

Hypertrophic Cardiomyopathy in Infancy

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ABSTRACT

Hypertrophic cardiomyopathy is a rare disorder in infancy. Signs of myocardial ischemia and cardiomegaly are the predominate manifestations of this lesion. The spectrum of the etiology and management of hypertrophic cardiomyopathy in infancy have been updated in the past several decades. Long-term small-dose digoxin combined with prednisone, supplemented by the angiotensin-converting enzyme inhibitor captopril is an accepted therapy for endocardial fibroelastosis in infancy. Treatment with recombinant human α -glucosidase enzyme replacement therapy can reverse the electrocardiographic changes of infantile Pompe's disease. Hypertrophic cardiomyopathy in infants of diabetic mothers is usually benign and transient, and treatment is not needed unless heart failure occurs. Differential diagnosis of hypertrophic cardiomyopathy from congenital heart defects is important for subsequent management.

Keywords: Diagnosis, hypertrophic cardiomyopathy, infant

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INTRODUCTION

Hypertrophic cardiomyopathy in infancy has been a topic of concern. The cardiac chambers, usually the left ventricle, response to some acyanotic and cyanotic congenital heart defects, including aortic stenosis, tricuspid atresia, single left ventricle and pulmonary atresia with intact septum, *etc.*, consists of wall thickening and enlargement of cavity size (1). Under these circumstances, pressure overload causes left ventricular remodeling and ultimately hypertrophy. Moreover, increased left ventricular mass subjected to remodeling in the context of volume or pressure overload in pediatric hypertension may lead to eccentric or concentric left ventricular hypertrophy (2). However, these conditions are of primary myocardial origins, thereby being excluded from the conceptual extension of “left ventricular hypertrophy syndrome”. According to Blumenthal and Sapin (3), the diagnosis of left ventricular hypertrophy syndrome in infancy should meet the requirements of three essential and two nonessential conditions (Table 1). They also divided the lesions into three: endocardial, myocardial and coronary disorders (Table 2). However, the concept of “left ventricular hypertrophy syndrome” has been outdated, and the spectrum of etiology and management of hypertrophic cardiomyopathy in infancy were updated in the past several decades. This article aims to describe the representative disorders of hypertrophic cardiomyopathy.

Endocardial fibroelastosis (EFE)

EFE is an uncommon disease that presents as unexplained heart failure in infants and children. Lurie (4) proposed that EFE is not a disease but a reaction of the endocardium. It is characterized by diffuse thickening of the endocardium resulting from proliferation of

collagen and elastic fibers. Gross examination of the explanted heart showed globular enlargement and an extensive endocardial fibrosis of the left ventricle with involvement of the aortic and mitral valves, the papillary muscles and chordae tendineae (5). It was divided into two kinds: primary (lack of associated cardiac malformations) and secondary (secondary to hemodynamic changes caused by associated cardiac malformations) (3). The etiologies of EFE remain uncertain. However, it was considered to be the result of developmental defects, inflammatory process, endocardial anorexia, or myocardial metabolic enzyme deficiency. As a result, deprivation of myocardial nourishment and myocardial capillary stasis develop, leading to subsequent myocardial ischemia and even heart failure (3). Newbould et al (6) hypothesized that EFE is an endocardial response to chronic prenatal myocardial stress. Most authors thought it is caused by myocardial inflammation secondary to viral infections during fetal or postnatal period. In addition, it might be related to endocardial hypoplasia due to *in utero* hypoxia, genetic factors, or autoimmunity.

It can be divided into expansion and contracted types according to the left ventricular size. The expansion type accounts for about 95%, characterized by enlargement of the left ventricle and thickening of the endocardium, mitral and aortic leaflet thickening and annulus dilation. Right ventricular endocardial thickening might be seen in a few of the infants. The contracted type accounts for about 5%, mainly found in neonates in whom the left ventricular chamber is reduced or normal with diffuse thickening of the endocardium. Left atrial and right ventricular enlargements are present in most of the cases and the pathological changes are similar to those of restrictive cardiomyopathy and the patients may present with left ventricular obstruction (7).

