The normal function of the human myocardium requires the proper generation and utilization of energy and relies on a series of complex metabolic processes to achieve this normal function. When metabolic processes fail to work properly or effectively, heart muscle dysfunction can occur with or without accompanying functional abnormalities of other organ systems, particularly skeletal muscle. These metabolic derangements can result in structural, functional, and infiltrative deficiencies of the heart muscle. Mitochondrial and enzyme defects predominate as disease-related etiologies. In this review, left ventricular noncompaction cardiomyopathy, which is often caused by mutations in sarcomere and cytoskeletal proteins and is also associated with metabolic abnormalities, is discussed. In addition, cardiomyopathies resulting from mitochondrial dysfunction, metabolic abnormalities, storage diseases, and inborn errors of metabolism are described. (Circ Res. 2017;121:838-854. DOI: 10.1161/CIRCRESAHA.117.310987.)

Key Words: cardiac failure ■ cardiomyopathy ■ infiltrative cardiomyopathy ■ metabolic cardiomyopathy ■ noncompaction cardiomyopathy

The normal function of the human myocardium requires the proper generation and utilization of energy and relies on a series of complex metabolic processes to achieve this normal function. When metabolic processes fail to work properly or effectively, heart muscle dysfunction can occur with or without accompanying functional abnormalities of other organ systems, particularly skeletal muscle. These metabolic derangements can result in structural, functional, and infiltrative deficiencies of the heart muscle. Mitochondrial and enzyme defects predominate as disease-related etiologies. Disrupted mitochondrial function and metabolic abnormalities have a causal role as well. Treatments focus on improvement of cardiac efficiency and reduction of mechanical stress in those with systolic dysfunction in these diseases. Further, arrhythmia therapy and implantation of an automatic implantable cardioverter-defibrillator (ICD) for prevention of sudden death are mainstays of treatment when deemed necessary and appropriate. Herein, we describe the causes and treatment options for left ventricular noncompaction (LVNC) cardiomyopathy, mitochondrial, and storage forms of cardiomyopathy.

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Left Ventricular Noncompaction

LVNC is a structural abnormality of the left ventricular (LV) myocardium of uncertain etiology and mechanism but is generally considered genetic in nature. In some patients, neuromuscular disorders and chromosomal defects are noted. LVNC is ally considered genetic in nature. In some patients, neuromuscular disorders and chromosomal defects are noted. LVNC is classified by the European Heart Association in 2008. Interestingly, LVNC cardiomyopathy (OMIM No. 604169) was first described at the time of autopsy because current imaging modalities were not available. Feldt et al. first reported bizarre spongy myocardium in both ventricles of a 3-month-old white female with complete situs inversus (1969), followed by a report by Westwood et al of a patient with endocardial fibroelastosis and biventricular noncompaction (1975). At the same time, Dusek et al speculated that there was postnatal persistence of a spongy-appearing myocardium similar to that seen during fetal development. The first report of an echocardiographically diagnosed case of LVNC was by Engberding and Bender in 1984. In 1990, the term noncompaction was first introduced by Chin et al. In 1997, cardiac magnetic resonance imaging (CMR) was initially used to identify LVNC by Hany et al. Since then, LVNC has been found to be isolated, as well as in association with systemic diseases such as mitochondrial disease, metabolic disease, and neuromuscular disease. In 2007, Menon et al documented LVNC for the first time in a fetus by echocardiography.

Etiology and Pathophysiology

The etiology of LVNC is uncertain, but it is speculated that it results from a disturbed compaction process during early development of the LV myocardium. It is believed that LVNC result from a failure of the final phase of cardiac development, the myocardial compaction process. During the normal process, the myocardium gradually compacts from the epicardial inward, and the intertrabecular recesses are compressed to capillaries. The compaction process continues with myocardial growth and increasing intracardial pressure. There are some indications that the compaction process is triggered by vascular endothelial growth factor or by angiopoietin. Failure of the compaction process results in deep intertrabecular recesses between the normal trabeculations. Mutations in the murine genes Casz1, Daam1, and Fkbpl1a and Bmp10, jmj and Jarid2, and Mib1 genes, which are involved in cardiac morphogenesis, have been shown to be implicated in the development of LV compaction during embryogenesis, consistent with this hypothesis.

Incidence and Prevalence

LVNC has been considered to be rare. However, Andrews et al reported that 9% of 104 children with a primary cardiomyopathy had LVNC. In adults referred for echocardiography, the prevalence of LVNC reportedly ranged from 0.01% to 0.3%. With the prevalence of LVNC being higher in patients with heart failure, reportedly 3% to 4%. The prevalence of LVNC in adults has been reported to be 0.05%, while in infants, the incidence was calculated as 0.8/100,000/year and in children, as 0.12/100,000/year. The low incidence and prevalence of LVNC might be because of the difficulty identifying the hypertrabeculation of LVNC on transthoracic echocardiography, but even on ventriculography and CMR may be difficult to identify. Males are more frequently diagnosed with LVNC than females (56%–82%), and LVNC is more prevalent in the black compared with the white population.

Nonstandard Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMP</td>
<td>adenosine monophosphate</td>
</tr>
<tr>
<td>AMP-K</td>
<td>adenosine monophosphate–activated protein kinase</td>
</tr>
<tr>
<td>BTHS</td>
<td>Barth syndrome</td>
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<tr>
<td>CDG</td>
<td>congenital disorders of glycosylation</td>
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<tr>
<td>CMR</td>
<td>cardiac magnetic resonance imaging</td>
</tr>
<tr>
<td>DNJAC19</td>
<td>DnaJ heat shock protein family member C19</td>
</tr>
<tr>
<td>Hsp40</td>
<td>heat shock protein family</td>
</tr>
<tr>
<td>ICD</td>
<td>implantable cardioverter-defibrillator</td>
</tr>
<tr>
<td>IEM</td>
<td>inborn errors of metabolism</td>
</tr>
<tr>
<td>KSS</td>
<td>Kearns–Sayre syndrome</td>
</tr>
<tr>
<td>LAMP2</td>
<td>lysosome-associated membrane protein-2</td>
</tr>
<tr>
<td>LS</td>
<td>Leigh syndrome</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>LVNC</td>
<td>left ventricular noncompaction</td>
</tr>
<tr>
<td>MERRF</td>
<td>myoclonic epilepsy with ragged red muscle fibers</td>
</tr>
<tr>
<td>PGM1</td>
<td>phosphoglucomutase 1</td>
</tr>
<tr>
<td>TAZ</td>
<td>tafazzin</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff–Parkinson–White</td>
</tr>
<tr>
<td>ZASP</td>
<td>Z-band alternatively spliced PDZ-motif protein</td>
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History

LVNC cardiomyopathy (OMIM No. 604169) was first described at the time of autopsy because current imaging modalities were not available. Feldt et al. first reported bizarre spongy myocardium in both ventricles of a 3-month-old white female with complete situs inversus (1969), followed by a report by Westwood et al of a patient with endocardial fibroelastosis and biventricular noncompaction (1975). At the same time, Dusek et al speculated that there was postnatal persistence of a spongy-appearing myocardium similar to that seen during fetal development. The first report of an echocardiographically diagnosed case of LVNC was by Engberding and Bender in 1984. In 1990, the term noncompaction was first introduced by Chin et al. In 1997, cardiac magnetic resonance imaging (CMR) was initially used to identify LVNC by Hany et al. Since then, LVNC has been found to be isolated, as well as in association with systemic diseases such as mitochondrial disease, metabolic disease, and neuromuscular disease. In 2007, Menon et al documented LVNC for the first time in a fetus by echocardiography.
The median age at diagnosis ranges from 40 to 50 years in adults and from 5 to 7 years in children. Clinical Presentation

