A Neonate with Acute Heart Failure: Chromosomally Integrated Human Herpesvirus 6–Associated Dilated Cardiomyopathy

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A 4-day-old neonate was transferred to a tertiary heart center for further evaluation and management of sudden-onset acute heart failure (HF). The birth history was significant for being born at 37 weeks' gestation to a 26-year-old mother with a probability 2 A0 blood type. There were no prenatal sonographic screenings of fetal cardiac status available. The mother had no history of smoking, diabetes, thyroid disease, autoimmune disorders, fever, or rash during pregnancy or before delivery. At birth, the patient's Apgar scores were 8 and 8 at 1 and 5 minutes, respectively, weight was 3200 g (25th percentile), length 48 cm (10th percentile), and head circumference 36 cm (80th percentile). He developed respiratory distress on day 1 of life and was treated empirically to rule out sepsis. There was no history of fever, skin rash, nasal congestion, diarrhea, or sick contact noted. His respiratory status improved by day 2 of life, and he began oral feeding and otherwise progressed well until day 4 of life, when he was scheduled for discharge home but was noted to have a gallop rhythm. His echocardiogram showed a structurally normal heart but markedly dilated left ventricle (LV end-diastolic diameter was 3.24 cm (Z-score 6.7) with moderate mitral regurgitation and severely decreased systolic function, shortening fraction (SF) 11% (mean normal SF value is 36% with 95% predicted limits of 28% to 44%; **Figure 1**).

When the patient arrived in cardiac intensive care unit, no dysmorphic features were noted on examination, his heart rate was 174 beats/min, he had delayed capillary refill (>5 seconds), diminished oxygenation (by near infrared spectroscopy), and had hypotension (systolic blood pressure in the range of 40-50 mm Hg). His S1 and S2 were normal, but a grade 1/6 systolic murmur at the left sternal border and gallop rhythm were noted. His lungs were clear to auscultation, but mild subcostal retractions were noted. The liver was palpable 3 cm below the right subcostal margin. The findings of his neurologic examination were normal, with normal muscle tone noted. He required resuscitation with inotropic support to achieve hemodynamic stability. Subsequently, a milrinone infusion was started for additional inotropic support. His respiratory status also deteriorated, and he required intubation and continuous positive airway pressure.

The initial chest radiograph revealed cardiomegaly (cardiothoracic ratio was 65%) with mild pulmonary venous congestion. His 12-lead electrocardiogram showed sinus tachycardia, right atrial enlargement, borderline prolonged QT interval, and low voltages in all limb leads (**Figure 2**). An echocardiogram was repeated in the cardiac intensive care unit showing no improvement in LV function with inotropic support. His initial N-terminal pro-B-type natriuretic peptide level was 85 000 pg/mL and ranged between 20 000 and 175 000 pg/mL during his course of treatment (N-terminal pro-B-type natriuretic peptide level >350 pg/mL is consistent with cardiac disease).

Work-up began for his acute-onset HF started with a careful review of family history and laboratory tests to identify the cause as described in the **Table** and **Figure 3** (available at www.jpeds.com). His laboratory tests came back normal for acylcarinitine, thyroid profile, alpha 1, 4-glucosidase activity, urine amino acid and organic acid profile, and serological screening for toxoplasma and HIV. Findings of whole-blood polymerase chain reaction (PCR) to exclude possible viral etiology of myocarditis including parvo B19, coxsackie virus, adenovirus, and cytomegalovirus were all negative. The only test that came back positive was human herpesvirus 6 (HHV-6) by PCR, with a viral load over 2 million copies per milliliter of whole blood, and therefore he was started on intravenous ganciclovir for HHV-6 infection.

His HHV-6 immunoglobulin M result was negative, but his immunoglobulin G for HHV-6 was positive; therefore, his HHV-6 viral DNA PCR was repeated 3 days after the first result, which was again positive with values more than 2 million copies per milliliter. He had no evidence of active HHV-6 infection such as fever or rash. His inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate were within normal limits, as well as his cardiac enzymes. His viral titers by HHV-6 PCR for DNA suggested he had amplifying viral DNA only, but no evidence of active viremia. The infectious disease service was consulted, who concluded the patient had a form of latent HHV-6 infection, called chromosomal integration of HHV-6 (ciHHV-6), which is different from acute HHV-6 viremia.[1] His antiviral therapy

ciHHV-6	Chromosomal integration of HHV-6
DCM	Dilated cardiomyopathy
ddPCR	Droplet digital polymerase chain reaction
EMB	Endomyocardial biopsy
HF	Heart failure
HHV-6	Human herpesvirus 6
LV	Left ventricle/ventricular
PCR	Polymerase chain reaction
SF	Shortening fraction

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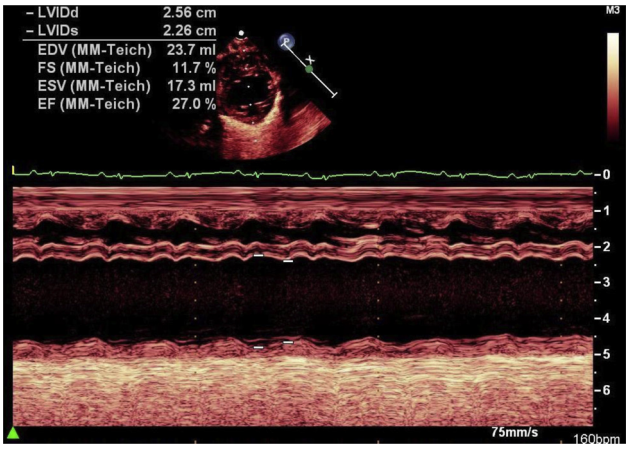

