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Case Reports

Pathogenic *BCS1L* Mutation Resulting in Hypertrophic Cardiomyopathy: A Unique Presentation of Nuclear Mitochondrial Disease

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Abstract

A 21-year-old man with sensorineural hearing loss and glaucoma presented with severely limited exercise capacity since childhood. He was found to have biventricular concentric hypertrophy with greatest wall thickening at the posterior and lateral walls of the left ventricle apex (1.7 cm) and the free wall of the right ventricle (1.1 cm). There was no inducible left ventricular outflow tract obstruction. Metabolic testing revealed marked lactic aciduria (1,650.1 µmol/mmol creatinine) and plasma lactate (3.9 mmol/L). A sarcomeric hypertrophic cardiomyopathy gene panel was unremarkable, but mitochondrial gene analysis revealed a homozygous c.385G>A (p.Gly129Arg) pathogenic mutation in the *BCS1L* gene. This gene is responsible for an assembly subunit of cytochrome complex III in the respiratory transport chain and is the rarest respiratory chain defect. This gene has not frequently been implicated in cardiomyopathy. Mitochondrial hypertrophic cardiomyopathy is more rare than hypertrophic cardiomyopathy resulting from sarcomeric mutations and is more likely to be symmetric, less frequently results in left ventricular outflow tract obstruction, and is more likely to progress to dilated cardiomyopathy. Evidence-based screening protocols have not been established; treatment follows guideline-directed medical therapy for congestive heart failure, including evaluation for heart transplantation. This report expands the phenotype of the *BCS1L* mutation and suggests that affected patients may need screening for underlying cardiomyopathy.

Keywords: BCS1L protein, human; cardiomyopathy; mitochondrial diseases

Introduction

Mitochondrial disorders (MIDs) are a rare group of heterogenous diseases caused by a deficiency in the electron transport chain. The diversity of symptoms and organs involved makes classification and evidence-based screening difficult.[1-3] Involvement of the cardiovascular system is frequent and can result in cardiomyopathy, conduction abnormalities, and arrhythmias.[1] This report describes a 21-year-old man from Abu Dhabi who presented with dyspnea on exertion and severely limited exercise capacity who was found to have biventricular concentric hypertrophic cardiomyopathy (HCM) caused by a pathologic variant of the *BCS1L* gene (c.385 G>A [p.Gly129Arg]), which codes for a component of the complex III in the electron transport chain.

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Case Report

A 21-year-old man from Abu Dhabi presented to an outpatient clinic for evaluation of symptoms he had experienced since childhood: progressive exertional dyspnea and exercise intolerance that limited his activities of daily living. His medical history included recently diagnosed bilateral sensorineural hearing loss (SNHL), bilateral primary open-angle glaucoma, and inappropriate sinus tachycardia. Pertinent cardiac medications included bisoprolol and ivabradine. His family history was notable for consanguinity but unremarkable for cardiac or genetic disorders.

On examination, the patient was bradycardic (pulse rate, 55/min) with a blood pressure of 133/82 mm Hg. His oxygen saturation was 100% on room air, although his 6-minute walk test distance was 40% of predicted. Electrocardiography showed sinus bradycardia (heart rate, 53/min), left ventricle (LV) hypertrophy by Sokolov-Lyon criteria, lateral and inferior T-wave inversions, and high-voltage QRS complexes (Fig. 1). Physical examination revealed no evidence of decompensated congestive heart failure (HF) but was notable for multiple craniofacial dysmorphisms, including synophrys (fusion of the eyebrows), dolichocephaly (anterior-posterior elongation of the skull), low-set ears with small lobes, and a high-arched palate.