The diagnostic approach to LVNC can be variable and center-dependent. Index cases, whether pediatric or adult, should undergo a thorough history and physical examination, with specific attention to cardiac symptoms such as unexplained syncope. In addition, a 3-generation pedigree should be obtained on all patients. LVNC is typically diagnosed by noninvasive imaging in the form of transthoracic echocardiography. Echocardiographic diagnostic criteria have been proposed for the isolated form of LVNC and include (1) absence of coexisting cardiac abnormalities, (2) noncompaction to compaction ratio of ≥2.1 at end systole, (3) segmental thickening of the LV myocardium with a thin compacted epicardial layer and a thick noncompacted endocardial layer with trabeculations and deep recesses, (4) color Doppler evidence of deep intertrabecular recesses, and (5) predominant localization in the apical, midlateral, and midinferior regions. However, the diagnosis is increasingly verified or made by the use of CMR. Diagnostic criteria as proposed by Petersen et al are generally accepted. These include (1) the presence of 2 distinct layers of myocardium, including a compacted epicardial layer and a noncompacted endocardial layer, (2) the presence of trabeculations and deep intraventricular recesses within the noncompacted endocardial layer, and (3) a noncompacted to compacted ratio of ≥2.3:1 in end diastole. Prior studies such as the MESA study (Multi-Ethnic Study of Atherosclerosis) have found that a ratio of >2.3:1 is not uncommon in the general population, suggesting that different CMR criteria may be needed. Additional CMR diagnostic criteria have been proposed by Grothoff et al, which include assessment of the amount of noncompacted LV mass involved, as well as the presence of a noncompacted to compacted ratio of ≥3:1 in 1 segment excluding the apex. The use of both modalities is not routinely recommended for all patients, especially in younger children who would require general anesthesia for CMR. However, CMR may be useful in establishing a diagnosis if echocardiography is equivocal or in the setting of poor acoustic windows. In addition, CMR offers the opportunity to characterize the myocardium and assess for late gadolinium enhancement, which in adults has been associated with clinical findings, including reduced LV systolic function and echocardiographic abnormalities. Concomitant congenital heart disease may also be seen by noninvasive imaging as discussed later. Individuals with LVNC most commonly are asymptomatic and incidentally diagnosed. However, index cases with LVNC typically present with signs of heart failure. In addition to heart failure, arrhythmias, conduction disturbances, and thromboembolism can occur. Ultimately, approximately two thirds of the patients with LVNC develop heart failure because of ventricular dysfunction during the disease course. Children may have an undulating phenotype, in which the cardiomyopathic features change abruptly, most commonly from having echocardiographic features of a dilated and hypertrophic LV with depressed systolic function to a hypertrophic and hypercontractile form before reverting to its final destination, a dilated and dysfunctional form with heart failure, usually occurring over several months.

Symptomatic LVNC typically manifests clinically as chest pain, dyspnea, palpitations, syncope, peripheral edema, exercise intolerance, embolic ischemic stroke, myocardial infarction, embolism, or sudden cardiac death. When associated with a neuromuscular disorder, affected patients may present with easy fatigability, exercise intolerance, myalgias, muscle cramps, muscle stiffness, myotonia, and muscle weakness or falling may occur. Elevated muscle form of creatine kinase, CK-MM (creatine kinase, muscle isoform), may be found and is consistent with skeletal myopathy, and needle electromyography may show a myogenic or neurogenic pattern.

Causes of Heart Failure

The underlying pathophysiologic etiologies of heart failure remain unclear but occur with systolic or diastolic dysfunction. Systolic dysfunction in LVNC is thought to be because of hypoperfusion of the subendocardium in the face of normal coronary arteries, while diastolic dysfunction is believed to occur because of a restrictive filling pattern and abnormal relaxation because of ventricular hypertrophy and dilatation. Perfusion of the noncompact layer is typically worse than perfusion of the compact layer, which has been demonstrated on cardiac magnetic resonance imaging. Positron emission tomography, thallium scintigraphy, and histological investigations at autopsy, all showing subendocardial perfusion defects. Positron emission tomography studies have shown a reduced coronary flow reserve in compact and noncompact segments as well. In adults with LVNC, systolic dysfunction occurs in 58% to 76% of subjects, with heart failure occurring in 53% to 73% of subjects. Diastolic dysfunction is reported in 50% of adult patients, with 36% having a restrictive filling pattern. In children with LVNC, systolic dysfunction occurs in 60% to 63% of subjects with heart failure seen in 30% to 63% of cases. Children with LVNC may present with a restrictive filling pattern as well.

Electric Abnormalities and Sudden Cardiac Death

The frequency of electrocardiographic abnormalities in both adults and children with LVNC is high, ranging from 88% to 94% in adults and children. Ventricular arrhythmias are prevalent with a frequency of 18% to 47% in adults and 0% to 38% in children. Sudden cardiac death has been reported in 18% of adults and 0% to 13% of children. Supraventricular arrhythmias or conduction defects occur in ≥25% of patients with LVNC, including atrial fibrillation, atrial flutter, paroxysmal supraventricular tachycardia, or complete atioventricular block. Wolff–Parkinson–White (WPW) preexcitation syndrome occurred in 0% to 3% of adults and in 13% to 15% of pediatric cases. Brescia et al showed that rhythm-related sudden deaths are a predominant feature in children who do poorly. Atrial fibrillation is reported in 5% to 29% of adults but is rare in children. Sinus node dysfunction is the initial clinical manifestation of LVNC in some patients. Bundle–branch block was reported in 26% to 56% of the adult cases and 15% to 25% in children. The relative risk differences in children versus adults regarding
arrhythmia risk in the setting of LVNC is unknown. There may be some correlations with worsening of ventricular function, but the specific genetic trigger (eg, SCN5A) may also contribute to underlying arrhythmia risk. The true prevalence of arrhythmias in the setting of LVNC is likely underrepresented, given the infrequent nature of arrhythmia monitoring in clinical practice.

**Thromboembolism**

Thromboembolism was initially thought to be common, especially in children with LVNC. The frequency of thromboembolism has been reported to range from 13% to 24% in adults and 0% to 38% in children. Thromboembolism may manifest as a stroke, transitory ischemic attack, mesenteric infarction, myocardial infarction, or peripheral embolism. Thrombi may originate from the ventricular cavity in case of severe systolic dysfunction or ventricular dilation, the intertrabecular recesses, the atrium in the restrictive cardiomyopathy form of LVNC or atrial fibrillation, or the right ventricle or right atrium via a ventricular septal defect or an atrial septal defect, respectively.

**LVNC With Congenital Heart Disease**

LVNC also occurs in association with congenital heart disease (the congenital heart disease form of noncompaction). Most commonly, obstruction of the LV or right ventricular outflow tracts and anomalies of the coronary arteries are associated. Stähli et al reported on 202 patients with LVNC, identifying 12% having the presence of congenital cardiac defects, with the most frequent being LV outflow tract abnormalities (46%), Ebstein’s anomaly (25%), tetralogy of Fallot (8%), and double outlet right ventricle. Patients with complex congenital heart disease, including those with single ventricle and heterotaxy, have also been shown to have associated LVNC. The association of LVNC with congenital heart disease complicates the surgical course and outcomes of these patients.