Figure 1. M-mode showing dilated LV with markedly decreased LV SF. *EDV,* end-diastolic volume; *EF,* ejection fraction; *ESV,* end systolic volume; *FS,* fractional shortening; *LVIDd,* left ventricular internal diameter in diastole; *LVIDs,* left ventricular internal systolic diameter.

ganciclovir was then discontinued. A whole blood sample was sent for quantitative PCR and droplet digital PCR (ddPCR) assay for HHV-6 to confirm his ciHHV-6 status.[2] Parents were not tested for HHV-6 as a part of his work-up.

A heart transplant evaluation concluded that the patient was not a transplant candidate because of a high risk for poor outcome such as acute rejection after transplant due to ciHHV-6. The patient further deteriorated with metabolic acidosis and abdominal distension on his 14th day of hospitalization as the result of intestinal ischemia and sepsis and subsequently died on his 16th day of hospitalization.

An autopsy was completed that revealed a thickened endocardium composed of bland fibroblasts in a myxoid background in both ventricles. Elastic stain demonstrated a deposition of parallel elastic fibers in the thickened endocardium. Trichrome stain highlighted collagen that was also deposited in the thickened endocardium. The endocardial changes were shown to be more prominent in the LV than the right ventricle. The interstitium of the myocardium was edematous, no inflammatory infiltrate was seen, and there was no evidence of myocyte necrosis. A viral culture from the cardiac tissue autopsy specimen resulted as negative, which is expected in cases with ciHHV-6 infection.[1]

The patient's blood test for ciHHV-6 was confirmed by HHV-6 chromosomal integration study,[2] the result was only available after the patient died. His final diagnosis was neonatal dilated cardiomyopathy (DCM) with endocardial fibroelastosis associated with ciHHV-6.

Differential Diagnosis of Neonatal DCM and Management

This case provides an opportunity to review the differential diagnosis of neonatal DCM and a step wise approach to management (Table and Figure 3). Neonatal DCM refers to a diverse group of myocardial disorders in which the myocardium is affected predominantly without structural abnormalities or evidence of infection such as myocarditis. The exact incidence of DCM in the newborn is unknown; however, the incidence of neonatal cardiomyopathy is

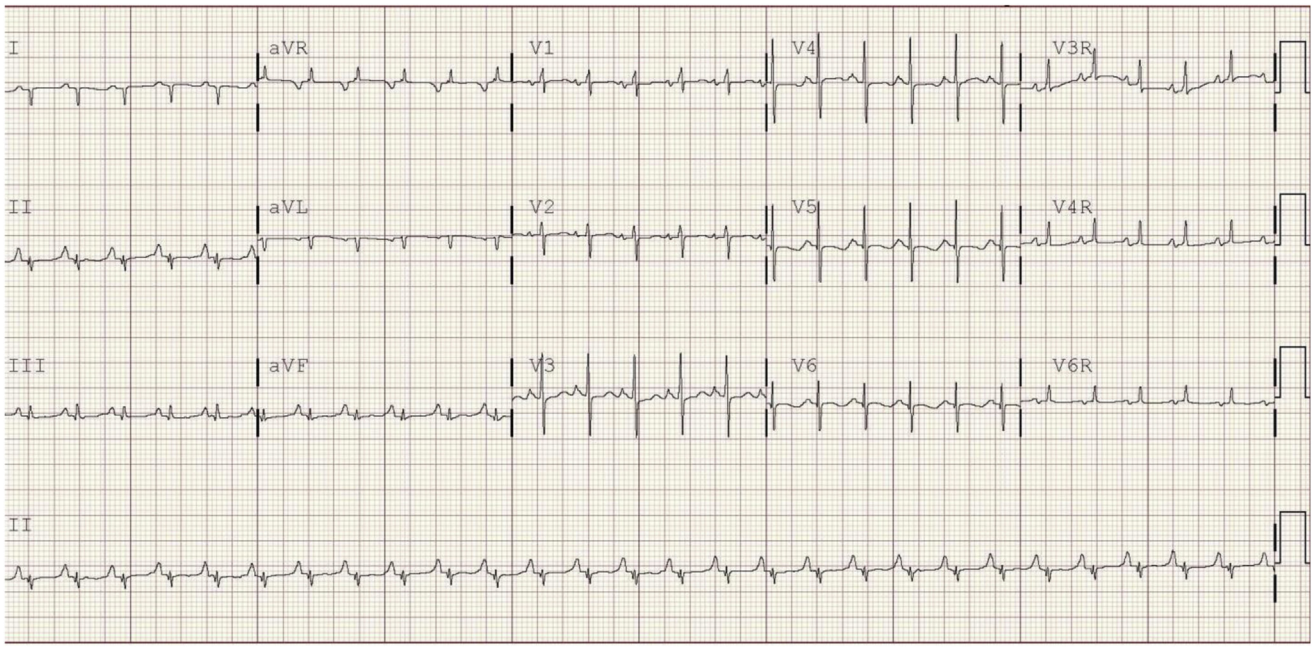

Figure 2. A 12-lead electrocardiogram shows sinus tachycardia, right atrial enlargement, borderline prolonged QT interval, and low voltages in all limb leads.