Initial laboratory testing showed normal plasma creatinine (0.8 mg/dL) and N-terminal pro B-type natriuretic peptide levels (<50 pg/mL) (Table I). Stress transthoracic echocardiography showed an LV ejection fraction of 66% with biventricular hypertrophy. The free wall of the right ventricle (RV) measured 1.1 cm in thickness (Fig. 2). The LV had concentric hypertrophy, most notable at the posterior and lateral walls of the apex, which measured 1.7 cm (Fig. 3). The LV basal septum measured 1.3 cm, and the LV basal posterior wall measured 1.1 cm (Fig. 4 and Fig. 5). There was moderate chordal systolic anterior motion (Fig. 6) with no resting left ventricular outflow tract (LVOT) gradient (parasternal view, Fig. 7; apical view, Fig. 8). There was no provokable LVOT obstruction with the Valsalva maneuver or administration of amyl nitrate. Cardiac magnetic resonance imaging (MRI) showed no evidence of fibrosis and demonstrated normal perfusion and viability. There were increased trabeculations in the RV apex and in the lateral wall and apex of the LV, but no wall-motion abnormalities or abrupt transition in the thickness of compacted myocardium; thus, these findings did not meet criteria for LV noncompaction cardiomyopathy.

Metabolic stress testing showed peak oxygen uptake at 13% of predicted and a blunted chronotropic response (63% of predicted for age) despite excellent effort. Right

Abbreviations and Acronyms

Cr	creatinine
HCM	hypertrophic cardiomyopathy
HF	heart failure
LV	left ventricle
LVOT	left ventricular outflow obstruction
MID	mitochondrial disorder
MRI	magnetic resonance imaging
RV	right ventricle
SNHL	sensorineural hearing loss

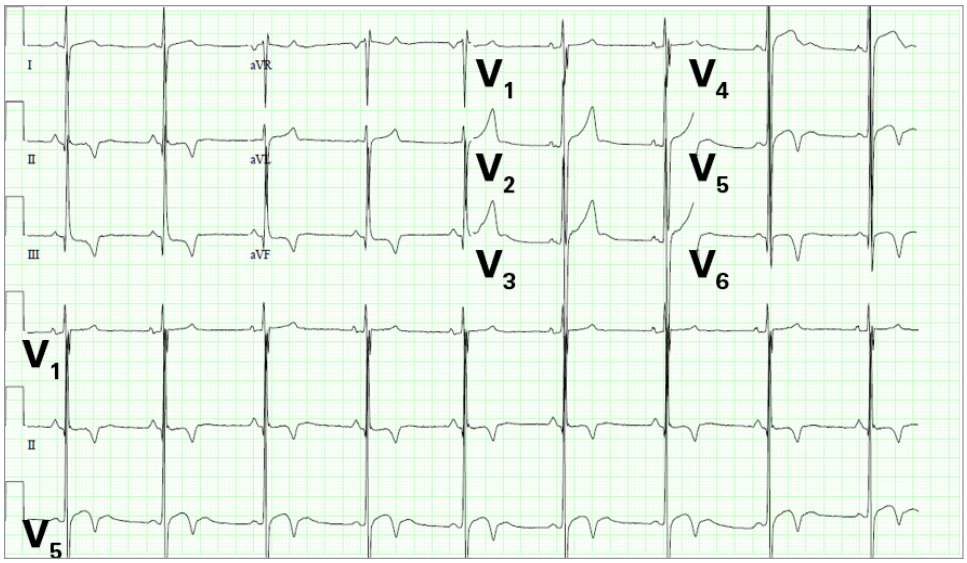

Fig. 1 Electrocardiography shows sinus bradycardia (heart rate, 53/min), left ventricular hypertrophy by Sokolov-Lyon criteria, lateral and inferior T-wave inversions, and high-voltage QRS complexes.

TABLE I. Laboratory Results and Reference Ranges

Test	Reference range	Patient result
Urine lactate, µmol/mmol Cr	2.9-47.2	1,650.1
Urine pyruvate, µmol/mmol Cr	0.1-2.6	0.8
Serum creatinine, mg/dL	0.73-1.22	0.80
Plasma lactic acid, mmol/L	0.5-2.2	3.9
Plasma pyruvic acid, µmol/L	20-140	147
Plasma iron, µg/dL	41-186	137
TIBC, µg/dL	232-386	391
Plasma ferritin, ng/mL	30.3-565.7	44.2
Transferrin saturation, %	15-57	35
Plasma NT-proBNP, pg/mL	<125	<50
Plasma aldolase, U/L	1.2-7.6	4.4
Plasma CK, U/L	51-298	74

CK, creatine kinase; Cr, creatinine; NT-proBNP, N-terminal pro B-type naturetic peptide; TIBC, total iron binding capacity.

