Review: Metabolic Cardiomyopathy and Conduction System Defects in Children

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Abstract. Metabolic cardiomyopathies include amino acid, lipid and mitochondrial disorders, as well as storage diseases. A number of metabolic disorders are associated with both myopathy and cardiomyopathy. These include the glycogen storage diseases, ie, acid maltase deficiency (infantile, childhood, and adult onset), McArdle disease, and debrancher and brancher deficiencies. Disorders of lipid metabolism include systemic carnitine deficiency and abnormalities of carnitine palmitoyltransferase (CPT), long-chain acyl-CoA dehydrogenase, and multiple acyl-CoA dehydrogenase. Disorders of mitochondrial metabolism affect complex I, II, III, IV and V, in addition to multiple respiratory chain defects. These may cause either hypertrophic or dilated cardiomyopathy. In addition, cardiomyopathy is frequently a component part of the storage disorders, including mucopolysaccharidosis, mucolipidosis, Fabry disease, gangliosidosis, and neuronal ceroid lipofuscinosis. Primary hypertrophic cardiomyopathy is caused by mutations in one of the genes that encode proteins of the cardiac sarcomere. Mutations in different genes are attended by different prognoses and different risks of sudden death. Mutations of the genes for myosin binding protein C (MBP-C) and tropomyosin have low penetrance and cause mild forms of primary hypertrophic cardiomyopathy, while mutations of the troponin T and B-myosin genes carry a worse prognosis. Conduction disorders result in cardiac arrhythmias that may be fatal. Histiocytoid cardiomyopathy is usually an autosomal recessive disorder that results in the presence of abnormal Purkinje cells that interfere with normal cardiac conduction. Other conduction defects include arrhythmogenic right ventricular dysplasia (ARVD), congenital heart block, noncompaction of the left ventricle, and long Q-T syndrome (LQTS). The genetic loci for LQTS reside usually in the potassium channel, and, less frequently, in the sodium channel (channelopathies). Although the histological appearance of some of these disorders may be diagnostic, molecular analysis is necessary to define clearly the particular type of cardiomyopathy. (received 3 July 2003; accepted 17 July 2003)

Keywords: cardiomyopathies, mitochondrial disorders, glycogen storage diseases, lipid disorders, cardiac conduction disorders, mucopolysaccharidoses

Introduction

Cardiomyopathy is an intrinsic abnormality of myocardial function and excludes structural abnormalities of the heart. There are three functional types: dilated or congestive; obstructive, as in hypertrophic cardiomyopathy; and restrictive, as in infiltrative disorders such as the storage diseases. The principal metabolic disorders that both frequently and predominantly affect the cardiovascular system are listed in Table 1.

Metabolic Cardiomyopathies

Alkaptonuria, a recessive trait, results in deposition of pigment produced by the oxidation and polymerization of homogentisic acid, a metabolite of tyrosine and phenylalanine. Ochronotic pigment
myocardial infarction [1,2]. The melanin-like pigment is deposited both intra- and extra-cellularly.

Homocystinuria. A defect in the activity of cystathionine synthetase, which converts homocysteine to cystathionine, results in homocystinuria with mental retardation, seizures, skeletal deformities, ectopia lentis similar to that seen in the Marfan syndrome, and occlusive vascular disease. Histologically, the aorta shows intimal thickening, fragmentation of the internal elastic lamella, assuming a “basket weave” pattern, and medial fibrosis [3] (Fig. 1). Thrombosis follows an increase in platelet survival time, and marked fragility of the endothelium that predisposes it to the formation of platelet thrombi.

Oxalosis. Primary oxalosis, a peroxisomal disorder, is an autosomal recessive trait and includes two rare disorders of glyoxylate metabolism [4]. Oxalosis is characterized by nephrocalcinosis and by extrarenal deposits of calcium oxalate especially in bone (Fig. 2). In type I, the most common form of the disease, deficiency of 2-oxoglutarate:glyoxylate carboligase, results in systemic accumulation of glyoxylic and glycolic acids. In type II (L-glyceric aciduria), deficiency of D-glyceric dehydrogenase results in accumulation of hydroxypyruvate and excessive urinary excretion of oxalic and glycolic acids.

The heart is the site of widespread deposition of oxalate crystals, including the conduction system.

Table 1. Tabulation of metabolic cardiomyopathies.

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<th>Disorders of amino acid metabolism</th>
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and results in a dilated cardiomyopathy. Oxalate crystals in arterioles and capillaries are often larger than the vessel wall and may extrude from them. Secondary oxalosis is due to ingestion of oxalic acid, oxalates, or ethylene glycol; hyperalimentation or enteric hyperoxaluria occurring in patients with severe disease of the small bowel; and pyridoxine deficiency caused by chronic renal insufficiency; which all can result in oxalate deposition in the heart and blood vessels [5-7].

