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# Infantile Hypertrophic Cardiomyopathies: Starting from the Pathogenesis

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Research Article

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## Abstract

Hypertrophic cardiomyopathy (HCM) rarely affects infants. The spectrum of infantile HCMs has been updated in the past decades. This article aims to present an review of the representative infantile HCMs in addition to a renewed classification at a pathogenesis level. The typical signs of myocardial ischemia and cardiomegaly are the predominate manifestations of this lesion. The early diagnosis of infantile HCMs rely on the pertinent signs on medical imaging and even genetic analysis. 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. HCM in infants of diabetic mothers usually follows a benign and transient course, and treatment is not needed unless heart failure occurs. Enzyme replacement therapy with recombinant human α-glucosidase is effective for the infantile Pompe disease. Supportive treatments are necessary for symptomatic cases especially for those with congestive heart failure. Infants with HCM due to mitochondrial disorders or RASopathies often have dismal prognoses, response poorly to treatments and early deaths. The prognosis of Friedreich ataxia was also poor and patients often die of cardiac causes, especially in those with the presence of HCM. The prognoses of infantile HCMs vary depending on etiologies: infants of diabetic mothers > Pompe disease > endocardial fibroelastosis > Friedreich ataxia > RASopathies > mitochondrial disorders in a decreasing hierarchy.

**Keywords:** diagnosis; hypertrophic cardiomyopathy; infant.

## Introduction

Infantile hypertrophic cardiomyopathy (HCM) has been a topic of concern, as it differs considerably from that of adults in terms of pathogenesis and prognosis. Hitherto, infantile HCMs is lack of a systematic classification at a pathogenesis level. In 1959, Blumenthal and Sapin [1] proposed the concept of left ventricular hypertrophy syndrome in order to interpret infantile HCM. They divided the lesions into three types: endocardial (endocardial fibroelastosis (EFE)), myocardial (idiopathic myocarditis, Pompe disease, primary cardiac tumors and nutritional deficiencies) and coronary disorders (anomalous origin of the left coronary artery and coronary occlusive disease). However, the spectrum of infantile HCMs updated with time. Colan et al. [2] classified pathogeneses of HCMs into four types based on the information of their 855 pediatric patients: idiopathic, inborn errors of metabolism, malformation syndromes and neuromuscular disorders. Patients with no specific etiology were defined as idiopathic HCM [2]. Pompe disease accounted for 33.8% of inborn errors of metabolism, Noonan syndrome accounted for 77.9% of the cases with malformation syndromes and Friedreich ataxia accounted for 87.5% of neuromuscular disorders [2]. Denfield and Towbin [3] divided causes of HCM into 3 types: familial, metabolic (Pompe disease) and syndrome-associated (Noonan syndrome, LEOPARD syndrome, Friedreich ataxia and mitochondrial myopathy, etc.). The pathogenesis classifications were nevertheless incomplete, and they were unable to represent the entire spectrum of HCMs. For instance, left ventricular noncompaction cardiomyopathy (LVNC) did not fall into these classifications.

EFE may be associated with viral infection, heredity, immunity and genetic metabolism, etc. Some authors believe that there might be of no specific cause, but rather a joint action of a variety of different causes [4]. The specific pathogenesis of LVNC is not very clear. The genesis has been recognized as arrest of myocardial morphogenesis during the embryonic period [5]. LVNC has variable phenotypic presentations and can be difficult to diagnose. It has been associated with multiple phenotypes of cardiomyopathy, structural heart defects and also has a possible arrhythmogenic

component associated with LVNC as well. Its prognosis depends on the severity of associated dysarrhythmias [6]. LVNC has been found overlapping phenotypes with mitochondrial cardiomyopathies and infantile dilated cardiomyopathy in Barth syndrome (LVNC, skeletal myopathy, cyclic neutropenia, 3-methylglutaconic aciduria and deficiency of cardiolipin) [7]. The genetic causes of LVNC are heterogeneous, but the causes of the cardiomyopathy phenotype were identified to be X-linked TAZ, which encodes tafazzin, a phospholipid transacylase responsible for membrane function. Mutations of TAZ gene typically results in Barth syndrome [5]. Therefore, HCMs in both EFE and LVNC ought to be termed as of undetermined pathogenesis. In brief, infantile HCMs can be categorized into 6 types (Table 1). This article is focusing on the clinical features of the representative HCMs of different pathogeneses.