**Genetics**

Familial occurrence of LVNC, particularly in first-degree relatives of affected patients, has been reported in 13% to 50% of the cases. and, for this reason, it is recommended that first degree relatives of patients with LVNC be investigated for LVNC (or other cardiomyopathy) as well. Genetic transmission of LVNC is usually an autosomal dominant, but autosomal recessive, X-linked, or mitochondrial inheritance has been reported. In addition, LVNC has been reported to be associated with several chromosomal defects and syndromes.

Sarcomeric gene mutations are the most common genetic cause of LVNC. These include mutations in MYH7, ACTC1, TNNT2, TNNI3, MYL2, MYL3, and MYH7. In adults with LVNC, MYH7 is the most frequently documented sarcomeric gene involved. This underscores the phenotypic overlap that is seen between cardiomyopathies because these same genes may also be responsible for both dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). Mutations in cytoskeletal genes encoding α-dystrobrevin and LIM domain protein binding and the gene encoding nuclear membrane protein lamin A/C have also been implicated in LVNC. Mutations in ion channel genes such as SCN5A have also been associated with LVNC and arrhythmias. Mutations in the HCN4 gene have been reported causing bradycardia and LVNC phenotype. LVNC may have a familial occurrence, and the proportion of patients with LVNC can be high in some disorders, such as Barth syndrome (BTHS).

**Treatment Options**

There are only limited data available about treatment options for LVNC. The crucial points of treatment are heart failure therapy, including heart transplantation, antiarrhythmic therapy, including ablation and implantation of an ICD, and oral anticoagulation.

Heart failure in LVNC should be treated in the same way as heart failure because of other causes. Beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, aldosterone antagonists, and diuretics may be given to manage systolic or diastolic dysfunction.

In patients with life-threatening arrhythmias, implantation of an automatic internal cardioverter-defibrillator is appropriate. The strongest indication for placement of an ICD is nonsustained ventricular tachycardia because 7% of those receiving the ICD for primary prevention and 8% of those who received the ICD for secondary prevention had ventricular tachycardia. Catheter ablation for treating ventricular arrhythmias has been successful in some patients.

In patients with refractory heart failure, heart transplantation may be necessary. In the current era, implantation of a ventricular assist device is commonly placed before transplantation and may be used as destination therapy or as a bridge to recovery or transplantation. In patients with congenital heart disease and LVNC, surgery for the congenital abnormalities takes precedence when technically feasible, but in many cases, the palliative surgery ultimately fails because of the myocardial abnormality, and cardiac transplantation is required.

**Outcome and Prognosis**

The outcome of patients with LVNC is usually determined by the development of complications, including ventricular arrhythmias, heart failure, and thromboembolism. It seems that outcomes and phenotypes may differ between children and adults. Initial reports suggested the mortality rate in children with LVNC to be 13%, mostly within the first year after diagnosis, with the highest risk being associated with ventricular arrhythmias and heart failure. Subsequently, better outcomes were seen initially; however, 90% of children developed systolic dysfunction during a follow-up of 10 years. In the National Australian Childhood Cardiomyopathy study, the incidence of sudden cardiac death was 23% over a median follow-up of 11.9 years. Brescia et al retrospectively reviewed 242 children diagnosed with LVNC and found that 150 (62%) presented with or developed cardiac dysfunction, 80 (33.1%) had an arrhythmia, 31 (12.8%) died, and 13 (5.4%) received were transplanted. The presence of cardiac dysfunction was strongly associated with mortality (hazard ratio, 11: P<0.001). Abnormalities were present in 87% of electrocardiograms,
with ventricular hypertrophy and repolarization abnormalities occurring most commonly. Repolarization abnormalities were associated with increased mortality (hazard ratio, 2.1; \( P=0.02 \)). Children with arrhythmias had increased mortality (hazard ratio, 2.8; \( P=0.002 \)) as well, with 42 (17.4%) having ventricular tachycardia and 5 presenting with resuscitated sudden cardiac death. In total, there were 15 cases of sudden cardiac death in the cohort (6.2%). Nearly all patients with sudden death (14 of 15) had abnormal cardiac dimensions or cardiac dysfunction. Preceding cardiac dysfunction or ventricular arrhythmias was associated with increased mortality.

In adults, \( \approx 50\% \) of patients died and 12% underwent transplantation within 6 years after diagnosis in early reports. \(^{36}\) More recently, Stöllberger et al \(^{81}\) reported 172 adult patients with LVNC (72% had associated neuromuscular disease), with only a 4% to 6% mortality during a mean follow-up of \( \leq 4.5 \) years. In 2014, Peters et al \(^{82}\) reported 55 adults with LVNC and systolic dysfunction, with 12.7% mortality during a mean follow-up of 17 months. Predictors of mortality have been thought to include heart failure, atrial fibrillation, and diabetes mellitus. \(^{83}\) It has been suggested that the use of ICDs should not be pursued in all patients with LVNC but may be considered in those with significant risk factors, such as systolic dysfunction, nonsustained ventricular tachycardia, and unexplained syncope.

**Cardiac Physiology and Metabolism**

The adult human heart pumps \( \approx 2000 \) gallons (7571 L) of blood each day and beats \( \approx 100,000 \) times daily. Thus, under normal conditions, there is complete replenishment of the myocardial ATP pool every 10 seconds. To support its contractile function, the human heart uses \( \approx 6 \) kg of ATP per day, 70% of which is derived from oxidation of fatty acids in mitochondria, the so-called power plant of the cell.\(^{84,85}\) The heart has a relatively low ATP content (5 \( \mu \)mol g/wet weight) and a high rate of ATP hydrolysis (30 \( \mu \)mol g/wet weight per minute) at rest. Thus, under normal conditions, there is complete replenishment of the myocardial ATP pool every 10 seconds.\(^{86}\) Because of the extraordinary demand for continuous ATP synthesis by oxidative metabolism, cardiomyocytes have the highest density of mitochondria of any cell in the body, occupying \( \approx 30\% \) of the volume of the adult cardiomyocyte (Figure 1A). Mitochondria are composed of outer and inner mitochondrial membranes, defining 2 sub mitochondrial compartments: the intermembrane space, and the mitochondrial matrix in the interior compartment of the mitochondria. Mitochondrial inner membranes form multiple invaginations called cristae (Figure 1A). The 2 membranes have different properties: the outer membrane is permeable for a variety of metabolites, while the inner mitochondrial membrane is only permeable to oxygen, carbon dioxide, and water. Specialized transporters exist to allow specific molecules to cross the inner mitochondrial membrane. This compartmentalization is a fundamental feature for mitochondrial energy metabolism.

Mitochondria can use either glucose or fatty acids as a source of energy (Figure 1B). Pyruvate, derived from glucose oxidation via the glycolytic process, is transported into mitochondria and enters the tricarboxylic acid cycle, producing reducing equivalents FADH\(_2\) and NADH. These reducing equivalents are used in the electron transport chain, ultimately generating ATP during oxidative phosphorylation. Fatty acid oxidation starts from the cellular uptake of fatty acids from the blood, which are esterified to form Acyl-CoAs. Esterified fatty acids are further transported into mitochondria and oxidized in a multistep enzymatic process termed \( \beta \)-oxidation, generating reducing equivalents in the form of NADH and FADH\(_2\), which also pass down the oxidative phosphorylation system to generate ATP.