**Glycogen storage diseases (GSD).** Cardiac involvement most commonly occurs in types II (Pompe disease), III, and IV GSD. The heart is grossly enlarged [8]; fibroelastic thickening of the endocardium occurs in about 20% of patients with Pompe disease [9]. Glycogen deposits are also present in vascular smooth muscle and endothelium [10,11]. The infantile form of type II GSD is a generalized and invariably fatal disease of infancy, characterized by massive cardiomegaly due to glycogen accumulation in the myocardial cells in the first few weeks or months of life, with failure to thrive and generalized hypotonia and weakness [12]. Chest radiography reveals an enlarged cardiac profile. Electrocardiographic (ECG) alterations include marked left axis deviation, short PR interval, large amplitude of the QRS, and inversion of the T waves. Echocardiography shows hypertrophy of both ventricular walls. Serum creatine kinase (CK) is invariably increased. The diagnosis is relatively simple because of multiorgan involvement, and is confirmed by liver and muscle biopsy that shows glycogen storage and severe vacuolar myopathy. Ultrastructurally, some of the glycogen is free in the cytoplasm and some is contained within membrand-bound vacuoles. Endomyocardial biopsy shows both free and intralysosomal glycogen [13].

Acid α-glucosidase (acid maltase) deficiency can be documented biochemically in muscle, lymphocytes, fibroblasts, or urine. Lysosomal GSD simulating GSD II with normal acid maltase has been described in some families [13-15]. Age at onset varies between 2.5 and 19 yr, and males are more severely affected than females. Myopathy, which may be clinically inapparent, nonobstructive hypertrophic cardiomyopathy, which can cause sudden death, an electrocardiogram showing both right and left ventricular wall hypertrophy, and mental retardation characterize this disorder. Inheritance suggests X-linked dominant or autosomal dominant trans-mission with different expressivity in males and females.

In debrancher deficiency (GSD III), clinical cardiomyopathy is rare, but electrophysiologic evidence of heart dysfunction is virtually universal [16,17]. In brancher enzyme deficiency (GSD IV), the rare occurrence of cardiomyopathy may be explained by the fact that most patients die of liver disease before the onset of cardiomyopathy. The cardiomyopathy is characterized by myocardial periodic acid-Schiff (PAS)-diastase-resistant cytoplasmic deposits [18].

Patients with myophosphorylase deficiency (GSD V, McArdle disease) have a partial defect of phosphorylase in the heart, but since the cardiac isoenzyme predominates, the residual activity is sufficient to be protective from heart disease. A rare fatal infantile form of McArdle disease with cardiac involvement has been reported [19].

**Mucopolysaccharidoses (MPS)** are characterized by deficiencies in lysosomal enzymes involved in the degradation of various glycosaminoglycans. Severe cardiac involvement occurs in MPS I (Hurler syndrome), MPS I-H (Scheie syndrome), MPS IHS (Hurler-Scheie syndrome), MPS II (Hunter syndrome), and MPS III A-D (Sanfilippo
syndrome). Cardiovascular lesions (Fig. 3) involve the valves, endocardium, myocardium, coronary arteries and large systemic arteries. The valves are thickened and chordae tendineae of the atrioventricular valves are moderately shortened and thickened. The large extramural coronary arteries are rigid and thickened, and their lumina are severely narrowed. The myocardial cells are distended with storage material. The aorta and large systemic arteries have raised intimal plaques. Endocardial fibroelastosis may be present in infants under 1 yr of age [20-22].

Mucolipidosis II (I-cell Disease). In mucolipidosis II (I-cell disease) (Fig. 4), an autosomal recessive trait, there is a deficiency of multiple lysosomal hydrolases active in the degradation of lipids and mucopolysaccharides. The changes in the cardiovascular system are similar to those seen in the mucopolysaccharidoses. Myocardial involvement is prominent and death usually results from congestive heart failure [23-27]. Ultrastructural studies show membrane-bound lysosomes with vacuoles containing pleomorphic inclusions with concentric membranous arrays and membrano-granular material [25].

Sphingolipidoses. In the adult form of Gaucher disease (glucosyl ceramide lipidosis, caused by deficiency of lysosomal glucocerebrosidase), pulmonary hypertension or cor pulmonale due to occlusion of alveolar capillaries by Gaucher cells may occur [28]; these changes are not seen in the infantile form. Constrictive calcific pericarditis may result from intrapericardial hemorrhage due to a bleeding diathesis that is frequent in Gaucher disease [28,29].

Fabry disease, caused by a deficiency of lysosomal α-galactosidase A (ceramide trihexosidase), is an X-linked recessive disorder manifested by skin lesions (angiokeratomas), pain, and paresthesias in the extremities, and progressive renal and cardiovascular disease. Cardiac hypertrophy and dilatation, congestive heart failure, anginal pain, and hypertension are related to the presence of deposits of ceramide trihexoside in lysosomes in endothelial and smooth muscle cells throughout the vascular system.
system, especially in the coronary arteries, cardiac muscle cells, specialized tissues of the atrioventricular conduction system and valvular tissue, as well as in renal glomeruli and tubules.

Myocardial infarction at an early age has been reported in patients with Fabry disease [30,31], and hypertrophic obstructive cardiomyopathy may occur [32]. Cardiac valvular lesions have been described in patients with Fabry disease and include mitral stenosis [33], aortic regurgitation [34], mitral insufficiency [35], and pulmonary regurgitation [36]. Deposits of ceramide trihexoside appear as vacuoles in frozen sections; they are sudanophilic, PAS positive, and strongly birefringent. In cardiac muscle cells these deposits show a lacework pattern (Fig. 5) similar to that in type II glycogenosis. By electron microscopy, ceramide trihexoside deposits form intralysosomal aggregates of concentric or parallel lamellae spaced 4 to 5.5 nm apart [37-39] (Fig. 6). The lamellar structures of the deposits are seen on freeze-fractured preparations [39].