## Materials and Methods

English language literature was comprehensively retrieved in the PubMed, Google Scholar, and "Baidu" Scholar without time limitations. The keywords entered in this search to identify articles were "infantile", "infants", "neonates", "hypertrophic cardiomyopathy", "endocardial fibroelastosis (EFE)", "infants of diabetic mothers", "Pompe disease", "mitochondrial cardiomyopathy", "RASopathy", and "Friedreich ataxia". The inclusion criteria were clinical research, case series, case report or proceeding abstracts on hypertrophic cardiomyopathies of any etiologies. As a result, 75 typical articles were included.

**Table 1:** The pathogenesis classification of infantile hypertrophic cardiomyopathies

| Type | Representative disorder |
|---|---|
| Idiopathic | |
| Metabolic | Pompe disease, infants of diabetic mothers |
| Mitochondrial disorder | Sengers syndrome, Leigh disease |
| RASopathy | Noonan syndrome |
| Neuromuscular disorder | Friedreich ataxia |
| Undetermined | Endocardial fibroelastosis (EFE), left ventricular noncompaction cardiomyopathy (LVNC) |

## Results

### Endocardial Fibroelastosis (EFE)

EFE is an uncommon disease characterized by diffuse thickening of the endocardium resulting from proliferation of collagen and elastic fibers. It represents unexplained heart failure in infants and children. This lesion can be divided into two categories: primary (lack of associated cardiac malformations) and secondary (secondary to hemodynamic changes subsequent to associated cardiac malformations) [1]. The etiologies of EFE remain uncertain. In the past, it was once believed to be a reaction of the endocardium [8], or an endocardial response to chronic prenatal myocardial stress [9]. Nowadays, it is hypothesized a result of myocardial inflammation secondary to viral infections during fetal or postnatal period. It is believed that developmental defects, inflammatory process, endocardial anorexia, or myocardial metabolic enzyme deficiency play an important role in the pathogenesis of EFE. As a result, deprivation of myocardial nourishment and myocardial capillary stasis develop, leading to subsequent myocardial ischemia and even heart failure [1]. In addition, endocardial hypoplasia due to in utero hypoxia, genetic factors, or autoimmunity might be an alternative etiology [10]. Recent studies determined endothelial-to-mesenchymal transition to be an underlying mechanism of EFE formation [11]. Gross examination of the explanted heart revealed left ventricular globular enlargement with extensive endocardial fibrosis and involvements of heart valves and valvular apparatus [12].

EFE is more common in neonates and infants, especially in infants <6 month. Of them, congestive heart failure is the major clinical manifestation [13, 14]. On electrocardiogram, nonspecific myocardial ischemia changes, such as T wave flattening or inversion, or ST depression, are usual, whereas deep Q wave with marked ST segment deviation is unusual [1]. Prolonged PR interval was present in less than one-third of the cases [15]. Left and right ventricular hypertrophies were recorded in 70% and 13% of the cases, respectively [15]. Echocardiography is very helpful for the diagnosis of EFE. It is necessary to differentiate EFE from pneumonia complicated by acute congestive heart failure, viral myocarditis and anomalous origin of the left coronary artery [14]. On echocardiogram, enhancement and thickening of the endocardium, left ventricular wall thickening and cardiac chamber (particularly the left ventricle) dilation could be seen [13]. The systolic and global cardiac functions can be normal, whereas the diastolic function can be abnormal [16]. Magnetic resonance imaging may show rim hypo-intense signal at the endocardial surface in the perfusion sequences and rim hyperintense signal in the myocardial delayed-enhancement sequence [17]. Levin [18] observed, in an autopsic case of an 8-month-old infant with EFE, significant increase of myocardial fibers and diffuse inflammation infiltration of the interstitial fibers. Nishikawa et al. [19] found immune-reactive cardiomyocytes in the ventricles of 10 hearts of infants with EFE, while the distribution of atrial natriuretic polypeptide-positive cells was most common in the inner third of the ventricular wall.