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It is more commonly seen in neonates or infants, especially infants younger than 6 months, with congestive heart failure being the predominant clinical manifestation (8). On electrocardiogram, nonspecific myocardial ischemia (T wave flattening or inversion, or ST depression) are often seen, whereas deep Q wave with marked ST segment deviation are unusual (3). The P-R interval was prolonged in less than one-third of the cases. Predominant signs of left and right ventricular hypertrophy were recorded in 70.0% and 13.0% of the cases, respectively (9). On magnetic resonance imaging, EFE manifested at the endocardial surface as a rim of hypointense signal in the perfusion sequences and as a rim of hyperintense signal in the myocardial delayed-enhancement sequence (10). On echocardiogram, enhancement and thickening of the endocardium, left ventricular wall thickening and cardiac chamber (particularly left ventricle) dilation could be visible (8). The systolic and global cardiac functions can be normal but the diastolic function can be abnormal (11). Levin (12) reported, in an autopsy case in an 8-month-old infant, significant increase of myocardial fibers and diffuse inflammation infiltration of interstitial fibers with lymphocytes and plasmocytes. Circular virus particles or analogs of the virus particles were observed in the nucleus under electron microscope. Nishikawa et al (13) noted immunoreactive myocytes in the ventricles of 10 hearts with EFE, where the distribution of atrial natriuretic polypeptide-positive cells was most frequent in the inner one-third of the left ventricle.

The natural course of EFE in infancy does not seem to be promising, and persistent heart failure is responsible for the 30% mortality of the patients (14). At present, there is no special treatment for EFE. However, there is an agreement on long-term small-dose digoxin combined with prednisone, supplemented by the angiotensin-converting enzyme inhibitor

captopril. An alternative is digoxin plus two immunosuppressive agents, *i.e.*, use of prednisone for 3-4 weeks and then the dose is reduced, and then cyclophosphamide monohydrate at a dose of 200 mg/m² *i.v.*, or 2 mg/kg/day *p.o.*

Infants of diabetic mothers

Hypertrophic cardiomyopathy has been recognized in 40% of infants of diabetic mothers, attributed to a compensatory increase in fetal insulin secretion (15). When it occurs it is usually benign and transient (16), but patients may develop heart failure (17). Because the fetal heart is particularly rich in insulin receptors, the increased synthesis of cardiac muscle protein, glycogen and fat, leading to neonatal hypertrophic cardiomyopathy (18). The electrocardiogram usually shows advanced left ventricular hypertrophy and abnormal Q waves in many leads as a result of septal hypertrophy (19). The newborns of the diabetic mothers with septal hypertrophy showed much longer QT and QTc dispersion intervals than control (20).

Echocardiography is the main basis for the diagnosis of the disease. On echocardiography, left and right ventricular systolic function can be normal, however, the diastolic function of the right ventricle was impaired in fetuses of diabetic mothers (Table 3) (21). Veille et al. (22) observed the fetuses of diabetic mothers by M-mode echocardiogram between 20-41 weeks of gestation and found the mean septal size increased during both diastole and systole. Ventricular septal hypertrophy was present in 75% of the cases. Gutgesell et al. (23) noted echocardiographic signs of marked septal hypertrophy with left ventricular outflow obstruction in 20.8% (5/24) and signs of hypertrophy of the right

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ventricular free wall in 20.8% (5/24) of infants of diabetic mothers.

Microscopic examination revealed hypertrophic fibers and scattered cellular disarray in the septum (23). Further studies revealed that ventricular and septal thickening may correlate with insulin, growth hormone, insulin like growth factor and leptin levels (24), and with endogenous catecholamine, nerve growth factor and maternal blood glucose control during pregnancy. Clinically, there is always a heart enlargement and myocardial enzyme elevations. The incidence of cardiac damage in infants of diabetic mothers were 71.9%, and serum creatine kinase (CK), MB isoenzyme of CK, aspartate aminotransferase and lactate dehydrogenase increased significantly within 24 hours postnatally. Genetic analysis showed all eight cases under investigation had K_{ATP} channel mutations (15). In most cases, the prognosis is good and the myocardial enzymes remarkably decreased after 7-10-day treatment (25). Most symptomatic infants require only supportive care with supplemental oxygen therapy, but β -blockers may be necessary for ventricular output improvement (26).

Pompe's disease

Pompe's disease, also called glycogen storage disease type II or acid maltase deficiency, is a rare autosomal recessive disease caused by an enzymatic deficiency of α -glucosidase, resulting in a massive lysosomal glycogen accumulation in cardiac and skeletal muscles (27). Pompe's disease is classified as a neuromuscular disease, a metabolic myopathy, and a glycogen storage disease. This deficiency causes an accumulation of intralysosomal glycogen in different organs. The classic form appears in the newborn with a very severe hypotonia and cardiomyopathy, which lead to death before age two. Less frequently, the disease appears only in childhood or in adult life, the so called

late-onset Pompe's disease (28). The infantile form is also considered a cardiac disorder because of the prominent cardiac involvement.