Fig. 4. Mucolipidosis II (I-cell disease). Left panel: child with coarse features and brushed-out appearance of hair. Upper right panel: opened heart with distortion of valves. Lower right panel: microscopic appearance of heart with large vacuolated cells.

Fig. 5. Fabry disease. Vacuolated cells of the myocardium (H&E stain).

Gangliosidosis. In type I and type II generalized GM1 gangliosidosis, cardiovascular lesions include cardiomegaly and diffuse, nodular thickening of the mitral and tricuspid valves. Microscopically, swollen histiocytes containing PAS and alcian blue positive...
cytoplasmic granules are seen. Similar cells have been found in the aortic valve, which is usually only slightly thickened, and the myocardial cells contain storage material [40,41]. Atheromatous plaques may be present in coronary arteries. On ultrastructural study, the myocardial cells show two types of deposits: membranous concentric bodies and membrane-bound vacuoles containing reticulogranular material [42].

Two types of GM2 gangliosidosis include Tay-Sachs disease (type I) with deficiency of hexosaminidase A (hex A), and Sandhoff disease (type II) with deficiency of hex A and β-N-acetyl hexosaminidase. Patients with Tay-Sachs disease have no clinical manifestations of cardiovascular disease but show nonspecific electrocardiographic changes and accumulations in heart tissue of a GM2 ganglioside similar to that found in excessive amounts in the brain [43]. Cardiomegaly and mitral regurgitation in Sandhoff disease [44-47] occur, and the changes are similar to those seen in GM1 gangliosidosis.

**Neuronal ceroid lipofuscinosis** (NCL) (Batten-Spielmeyer-Vogt syndrome). This condition is characterized clinically by progressive mental deterioration and loss of vision, seizures, and pathologically by the accumulation of lipopigment in neural and other tissues [48]. In the late infantile and juvenile forms, the heart is large and hypertrophied, and the valvular tissue is thickened (Fig. 7). Electron microscopy demonstrates curvi-linear bodies (Fig. 8) that seem specific for this disorder, as well as fingerprint patterns and electron-dense deposits of lipofuscin. The storage material stains positively for PAS and acid phosphatase and is autofluorescent, giving peak emission when stimulated at around 500 µm [49]. The storage material is far more abundant in neurons, but it can be found in almost all tissues. In skin, the inclusions are readily seen in capillary endothelial cells.
Multisystem triglyceride storage disease. Hyper- 
trophic cardiomyopathy in a patient with multi-
system triglyceride storage disease and normal 
carnitine is characterized clinically by weakness, 
ichthyosis, and steatorrhea [50]. Although the 
underlying metabolic defect is unknown, this 
disorder may be due to impaired degradation of 
endogenously synthesized triglycerides; inheritance 
seems to be autosomal recessive [51,52].

Carnitine deficiency. Carnitine is an essential 
cofactor in the transfer of long-chain fatty acids 
across the inner mitochondrial membrane. 
Carnitine deficiency results in the accumulation of 
neutral lipid within type I skeletal muscle fibers (Fig. 
9), the myocardium, and the liver. Skeletal muscle 
weakness, episodic weakness, episodic hypoglycemia, 
encephalopathy, dilated cardiomyopathy, and brady-
dysrhythmic cardiac arrests are common in carnitine 
deficiency [53,54]. The disease is diagnosed by 
muscle biopsy and by measurement of plasma 
carnitine concentrations.

Systemic carnitine deficiency is generally 
diagnosed early in life. Two clinical subtypes are 
recognized: (1) that associated with multiple 
episodes of acute encephalopathy, which resemble 
Reye syndrome [55-57], and (2) that associated with 
cardiomyopathy characterized by cardiomegaly and 
congestive failure at an early age [53], with striking 
T-wave changes in the EKG. The heart is large and 
globular. The endocardium may show mild endo-
cardial fibrosis; skeletal muscle contains myriad small 
vacuoles in type I fibers; modified Gomori stain 
shows large subsarcolemmal accumulations of mito-
ochondria are red and granular (ragged red fibers).

Ultrastructurally, myofibrils are disrupted, and 
there are large aggregates of mitochondria and lipid 
deposits within the skeletal muscle and myocardium 
(Fig. 10). The clinical response to L-carnitine may 
be dramatic. Determination of plasma carnitine and 
skeletal muscle biopsy seem justified in all patients 
with familial cardiomyopathy. Secondary carnitine 
deficiency may be due to genetic defects of 
metabolism, particularly those with acidemias, 
following hemodialysis, and other conditions [58].