The natural course of EFE in infants does not seem to be promising, and persistent heart failure is responsible for the 30% mortality of the patients [19]. At present, there is no special treatment for EFE. The treatment regimen is usually to control symptoms of congestive heart failure. Patients who respond well to digitalis with good medication compliance have a favorable prognosis [14]. An agreement has been reached on long-term small-dose digoxin combined with prednisone, supplemented by the angiotensin-converting enzyme inhibitor captopril. An alternative regimen is digoxin plus two immunosuppressive agents, i.e., prednisone use for 3–4 weeks with a subsequent dosage reduction, plus cyclophosphamide monohydrate 200 mg/$m^2$ via intravenous injection, or 2 mg/kg/day orally taken.

### Infants of Diabetic Mothers

Infants of diabetic mothers carry an increased risk of development of fetal HCM, with predominant thickening of the ventricular septum and ventricular free wall [20]. HCM accounts for 40% of infants of diabetic mothers [21]. The development of HCM in infants of diabetic mothers is attributed to fetal hyperinsulinemia and increased expression and affinity of insulin receptors responsible for cardiomyocyte proliferation and hypertrophy [20-22]. The clinical and pathological phenotypes are a consequence of activations of growth factors and regulatory factors, such as insulin-like growth factor-1, transforming growth factor-$\beta_1$ and angiotensin II [23].

Infants of diabetic mothers with HCM often follow a benign and transient course, and they are usually asymptomatic [20]. Nevertheless, some patients may develop heart failure early after birth [24]. The electrocardiogram usually shows advanced left ventricular hypertrophy and abnormal Q waves in many leads as a result of septal hypertrophy [25]. The newborns of the diabetic mothers with septal hypertrophy showed much longer QT and QTc dispersion intervals than control [26]. Echocardiography is the main imaging technique for the diagnosis of this lesion. Wu et al. [27] investigated the early changes of heart function in 19 neonates and infants of diabetic mothers comparing with 20 cases of normal newborns with similar gestational age and birth weight. Results showed normal left and right ventricular systolic functions but impaired right ventricular diastolic function in infants of diabetic mothers (Figure 1). Veille et al. [28] investigated fetuses of diabetic mothers at 20–41 weeks of gestation by M-mode echocardiogram and found the mean septal size increased during both diastole and systole, and ventricular septal hypertrophy accounted for 75% of the cases. Gutgesell et al. [29] observed echocardiographic signs of marked septal hypertrophy with left ventricular outflow tract (LVOT) obstruction in 20.8% (5/24) and signs of hypertrophy of the right ventricular free wall also in 20.8% (5/24) of infants of diabetic mothers. Microscopic examination revealed hypertrophic fibers and scattered cellular disarray in the septum [29]. Further studies demonstrated that ventricular and septal thickening correlated with insulin, growth hormone, insulin-like growth factor and leptin levels [30]. Clinically, there was always a heart enlargement and myocardial enzyme elevations. The incidence of cardiac damage in infants of diabetic mothers were 71.9%, with significant increases of serum creatinine kinase, MB isoenzyme of creatinine kinase, aspartate aminotransferase and lactate dehydrogenase within 24 hours postnatally. Genetic analysis revealed adenosine triphosphate-sensitive potassium channel mutations [21].

Most symptomatic infants of diabetic mothers require only supportive care with supplemental oxygen therapy, but β-blockers may be necessary for ventricular output improvement [31]. In most cases, the prognosis is good and the myocardial enzymes remarkably decreases after a 7–10 day supportive treatments (correcting hyperglycemia, nourishing myocardium, improving heart function, correcting acidosis and expansion of the blood volume) and all infants survived [32].