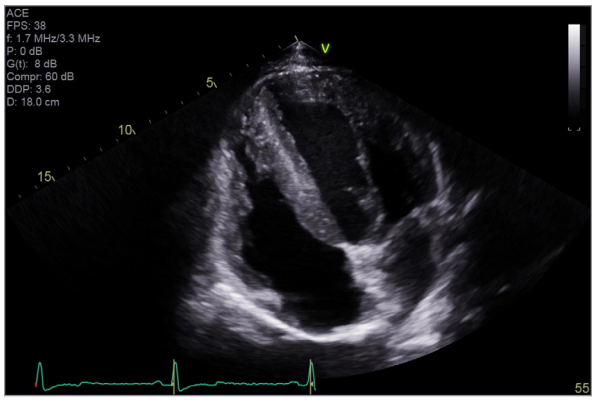

Fig. 2 Apical 4-chamber axis echocardiogram view shows right ventricular hypertrophy most notable at the free wall (1.1 cm).

Supplemental motion image is available for Figure 2.

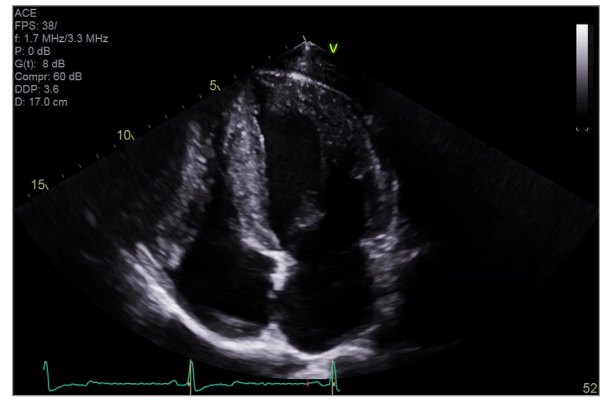

Fig. 3 Apical 4-chamber axis echocardiogram view shows concentric left ventricular hypertrophy most notable at the apical posterior and lateral walls (1.7 cm).

Supplemental motion image is available for Figure 3.

heart catheterization showed a mildly reduced cardiac output using the Fick method (3.67 L/min), an elevated pulmonary capillary wedge pressure (16 mm Hg), tall A and V waves (both 24 mm Hg), and rapid X and Y descents. The pulmonary artery pressure (34/16 mm Hg; mean, 22 mm Hg), RV pressure (40/10 mm Hg), and right atrial mean pressure (8 mm Hg) were at the upper limit of normal.

Metabolic testing (Table I) revealed marked lactic aciduria (1,650.1 µmol/mmol creatinine [Cr]; reference range, 2.9-47.2 µmol/mmol creatinine) and elevated plasma lactate (3.9 mmol/L; reference range, 0.5-2.2 mmol/L). Creatine kinase (74 U/L) and aldolase (4.4 U/L) levels were normal. The plasma acylcarnitine profile showed increased levels of medium-chain species and multiple long-chain species. The plasma amino acid profile revealed a moderately elevated alanine level of 620 µmol/L (reference range, 177-583 µmol/L). The chromosome single-nucleotide polymorphism array was normal, and the HCM multigene panel—including cardiac β-myosin heavy chain, myosin binding protein gene, and cardiac troponin T—was unremarkable. Mitochondrial genetic testing revealed a pathogenic homozygous c.385G>A (p.Gly129Arg) mutation in the *BCS1L* gene. The patient did not undergo muscle or cardiac biopsy. Evaluation for cardiac transplantation is ongoing.