Fatty acid oxidation disorders. Carnitine palmitoyl 
transferase-II deficiency, in its most severe form, 
causes hypoketotic hypoglycemia, metabolic 
acidosis, hepatomegaly, congestive heart failure, and 
lethal arrhythmias in the newborn period [59]. 
Deficiency of very long-chain acyl coenzyme A 
(CoA) dehydrogenase (VLCAD), which catalyzes 
the first step in β-oxidation of long chain fatty acids, 
or long chain 3-hydroxy-acyl-CoA dehydrogenase 
(LCHAD) may result in severe, dilated cardio-
myopathy in the early weeks of life [60,61].
Mitochondrial Disorders

Features of mitochondrial disorders [62,63] allow mutated mitochondrial DNA to coexist in the same cell with normal mitochondrial genomes, a condition known as “heteroplasmy.” Different cells and tissues may contain vastly different percentages of mutant mitochondrial genomes, resulting in extraordinary phenotypic variation in expression, even within the same family. In the process of oxidative phosphorylation (OXPHOS), molecular oxygen is consumed and ATP is produced as protons fall back down the electrochemical gradient. All 13 of the proteins encoded by the mitochondrial genome are subunits of these OXPHOS complexes. Thus, mitochondrial DNA mutations alter the crucial OXPHOS process. In mitochondrial disorders, myocardial biopsy demonstrates an absolute increase in the number and size of mitochondria, while the activity of mitochondrial enzymes is decreased [64].

The types of cardiomyopathy in mitochondrial disorders are shown in Table 2. Biopsies of skeletal muscle stained by a modified Gomori trichrome stain show intracellular aggregates of coarse, red, granular material predominantly involving the aerobic type I fibers (so-called “ragged red fibers”) [65]. By electron microscopy, these aggregates consist of masses of abnormally large mitochondria with bizarre morphological features.

**Kearns-Sayre syndrome** is a mitochondrial cytopathy that includes ophthalmoplegia, degenerative retinopathy, renal tubular dysfunction, delayed growth, short stature, and slow mental and neurologic deterioration with progressive heart block [66,67].

**MELAS syndrome** (mitochondrial encephalopathy, lactic acidosis, and stroke) and **MERRF syndrome** (myoclonic epilepsy and ragged red fibers) are characterized by dilated cardiomyopathy.

**Barth syndrome** (3-methylglutaconic acidemia), an X-linked form of mitochondrial myopathy with a high variable penetrance, is characterized by abnormalities in carnitine metabolism with dramatic response to L-carnitine therapy [68]. The mitochondria show concentric, tightly packed cristae and occasional inclusion bodies. Skeletal muscles are weak, with sparing of the extraocular and bulbar muscles; granulocytopenia with arrest of development at the myelocyte stage; and mild mental retardation. Increased levels of urinary 3-methylglutaconic acid with severe lethal cardiomyopathy are components of Barth syndrome [69]. Cardiac pathology shows left ventricular hypertrophy and dilation with EFE. It is not certain that Barth syndrome is separate from X-linked EFE [70]. Barth syndrome has been mapped to Xq28 [71].

**Mitochondrial respiratory chain defects.** Complex I deficiency (reduced nicotinamide-adenine dinucleotide-coenzyme Q (NADH-CoQ) causes three major clinical syndromes: fatal infantile multisystem disorder, myopathy, and mitochondrial encephalomyopathy. Cardiomyopathy has been observed clinically in infants with the fatal form in association with severe lactic acidosis, psychomotor delay, generalized hypotonia, and weakness. Cardiac failure is the most common cause of death [72].

Complex III deficiency (reduced CoQ-cytochrome c reductase) is heterogeneous and can be divided into two major groups: those with multisystem disease (encephalomyopathy) and those with tissue-specific defects such as the myopathy of congenital myopathic dystrophy, Steinert disease. Echocardiography demonstrates hypertrophy of
both ventricles and septum with diminished contractility. Complex III activity is normal in muscle and liver, which suggests that the defect involves a tissue-specific subunit.

Complex IV deficiency (cytochrome c oxidase) causes two major syndromes: one is characterized by myopathy and the other is dominated by brain dysfunction [73,74]. The two forms of myopathy cause severe generalized weakness at or soon after birth, with respiratory distress and lactic acidosis, but they have different prognoses. Children with benign infantile myopathy improve spontaneously and are normal by 2 yr of age. Children with fatal infantile myopathy have a relentlessly downhill course, and death from respiratory failure occurs before 1 yr of age. The fatal infantile form is frequently associated with renal disease (de Toni-Fanconi-Debré syndrome), or, less frequently, with hypertrophic cardiomyopathy [75,76].

Complex V Deficiency (ATP-synthase) is characterized by congenital lactic acidosis, respiratory distress and hypertrophic cardiomyopathy (HCM). Combined deficiencies of respiratory chain enzymes in muscles, especially those involving complexes I and IV, have been observed in a syndrome characterized by HCM and mitochondrial myopathy but with general sparing of the central nervous system [77,78]. In most of these cases, muscle histology show accumulation of lipids and glycogen. Clinical features include onset during the first months of life, followed by early death.

**Disorders of Metal Metabolism**

**Hemosiderosis and hemochromatosis.** Cardiac iron deposits occur in hemochromatosis as well as in hemosiderosis, secondary to iron overloading (Fig. 11). Supraventricular arrhythmias correlate with the extent of iron deposit in atrial myocardium [79]. The heart has rusty brown discoloration with hypertrophy and dilatation. The coronary arteries and heart valves are uninvolved [80,81]. Cardiac muscle has greater affinity for iron than does skeletal or smooth muscle. Iron deposits are localized in lysosomes that contain electron-dense particles, 6 nm in diameter. Iron is seen by histochemical staining and energy-dispersive X-ray microanalysis.

