, brain tumor	+/+	N/A	ND	ND	Fever	Encephalitisstatus epilepticus	Rantala *et al.*, 2000[38]
2 years, female	+ (64,600 copies/mL)	ND	ND	ND	+ (immunofluorescence)	ND	A	Exanthem subitum	N/A	Stefanski *et al.*, 2016[39]
6 years, male	ND	+	Thoracic lymph nodes	ND/-	Unclear (IHC)	ND	ND	Maculopapular rash	Liver and kidney failure	Sergi 2007[25]
11 years, female	ND	+	Large bowel, small bowel, lymph nodes	ND	+ (IHC)	ND	B	N/A	N/A	Sergi *et al.*, 2007[25]
<18 months, female	2/11+	ND	ND	ND	ND	ND	ND	ND	N/A	Simpson *et al.*, 2016[9]
1-19 years, male/female	ND	7/16 + (mean 2.96×10^2 copies/μg DNA)	ND	ND	ND	ND	B	ND	N/A	Comar *et al.*, 2008[10]
At birth male	+ (2×10^6+ copies/mL)	-	ND	+/-	+ (ISH)	+ (ddPCR)	B	N/A	N/A	Das *et al.*, 2016[23]
1 months, female	ND	+	ND	ND	N/A	ND	ND	N/A	N/A	Papadopoulou-Legbelou *et al.*, 2016[24]

ddPCR: droplet digital PCR, EM: Electron microscopy, IHC: immunohistochemistry, ISH: *In situ* hybridization, ND: Not done, N/A: Not applicable, PCR: Polymerase chain reaction, ciHHV-6: Chromosomally integrated HHV-6, +: Positive, -: Negative

The severe clinical course of HHV-6-associated myocarditis in our review also associated with the relatively young age of the patients. For other causative agents, such as Coxsackie B, mortality rates for pediatric myocarditis are significantly higher in infants (75%) than in older children (25%).[15] Seven out of 11 (64%) HHV-6 myocarditis patients in our review were under 2 years of age and most were suffering from a presumed primary HHV-6B infection. The immature nature of the myocardium in neonates and infants increases susceptibility to injury. In addition, cardiac catheterization poses higher risk in infants, increasing the difficulty of obtaining an EMB, and potentially delaying diagnosis and pathogen-specific antiviral treatment.[15]

Patients with HHV-6-associated myocarditis in this review demonstrated organ involvement outside of the heart. Two patients had signs of central nervous system (CNS) dysfunction, including convulsions and/or status epilepticus. Seizures are associated with HHV-6 infection as one study reports 32% of infants with status epilepticus as positive for active HHV-6 infection confirmed by plasma quantitative PCR testing.[16] Two patients also demonstrated kidney and/or liver failure. Hepatitis and end-stage renal disease have been commonly reported in transplant patients with HHV-6 reactivation.[17,18] As these extracardiac findings (i.e., CNS dysfunction, liver failure, and kidney failure) are associated with HHV-6 infection, they may provide evidence to HHV-6 being etiologically involved with multiple organs in our review.

The clinical course of HHV-6-associated myocarditis may also be complicated by drug exposure. HHV-6 reactivation is commonly triggered by drug responses as seen in cases of drug-induced hypersensitivity disorder (DIHS) and drug reaction with eosinophilia and systemic symptoms (DRESS). In DIHS and DRESS, a severe cutaneous reaction erupts in response to prolonged exposure to a drug, typically an anticonvulsant or sulfonamide.[19] Myocarditis has been noted in the sequelae of adult DIHS/DRESS cases with active HHV-6 infection.[20] In seven patients whom amoxicillin-induced flare with DRESS demonstrated a direct effect of amoxicillin on HHV-6 replication *in vitro*.[21] DIHS/DRESS should be considered as a potential cause for HHV-6-associated myocarditis in pediatric patients, particularly those with prolonged exposure to a common culprit drug for the disease.

There remains significant controversy and a lack of standardized procedure in diagnosis for HHV-6-associated myocarditis. While the diagnosis of myocarditis was not in question for many of our cases, determining the subtype and etiology posed a serious challenge. Findings from EKG, chest X-ray, and echocardiography (i.e., arrhythmia, sinus tachycardia, decreased ventricular function) contribute to the evidence for myocarditis. Still, histopathological testing remains the definitive method for diagnosis of viral myocarditis, and specifically, viral myocarditis caused by HHV-6. Only 3/11 (27%) cases featured the use of biopsy to confirm the presence of HHV-6 in cardiac tissue. Other patients in this review faced a rapidly deteriorating condition in which biopsy would pose significant risk. Quantitative PCR blood tests can indicate viral load levels and provide evidence toward active viremia in acute infections. While serological testing for IgM and IgG antibodies can be used to confirm the presence of HHV-6 infection 2–4 weeks after the onset of the myocarditis, it may take up to 2 weeks to develop detectable IgM responses. Children develop primary infections from 4 months to 30 months, and they are protected for the first few months by their maternal antibodies. However, new studies reveal that fetuses and newborns are vulnerable to HHV-6 infection from mothers with inherited ciHHV-6 who can reactivate during pregnancy and pass HHV-6 virus transplacentally.[22] Two of the cases in this review fall into this category.[23,24]

