Hypertrophic Cardiomyopathy as a Clinical Component of Congenital Cytomegalovirus Infection

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ABSTRACT

We report hypertrophic cardiomyopathy in a newborn with congenital cytomegalovirus infection. The neonate had distinct signs of congenital cytomegalovirus infection including petechiae, jaundice, intracranial calcifications, cerebral ventriculomegaly and chorioretinitis together with hypertrophic cardiomyopathy. Following determination of anti-cytomegalovirus IgM, viral DNA was also isolated from the plasma of the patient by polymerase chain reaction. Although cytomegalovirus is a relatively frequent cause of myocarditis in childhood, it was rarely reported to be associated with cardiac abnormalities such as structural heart disease, atrioventricular block, or dilated cardiomyopathy. To our knowledge, this is the first case with congenital cytomegalovirus infection and hypertrophic cardiomyopathy.

Keywords: Congenital, cytomegalovirus, hypertrophic cardiomyopathy

La miocardiopatía hipertrófica como componente clínico de la infección congénita por citomegalovirus

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RESUMEN

Reportamos una cardiomiopatía hipertrófica en un recién nacido con infección congénita por citomegalovirus. El neonato exhibía claros signos de infección congénita por citomegalovirus incluyendo petequias, ictericia, calcificaciones intracraneales, ventriculomegalia cerebral, y coriorretinitis con cardiomiopatía hipertrófica. Tras la determinación de IgM anti-citomegalovirus, también se aisló el ADN viral del plasma del paciente mediante reacción en cadena de la polimerasa. Aunque el citomegalovirus es una causa relativamente frecuente de miocarditis en la infancia, raras veces se le ha reportado en asociación con anormalidades cardiacas, tales como la enfermedad cardíaca estructural, el bloqueo auriculoventricular, o la miocardiopatía dilatada. Hasta donde sabemos, éste es el primer caso con infección congénita por citomegalovirus y cardiomiopatía hipertrófica.

Palabras claves: Congénita, citomegalovirus, miocardiopatía hipertrófica

INTRODUCTION

Human cytomegalovirus (CMV) is the most common cause of congenital infections, accounting for 0.2 to 2.2% of all live births (1). Approximately a third of the pregnant women with primary infection and 1.4% of the women with recurrent infection transmit CMV to their fetuses (2). Only 10% of the infected fetuses become symptomatic and usual present with anaemia, thrombocytopenia, petechiae/purpura, hepatosplenomegaly, jaundice, growth retardation, microcephaly, cerebral calcifications and/or ventriculomegaly, and chorioretinitis in the antenatal or early postnatal period (2, 3). Nevertheless, hypertrophic cardiomyopathy (HCM) associated with CMV infection has not been reported so far. In this article, we present the first patient with congenital CMV infection and HCM, to the authors' knowledge.

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CASE REPORT

A female newborn was born after 36 weeks of gestation by emergency Caesarean section due to fetal distress. The neonate was stabilized quickly, but one hour after the delivery, she was noted to have poor sucking and petechial lesions on her abdomen. She was born of a 23-year old woman and was her first pregnancy. Her mother had no prenatal problem identified including viral illnesses. None of the family members had known myocardial disease, arrhythmia, syncope and history of sudden death. On physical examination, the newborn had hypotonia, petechial skin lesions and hepatomegaly. The liver was palpable 4 cm below the right costal margin at the mid-clavicular line. She had a body weight of 2800 (50–75th percentile), a head circumference of 36 cm (75–90th percentile), and a height of 50 cm (75–90th percentile). She had thrombocytopenia (90 x 10^9/L [normal ranges: 84 – 478 x 10^9/L]) and increased liver enzymes (alanine aminotransferase: 278 IU/L [normal ranges: 6–50 IU/L], aspartate aminotransferase: 913 IU/L [normal ranges: 35–140 IU/L]). After obtaining blood and urine cultures, ampicillin (50 mg/kg/dose every 12 hours) and gentamicin (2.5 mg/kg/dose every 12 hours) were initiated intravenously. As she developed significant and rapidly progressive jaundice (total serum bilirubin: 19.3 mg/dL [normal < 2 mg/dL] and conjugated bilirubin: 11.8 mg/dL [normal < 0.3 mg/dL]) within hours, exchange transfusion was performed. Cranial ultrasonography revealed marked dilatation of the lateral ventricles. Parenteral ganciclovir therapy (6 mg/kg/dose every 12 hours) was started on the second day following determination of anti-CMV IgM antibodies in the serum obtained just before transfusion. The cranial computed tomography confirmed the lateral ventricular dilatations and showed periventricular calcifications. Ophthalmological examination revealed bilateral chorioretinitis, characterized by areas of active inflammation and mild necrosis just around the optic discs. A systolic murmur heard over the cardiac apex on day four led us to a cardiac assessment. Electrocardiogram was normal. Echocardiographic examination revealed global thickening of the left ventricular walls together with a moderate sized patent ductus arteriosus [PDA] (2 mm) and mild mitral insufficiency. Left atrium-to-aortic root ratio was measured as 1.5/1 [normal < 1.4/1]. The thickening of the septal wall was more pronounced. The interventricular septum and the left ventricular posterior wall diastolic thicknesses were measured as 14 and 11 mm, respectively [both normal values < 5.5 mm] (Figure).