## Pompe Disease

Pompe disease, also termed as 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 [33]. The enzyme deficiency causes an accumulation of intra lysosomal glycogen in different organs, leading to HCM, weakness of respiratory muscles and subsequent death within the first year of life [34]. The classic form appears in the newborn with a very severe hypotonia and HCM, and patients often die before age two. The infantile form is considered a cardiac disorder because of the prominent cardiac involvement. Less frequently, the disease appears only in childhood or in adult life, the so called late-onset Pompe disease [35].

Patients with Pompe disease may present with fatigue, tachypnea, tachycardia, hypoxia and respiratory failure [36]. Respiratory dysfunction and diaphragmatic weakness can be found in over half of the patients [37]. A progressive cardiac hypertrophy is characteristic for infantile Pompe disease [38]. The creatinine kinase levels can be 3–4 times elevated. Assay of α-glucosidase enzyme activity in whole blood shows significantly reduced activity, and eight point mutations of GAA gene has been detected [39]. Muscle biopsy is commonly used as an early diagnostic tool for diagnosing Pompe disease by differentiating it from other neuromuscular diseases [40]. Patients are of an ultrastructural evidence of glycogen deposition in muscle [41].

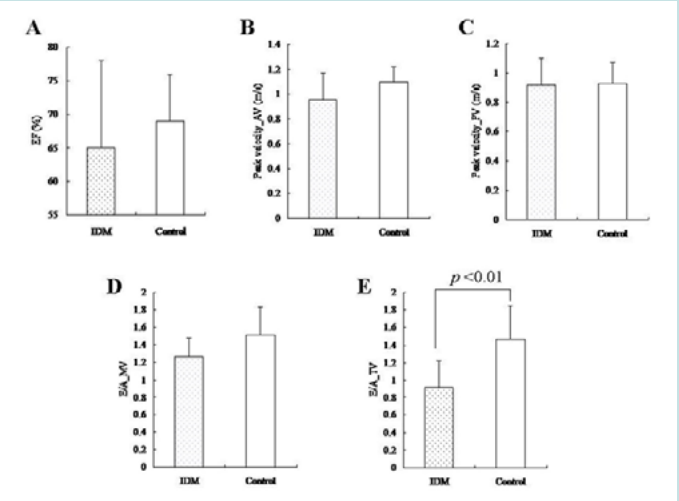


**Figure 1:** Echocardiographic evaluation of heart function in infants of diabetic mothers (n=19) in comparison to matched healthy newborns (n=19) [27]. No intergroup differences were found in ejection fraction (A), peak velocity across the aortic valve (B), peak velocity across the pulmonary valve (C) and E/A ratio of the mitral valve (D). E/A ratio of the tricuspid valve of infants of diabetic mothers was much lower than that of the control group ($p<0.01$) (E). AV: aortic valve; EF: ejection fraction; IDM: infants of diabetic mothers; MV: mitral valve; PV: pulmonary valve; TV: tricuspid valve.

Ding et al. [42] reported six patients with Pompe disease had enlarged cardiac chambers, three of them had an enlarged heart shadow on chest X-ray films and four patients had an echocardiographically myocardial hypertrophy. The electrocardiogram in three patients showed short PR intervals and a high voltage. Interventricular septum and left ventricular free wall thickening were disclosed by echocardiography [39]. The magnetic resonance imaging revealed hypertrophy of the right and left ventricles and the interventricular septum with an irregular inhomogeneous appearance of the myocardium [43].

The diagnosis of infantile Pompe disease is based on profound deficiency of α-glucosidase in fibroblasts, gene mutation analysis and the presence of HCM [44]. Blood α-glucosidase enzyme level is a reliable biomarker, and genetic mutation analysis can be helpful for the diagnosis of Pompe disease. Ngiwsara et al. [45] examined the molecular characteristics of 12 patients with typical presentation of Pompe disease, all of whom had HCM and proved mutations of GAA gene.