**Mitochondrial Diseases**

Mitochondrial disease is a heterogeneous group of multisystem diseases that develop consequent to mutations in nuclear or mitochondrial DNA. Mitochondrial disease may be diagnosed at any age given the spectrum of clinical presentation can be broad. However, more severe forms of mitochondrial disease typically present in infancy or early childhood. The prevalence of inherited mitochondrial disease has been estimated to be \( >1 \) in 5000 births; however, the diagnosis and treatment of this disease are not taught in most adult-cardiology curricula. Because mitochondrial diseases often occur as a syndrome with resultant multiorgan dysfunction, they might not immediately seem to be specific to the cardiovascular system. Mitochondrial cardiomyopathy can be described as a myocardial condition characterized by abnormal heart–muscle structure, function, or both, secondary to genetic defects involving the mitochondrial respiratory chain, in the absence of concomitant coronary artery disease, hypertension, valvular disease, or congenital heart disease. The typical cardiac manifestations of mitochondrial disease—hypertrophic and dilated cardiomyopathy, arrhythmias, LV myocardial noncompaction, and heart failure—can worsen acutely during a metabolic crisis. The optimal management of mitochondrial disease necessitates the involvement of a multidisciplinary team, careful evaluations of patients, and the anticipation of iatrogenic and noniatrogenic complications.

**Cardiovascular Disorders of Mitochondrial Function**

Referrals for cardiac evaluation typically come from neurologists or geneticists who have diagnosed a mitochondrial disorder. Cardiologists who evaluate patients for cardiomyopathies or conduction abnormalities should be aware of the role and spectrum of mitochondrial disease so that they can collaborate with neurologists, geneticists, and mitochondrial-disease specialists to make accurate diagnoses and arrange appropriate care for these patients.

Certain syndromes predispose patients to specific cardiac abnormalities.\(^{13}\) For example, patients with Kearns–Sayre syndrome (KSS) are predisposed to atrioventricular conduction defects that can present as syncope, Adams–Stokes syndrome, or sudden death. In these patients, retinopathy and ophthalmoplegia tend to occur before heart block develops. Therefore, when ophthalmoplegia has been noted, affected patients should be monitored closely by electrocardiograms and Holter monitors. Patients with myoclonic epilepsy with ragged red muscle fibers (MERRF) and mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) should be monitored for the development of hypertrophic and dilated cardiomyopathies.\(^{13,14}\) Patients with MERRF can have myoclonus, generalized convulsions, cerebellar ataxia, muscular atrophy, and
Figure 1. A, Organization of the mitochondrial respiratory chain. Mitochondria are elongated organelles consisting of an outer mitochondrial membrane (permeable to small molecules), an intermembrane space, an inner mitochondrial membrane (which is permeable to specific ions only), the cristae, and the mitochondrial matrix, where ions, metabolites, and mitochondrial deoxyribonucleic acid (DNA) are located. The mitochondrion uses oxygen and substrates mainly derived from glucose to produce cell energy in the form of ATP. Electrons from oxidized substrates are transferred to oxygen by a series of reduction reactions to generate water; protons are pumped from the mitochondrial matrix to cross the inner mitochondrial membrane through the respiratory complexes. (Continued)
elevated blood lactate and pyruvate levels, as well as ragged red fibers on muscle biopsy. Patients with MELAS can also have ragged red fibers on muscle biopsy; however, unlike MERRF patients, MELAS patients have normal early development and start to show symptoms only between 3 years of age and adulthood. Patients with MELAS tend to have short stature, seizures, hemiparesis, hemianopia, and blindness. Mitochondrial mutations are also associated with LVNC, \(^\text{4,15,16}\) as described earlier. Advances in diagnostic imaging and its widespread availability have led to more frequent diagnosis of LVNC, although there is limited agreement about the various diagnostic criteria that have been proposed (Table).

### KSS (OMIM No. 53000)

KSS (OMIM No. 53000) is a mitochondrial myopathy characterized by the clinical triad of ptosis, chronic progressive external ophthalmoplegia, and abnormal retinal pigmentation. Cardiac conduction defects, as well as DCM, are commonly observed in patients with KSS, sometimes requiring heart transplantation.\(^\text{48}\) Approximately 50% of patients with KSS have cardiac involvement, including recurrent syncope, bundle-branch blocks, fascicular blocks, and nonspecific intraventricular conduction disturbances, and \(^\text{20}\%\) of deaths in these patients is attributed to cardiac causes. The American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines give a class I, level of evidence B rating to implantation of pacemakers for third-degree and advanced second-degree ativoventricular block at any anatomic level when associated with neuromuscular diseases. Endocrinopathies including diabetes mellitus, hypothyroidism, and parathyroid disorders also occur commonly. Skeletal muscle histopathology demonstrates ragged red fibers. The genetic abnormalities seen in KSS consist largely of single large-scale mitochondrial DNA deletions, although mitochondrial DNA point mutations, such as m.3249G>A in the tRNA (Leu) gene, m.3255G>A in the tRNA (Leu) gene, or m.3243A>G in the tRNA (Leu) gene, have also been reported.

### MERRF Syndrome

MERRF syndrome (OMIM No. 545000) is a multisystem disorder characterized initially by myoclonus that is followed by generalized epilepsy, ataxia, weakness, and dementia, with onset usually in childhood after normal early development has occurred. Common findings are hearing loss, short stature, optic atrophy, and cardiomyopathy with WPW syndrome. Pigmentary retinopathy and lipomatosis are occasionally observed. Skeletal muscle histopathology demonstrates ragged red fibers. The mitochondrial DNA gene \(MT-TK\), which encodes tRNA\(^{\text{19}}\), is the most commonly associated gene with MERRF; and the most common variant is an A-to-G transition at nucleotide 8344 (m.8344A>G), which is present in over 80% of individuals. Pathogenic variants in \(MT-TF, MT-TL1, MT-TL2,\) and \(MT-TP\) have also been described in a subset of individuals with MERRF. Pathogenic variants are usually present in all tissues and blood leukocytes.\(^\text{91}\) Other reports have also outlined various other disease-causing mutations.\(^\text{88,92}\)

### Leigh Syndrome

Leigh syndrome (LS; OMIM No. 256000), a progressive neurodegenerative disorder, is the most common infantile mitochondrial disorder affecting 1 in 4000 live births. It is associated with gliosis, demyelination, capillary proliferation, and necrosis in the brain on magnetic resonance imaging and behavioral symptoms that include developmental retardation, hypotonia, ataxia, dystonia, optic atrophy, hearing impairment, breathing abnormalities, dysarthria, swallowing difficulties, and failure to thrive.\(^\text{93,94}\) Respiratory arrest, the most common cause of death for LS patients, is observed in ≤75% of cases. The necessity for mechanical ventilation or the occurrence of sudden death of LS patients is associated with brain stem lesion.\(^\text{94}\) Non-neurological abnormalities may predominate the clinical picture and include cardiac abnormalities, mostly hypertrophic cardiomyopathy, as well as dilated cardiomyopathy and arrhythmia/conduction defects, such as WPW syndrome, renal abnormalities (renal tubulopathy), hepatic abnormalities with elevated transaminases, hepatomegaly, or liver failure. In ≥50% of cases, the gene is known; however, genetic heterogeneity is the rule in LS with ≥60 genes, mostly in the nuclear DNA, but with 25% in mitochondrial DNA, identified to date, affecting all 5 respiratory chain complexes. Mutations leading to LS have been found in proteins involved in other mitochondrial processes, like pyruvate metabolism, coenzyme Q10 biosynthesis, and the oxidation of fatty acids, and nonmitochondrial processes like thiamine metabolism, which indirectly affects mitochondrial function.\(^\text{97-99}\)