However, left ventricular outflow tract obstruction or systolic anterior motion of the mitral valve was not detected. Systolic and diastolic functions were found as normal (fractional shortening was 41%, mitral valve E-to-A ratio was 1.9). Oral ibuprofen therapy (10 mg/kg/dose every 24 hours) was started for closure of PDA.

The diagnosis of congenital CMV infection was established definitively after detection of CMV DNA by polymerase chain reaction (PCR). Ampicillin and gentamicin were stopped after negative culture results. Patent ductus arteriosus
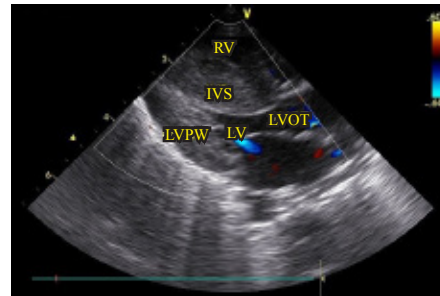

Figure: Parasternal long axis view demonstrating hypertrophic cardiomyopathy. IVS: interventricular septum, LV: left ventricle, LVOT: left ventricular outflow tract, LVPW: left ventricular posterior wall, RV: right ventricle.

closed following three days of ibuprofen therapy. Her hypotonia, poor sucking and petechial lesions disappeared and activity returned to normal at the end of the first week. Hyperbilirubinaemia and liver enzymes improved to near normal values (total bilirubin: 3.3 mg/dL, conjugated bilirubin: 0.9 mg/dL, alanine aminotransferase: 54 IU/L, aspartate aminotransferase: 62 IU/L). Ganciclovir therapy was terminated two weeks later following disappearence of CMV DNA and she was discharged from the hospital. A ventriculo-peritoneal shunt was performed for hydrocephalus at the fourth postnatal month. Left ventricular septal thickness was 12.9 mm and posterior wall thickness was 8.8 mm one year after discharge. At the end of a follow-up of 25 months, left ventricular septal and posterior wall thicknesses were measured to be 11.8 and 7 mm, respectively [both normal values were < 7 mm for her current weight (13 kilograms)]. Her cardiovascular examination was normal and no other echocardiographic abnormality was determined. Her motor skills were delayed by a few months (not documented with any test).

DISCUSSION

Congenital CMV infection is generally asymptomatic and it is characterized by multi-organ involvement in 10% of the infected neonates. The brain, liver, spleen, pancreas, heart, lungs, kidneys and eyes are the most commonly affected organs (3). Thrombocytopenia and petechiae are frequent findings. Liver involvement is characterized by hepatomegaly, conjugated hyperbilirubinaemia and elevated liver transaminase levels. Central nervous system involvement is the predominant cause of adverse outcome such as mental retardation and hearing loss (2, 3).

Besides being a potential cause of myocarditis in the paediatric population, CMV is also associated with certain forms of cardiac involvement through its congenital infection. Cytomegalovirus nucleic acids were determined in myocytes of the majority of the cases with fatal myocarditis (4). The histologic features of myocarditis associated with CMV or other infectious agents consist of inflammatory infiltrates and necrosis of myocytes (5). Chronic viral myocardial infections including CMV were accused of causing dilated cardiomyopathy through partially unknown mechanisms. Cell-mediated autoimmune response to viruses or persisting viral particles

such as RNA and production of some autoantibodies, cross-reacting with viral proteins and cardiac myosin, may have roles in the pathogenesis of cardiomyopathy (6, 7). Some structural heart diseases associated with congenital CMV infection were also reported. Patent ductus arteriosus, atrial septal defect, ventricular septal defect (VSD), Fallot's tetralogy, complex cyanotic heart diseases, ventricular aneurysm and atrioventricular block were the major abnormalities denoted to be related with such infection (2, 8). The frequencies of ventricular septal defect and Fallot's tetralogy were found higher in the CMV-infected population than the general population, though the pathogenetic mechanisms were not determined (2).

Cytomegalovirus is a relatively common cause of myocarditis. Left ventricular hypertrophy was observed, albeit not frequently, in the course of various forms of myocarditis. Although such cases were accompanied by systolic dysfunction and generally reversible, the persistence of cardiac hypertrophy was encountered in a few patients (9). The incidence of symptomatic congenital CMV infection was found as 1% in a study from our country (10). Acquired and usually reversible causes of ventricular hypertrophy such as gestational diabetes and corticosteroid use were not present in our CMV-infected patient. The incidence of infantile HCM was reported as 30/1 000 000 cases (11). The cases with HCM often have several gene mutations, while sporadic, nonfamilial cases are occasionally determined and the cause of those remains unknown. There was no respiratory distress, persistent hypotonia, history of familial HCM or parental consanguinity and the blood creatine kinase level was normal. Therefore, Pompe disease was excluded. However, a further investigation including myocardial biopsy or mutation analysis was not performed. Although it cannot be proven that the ventricular hypertrophy in our case is not a coincidental finding, we think that HCM might have resulted from CMV-associated microRNA regulation or myocardin stimulation, as well as it might be a sequelae of CMV myocarditis through unknown pathogenetic mechanisms.

As congenital CMV infection may be associated with cardiomyopathy and congenital heart disease in some instances, fetal or transthoracic echocardiography may be of value, if available, in the cases with suspicion of such infection. To the best of our knowledge, the case presented here is the first CMV-infected patient diagnosed with HCM in the literature.

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