The diagnosis of Pompe disease is usually established at the age of 6 months. If left untreated, patients may die of cardiorespiratory failure at 2 years of age [36]. Current

developments toward enzyme replacement therapy has obtained promising results. Enzyme replacement therapy with recombinant human acid α-glucosidase prevents lysosomal glycogen accumulation and improves clinical outcomes by reducing cardiac hypertrophy and increasing overall and ventilator-free survivals [38, 46]. A retrospective study on 14 patients with Pompe disease demonstrated that enzyme replacement therapy brought about significant improvements of left ventricular mass index, left ventricular posterior wall thickness and diastolic and systolic functions in all patients, and this effect maintained for 13.9 years [44]. Moreover, enzyme replacement therapy leads to reduction of left ventricular voltage and disappearance of repolarization disturbances [44]. Furthermore, myozyme has been approved by the Food and Drug Administration and is used to treat Pompe disease, but it is very expensive and the medicine needs taking for life. The first response to treatment can be shown in vascular endothelium and in peripheral nerves after a 12-week treatment at an enzyme dose of 15–20 mg/kg, which can be increased to 40 mg/kg after a 72-week treatment. As a result, a reduction of glycogen storage and substantial improvement of muscle architecture can be noted in some patients [47]. After enzyme replacement therapy, the characterized electrocardiographic findings of a shortened PR interval, an increased QT dispersion and high left ventricular voltages for infantile Pompe disease alleviated [48], and heart dimension decreased after a 3-month treatment [49]. Recent development of enzyme replacement therapy with recombinant α-glucosidase has dramatically improved the life expectancy and quality of life of the infants [50]. The therapeutic effect of human α-glucosidase at high levels in knockout mouse model of glycogen storage disease type II resulted in degradation of lysosomal glycogen in heart, skeletal and smooth muscles [51].

## Mitochondrial cardiomyopathy

Mitochondrial dysfunction frequently affects the heart and may cause both hypertrophic and dilated cardiomyopathies. The cardiomyopathy is rarely an isolated disorder, but part of a mitochondrial disorder involves at least one other system [52]. Infantile mitochondrial cardiomyopathy can present with progressive neuromuscular disease, HCM and brain atrophy. The mitochondrial cardiomyopathy can be progressive and the cause of premature death [53]. Cardiomyopathy and cataract are common features of mitochondrial disorders associated with psychomotor retardation or progressive mental deterioration in most patients [54]. Sengers syndrome presents with mitochondrial myopathy, HCM, congenital cataract, lactic acidosis and normal mental development [55]. Echocardiography reveals HCM with mild LVOT obstruction [56].

It is of difficulty to diagnose hypertrophic obstructive cardiomyopathy in neonates as there are always an abnormally thickened septum or increased septum/left ventricular posterior wall ratio in them. Fortunately, the septal hypertrophy disappears with age [54]. Mitochondrial cardiomyopathy can be resulted from mutations of either nuclear or mitochondrial-encoded genes of respiratory chain enzymes [57]. Ultrastructural findings include mitochondrial hyperplasia, enlargement and abnormal structure [58] and myofibril loss in the cardiomyocytes [59]. Abnormal oxidative phosphorylation in pediatrics may lead to a hypertrophic or dilated cardiomyopathy, usually with no LVOT obstruction [52]. Of the five complexes of the respiratory chain, oxidative phosphorylation defects most frequently affect complex I (NADH-CoQ reductase) and complex IV (cytochrome c oxidase) [57]. Marin-Garcia et al. [60] inspected the skeletal muscles of patients with mitochondrial cardiomyopathy for changes of the respiratory chain enzymes. Decreased activities of complexes I, III, IV and V but not of II were found by muscle biopsy. Rustin et al. [61] described 3 patients with isolated HCM diagnosed in the first few weeks of life had respiratory enzyme deficiencies in endomyocardial biopsies. A mutation in nuclear gene COX10 responsible for complex IV deficiency was noted to be associated with infantile HCM [62]. In Sengers syndrome, in addition to the characteristic ANT1 deficiency, multiple mitochondrial enzyme complex dysfunctions and defective oxidative phosphorylation can be observed [56]. Patients with Leigh disease showed primarily a neurological disorder, while other systemic manifestations including HCM were less common. Cytochrome c oxidase deficiency was found in muscle biopsies of patients with severe Leigh disease [52]. Mutations in SURF1, a gene encoding a putative COX assembly factor, were found in Leigh syndrome with HCM [63].

