REVIEW

Hypertrophic Cardiomyopathy in Infancy

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ABSTRACT

Objective: *To report comprehensively the clinical features and the management strategies of hypertrophic cardiomyopathy in infancy.*

Methods: *Comprehensively retrieved studies published from 2000 to present constituted the study materials for this article.*

Results: *Signs of myocardial ischaemia and cardiomegaly are the predominate manifestations of this lesion. The spectrum of the aetiology 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. The treatment with recombinant human α-glucosidase enzyme replacement therapy can reverse the electrocardiographic changes of infantile Pompe's disease.*

Conclusion: *Hypertrophic cardiomyopathy in infants of diabetic mothers is usually benign and transient, and the 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

INTRODUCTION

Hypertrophic cardiomyopathy in infancy has been a topic of concern. The cardiac chambers, usually the left ventricle, in response to some acyanotic and cyanotic congenital heart defects, including aortic stenosis, tricuspid atresia, single left ventricle and pulmonary atresia with intact septum, *etc* consist of wall thickening and enlargement of cavity size (1). Under these circumstances, the pressure overload causes left ventricular remodelling and ultimately hypertrophy. Moreover, an increased left ventricular mass subjected to remodelling in the context of volume or pressure overload in paediatric 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 non-essential 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 aetiology and management of hypertrophic cardiomyopathy in infancy was

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

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DOI: 10.7727/wimj.2016.461

Table 2: Classifications of left ventricular hypertrophy syndrome in infancy

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

updated in the past several decades. This article aims to describe the representative disorders of hypertrophic cardiomyopathy.

Endocardial fibroelastosis (EFE)

Endocardial fibroelastosis 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 fibres. 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 haemodynamic changes caused by associated cardiac malformations) (3). The aetiologies 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 ischaemia and even heart failure (3). Newbould *et al* (6) hypothesized that EFE is an endocardial response to chronic prenatal myocardial stress. Most authors thought that it is caused by the myocardial inflammation, secondary to viral infections during foetal 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 the 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 like those of restrictive cardiomyopathy and the patients may present with left ventricular obstruction (7).

It is more commonly seen in neonates or infants, especially the infants younger than six months, with congestive heart failure being the predominant clinical manifestation (8). On an electrocardiogram, non-specific myocardial ischaemia (T-wave flattening or inversion, or ST depression). The ST segment is the period from the end of the QRS complex (J) to the beginning of the T wave and it mainly represents the short period from the end of ventricular depolarization to the beginning of ventricular repolarization are often seen, whereas deep Q wave with marked ST segment deviation are unusual (3). The P-R interval that is between the start of the P wave and the start of the QRS wave in the electrocardiogram, which lasts for 0.12–0.20 s, 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 the 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 an 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; however, the diastolic function can be abnormal (11). Levin (12) reported, in an autopsy case in an 8-month-old infant, a significant increase of myocardial fibres and diffuse inflammation infiltration of interstitial fibres with lymphocytes and plasmocytes. Circular virus particles or analogues of the virus particles were observed in the nucleus under the 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 and two immunosuppressive agents, that is, use of prednisone for 3–4 weeks and then the dose is reduced, and then cyclophosphamide monohydrate at a dose of 200 mg/m^2 *intravenously* or 2 mg/kg/day *orally*.

Infants of diabetic mothers

Hypertrophic cardiomyopathy has been recognized in 40% of infants of the diabetic mothers, attributed to a compensatory increase in foetal insulin secretion (15). When it occurs, it is usually benign and transient (16), but the patients may develop heart failure (17). Because the foetal 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 (the QT interval is the time from the start of the QRS complex to the end of the T wave in the electrocardiogram) and QTc (the corrected QT interval) dispersion intervals than the control (20).

Echocardiography is the main basis for the diagnosis of the disease. On the echocardiography, left and right ventricular systolic function can be normal; however, the diastolic function of the right ventricle was impaired in foetuses of diabetic mothers (Table 3) (21). Veille *et al* (22) observed the foetuses of diabetic mothers by M-mode echocardiogram between 20 and 41 weeks of gestation and found the mean septal size increased during both the 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 ventricular-free wall in 20.8% (5/24) of infants of the diabetic mothers.

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

Parameter	IDM	Control	*p*-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 the diabetic mothers; NS = non-significant

A microscopic examination revealed hypertrophic fibres and scattered cellular disarray in the septum (23). Further studies revealed that ventricular and septal thickenings correlated 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 the diabetic mothers were 71.9%, and serum creatine kinase (CK), the MB isoenzyme of CK, aspartate aminotransferase and lactate dehydrogenase increased significantly within 24 hours postnatally. Genetic analysis showed all the 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- to 10-day treatment (25). Most symptomatic infants require only supportive care with supplemental oxygen therapy, and 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 that 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. An assay of α-glucosidase enzyme activity in whole blood showed significantly reduced activity in the patients and gene sequencing in four patients who 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).

The 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, which is a lethal cardiac and muscular disorder (30). Current developments towards enzyme replacement therapy are promising. Myozyme has been approved by the Food and Drug Administration and is used to treat Pompe's disease; however, 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 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). The infants diagnosed with Pompe's 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

The infants with left ventricular hypertrophy syndrome were often healthy, without signs of cyanosis or heart murmur. Only they can present with recent fatigue or dyspnoea 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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