Some degree of respiratory dysfunction and obvious diaphragmatic weakness can be found in more than half of the patients (29). A progressive cardiac hypertrophy is characteristic for infantile Pompe's disease (30). Glycogen deposition in muscle has been noted by ultrastructural observations (31). Muscle biopsy is commonly used as an early diagnostic tool in the evaluation of muscle disease. However, a periodic acid-Schiff-positive vacuolar myopathy often leads to false-negative results and subsequent delays in the treatment of the disorder (32). Ding et al. (33) reported six patients with Pompe's disease had an enlarged heart, three of them had an enlarged heart shadow on chest X-ray examination and four patients had an echocardiographic myocardial hypertrophy. The electrocardiogram in three patients showed short P-R intervals and high voltage. The CK levels were three to seven times elevated. Assay of α -glucosidase enzyme activity in whole blood showed significantly reduced activity in the patients and gene sequencing in four patients showed eight pathogenic mutations. The magnetic resonance imaging findings of the heart in a 5-month-old infant with this disease revealed hypertrophy of the right and left ventricles and the interventricular septum with an irregular inhomogeneous appearance of the myocardium (34).

Detection of α -glucosidase enzyme level in blood plays an important role in correct diagnosis of the disease. Genetic mutation analysis can help detect the carriers. Enzyme replacement therapy for Pompe's disease is to provide the missing enzyme for the metabolic defect via intravenous infusions of recombinant human infantile Pompe's disease is a lethal

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cardiac and muscular disorder (30). Current developments toward enzyme replacement therapy are promising. Myozyme has been approved by the Food and Drug Administration and is used to treat Pompe's disease, but it is very expensive and needs to be taken for the patient's entire life. The first response to treatment can be shown in vascular endothelium and in peripheral nerves after 12 weeks of treatment at an enzyme dose of 15-20 mg/kg. The dose can be increased to 40 mg/kg, after 72 weeks of treatment, and a reduction of glycogen storage and substantial improvement of muscle architecture can be noted in some patients (35). After the treatment with recombinant human α -glucosidase enzyme replacement therapy, the characterized electrocardiographic findings of a shortened P-R interval, an increased QT dispersion (QTd), and large left ventricular voltages for infantile Pompe's disease could be alleviated (36), and heart size decrease can be observed after a 3-month treatment (37). Infants diagnosed with Pompe disease usually died within the first year of life, but recent development of recombinant α -glucosidase has dramatically improved the life expectancy and quality of life of infant (38). In addition, trials with human α -glucosidase at high levels in the milk of transgenic rabbits have been successful (39).

CONCLUSION

Infants with left ventricular hypertrophy syndrome were often healthy, without signs of cyanosis or heart murmur. Only can they present with recent fatigue or dyspnea as their onset symptoms, and gradual progression into heart failure. Electrocardiographic or radiographic signs of left ventricular hypertrophy might be noted. Differential diagnosis from congenital

heart defects is important for subsequent management.

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Table 1: Diagnostic criteria of left ventricular hypertrophy syndrome in infancy

Diagnostic criteria
Essential conditions
Heart chamber enlargement predominantly of the left ventricle
Absence of heart murmur
Absence of central cyanosis
Nonessential conditions
Electrocardiographic findings of myocardial damage or left ventricular hypertrophy
Manifestations of heart failure

Table 2: Classifications of left ventricular hypertrophy syndrome in infancy

Classifications
Endocardial
Endocardial fibroelastosis
Myocardial
Idiopathic myocarditis
Pompe's disease
Primary cardiac tumors
Nutritional deficiencies
Coronary
Anomalous origin of the left coronary artery
Coronary occlusive disease

Table 3: Echocardiographic evaluation of heart function in infants of diabetic mothers

Parameter	IDM	Control	<i>p</i> value
Ejection fraction (%)	65 ± 13	69 ± 7	NS
Peak velocity across the aortic valve (m/s)	0.96 ± 0.21	1.1 ± 0.12	NS
Peak velocity across the pulmonary valve (m/s)	0.92 ± 0.18	0.93 ± 0.14	NS
E/A ratio of the mitral valve	1.27 ± 0.21	1.51 ± 0.32	NS
E/A ratio of the tricuspid valve	0.91 ± 0.31	1.47 ± 0.38	<0.01

IDM: infants of diabetic mothers; NS: nonsignificant