The management of mitochondrial disorders and cardiomyopathy is supportive treatment. Pharmacological regimens are inclusive of all kinds of dietary supplements. The typical “mitochondrial cocktails” include coenzyme Q10, creatinine, L-creatinine, thiamine, riboflavin, folic acid and vitamins C and E. The antioxidants may partially improve clinical features [64]

## RASopathy

RASopathies are developmental syndromes due to germline gain-of-function mutations of genes of the RAS/MAPK signaling pathway. RASopathies are a group of genetic disorders phenotypically related to Noonan syndrome often associated with HCM, including Noonan syndrome with multiple lentigines (NSML), cardiofaciocutaneous syndrome, Costello syndrome, and Noonan syndrome-like disorder with loose anagen hair. RASopathies have similar pathogenetic mechanisms and share many clinical features, such as distinct facial features, congenital heart defects, cardiomyopathy, skin anomalies and growth retardation. HCM is frequently observed in patients with RASopathies and might represent a major determinant of patients’ outcomes [65]. RASopathy-associated HCM is a genetically heterogeneous condition involving diverse genes within the RAS-MAPK pathway, frequently relating to NSML-associated PTPN11 mutations [66], as well as HRAS and RAF1 genes [67]. Different missense mutations in the RIT1 gene have been reported in patients with Noonan syndrome. RIT1 mutations are particularly of a high prevalence of cardiovascular manifestations, especially the HCM phenotype [68]. De novo mutation in exon 7 of the RAF1 gene: c.776C > A (p.Ser259Tyr) was identified by whole exome sequencing in infantile Noonan syndrome [69]. Pandit et al. [70] noted that Noonan syndrome patients with HCM carried gain-of-function RAF1 mutations resulting in increased ERK activation, whereas Noonan syndrome patients without HCM harbored loss-of-function RAF1 mutations. These findings suggest that enhanced ERK activation may underlie HCM [69]. Chen et al. [71] identified RASopathy gene mutations in 46 unrelated children with HCM, 3 patients with PTPN11 gene mutation died of cardiac failure at an early age, and the rest survived with 5 of them having

spontaneous regression of cardiac hypertrophy. NSML, also known as LEOPARD syndrome, is a rare congenital multisystem disorder. HCM manifests in these patients during infancy, and may be associated with severe LVOT obstruction. Conduction anomalies and HCM can result in sudden death or ultimately heart failure. In Noonan syndrome, PTPN11 mutations have been identified in approximately 50% of patients, and mutations have been described in other genes of the RAS-MAPK pathway (SOS1, RAF1, KRAS, MAP2K1, BRAF, NRAS, and SHOC2). In Leigh disease, about 85% of patients have mutations in PTPN11 [72].

Wilkinson et al. [73] found pediatrics with Noonan syndrome and HCM were characterized by younger age, more congestive heart failure, more family history of genetic syndromes and cardiomyopathy and smaller length/height z-score in comparison to children with non-Noonan HCM. Infants age <6 months and congestive heart failure were significant risk factors of infants with Noonan syndrome, with a 1-year survival of 64% and 34% for both conditions, respectively. Jaouadi et al. [69] reported a case of infantile Noonan syndrome had a severe clinical phenotype including neonatal HCM, facial dysmorphism, severe failure to thrive, cutaneous abnormalities, pectus excavatum and severe stunted growth, and she died at the age of 8 months. Echocardiography revealed concentric asymmetric hypertrophy of the ventricles and interventricular septum leading to a mild right ventricular outflow tract obstruction [69]. The molecular pathogenesis of HCM in RASopathies results from hyperactivation of several signaling pathways [74].