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**Figure 1 Continued.** Forming the oxidative phosphorylation chain consisting of 5 multi-polypeptide enzyme complexes that form the oxidative phosphorylation system: complex I (NADH-ubiquinone reductase); complex II (FADH2 succinate-ubiquinone reductase); complex III (ubiquinol-cytochrome C reductase); complex IV (cytochrome C oxidase and 2 mobile electron transporters, ubiquinone and cytochrome C\(\text{e}\)); and complex V (ATP synthase). Electrons generated from the reducing equivalents (NADH and FADH2) pass between the complexes and generate an increase in energy that allows for proton pumping to complexes I, III, and IV. Finally, the proton pump generated in the intermembrane space is used to generate ATP. Adapted from Hernández-Beltrán et al\(^\text{154}\) with permission of the publisher. Copyright ©2011 SEEN.

Published by Elsevier España. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. **B. Overview of fatty acid beta oxidation in the heart.** Plasma fatty acids bound to albumin or from fatty acids contained within chylomicron or very low-density lipoproteins (VLDL) triacylglycerol (TAG) are the primary source of fatty acids used for cardiac fatty acid beta oxidation. Lipoprotein lipase (LPL) converts TAG to fatty acids, that are then imported via CD36/FATP transporters. Once inside the cytosolic compartment of the cardiac myocyte, fatty acids (bound to fatty acid-binding proteins) are esterified to fatty acyl CoA by fatty acyl CoA synthase (FACS). The fatty acyl CoA can then be re-esterified to complex lipids such as TAG or the acyl group transferred to carnitine via carnitine palmitoyltransferase 1 (CPT1). The acylcarnitine is then shuttled into the mitochondrial matrix compartment via carnitine acylcarnitine translocase (CT), where it is converted back to fatty acyl CoA by CPT2. The majority of this fatty acyl CoA then enters the fatty acid beta oxidation cycle, producing acetyl CoA, NADH, and FADH2. Depending on the metabolic conditions, mitochondrial thioesterase (MTE) can cleave long-chain acyl CoA to fatty acid anions (FA\(-\)), which may leave the mitochondrial matrix via uncoupling protein (UCP) and dissipate the proton gradient. ADP indicates adenosine diphosphate; ATP, adenosine triphosphate; e, electrons; H, hydrogen; H\(_2\), water; NAD, nicotinamide adenine dinucleotide; NADH, reduced nicotinamide adenine dinucleotide; O\(_2\), oxygen; and Pi, phosphate. Adapted from Lopaschuk et al\(^\text{16}\) with permission of the publisher. Copyright ©2010, The American Physiological Society. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Sengers Syndrome
Sengers syndrome (OMIM No. 212350) is a rare autosomal recessive with the clinical features of congenital cataracts, HCM, mitochondrial myopathy, and lactic acidosis after exercise.95,96 Two forms of this syndrome have been described, a severe neonatal form that causes infantile death and a more benign form with a longer survival into the fourth decade.97–99 The longer surviving patients reportedly have had normal development milestones. The cause of mortality in Sengers syndrome is usually HCM with heart failure. Sengers syndrome is caused by mutations in the AGK gene, encoding acylglycerol kinase, which is located on chromosome 7q34 and consists of 16 exons.100 To date, different types of loss-of-function mutations in the AGK gene have been identified, including start codon mutations (compound heterozygous), nonsense (compound heterozygous), frameshift (compound heterozygous), and splice site mutations (homozygous and compound heterozygous).101,102

Acylglycerol kinase, a mitochondrial transmembrane enzyme, is a multisubstrate lipid with a likely role in cardiolipin biosynthesis. Acylglycerol kinase catalyzes the formation of phosphatidic acid and lysophosphatidic acid.103 that can participate in phospholipid synthesis or act as signaling molecules regulating several cell processes.103–105 Cardiolipin plays an important role in structural maintenance of mitochondria and in regulating the permeability of the inner membrane. Abnormal mitochondrial morphology has been seen in conditions with cardiolipin impairment, like Sengers and BTHSs (see below).105–107 Abnormal muscle cell histopathology with cardiolipin impairment, like Sengers and BTHSs, has been reported in a proband with mutations in AGK gene.108 Secondary to AGK mutations, a deficiency of the adenine

### Mitochondrial and Metabolic Cardiomyopathies

<table>
<thead>
<tr>
<th>Disease Name</th>
<th>Hallmarks of Phenotype</th>
<th>Affected Gene, Protein, Pathological Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fabry disease</td>
<td>X-linked, burning pain in the hands and feet, angiokeratoma, corneal opacities, renal failure, seizures, hypertrophic cardiacopathy, mitral insufficiency, conduction system abnormalities, myocardial infarction</td>
<td>Abnormalities in the GLA gene, causing deficiency in the enzyme α-galactosidase A, leading to massive accumulation of intralysosomal glycosphingolipids</td>
</tr>
<tr>
<td>Danon disease</td>
<td>X-linked, hypertrophic cardiacopathy, and skeletal myopathy, with or without conduction defect, WPW syndrome, or mental retardation</td>
<td>Mutations in the lysosomal-associated membrane protein 2 (LAMP2) gene cause reduction in LAMP2 protein and disrupts intracytoplasmic trafficking; leads to accumulation of autophagic material and glycogen in skeletal muscle and cardiac muscle cells</td>
</tr>
<tr>
<td>PRKAG2 deficiency</td>
<td>Hypertrophic cardiomyopathy, preexcitation, supraventricular tachycardia, atrioventricular block, Mental retardation, myalgia, epilepsy, early-onset hypertension</td>
<td>PRKAG2, enhances glucose and lipid metabolism to elevate intracellular ATP; dysfunction alters myocyte glidic uptake and metabolism, causes deposition of glycogen and amylopectin</td>
</tr>
<tr>
<td>Sengers syndrome</td>
<td>Congenital cataracts, HCM, mitochondrial myopathy, and lactic acidosis after exercise</td>
<td>AGK gene, mitochondrial transmembrane enzyme, acylglycerol kinase, a multisubstrate lipid with role in cardiolipin biosynthesis</td>
</tr>
<tr>
<td>Kearns–Sayre syndrome</td>
<td>Ptsis, chronic progressive external ophthalmoplegia (CPEO), abnormal retinal pigmentation, with cardiac conduction defects, dilated cardiomyopathy, ragged red fibers</td>
<td>Single large-scale mitochondrial DNA deletions, mtDNA point mutations in the tRNA (Leu) gene</td>
</tr>
<tr>
<td>Myoclonic epilepsy with ragged red muscle fibers (MERRF) syndrome</td>
<td>Myoclonus, generalized epilepsy, ataxia, weakness, dementia, hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff–Parkinson–White (WPW) syndrome, ragged red fibers</td>
<td>Mitochondrial tDNA gene MT-TK, encoding tRNA^Leu^; most common defect; m.8344A&gt;G mutation present in &gt;80% of individuals. Pathogenic variants in MT-TP, MT-TL1, MT-TL, and MT-TP</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>Gliosis, demyelination, capillary proliferation, and necrosis in the brain on MRI, behavioral symptoms that include developmental retardation, hypotonia, ataxia, dystonia, optic atrophy, hearing impairment, breathing abnormalities, dysarthria, swallowing difficulties, or failure to thrive, hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmia/conduction defects</td>
<td>Sixty genes, mostly in the nuclear DNA, 25% in mtDNA, affects all 5 respiratory chain complexes. Mutations also in pyruvate metabolism, coenzyme Q10 biosynthesis, oxidation of fatty acids, thiamine metabolism genes</td>
</tr>
</tbody>
</table>

