Cardiac Magnetic Resonance Aids in the Diagnosis of Mitochondrial Cardiomyopathy

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A 29-year-old woman presented with symptoms of cough, shortness of breath, and wheezing. She was diagnosed with bronchitis, but did not improve with empirical therapy, including antibiotics, inhalers, and prednisone. She subsequently developed chest pain that was worse when lying down, and a chest X-ray demonstrated cardiomegaly. This radiographic finding prompted further investigations. Her past medical history was notable for respiratory distress at birth and small stature growing up. She was diagnosed with a heart murmur at age 15, but investigations performed at that time were unrevealing. She also suffered from hearing loss. In retrospect it was discovered that several members in her maternal family, including her mother, grandmother, and aunt, also suffered from hearing loss. In addition, her mother had type 2 diabetes and a history of stroke and seizures.

On physical examination, she was a short, thin young woman with a body mass index of 17, wearing bilateral hearing aids. Her vital signs were normal. Cardiac auscultation revealed a 2/6 systolic ejection murmur. Laboratories revealed an elevated serum creatinine level of 1.36 mg/dL and a markedly elevated B-type natriuretic peptide level of 1417 pg/mL. The electrocardiogram was abnormal with evidence of right atrial enlargement, inferior Q waves, poor R wave progression, and inferolateral T wave inversions.

Transthoracic echocardiography revealed severe, concentric left ventricular (LV) hypertrophy with a septal wall thickness of 17 mm (Figure 1). LV systolic function was hyperdynamic (Movie I of the online-only Data Supplement), while diastolic filling demonstrated a restrictive pattern. The right ventricle also demonstrated increased wall thickness but was of normal chamber size and function. There was a moderate-sized pericardial effusion measuring 1.8 cm inferiorly with no evidence of hemodynamic compromise.

A cardiac magnetic resonance (CMR) scan was performed for better assessment of cardiac morphology and to rule out an infiltrative process. CMR confirmed severe concentric LV hypertrophy with an LV ejection fraction of 55% (Figure 2; Movie II of the online-only Data Supplement). Right ventricular dimensions and function were normal. T2-weighted imaging demonstrated high signal intensity globally with evidence of focal increased signal intensity in the subepicardial anterior and midwall anterolateral regions consistent with generalized edema with focal regions of increased edema (Figure 3A). On late gadolinium enhancement (LGE) imaging, extensive areas of hyperenhancement were seen in the basal to mid anterior and anterolateral walls corresponding to the focal regions of increased signal intensity on the T2-weighted images (Figure 3B). The territories of LGE are consistent with regions of edema or combined fibrosis and edema. Perfusion imaging revealed a circumferential global perfusion defect (worse with stress compared to rest) consistent with small vessel disease (Figure 4; Movies IIIA and IIIB of the online-only Data Supplement). These findings were suggestive of an infiltrative or myopathic process.

**Figure 1.** Transthoracic echocardiogram demonstrating the parasternal long (A) and short (B) axis images with increased LV mass and a moderate-sized pericardial effusion (arrow).
The concomitant presence of hearing loss, low skeletal mass, cardiac hypertrophy, and pericardial effusion raised the possibility of a mitochondrial cardiomyopathy. Along with deafness, the maternal history of diabetes, seizures, and stroke-like syndrome also suggested this diagnosis. Additional laboratories revealed evidence of anaerobic metabolism with an elevated lactic acid level of 2.1 mmol/L and abnormal Krebs cycle metabolism with an elevated pyruvate level of 0.15 mmol/L. Fasting blood glucose was 118 mg/dL, and hemoglobin A1c was mildly elevated at 6.4%.

The diagnosis of mitochondrial cardiomyopathy was confirmed, and other forms of infiltrative and inflammatory cardiomyopathies were ruled out by endomyocardial biopsy. Light microscopic evaluation revealed the hallmarks of mitochondrial myopathy, with myocyte hypertrophy, perinuclear vacuolar swelling (Figure 5A), and the absence of other infiltrative or inflammatory disorders. Electron microscopy (Figure 5B) revealed severe hyperplasia of the mitochondria, with marked variability in size, shape and morphology, including abnormalities in the structure of the cristae, along with an absence of specific findings of other cardiomyopathies.

This case highlights the important clinical and CMR characteristics in making the uncommon diagnosis of mitochondrial cardiomyopathy. The tissue-characterizing capability of CMR was effective in ruling out other causes of increased LV mass. Familial hypertrophic cardiomyopathy due to sarcomeric gene mutations can have LGE in variable locations and distributions, but most commonly at the junction of the interventricular septum and right ventricular wall, and pericardial effusion is not a common finding. Fabry’s disease specifically involves LGE in the inferolateral basal or mid basal segments. The CMR findings were not typical of an infiltrative cardiomyopathy. Cardiac amyloid shows diffuse subendocardial LGE not present in this patient. In addition, the gadolinium washout kinetics in blood compared to myocardium were not consistent with cardiac amyloidosis. Myocardial sarcoid does not typically result in generalized hypertrophy.

Mitochondrial disorders result in problems with oxidative phosphorylation, limiting the production of adenosine triphosphate. Mitochondrial diseases represent a heterogeneous group of disorders, but the brain, heart, and skeletal muscle are most commonly affected, because these systems are particularly vulnerable to defects in energy metabolism. Other multisystem abnormalities can occur, including sensorineural hearing loss, endocrine dysfunction (diabetes), and short stature. Although LV hypertrophy is not common in all forms of mitochondrial disease, in 1 large series of children with various subtypes of mitochondrial myopathies, 17% had an associated cardiomyopathy. The cardiomyopathy frequently results in concentric hypertrophy with significant variability in LV volume and function. Pericardial effusions are present in up to 1 quarter.

The combination of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episode (MELAS), often accompanied by seizures, represents a clinically distinct subgroup of patients with mitochondrial disease. Symmetrical...
LV hypertrophy is prevalent among patients with MELAS.\(^5\) Although the genetic tests to confirm the diagnosis of MELAS are pending, our patient’s clinical symptoms, laboratory work, and family history are suggestive of this diagnosis. Previous reports of CMR in MELAS also showed a pericardial effusion, increased signal with T2-weighted imaging, and LGE.\(^6\)

The presence of cardiomyopathy in patients with mitochondrial disease has prognostic implications because it is associated with increased mortality.\(^4\) The diagnosis can be made with a skeletal muscle biopsy and screening for cardiac involvement. Although in this case CMR was used to assess the etiology of cardiomyopathy in a patient without known mitochondrial disease, CMR could also be used to screen for myocardial involvement in patients with known mitochondrial myopathy. This case also illustrates the importance of taking a careful family history. Treatment consists of standard heart failure therapy, and dietary supplements that increase adenosine triphosphate production, such as creatine, carnitine, and coenzyme Q10.

Our patient’s presenting symptoms, which included cough, shortness of breath, and positional chest pain, were presumed to be due to myopericarditis, and her chest pain improved with nonsteroidal antiinflammatory therapy. Our patient was also treated with metoprolol, with consideration of coenzyme Q10 and carnitine supplementation. Genetic testing was negative for the known genes responsible for hypertrophic cardiomyopathy and dilated cardiomyopathy. Mitochondrial genome analysis is pending.

**Disclosures**

None.

**References**

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