**Neonatal iron storage disease** is a disorder in which iron is stored, particularly in the liver. Extrahepatic sites for iron accumulation include pancreatic acinar and islet cells, renal tubules, adrenal cortex, thyroid follicular cells, and myocardial fibers; the reticuloendothelial system is spared. Most patients die in the first week of life. With continuous iron transport, saturation of fetal transferrin develops, leading to an increased concentration of nontransferrin-bound iron in the infant and accumulation of iron in hepatic and extrahepatic sites [81].

**Wilson disease** (hepatolenticular degeneration) is an autosomal recessive trait characterized by cirrhosis of the liver, degenerative changes in the brain (especially in the basal ganglia), Kayser-Fleischer corneal rings, low serum copper concentration, decreased serum ceruloplasmin level, increased urinary copper, and deposition of copper in various tissues [82]. Cardiac hypertrophy and increased cardiac copper concentration have been described, and lenticular degeneration in basal ganglia [83,84].
Menkes kinky hair syndrome is a sex-linked, recessively transmitted copper deficiency state related to impaired absorption of copper from the gastrointestinal tract [85]. Copper is a cofactor for the enzyme responsible for the formation of cross-links between lysine residues in elastin and collagen. The heart in Menkes syndrome is normal, but superficial vessels often appear tortuous or dilated [86], and aneurysm formation often involves major arteries and veins. In the arterial wall there are fragmentation, splitting, and duplication of the internal elastic lamina. Vascular lumina often are compromised and occasionally are obliterated [87,88]. Ultrastructural study of the aorta shows elastin surrounded by large numbers of connective tissue microfibrils.

Primary Hypertrophic Cardiomyopathy

Primary hypertrophic cardiomyopathy is a disease of the myocardium with an incidence of >1 per 500 [89]. Idiopathic hypertrophic subaortic stenosis (IHSS), hypertrophic obstructive cardiomyopathy, muscular subaortic stenosis, and asymmetric septal hypertrophy (ASH) are among its many synonyms. Although primary HCM has been described in stillborns, newborns, and infants, it is rare in the first two decades of life. Fifty percent of cases are familial, and are inherited as an autosomal dominant trait. The disease can be caused by one of over 100 mutations in seven genes that encode proteins of the cardiac sarcomere, –

• Tropinin T (chromosome 1q3), worst prognosis, arrhythmogenic, autosomal dominant inheritance;
• MLC-1 (chromosome 3p); risk of sudden death unknown;
• MLC-2 (chromosome 12q); risk of sudden death unknown;
• MBPC (chromosome 11p11), low penetrance, mild form of the disease;
• B-Myosin (chromosome 14q12), high incidence of sudden death;
• Tropomyosin (chromosome 15q22), low penetrance, mild form of the disease;
• Troponin I (chromosome 19q13), risk of sudden death unknown.

Molecular diagnosis of HCM in asymptomatic children and fetuses is now possible [90-97]. The clinical expression of mutations of the gene for cardiac myosin-binding protein c (MBPC) is often delayed until middle age or old age. Delayed expression of cardiac hypertrophy and a favorable clinical course may hinder recognition of the heritable nature of mutations in the MBPC gene. Clinical screening in adult life may be warranted for members of families characterized by hypertrophic cardiomyopathy [98].

Clinical findings in patients with hypertrophic cardiomyopathy include jerky pulse, palpable atrial beat, late systolic outflow tract murmur, pulse with rapid upstroke, and nondilated left ventricle with disproportionate thickening of the ventricular septum. The ECHO 3 patterns show asymmetric septal hypertrophy (80%), concentric left ventricular hypertrophy (LVH) (25%), distal LVH (10%), and other patterns of LVH (5%). The incidence of sudden death post-exercise is 6% per yr until 15 yr old and 2.5% per yr from 15 to 30 yr of age.

Criteria for the diagnosis of familial HCM in infants include:
• Characteristic clinical and hemodynamic features of HCM;
• An abnormal septal-to-free wall ratio;
• A ventricular septum clearly thicker than normal in absolute terms;
• Evidence of genetic transmission of asymmetric septal hypertrophy in first-degree relatives, and
• Marked myocardial fiber disarray of ventricular septal myocardium in necropsy materials.

Because of the asymmetric hypertrophy of the interventricular septum and the close proximity of the anterior mitral valve (AMV) leaflet with increased filling of the left ventricle after exercise, the AMV leaflet slams shut against the bulging septum (Fig. 12), because of a Bernoulli effect. The resultant obstruction to left ventricular outflow explains the death that may occur after exercise. This is particularly seen in teenage athletes who undergo stress from swimming, football, and basketball.

Pathologically, there is asymmetric septal hypertrophy with an abnormally high ratio of ventricular septal thickness to that of the posterior wall of the LV (>1.3:1); ratios 2.5:1 are not uncommon. Occasionally, midseptal or atypical hypertrophy may be present. The ratio is inappropriate for evaluating
HCM in the stillborn or neonate because the ventricular septum is thicker in the developing heart. HCM may involve the left, right, or both ventricles. Hypertrophy is usually symmetric in the right ventricle, but in the left ventricle it may be symmetric or asymmetric, involving the septum, free wall, or posterior wall, or occasionally is isolated to the distal ventricle.