Trametinib, an inhibitor of MEK1/2 activity, has been proved to generate beneficial effects of reversing progressive myocardial hypertrophy, in either preclinical mouse models or human infants of RASopathies [75]. Clinically, trametinib treatment (0.02–0.027 mg/kg/day) for 3 months in infants brought about significant cardiac functional improvement and reversed HCM and valvular obstruction in patients with RIT1-associated Noonan syndrome [75]. The severity of heart failure assessed by New York Heart Association class and brain natriuretic peptide levels improved markedly with everolimus treatment, suggesting that HCM in NSML patients can principally be treated with mammalian target of rapamycin (mTOR) antagonists. Short-term and low-dose rapamycin could be beneficial in NSML patients with severe or rapidly progressive HCM. Clinical trials of rapamycin and analogs should be considered for treatment of severe NSML-associated HCM [67]. Marin et al. [76] reported that treatment of NSML mice with rapamycin prevented the onset of disease when administered early, and reversed HCM. Based on the latter finding, mTOR inhibitors, such as rapamycin, can be used for HCM treatment in NSML patients.

### Friedreich Ataxia

Friedreich ataxia is the result of hereditary progressive and recessively transmitted spinocerebellar degeneration. It is estimated that one third to one half the patients with Friedreich ataxia have cardiovascular involvements. In the child with Friedreich ataxia the diagnosis of the cardiac disease preceded the systemic disorder [77]. Left ventricular hypertrophy may have a variety of types and extents of the increased wall thickness, from mild, severe to diffuse or predominantly septal [78]. The transition from the hypertrophic to the hypokinetic dilated form is not rare in children with Friedreich ataxia [78]. The myocardial disease may have several forms of expression and some patients have hypertrophic obstructive cardiomyopathy. Still unclear is the association between Friedreich ataxia and HCM [77]. There was no association between the presence of HCM and patient age or severity of the neurologic disorders [79]. Pathogenesis is multifactorial, but predominantly relating to genetically neural dysfunction [79]. Studies with Friedreich ataxia fibroblasts demonstrated a deficiency of mitochondrial malic enzyme (MEm). The MEm activity in patients with Friedreich ataxia was only 10% of the mean activity of normal and neurological disease controls. MEm deficiency could produce the Friedreich ataxia phenotype [80]. The symmetrical concentric HCM in Friedreich ataxia has been reported to show good response to high-dose propranolol treatment, which lead to a significant reduction of septal and posterior left ventricular wall thickness and complete normalization of repolarization abnormalities [81]. The prognosis of Friedreich ataxia was nevertheless poor as 50% of patients with Friedreich ataxia died of cardiac cause, especially in those with the presence of HCM [79].

## Discussion

HCM is characterized by asymmetric ventricular wall hypertrophy, and there are many phenotypes. According to the hemodynamic characteristics, it can be divided into obstructive, occult obstructive and non-obstructive hypertrophies. According to the anatomical locations, it can be divided into left ventricular, right ventricle and biventricular hypertrophies. Left ventricular hypertrophy can be further divided into ventricular septal and (or) lateral wall, apical and midventricular papillary hypertrophic and hypertrophic dilated types, with asymmetrical hypertrophy of the left ventricular septum being the most common [82]. In the classic form of HCM, the hypertrophy is apparent in the cephalic portion of the ventricular septum, which results in both left and right ventricular outflow obstructions when the hypertrophied septum protrudes into both the left and right ventricles [83].