DCMA indicates dilated cardiomyopathy with ataxia, HCM, hypertrophic cardiomyopathy; MERRF, myoclonic epilepsy with ragged red muscle fibers; MRI, magnetic resonance imaging; mtDNA, mitochondrial; OXPHOS, oxidative phosphorylation; PMR, psychomotor retardation; and WPW, Wolff–Parkinson–White.
nucleotide translocator and impairment of ATP synthesis has been reported and seems to play a central role in the pathophysiology of Sengers syndrome.\textsuperscript{100,108,109}

**Barth Syndrome**

An X-linked genetic disorder, BTHS (OMIM No. 302060) affects boys and is characterized by cardiomyopathy, intermittent neutropenia, skeletal muscle weakness, and 3-methylglutaconic aciduria. It is caused by mutations in the tafazzin (TAZ) gene (formerly known as G4.5), which encodes the mitochondrial transacylase protein called tafazzin.\textsuperscript{110–112} Tafazzin catalyzes the final step of the remodeling of cardiolipin, a mitochondrial phospholipid that is predominately found in the inner mitochondrial membrane where it constitutes \(\approx 20\%\) of the total phospholipid. Mortality during infancy is high and usually secondary to cardiac dysfunction, although sudden, unexplained death has also been observed. Cardiomyopathy was the primary diagnosis in \(\approx 70\%\) of cases diagnosed with BTHS in a recent UK study, with almost half of them diagnosed during the first month of life.\textsuperscript{113} In some infants, the myocardial abnormalities display the typical, pathological features of endocardial fibroelastosis on autopsy. By echocardiography, LV noncompaction is common, although DCM and HCM also occur.\textsuperscript{79} The appearance of the myocardium by echocardiography can also change over time from, for example, a dilated and hypertrophic form with hyperdynamic function to a purely hypertrophic form with normal function and then to a purely dilated form with poor function. This remodeling process is termed an undulating phenotype.\textsuperscript{2,4,52,74} Severe neutropenia may also result in fatal sepsis. The distinct facial appearance may present in childhood and early adolescence.\textsuperscript{114}

After about age 3 years, the boys can develop a so-called honeymoon period, during which cardiac function improves and morbidity lessens.\textsuperscript{115} Decreased linear growth may become apparent during infancy and early childhood. By about age 10 years, however, these patients develop chronic fatigue, substantially reduced exercise capability, worsening of cardiomyopathy, psychomotor retardation, 3-methylglutaconic aciduria, hyperammonemia, and lactic acidosis present in the neonatal period with a muscular hypotonia, hypertrophic cardiomyopathy, potentially lethal cardiac arrhythmias, and diminished body mass. Mild forms of cognitive difficulties, mostly in mathematics and visual spatial tasks, have been reported in BTHS boys.\textsuperscript{116} The incidence of BTHS is low, estimated as 1 in 300,000 live births, although this figure is controversial. A recent study on 6 kindreds with genetically and biochemically proven BTHS demonstrated a broad phenotype, including male fetal loss, stillbirth, and severe neonatal illness or death. In these families, 9 males were stillborn and 14 died as neonates or infants, but there were no losses of females.\textsuperscript{113}

The hallmark features of cardiomyopathy, neutropenia, and 3-methylglutaconic aciduria may not occur consistently in any individual patient\textsuperscript{117} as demonstrated by the study of young males who exhibited only cardiomyopathy, either as LVNC or endocardial fibroelastosis, with TAZ mutations but no other features of BTHS.\textsuperscript{118} This suggested that it is likely that TAZ deficiency is a more common cause of cardiomyopathy than previously thought. This observation has major clinical implications, raising the possibility that all boys with cardiomyopathy should be assessed for TAZ mutations. An observational cardiorespiratory study on 15 BTHS patients and 9 healthy controls demonstrated exercise intolerance, greatly exaggerated heart rate response to graded exercise, and impaired ability of muscles to extract oxygen from the blood in BTHS patients. When subjected to aerobic exercise on the treadmill, BTHS patients and TAZ-knockdown mice exhibited significantly a higher respiratory exchange ratio values compared with the control group, indicating increased anaerobic energy supplementation (Figures 2–5).\textsuperscript{119,120}

**Mitochondrial Dysfunction Disorders With 3-Methylglutaconic Aciduria**

In addition to BTHS, disorders associated with cardiomyopathies with mitochondrial dysfunction and 3-methylglutaconic aciduria include defects in DNJAC19 (DnaJ Hsp40 [heat shock protein family] member C19) and TMEM70 genes.

**DNJAC19 Defect (DCMA [dilated cardiomyopathy with ataxia] Syndrome)**

DNJAC19, a gene located at chromosome 3q26.33, encodes a protein thought to be part of a complex involved in the ATP-dependent transport of transit peptide-containing proteins from the inner cell membrane to the mitochondrial matrix. Hutterite patients with DNJAC19 defect or DCMA syndrome (MIM No. 610198) show the characteristic combination of childhood-onset dilated cardiomyopathy, nonprogressive cerebellar ataxia, testicular dysgenesis, growth failure, and 3-methylglutaconic aciduria.\textsuperscript{121}

**TMEM70 Defect**

The TMEM70 gene, located on chromosome 8q21.11, encodes a mitochondrial membrane protein, the mitochondrial transmembrane protein 70, that plays a role in the biogenesis of mitochondrial ATP synthase. Mutations in this gene have been associated with neonatal mitochondrial encephalomyopathy because of ATP synthase deficiency. Patients mostly present in the neonatal period with a muscular hypotonia, hypertrophic cardiomyopathy, psychomotor retardation, 3-methylglutaconic aciduria, hyperammonemia, and lactic acidosis (MIM No. 604273). Patients surviving the neonatal period later show developmental delay. All patients show a deficiency of the ATPase (complex V) of the oxidative phosphorylation system.

**Inborn Errors of Metabolism**

Inborn errors of metabolism (IEM) can cause a range of cardiomyopathy subtypes, including hypertrophic, dilated, restrictive, or mixed forms. As might be expected, IEM are a much more important diagnostic consideration in the pediatric age group versus adults, where they account for \(\approx 5\%\) of cases (with many presenting in the first year of life), compared with \(<1\%\) in adults. Over 40 different IEM have been identified and can be grouped into glycogen and lysosomal storage disorders, fatty acid oxidation and mitochondrial disorders, organic acidemias, amino acidopathies, peroxisomal biogenesis disorders, and congenital disorders of glycosylation. IEM are important to recognize because, for many, treatment strategies have been developed that can reverse or at least slow disease progression.