The histologic findings in HCM are distinctive and provide an almost specific morphology. Within areas of affected myocardium, there is considerable interstitial fibrosis with gross disorganization of the muscle bundles resulting in a characteristic whorled pattern (Fig. 13). The cell-to-cell orientation of muscle cells is lost (disarray) and there is disorganization of the myofibrillar architecture within a given cell. Myocardial cells are wide, short, stubby, hypertrophied, and often bizarre in shape, and shows disarray deep in the septum.

Neuromuscular Diseases

Neuromuscular disorders with cardiac involvement are listed in Table 3. In Duchenne muscular dystrophy (DMD), an X-linked recessive disorder, cardiomegaly is usually present, with dilatation, hypertrophy and fibrosis within the ventricular myocardium [99,100]. Dystrophin, the defective gene product, is a large, membrane-associated protein that forms an oligomeric complex with several transsarcolemmal proteins leaking intracellular microtubules to the extra-cellular matrix.

The heart is dilated and fragmentation of myocardial cells is seen. By electron microscopy, the myocardium shows myofibrillar lysis, with loss of actin and myosin filaments, disorganization of Z-band material, and preservation of the structure of the transverse tubular system [101-103].

Connective Tissue Disorders

*Marfan syndrome* is transmitted as an autosomal dominant trait and is characterized by musculoskeletal abnormalities, ectopia lentis, cardiovascular alterations, and abnormality of fibrillin. The most

Table 3. Cardiac involvement in neuromuscular disorders.
striking cardiovascular lesions include dilation of the aortic root and mitral and aortic regurgitation, dissecting aneurysms of the ascending aorta with dissection of the entire aorta due to cystic medionecrosis, and mitral valve prolapse (Fig. 14) [104-111]. Marfan syndrome includes coarctation of the aorta, truncus arteriosus, and atrial septal defect [110]. Eighty percent of patients inherit the Marfan trait from a parent; the remaining cases are new mutations. The fibrillin gene is located on chromosome 15q21.1 [112-119]. More than 50 mutations of fibrillin have been defined. Mutant fibrillins have a negative effect on formation of microfibrils.

Ehlers-Danlos syndrome. The cardiovascular lesions in type I Ehlers-Danlos syndrome, the gravis type, notably aortic dissection and tears in peripheral arteries, are probably no more common than in the general population [120]. In type II, the mitis type, atrial septal defects (ASDs), congenital AV block, aneurysms of the ascending aorta, and aneurysms of the brachial artery and the abdominal aorta occur [120-126]. Mitral valve prolapse occurs in types II and III. Arterial rupture (especially in the abdomen, thorax, or limbs) and other vascular complications are most common in type IV.

Osteogenesis imperfecta is a generalized disorder of connective tissue [127]. There are at least four well-defined forms of the disorder and a number of presently unclassified examples [128]. There appears to be marked heterogeneity of these defects, but principally they involve the synthesis of pro-alpha chains of procollagen monomers. The most common valvular lesion is aortic regurgitation; less common is mitral regurgitation. Dilatation of the aortic root and deformity of the valvular leaflets result from an abnormally dilated mitral annulus; the mitral leaflets are attenuated and redundant, and tend to prolapse; and the chordae tendineae may rupture [129].

In lethal perinatal osteogenesis imperfecta (01 type II), the chordae tendineae are short and fragile; both the AV valves and the chordae tendineae are hypocellular and the myocardial fibers are separated by ground substances. In fetuses, electron microscopy shows organized collagen in the chordae tendineae with marked decrease in the adventitial and intramural collagen of the intramyocardial arteries and great vessels [129].

Pseudoxanthoma elasticum, a recessive disorder, is manifested by cutaneous lesions, retinal angioid streaks, gastrointestinal hemorrhages, and fragmentation and calcification of elastic fibers [130]. Cardiovascular manifestations result from enlargement and calcification of elastic fibers in the intima and media of peripheral muscular arteries [131]. Endocardial plaques composed of degenerated, calcified elastic fibers are located in deeper areas of endocardium principally involving the atria [131-132].

Neonatal Effects of Maternal Disease

Infants of diabetic mothers (IDM) show cardiomyopathy with the following characteristics:

- occurrence in 50% of IDM;
- the cardiomyopathy usually mild;
- non-obstructive cardiomyopathy with increased thickness of interventricular septum occurs in 80% of cases and obstructive cardiomyopathy in 20%;
- there is septal hypertrophy and left ventricular outflow obstruction with disorganization of myocardial fibers;
- biochemical findings include in utero hyperinsulinemia, increase of insulin receptor sites in myocardial cells, and increase of myocardial glycogen.