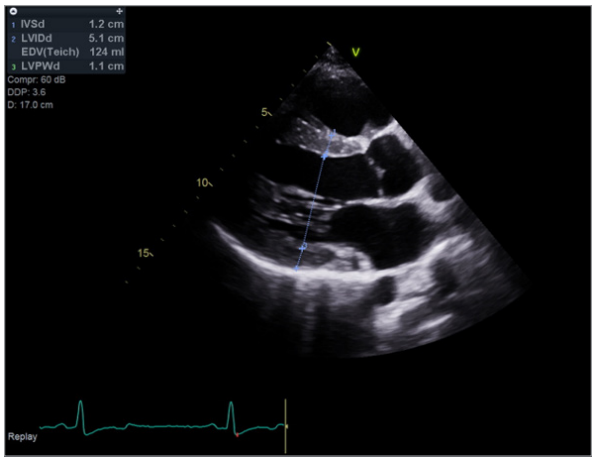

Fig. 4 Parasternal long-axis echocardiogram demonstrates thickening of the basal septum and basal posterior wall of the left ventricle (the latter measures 1.1 cm).

EDV, end-diastolic volume; IVSd, interventricular septum end diastole; LVIDd, left ventricular internal diameter end diastole; LVPWd, left ventricular posterior wall dimension.

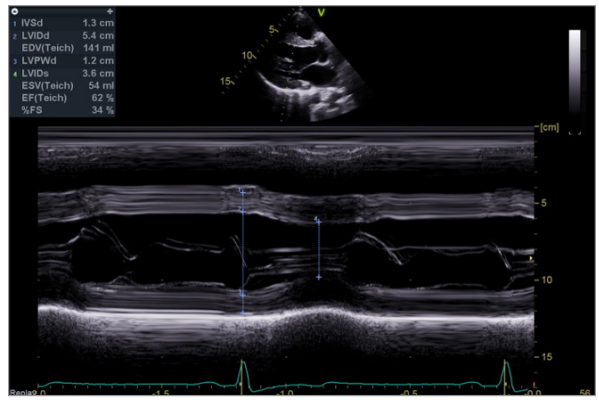

Fig. 5 Parasternal long-axis M-mode echocardiogram view demonstrates thickening of the left ventricle basal septum (1.3 cm) and the left ventricle basal posterior wall.

EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; %FS, fractional shortening; IVSd, interventricular septum end diastole; LVIDd, left ventricular internal diameter end diastole; LVIDs, left ventricular internal diameter end systole; LVPWd, left ventricular posterior wall dimension.

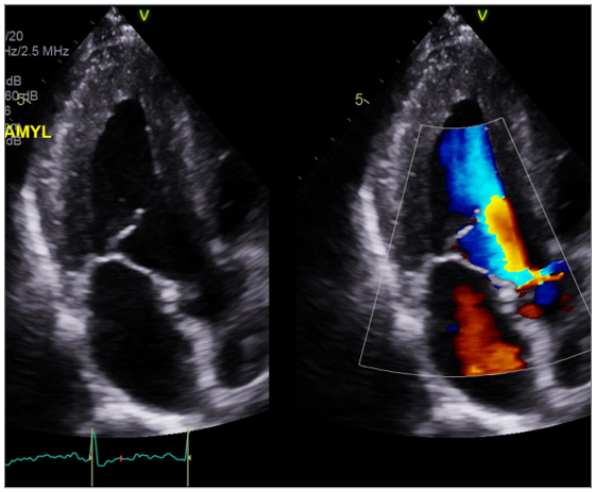

Fig. 6 Apical 3-chamber echocardiogram demonstrates chordal systolic anterior motion of the mitral valve with amyl nitrate (left, without Doppler; right, with Doppler).

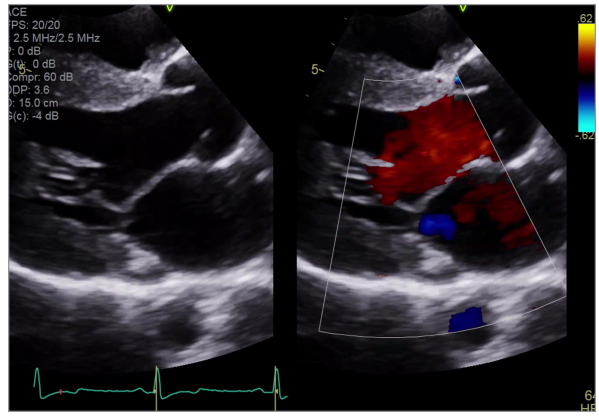

Fig. 7 Parasternal long-axis echocardiogram demonstrates no resting obstruction of the left ventricular outflow tract (left, without Doppler; right, with Doppler; video, without Doppler).)