**Glycogen and Lysosomal Storage Disorders**

The storage disorders are some of most common IEM and can present with marked thickening and enlargement of the heart
that mimics HCM. Pompe disease (glycogen storage disease, type II; OMIM No. 232300) occurs in 1 in 40,000 births\textsuperscript{122–124} and is caused by a deficiency of acid α-glucosidase and is characterized by large cytoplasmic inclusions of glycogen. It presents in infancy and is associated with high mortality unless treated. Infants often present with hypotonia and a HCM with normal or depressed function. Early diagnosis by the recommended newborn screening panel is critical to prevent irreversible myopathy. Enzyme replacement therapy is readily available and is a lifelong treatment with infusions every 2 weeks.

Danon disease is an X-linked disorder caused by a defect in the gene encoding the LAMP2 (lysosome-associated membrane protein-2)\textsuperscript{124,125} and is characterized as a vacuolar or lysosomal disorder.\textsuperscript{126,127} In addition to ventricular thickening, which can range from mild to severe in males (and exceedingly rarely in young females), boys often have associated skeletal muscle weakness. The cardiomyopathy is often rapidly progressive and may be associated with ventricular preexcitation and atrial fibrillation, progressive systolic dysfunction, and intractable heart failure.\textsuperscript{126,128} In these boys, the condition typically begins as HCM with progression to dilation as systolic dysfunction progresses. The mothers of the affected boys typically present with DCM in their 30s or 40s and may present concurrently with their sons. A similar cardiac phenotype is seen in individuals with PRKAG2 mutations.\textsuperscript{129,130} PRKAG2 encodes for 5′-adenosine monophosphate (AMP)–activated protein kinase subunit γ-2, an enzyme involved in the regulation of fatty acid and cholesterol biosynthesis. Affected individuals demonstrate cardiac

Figure 2. Echocardiographic LV noncompaction phenotypes. The heterogeneous features that cover the spectrum of patients with the different forms of LV noncompaction. Four-chamber views demonstrate normal atrial and ventricular sizes and thickness with a hypertrabeculated LV wall and apex (arrow; A); 7-year-old female with normal atrial sizes with a dilated (yellow star) and hypertrabeculated LV wall and apex (arrow; B); 15-year-old male with hypertrophic and hypertrabeculated ventricular walls and apex (arrow) with a hypertrophic septum (black star; C); 2-year-old male with normal to small ventricular sizes with dilated atria bilaterally (yellow stars) and a hypertrabeculated LV (arrow; D); 19-year-old male with normal atrial sizes with severely hypertrabeculated LV and RV wall and apices (arrows; E). LA indicates left atrium; LV, left ventricle; RA, right atrium; and RV, right ventricle.

Figure 3. ECG in left ventricular noncompaction (LVNC). Note the prominent precordial voltage (1/4 standard) on a 4-year-old male.
hypertrophy, which can be severe, ventricular preexcitation, and progressive conduction system disease. It is characterized by vacuolar accumulation of glycogen selectively in cardiac myocytes.

Other glycogen storage disorders can result in HCM (glycogen storage disease, type III; glycogen storage disease, type IX; OMIM Nos. 232400 and 261750) or, less commonly, DCM (glycogen storage disease, type IV; OMIM NO. 232500). Likewise, other lysosomal storage disorders such as the mucopolysaccharidoses can result in an HCM (mucopolysaccharidoses-I, -II, -III, -IV, and -VII; OMIM No. 607014, 309900, 252920, 253000, 253220) or DCM (mucopolysaccharidoses-I, -VI) phenotype and most commonly presents during childhood.

Organic Acidemias and Amino Acidopathies
Organic acidemias and amino acidopathies are rare disorders that cause a build-up of toxic metabolites within cells in the heart and other tissues, leading to organ dysfunction. In the heart, this can lead to a dilated (propionic acidemia, methylmalonic aciduria, and β-ketothiolase deficiency) or hypertrophic cardiomyopathy (tyrosinemia and oxalosis). These conditions are rare and usually present in infancy as a result of newborn screening or with hepatic dysfunction, seizures, hypotonia, and developmental delay.

Fabry Disease
Fabry disease (OMIM No. 301500) is an X-linked recessive disorder affecting males, triggered by abnormalities in the GLA gene at Xq22, which leads to a deficiency in α-galactosidase A and massive accumulation of intralysosomal glycosphingolipids. It occasionally has mild expression in carrier females as well. Deficiency in α-galactosidase A enzymatic activity, which is responsible for hydrolysis of the terminal α-galactosyl moieties from glycolipids and glycoproteins, results in cellular accumulation of globotriaosylceramide and other neutral glycosphingolipids in various organ systems. The progressive glycosphingolipid accumulation within cardiac myocytes, valvular fibroblasts, neuronal, vascular smooth muscle, and vascular endothelial cells leads to cellular dysfunction and result in life-threatening cardiovascular disease. Young adults may be prone to renal failure and myocardial infarction. Fabry disease usually has its onset in adolescence and manifests with sensations of burning pain in the hands and feet. With increasing age, multiple angiokeratomas become noticeable, especially around the umbilicus and
genitalia. Corneal opacities are often noted. Progressive renal failure develops with age. Central nervous system manifestations include seizures and headaches, as well as hemiplegia associated with an increased risk of stroke. Primary cardiac manifestations in affected males include HCM and mitral insufficiency, with the diagnosis usually based on echocardiographic findings, although cardiac magnetic resonance may also be helpful. Bradycardia and conduction system abnormalities, related to abnormal accumulation of glycolipids in the lysosomes of conduction tissues, are common. The LV myocardium and mitral valve tend to be areas of greatest storage of lipid material. On ECG, the PR interval is usually short. Deposition of sphingolipids in the coronary arteries can lead to myocardial ischemia and infarction. Direct muscle involvement with mild glycosphingolipid accumulation may occur. However, skeletal muscle involvement may be milder and delayed compared with that in the heart. Cardiac complications are the main cause of late morbidity, as well as early mortality in both hemizygous men and heterozygous women.

**Danon Disease**

Danon disease (OMIM No. 300257) is an X-linked dominant disorder characterized by intracytoplasmic vacuoles containing autophagic material and glycogen in cardiac and skeletal muscle cells, cardiomyopathy, and skeletal myopathy, with or without conduction defect, WPW syndrome, or mental retardation. The underlying abnormality affects lysosomal function and is because of mutations in the LAMP2. The clinical phenotypic expression of Danon disease is variable. Charron et al screened 50 cases of HCM for LAMP2 mutations and identified mutations in 2 patients with HCM and skeletal myopathy. Both of these individuals presented during their teenage years, and other younger affected individuals in the family were also identified as young as 7 years of age. WPW syndrome and high-voltage QRS complexes on ECG were notable along with high creatine kinase plasma levels. In addition, late LV dilation and dysfunction occurred with symptoms of heart failure. Atrial and ventricular arrhythmias and conduction disease was notable along with death during their twenties. Visual acuity abnormality was also common because of choriocapillary ocular atrophy. In at least 1 family, X-linked cardiomyopathy was the presenting form of Danon disease, despite a family history of the more commonly associated HCM. This confirmed a LAMP2 mutation, as opposed to a dystrophin mutation, as the cause of DCM.