Two forms of cardiomyopathy occur in infants of diabetic mothers. In the hypertrophic form, the
interventricular septum is hypertrophied [133-135]. This appears related to maternal hyperinsulinemia. The septum exceeds 6 mm in thickness (normal, 3 to 4 mm) and the hypertrophy is transient, resolving in 2 to 12 mo [136]. Fiber disarray, focal hydric change, hypertrophy of myocardial fibers, and focal fiber necrosis are histologic features [137-138]. A dilated form of cardiomyopathy is less common in infants of diabetic mothers, and is usually related to severe hypoglycemia and acidosis.

Cardiomyopathy of neonatal thyrotoxicosis. Infants of thyrotoxic mothers may show irritability, hyperactivity, tachypnea, tachycardia, and palpable thyroid; these findings usually resolve by 6 to 12 weeks of age; cardiomegaly is rare. In hyperthyroidism, the excess thyroid hormone partially uncouples oxidative metabolism, with production of high-energy phosphate bonds. Cardiac inefficiency may occur and arrhythmias and congestive heart failure may result [139]. The present author has observed a neonate with fatal thyrotoxic cardiomyopathy and massive cardiomegaly, born to a mother with thyrotoxicosis treated with propylthiouracil.

Conduction System Disorders

Histiocytoid (oncocytic) cardiomyopathy is characterized by cardiomegaly, incessant ventricular tachycardia, and, frequently, sudden death in the first 2 yr of life [140-143]. Female preponderance is approximately 4:1. Most cases (90%) occur in female children under 2 yr of age, leading to intractable ventricular fibrillation or cardiac arrest. The lesion resembles a hamartoma with histiocytoid or granular cell features [143]. It has clearly been defined as a mitochondrial disorder of complex III (reduced coenzyme Q-cytochrome c reductase) of the respiratory chain of the cardiac mitochondria [143]. It has been associated with congenital cardiac defects [143]. The etiology favors either an autosomal recessive gene or an X-linked condition. Female predominance may be explained by gonadal mosaicism for an X-linked mutation. The latter seems likely because of the reported association with another rare X-linked condition, microphthalmia with linear skin defects (MLS) that is monosomic for Xp22 [144]. An X-linked dominant mutation has been associated with lethality in the male.

Histopathological findings in patients with histiocytoid cardiomyopathy include multiple flat-to-round, smooth, yellow nodules located beneath the endocardial surface of the left ventricle, the atria, and the four cardiac valves. The nodules are composed of demarcated, large, foamy granular cells. Glycogen, lipid, and pigment may be seen in these cells, as well as a lymphocytic infiltrate (Figs. 15-17). Immunostaining shows perimembranous immunoreactivity for muscle-specific actin, but not for the histiocytic markers, S-100 protein and CD69 (KP) [145-149]. These cells may be abnormal Purkinje cells, but a primitive myocardial precursor cannot be excluded. Radiofrequency ablation of a conduction defect may be an effective treatment for dysrhythmias [150]. Surgical intervention with prolonged survival has been reported [151].

Arrhythmogenic right ventricular dysplasia is occasionally present in infants. Ventricular tachycardia, left bundle branch block, and right ventricular dilation characterize the clinical features [152]. A recent infection frequently precedes the onset of symptoms. The principal histologic finding in a biopsy of the right ventricle of an affected patient is fatty infiltration (Fig. 18), with or without interstitial fibrosis of the myocardium; cardiac enlargement is mostly localized to the right ventricle, although similar abnormalities may be present on
the left side of the heart [153]. There are more than 200 reported cases, with a mean age of presentation of 30 yr and a 2:1 to 3:1 male preponderance. At least 30% of cases are familial. The gene for this disease has been mapped to chromosome 14q23-q24 and there is speculation that a mutation in this region may lead to defective cardiac isoforms of gene products [154]. There is an autosomal dominant mode of inheritance with variable penetrance and expression. In a study of 60 cases of sudden death in young northern Italians, at least 20% had histological evidence of right ventricular dysplasia at autopsy. Although 10% of such patients are asymptomatic [155], they may present with palpitations, syncope, congestive heart failure, or even sudden death, and these episodes are commonly precipitated by exertion. The classic electrocardiographic finding is ventricular tachycardia, often with left bundle branch block.

*Isolated noncompaction of the left ventricle myocardium* (persistence of spongy myocardium) is a rare form of congenital cardiomyopathy in which the left ventricular wall fails to become flattened and smoother than it normally would during the first 2 months of embryonic development. This developmental arrest results in decreased cardiac output with subsequent left ventricular hypertrophy. The aberrant left ventricular trabeculae (Fig. 19) predispose to cardiac conduction abnormalities and potentially fatal cardiac arrhythmias. The interstices within the trabeculated left ventricle predispose to thrombus formation with secondary systemic embolic events. Fibroelastosis of the adjacent ventricular endothelium is a secondary phenomenon, resulting from an abnormal blood flow pattern in the left ventricular chamber [156].

*Long QT syndrome* (LQTS) is a heterogeneous group of disorders characterized by prolongation of the corrected QT interval (Qtc) on the surface electrocardiogram, seizures, syncope and sudden death. Mortality is presumably due to cerebral hypoperfusion during malignant ventricular tachycardia,
known as “torades de pointes.” The defect lies in abnormal myocardial repolarization, creating a vulnerable refractory period at risk for ventricular tachycardia. Patients are usually detected during the evaluation for syncope or seizures, though for many the initial presentation is aborted sudden death. The several genetic defects are listed in Table 4.