Supplemental motion image is available for Figure 7.

Discussion

Mitochondria are organelles found in nearly every cell of the human body; they play diverse roles in energy production via oxidative phosphorylation, apoptosis, production of reactive oxygen species, calcium homeostasis, and cellular innate immunity.[4,5] One of their main functions is to convert free fatty acids and carbohydrates into adenosine triphosphate through the Krebs cycle and the electron transport chain.[4,5] Mitochondrial disorders (MIDs) are a heterogeneous group of diseases resulting from a deficiency in the electron transport chain or its precursor chemicals. These disorders occur in approximately 1 in 5,000 to 8,500 individuals, although classification is difficult because the clinical manifestations are diverse.[1,2] The heart, brain, and eyes are heavily reliant on oxidative phosphorylation for energy production and are commonly affected by MIDs.[5] Common presenting symptoms are neurologic (eg, psychiatric, seizures) or myopathic; patients may also have renal tubulopathy, endocrine disorders, or SNHL.[5]

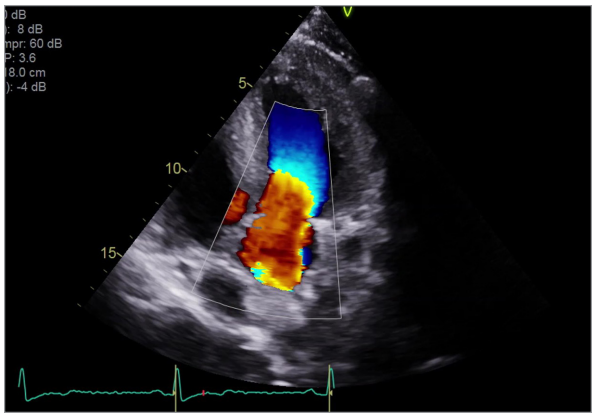

Fig. 8 Apical 5-chamber echocardiogram with Doppler demonstrates no resting obstruction of the left ventricular outflow tract.

Supplemental motion image is available for Figure 8.

A ventricular end-diastolic wall thickness greater than 13 mm defines HCM.[6] More than 100 mutations across 24 genes in the sarcomeric and mitochondrial genomes have been implicated in HCM.[7] Two-thirds of the sarcomeric mutations are the result of a mutation in cardiac β-myosin heavy chain, myosin binding protein gene, or cardiac troponin T.[3] Other causes of unexplained LV hypertrophy that must be explored include sporadic mitochondrial DNA mutations, amyloidosis, physiologic hypertrophy (caused by hypertension or aortic stenosis), or glycogen storage diseases (eg, Fabry, Danon, or Pompe disease).[6]

Many MIDs lack reliable screening tests, and there are no consensus-based parameters for diagnosis.[2] Generally, biochemical testing of the urine and serum is used for screening; elevated plasma lactate (sensitivity, 34%-62%; specificity, 83%-100%) and amino acids are common.[2] Serum mitochondrial DNA heteroplasmy analysis and tissue diagnosis (ie, muscle biopsy showing "ragged red fibers") can also be used to confirm the diagnosis if serum analyses are indeterminate.[2] However, endomyocardial biopsy has a high false-negative rate in patients with suspected cardiac involvement because of the patchy distribution of myocyte disarray; this further complicates diagnosis.[3] Montaigne et al[4] proposed screening patients for MIDs if they have cardiomyopathies or arrhythmias and (1) a family history with maternal inheritance, (2) other classic MID symptoms including SNHL or unexplained neurologic symptoms, (3) biventricular hypertrophy, or (4) lactic acidosis. Mitochondrial HCM and sarcomeric HCM have differing underlying pathogeneses and natural histories, which makes early identification of the etiology important.