HCMs can be diagnosed by echocardiography and clinical and metabolic investigations [84]. For asymptomatic infants, family screening is necessary. Symptomatic infants may present with dyspnea, chest pain, syncope/presyncope or even sudden death [85]. Patients with Noonan syndrome or LEOPARD syndrome have characteristic facial features and skin and chest wall manifestations [85]. Echocardiography reveals cardiac chamber dimension, LVOT obstruction and diastolic performance [86]. Ergometric exercise testing is helpful for assessing disease severity. Most patients with HCM usually have a reduced peak oxygen consumption comparing with healthy controls [85].

Physical activity restrictions are often the first step of treatment. In addition to specific therapeutic regimens described as above-mentioned, medical therapy is based on the use of β-blockers alone or in combination with disopyramide to alleviate the symptoms and to ameliorate resting or induced LVOT obstruction [86]. Verapamil is used in patients with intolerance to β-blockers [85]. Implantable cardioverter defibrillator therapy prevents sudden cardiac death in patients with HCM. The indications for implantable cardioverter defibrillator therapy in infants were left ventricular wall thickness >30 mm, syncope/presyncope, family history of sudden cardiac death, non-sustained ventricular tachycardia, poor blood pressure response during exercise and previous cardiac arrest [87]. Percutaneous alcohol septal ablation induces a myocardial infarction in the cephalic portion of the ventricular septum by injecting absolute alcohol into the septal perforator branch of the left anterior descending coronary

artery. Septal hypokinesis and more remote remodeling occur, thereby relieving LVOT obstruction [86]. Surgical treatment like left ventricular myectomy has been recommended for children with HCM and LVOT obstruction with poor response to β-blockers or calcium antagonists [83]. In infants, septal myectomy with or without a modified Konno procedure is a surgical treatment of choice for relieving LVOT obstruction. The extensive endocardial and myocardial resection through a transaortic approach poses special problems in infants for limited exposure and risks of injury of the conduction system, heart valves and coronary arteries, whereas incision of the ventricular septum greatly facilitates the exposure of the left ventricular cavity [83]. The procedure had resulted in a significant reduction of thicknesses of the left ventricular septum and the left ventricular posterior free wall and an increase of the left ventricular end-diastolic volume. Maron et al. [88] reported that sudden death occurred in 40% of patients with LVOT obstructions who had not undergone operations versus only 8% of patients without obstruction. Laredo et al. [89] reported the results of modified Konno procedure in children with severe forms of hypertrophic obstructive cardiomyopathy. A 6% rate of postoperative mortality was considered to be due to younger age at operation <15 months, an etiology of Noonan syndrome and biventricular obstruction. They concluded that older children might tolerate the operation better than younger ones.

## Conclusions

The diagnoses of infantile HCMs are based on clinical signs of cardiomyopathy on medical images. Differential diagnosis from congenital heart defects is important for proper managements. Infantile HCM due to EFE may have persistent heart failure with a relatively high mortality rate, and the treatment of choice is standardized anti-heart failure therapy. Infants of diabetic mothers with HCM are often asymptomatic, with no signs of cyanosis or heart murmur, and they usually do not need a treatment. Treatment becomes necessary only when patients present with recent fatigue, dyspnea, or heart failure. Infants with Pompe disease may develop cardiorespiratory failure. Apart from supportive treatments, enzyme replacement therapy with recombinant α-glucosidase for Pompe disease is always necessary. Infants with HCM due to mitochondrial disorders or RASopathies often have dismal prognoses, poor response to treatments and early deaths. The prognosis of Friedreich ataxia was also poor and patients often die of cardiac cause. The prognoses of infantile HCMs vary depending on etiologies: infants of diabetic mothers > Pompe disease > endocardial fibroelastosis > Friedreich ataxia > RASopathies > mitochondrial disorders in a decreasing hierarchy.

## Abbreviations

EFE: endocardial fibroelestosis

HCM: hypertrophic cardiomyopathy;

LVNC: left ventricular noncompaction cardiomyopathy;

LVOT: left ventricular outflow tract;

Mem: mitochondrial malic enzyme;

NSML: Noonan syndrome with multiple lentigines.

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