ACTIVE HUMAN HEREPESVIRUS-6 IINFECTION VERSUS CIHHV6

Sergi *et al.* describe two cases showing positive nested PCR testing of HHV-6 DNA, but negative RT-PCR testing of HHV-6 mRNA.[25] These researchers note that the HHV-6 mRNA testing was negative. However, the presence of HHV-6 DNA in plasma widely accepted as a sign of active infection, and best methods and tools for the detection of HHV-6 mRNA are still under investigation and samples collected without RNA preservative are unlikely to produce reliable results. In addition, there is evidence that HHV-6 latent infection can continue to produce inflammation in the absence of replication, with significant production of chemokines and cytokines resulting from nonlytic gene expression.[26]

Only two of the cases in our review consider ciHHV-6 in the differential diagnosis for HHV-6-associated myocarditis. ciHHV-6 status should be determined to assist with evaluation of plasma PCR DNA loads (since plasma DNA load is irrelevant in a ciHHV6 patient), but ciHHV-6 status does not help the physician determine if the HHV-6 is active.[27] In both cases of ciHHV-6 in this review, we see extremely high viral loads of 2×10^6 and 6×10^5 copies/mL, respectively. In addition, both patients presented with DCM and failed to respond to short courses (<2 weeks) of antiviral treatment. HHV-6 DNA loads of ciHHV6 patients would not be expected to demonstrate a significant response to antiviral therapy, even those with active HHV-6 infection, given the high background levels of HHV-6 DNA in these patients. In cases of unexplained LV dysfunction with high HHV-6

viral loads and absence of markers of active HHV-6 infection, ciHHV-6 should be included in the diagnostic workup.[28] According to this study, in ciHHV-6 cases, the HHV-6 may be incidental or it may be reactivated; prolonged treatment with valganciclovir resulted in significant improvement of heart failure symptoms.

POTENTIAL HUMAN HERPESVIRUS-6 SPECIFIC TREATMENT STRATEGIES

Conventional treatment of HHV-6 infection consists of the antivirals ganciclovir, cidofovir, and foscarnet. Due to the frequent acute onset of heart failure, antiviral treatment was not started in the majority of cases or was initiated the day before death. HHV-6 reactivation is more likely to occur in patients who receive prednisone or other immunosuppressant therapy.[29] As steroids can increase viral loads of HHV-6, they should be used with caution in patients with a suspected reactivation and preferably in conjunction with antiviral therapy.

Successful implantation of a LVAD was used to manage heart failure from HHV-6-associated chronic myocarditis.[12] This mechanical circulatory support can restore LV function by unloading the failing LV and allow the patient to be discharged – acting as a bridge to recovery. Implantation of an LVAD has the added benefit of obtaining the core biopsy at time of LVAD implant for histopathological and molecular study to make a specific etiological diagnosis of myocarditis.[30]

Hakacova *et al.* describe a case in which the antimalarial drug artesunate was used to treat HHV-6 viremia.[12] After a 2-week treatment with ganciclovir showed no improvement, the patient was started on a course of artesunate and showed an immediate decrease in HHV-6 viral load. Artesunate has shown antiherpes viral properties *in vitro* and *in vivo*, with good tolerability and a low rate of adverse side effects.[31,32] While ganciclovir, cidofovir, and foscarnet target viral DNA polymerase, artesunate is thought to inhibit cellular activation pathways. This lends artesunate the ability to significantly reduce viral early protein synthesis, which cannot be accomplished with drugs targeting viral DNA polymerase.[33] Considering the tolerability, limited viral resistance, anti-inflammatory action, and good safety profile when used for malaria, artesunate should be explored as a treatment for patients who demonstrate HHV-6-associated myocarditis.[34]

CONCLUSIONS

The exact role of HHV-6 as a causal factor of inflammatory cardiomyopathy is still a matter of discussion. Nevertheless, the majority of studies suggest that HHV-6 viral persistence or presence is responsible for progression of disease in myocarditis and ultimately develops DCM. Therefore, the diagnosis of HHV-6-related inflammatory cardiomyopathy should be considered when a patient presents with an unexplained heart failure, especially a child who is within the peak period for primary infections (4–24 months) or with a rash similar to exanthem subitum. These cases should be fully evaluated with histological, immunohistochemical, serological, and molecular methods. The identification of the exact etiology for inflammatory cardiomyopathy may facilitate patient-tailored management with specific antiviral therapy. Therefore, future studies are needed to gain a better understanding of the prognostic relevance of HHV-6 viral load, replicative status, and virus coinfections as well to gain more specific insight on how to evaluate diagnostic markers such as HHV-6 viral DNA and mRNA in the pathogenesis of inflammatory cardiomyopathies. In addition, the immunogenetic background of inflammatory cardiomyopathy patients that makes them susceptible to develop heart failure on the presence of HHV-6 should be more thoroughly investigated.

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Conflicts of interest

There are no conflicts of interest.

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