Sarcomeric mutations—often single-point missense mutations, deletions, or insertions—result in myocyte hypertrophy and disarray.[3] Although there are several patterns of myocardial disarray, they have not been found to be useful for prognostication.[3] Myocyte dysfunction results in LV hypertrophy, most commonly in an asymmetric pattern involving the basal interventricular septum.[3] During systole, the anterior mitral leaflet can make contact with the septum and obliterate the LVOT, causing subaortic obstruction and reduced cardiac output.[3,8] Approximately one-third of patients with sarcomeric HCM have a resting LVOT gradient (defined as >30 mm Hg), and an additional one-third have a provokable LVOT gradient.[3] The repetitive contact of the mitral valve leaflet against the interventricular septum results in compensatory endomyocardial fibrosis.[3] Approximately 10% of patients with sarcomeric HCM will progress to a "burnout" phase of LV dilatation caused by a combination of underlying patchy fibrosis and transmural myocardial ischemia from hypertrophy of small myocardial arteries.[3]

Mitochondrial HCM is caused by a complex interaction between abnormal cardiac structure and function as a result of ineffective aerobic respiration from dysfunctional cardiac mitochondria.[1,5] The heart is involved in up to 40% of patients with MID; this involvement has important prognostic implications because of reduced survival.[1] Cardiac involvement most commonly affects the myocardium, resulting in cardiomyopathy, but it can affect any structure, including the coronary arteries, pericardium, conduction system, autonomic nervous system, and aortic root.[1] Although HCM can be seen in pediatric patients as early as the antenatal period, it more commonly arises in early adolescence.[1] Older patients develop LV systolic dysfunction that leads to LV dilatation and, ultimately, dilated cardiomyopathy.[1]

Dilated cardiomyopathy in young patients carries a poor prognosis: only 18% survive to age 16 years.[1] Abnormal calcium homeostasis can cause a wide range of arrhythmias in 22% of patients with MIDs, including sinus node dysfunction, atrioventricular prolongation, supraventricular tachycardia, or, more rarely, ventricular arrhythmias.[1,4] Fibrosis can be detected in patients in the late stages of cardiomyopathy as late gadolinium enhancement on cardiac MRI.[1] The severity of fibrosis is an important predictive marker for the risk of mortality, HF exacerbations, and malignant arrhythmias in

patients with HCM.[9,10] Nonobstructive HCM has been described in multiple MIDs, including mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes; myoclonic epilepsy with ragged red fibers; chronic progressive external ophthalmoplegia; Leigh syndrome; and neuropathy, ataxia, and retinitis pigmentosa, even in the absence of cardiac risk factors.[1]

Mitochondrial HCM can be difficult to differentiate from sarcomeric HCM on echocardiography. Mitochondrial HCM is more likely to present as LV hypertrabeculation; it results in LVOT obstruction less frequently than does sarcomeric HCM.[5] Mitochondrial HCM generally causes symmetric hypertrophy and more frequently involves the RV.[4] In addition, mitochondrial HCM is more likely to result in dilated cardiomyopathy, with the degree of LV hypertrophy correlating positively with the degree of dilation and inversely with the degree of LV systolic function.[11] In contrast, sarcomeric HCM is frequently asymmetric and involves the basal interventricular septum and the free wall of the LV.[3] The apex, posterior LV, and lateral LV are rarely involved.[3] The RV is hypertrophied in only 17.6% of patients.[3] Lack of LV enlargement, asymmetric hypertrophy, and higher left atrial strain values (using mitral and pulmonary venous inflow signals) and left atrial volumes on echocardiography can help differentiate HCM from physiologic (secondary) hypertrophy.[8]