![Fig. 19. Noncompaction of the left ventricle with coarse trabeculation.](image)

From 1976 to 1984, electrocardiograms were recorded in 34,442 Italian newborns on the third and fourth day of life. The infants were followed prospectively for 1 yr. During this period, 34 of the infants died, including 24 from SIDS. The victims of SIDS had longer QT intervals [157].

**Concluding Observations**

In evaluating a case of cardiomyopathy in childhood, a thorough investigation for the possibility of a metabolic disorder should be made. Neuromuscular evaluation should be done in all patients with congestive cardiomyopathy. Muscle biopsy and electromyography can be useful since skeletal muscle involvement in cardiomyopathy may be clinically silent and a myopathy not suspected. The diagnostic approach to cardiomyopathies is summarized in Table 5.

In managing a case of cardiomyopathy in childhood, it is important that the underlying cause of myocardial dysfunction be defined. If secondary

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Table 4. Molecular genetics of long QT syndrome (LQTS)*§

<table>
<thead>
<tr>
<th>LQTS type and (year discovered)</th>
<th>Mutant gene and (alternate name)</th>
<th>Chromosomal locus</th>
<th>Ion currents affected by the mutant gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1 (1991)</td>
<td>KCNQ1 (KVLQT1)</td>
<td>11p15.5</td>
<td>Decreased slowly activating delayed rectifier K+ repolarization current (I_{Ks})</td>
</tr>
<tr>
<td>LQT2 (1994)</td>
<td>HERG</td>
<td>7q35-36</td>
<td>Decreased rapidly activating delayed rectifier K+ repolarization current (I_{Kr})</td>
</tr>
<tr>
<td>LQT3 (1994)</td>
<td>SCN5A</td>
<td>3p21-24</td>
<td>Increased Na+ current (I_{Na}) due to late reopening of the sodium channel</td>
</tr>
<tr>
<td>LQT5 (1997)</td>
<td>KCNE1 (minK)</td>
<td>21q22.1-22.2</td>
<td>Decreased slowly activating K+ repolarization current (I_{Ks})</td>
</tr>
<tr>
<td>LQT6 (1999)</td>
<td>KCNE2 (MRP1)</td>
<td>21q22.1-22.2</td>
<td>Decreased rapidly activating K+ repolarization current (I_{Kr})</td>
</tr>
<tr>
<td>LQT7 (2001)†</td>
<td>KCNJ2</td>
<td>17q23</td>
<td>Decreased inwardly rectifier K+ current (I_{Kr2.1})</td>
</tr>
</tbody>
</table>

* This table is adapted from Moss AJ. Long QT syndrome. JAMA, 2003;289:2041-2044.
§ A single mutation (heterozygous state) in any one of the LQT1 through LQT7 genes results in an autosomal dominant form of LQTS (Roman Ward syndrome). The presence of 2 mutations (homozygous state) in either the LQT1 or LQT5 gene results in a severe autosomal recessive form of LQTS with associated deafness (Jervell and Lange-Nielsen syndrome).
†Mutations in LQT7 are responsible for Andersen syndrome, a rare neurologic disorder characterized by periodic paralysis, skeletal developmental abnormalities, and QT prolongation.
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cardiomyopathy is present, such as in carnitine deficiency, pheochromocytoma, or hemosiderosis, specific therapy should be instituted. Routine therapy for congestive heart failure is relatively ineffective in primary metabolic disorders, and the inotropic effects of digitalis may be negligible [158].

Major complications of congestive cardiomyopathy are dysrhythmias and thromboembolism [159]. Cautious, specific drug therapy and timely implantation of cardiac pacemakers may avoid sudden and unexpected death in children with dysrhythmias. Patients with atrial fibrillation or atrial standstill, with known mural thrombi, or with a definite or probable history of thromboembolus should be given anticoagulants [160]. Intercurrent infections should be treated with appropriate antibiotics, antipyretics, bed rest, and oxygen. Radiofrequency ablation of a conduction defect may be an effective treatment for dysrhythmias [151].

References

21. Haust MD, Gordon BA, Hong R et al. Cardiomyopathy pathophysiology is present, such as in carnitine deficiency, pheochromocytoma, or hemosiderosis, specific therapy should be instituted. Routine therapy for congestive heart failure is relatively ineffective in primary metabolic disorders, and the inotropic effects of digitalis may be negligible [158].

Table 5. Diagnostic approach to cardiomyopathies.*

| Cardiologic investigations
| Electrocardiogram
| Echocardiography
| Hemodynamic studies
| Muscle biopsy
| Morphology (histochemistry, histoenzymology)
| Biochemistry
| Molecular genetics
| Biochemical tests (overnight fasting)
| Plasma glucose
| Plasma lactate (lactate/pyruvate ratio)
| Plasma pyruvate
| Plasma free fatty acids
| Plasma ketones (β-hydroxybutyrate/acetoacetate ratio)
| Serum creatine kinase
| Serum transaminases
| Plasma carnitine (total and free)
| Urine organic acids, assayed by GC/MS
| Fibroblast cultures for enzyme assays


94. Thierfelder L, Watkins H, MacRae C et al. α-Tropo-


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