**Figure 5. Left ventricular noncompaction (LVNC) associated with congenital heart disease.** A, LVNC in a female neonate with tricuspid atresia. The top arrow demonstrates the tricuspid valve abnormality, and the bottom arrow points to the apical hypertrabeculation; B, LVNC in a 1-year-old male with a large ventricular septal defect. The top arrow demonstrates the ventricular septal defect, and the bottom arrow points to the apical hypertrabeculation; C, LVNC in a male neonate with Ebstein anomaly. The top arrow demonstrates the Ebstein’s tricuspid valve abnormality, and the bottom arrow points to the apical hypertrabeculation.
in these patients. Skeletal myopathy may develop with age, and severity seems to correlate with number of vacuolated skeletal muscle fibers.\textsuperscript{141,142} Danon disease seems to be under recognized and may play a significant role in pediatric heart failure. Importantly, female carriers of LAMP2 mutations may develop a cardiomyopathy (dilated and hypertrophic), heart failure, and arrhythmias.

**Adenosine Monophosphate–Activated Protein Kinase**

AMP-K (AMP-activated protein kinase; OMIM No. 602743), encoded by the \( \gamma \)2 regulatory subunit of the PRKAG2 gene on chromosome 7q31,\textsuperscript{143} is an enzyme that modulates glucose uptake and glycolysis. AMP-K is activated by high AMP levels and by AMP-K kinase. It enhances glucose and lipid metabolism to elevate intracellular ATP and regulates the creatine kinase activity to reduce ATP depletion. AMP-K is also involved in cardiac development, growth, and regeneration acting through PKB activation and insulin sensitivity. Mutations in the AMP-K \( \gamma \)2 regulatory subunit results in dysfunction of the enzyme and causes alterations in secondary pathways and nuclear transcriptional factors, which can lead to cardiac hypertrophy, improper glycogen accumulation, ion channel dysfunction, altered atrioventricular septation, and ATP utilization by the sarcomere. Dominant mutations in this gene were first identified in 2001\textsuperscript{128,129,144,145} in subjects with HCM, preexcitation, supraventricular tachycardia, and atrioventricular block. Myalgia, epilepsy, and early-onset hypertension may occur. Cardiac pathology differed from that in other forms of HCM, with no myocyte and myofibrillar disarray seen, but instead pronounced formation of vacuoles that were filled with glycogen-associated granules was noted.\textsuperscript{128} As AMP-K dysfunction alters the myocyte glucidic uptake and metabolism, deposition of glycogen and amylopectin occurs, mimicking that seen in glycogen storage cardiomyopathies.

**Congenital Disorders of Glycosylation**

These disorders are a growing group of inborn errors of protein glycosylation in which cardiac involvement is frequently observed and is classified into 4 major biochemical categories: 3 involving protein glycosylation (disorders of N-linked glycosylation, O-linked glycosylation, and combined N- and O-glycosylation) and 1 involving lipid glycosylation.\textsuperscript{146,147} The process of N-linked protein glycosylation occurs via a pathway involving the cytoplasm to the endoplasmic reticulum and the Golgi compartment. Protein N-glycosylation is a ubiquitous process in all organ systems. During N-glycosylation, glycan precursors are assembled from monosaccharide units and then covalently attached to asparagine residues in the nascent peptide chain of a protein. The protein-bound glycans undergo further processing to generate mature glycoproteins. Plasma transferrin isoelectric focusing is used as a biochemical screening tool for congenital disorders of glycosylation (CDG). CDG is generally associated with multiorgan syndromes, including psychomotor retardation, ataxia, polynuropathy, epilepsy, endocrine abnormalities, growth retardation, visual and hearing loss, ichthyosis, cardiac, renal, liver, and gastrointestinal involvement.\textsuperscript{147} In the most common form of CDG, PMM2-CDG (phosphomannomutase 2-congenital disorder of glycosylation; OMIM No. 601785) cardiomyopathy, especially HCM, is common. Dilated cardiomyopathy has only been observed in a few CDG subtypes, usually with a lethal outcome.\textsuperscript{148,149}

Cardiac symptoms vary from asymptomatic with discrete, mild LV dilation to overt heart failure with death. Children with mild DCM at the time of the diagnosis may deteriorate rapidly. In most cases, the cardiac findings dominate the clinical picture, without central nervous system or multisystem involvement, which is unique in CDG syndrome. Patients with isolated cardiomyopathy may remain stable on supportive treatment (angiotensin-converting enzyme inhibitors, \( \beta \)-blockers) while others deteriorate rapidly.

**Phosphoglucomutase 1 Deficiency**

Genetic defects in protein N-glycosylation lead to multisystem disorders in patients with phosphoglucomutase 1 deficiency (OMIM No. 171900).\textsuperscript{150} Mutations of genes involved in N-glycosylation may affect either the biosynthesis of the glycan precursor (CDG type I) or the processing of the glycan after its attachment to the protein (CDG type II). Glucose-1-phosphate is an important intermediate in the pathways leading to protein N-glycosylation and in glucose homeostasis. Phosphoglucomutase 1 (PGM1) catalyzes the interconversion of glucose-6-phosphate and glucose-1-phosphate and PGM1, previously designated as glycogenosis type XIV,\textsuperscript{151} and is associated with glycosylation abnormalities affecting both the attachment and the processing of N-glycans. PGM1 catalyzes the interconversion of glucose-6-phosphate and glucose-1-phosphate. PGM1 binds to the heart muscle cell–specific splice variant of ZASP (Z-band alternatively spliced PDZ-motif protein), and ZASP mutations that affect the binding of PGM1 are associated with DCM.\textsuperscript{152,153} The clinical disorder that develops includes DCM with possible cardiac arrest or need for heart transplantation, signs of hepatopathy (moderately elevated serum aminotransferase levels, steatosis, fibrosis, or a combination of these features), growth retardation (height at or below the 5th percentile), hypogonadotropic hypogonadism with delayed puberty, and hypoglycemia (fasting glucose level of <2.2 mmol/L [40 mg/dL]) in addition, the majority of the patients have muscle symptoms (maximal creatine kinase level >300 U/L), including exercise intolerance, muscle weakness, and rhabdomyolysis. Malignant hyperthermia with severe rhabdomyolysis has also occurred after the administration of general anesthesia. Most patients have a bifid uvula as well.

**Muscle Is Muscle: Cardiomyopathy and Skeletal Myopathy Genes Overlap**

Interestingly, nearly all of the genes identified for inherited cardiomyopathies are also known to cause skeletal myopathy in humans and mouse models. In the case of dystrophin, mutations cause Duchenne and Becker muscular dystrophy while \( \delta \)-sarcoglycan mutations cause limb girdle muscular dystrophy 2F. Lamin A/C has been shown to cause autosomal dominant Emery–Dreifuss muscular dystrophy and limb girdle muscular dystrophy 1B, whereas actin (ACTC) mutations are associated with nemaline myopathy. Desmin, tafazzin, \( \alpha \)-dystrobrevin, Cypher/ZASP, MLP/CSRP3, \( \alpha \)-actinin-2, titin, \( \delta \)-sarcoglycan mutations, and mitochondrial DNA and mitochondrial gene mutations also have associated skeletal
myopathy, suggesting that cardiac and skeletal muscle function is interrelated and that possibly the skeletal muscle fatigue seen in patients with cardiomyopathies with and without heart failure may be because of primary skeletal muscle disease and not only related to the cardiac dysfunction. Further support for this concept comes from studies of animal models. It suggests that both cardiologists and neurologists should consider evaluation of both sets of muscles in caring for these patients.

Disclosures
None.

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Cardiomyopathies Due to Left Ventricular Noncompaction, Mitochondrial and Storage Diseases, and Inborn Errors of Metabolism

Jeffrey A. Towbin and John Lynn Jefferies

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