The *BCS1L* gene encodes a protein that is a critical chaperone for complex III assembly factors in the electron transport chain.[12] It encodes an adenosine triphosphatase responsible for the addition of the Rieske iron-sulfur proteins to the main subunits of cytochrome *b* and cytochrome c_1.[12] Dysfunction of the *BCS1L* gene usually results in fatal neurologic deficits in children and has been associated with 4 distinct disorders: isolated mitochondrial complex III deficiency (usually renal tubulopathy, encephalopathy, liver dysfunction), GRACILE syndrome (growth restriction, aminoaciduria, cholestasis, iron overload, lactic acidosis, early death), Björnstad syndrome (SNHL, pili torti), and Leigh syndrome (neuromuscular symptoms), none of which classically have cardiac involvement.[12]

A total of 25 distinct *BCS1L* mutations in 66 patients and 20 case studies have been described in the literature.[12] Isolated complex III deficiencies are the least common respiratory chain deficiency, with only 25 isolated defects reported between 1982 and 1995.[5] Because of the low frequency and high heterogenicity of this disorder, the full spectrum of clinical presentations and progressions is not well described. There is only 1 other report of HCM in a patient with the same *BCS1L* mutation as that described in this report (c.385G>A [p.Gly129Arg]).[13] That patient presented at age 14 years with delayed cognition and SNHL. Echocardiography and cardiac MRI showed nonobstructive HCM with severe biventricular hypertrophy and fibrosis of the anterior LV septum. Muscle biopsy showed characteristic ragged red fibers, and genomic analysis identified the *BCS1L* mutation.[13]

The course for most adult patients with both sarcomeric and nonsarcomeric HCM is benign, with an annual mortality rate of less than 0.7%; mortality is higher in those with resting or provokable LVOT obstruction and massive LV hypertrophy.[6] The risk of sudden cardiac death ranges from 0.5% to 2% per year; the patients at highest risk include those with a history of cardiac arrest or syncope, a family history of HCM and sudden cardiac death, documented ventricular arrhythmias, massive interventricular septum hypertrophy (≥30 mm), or late gadolinium LV enhancement of 15% or greater on cardiac MRI.[6] For patients with these characteristics, primary or secondary prevention with an implantable cardioverter-defibrillator is recommended.[6]

Acute complications of mitochondrial cardiomyopathy are difficult to evaluate because of the limited patient population. Nguyen et al[4] evaluated 705 patients with mitochondrial metabolism disorders and found a 2.4-fold increased risk of major adverse cardiovascular events (including cardiac arrest, acute HF exacerbation, and all-cause in-hospital mortality) and a 14.2-fold increased risk of all-cause in-hospital mortality compared with a propensity-matched cohort without MIDs. Although the risk of acute HF exacerbation was not statistically significant compared with the control population, those with MIDs were 4.1-fold more likely to have an underlying cardiomyopathy.[14] Similarly, McCormack et al[15] evaluated healthcare use for adult patients with MID and found a 3.0% all-cause in-hospital mortality rate for adults, approximately 3-fold higher than for those without MIDs. Of note, cardiovascular complications—including acute HF exacerbation, syncope, cardiac arrest, or arrhythmia—were not in the top 5 reasons for hospitalization.[15] Although these analyses provide some insight into complications of MID, they provide limited specific information about patients with underlying cardiac involvement.

Management of cardiac complications for patients with MID follows recommendations similar to those of

guideline-directed medical therapy for congestive HF, although there are no data from randomized controlled trials to support this.[5] A meta-analyses by Pfeffer et al[16] showed no significant clinical or biomarker improvement in patients with MID treated with supplements, including coenzyme Q10, creatine monohydrate, lipoic acid, dichloroacetate, dimethylglycine, and whey-based supplements. For patients with severe LV hypertrophy, dual-chamber pacing, septal myomectomy, or alcohol ablation can be considered.[3] In severe cases, evaluation for cardiac transplantation is warranted.

Conclusion

The MIDs are a heterogeneous group of diseases, commonly involving the heart, that cause either cardiomyopathy or arrhythmias. The *BCS1L* gene is responsible for an assembly subunit of cytochrome complex III in the respiratory transport chain and is the rarest respiratory chain defect. This report expands the phenotype of the *BCS1L* mutation and suggests that affected patients may need screening for underlying cardiomyopathy.

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