

## Case Report

# Case Review of Cardiac Imaging Findings in Mitochondrial Disease

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### Abstract

Mitochondrial disease can be difficult to diagnose, as each case presents with unique manifestations. Mitochondrial cytopathies can result in cardiovascular disease, most commonly hypertrophic cardiomyopathy, left ventricular noncompaction, aortic root dilation and dilated cardiomyopathy. Identification of one of these cardiac disorders may prompt further investigation to exclude mitochondrial disease. We include a comprehensive literature review and discussion about cardiac imaging used to detect disease in patients with mitochondrial defects.

**Keywords:** Cardiac magnetic resonance imaging, cardiac computed tomography, dilated cardiomyopathy, hypertrophic cardiomyopathy, mitochondrial disease, left ventricular noncompaction

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Mitochondrial disorders have diverse clinical manifestations leading to a difficulty in diagnosis. Cardiac manifestations of mitochondrial disease can be effectively revealed on imaging with MRI and CT, which could prompt further investigation into the presence of mitochondrial disease. The most common findings on imaging include hypertrophic cardiomyopathy, left ventricular noncompaction, and dilated cardiomyopathy.

Mitochondrial disorders are a rare spectrum of diseases that have a variety of clinical manifestations. Mitochondrial disease (MD) emerges due to dysfunction of the mitochondrial respiratory chain, which can lead to a decrease of energy available for cell functions. The presentation is variable across organ systems but the greatest impact is seen with

organs that are most reliant on aerobic respiration, such as the heart.<sup>[1]</sup> Hypertrophic cardiomyopathy, left ventricular noncompaction, and dilated cardiomyopathy are the three most prevalent manifestations of cardiac disease associated with MD.<sup>[2]</sup> In this study, we present a series of cases demonstrating typical cardiac imaging findings in MD. The diagnosis of MD in these patients was based on objective criteria as defined by Bernier et al.<sup>[3]</sup> No protected health information was used for this work.

### Case Report

**Patient 1** is a 24-year-old female with a known history of Friedreich ataxia. The patient complained of intermittent episodes of palpitations associated with dyspnea and leth-

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argy occurring at least once a month. Initial ECG showed normal sinus rhythm with LV strain pattern and echocardiogram demonstrated hypertrophic cardiomyopathy. No significant cardiac arrhythmias, aside from a few premature ventricular contractions, were found on cardiac event monitoring. Cardiac MR performed five years later showed thickening of the mid septum measuring 16 mm in thickness at end diastole (z-score= 3.86). Myocardial hypertrophy was limited to the mid septum. No LV outflow tract obstruction or systolic anterior motion of the mitral valve anterior leaflet was demonstrated. Late gadolinium enhancement "grey-zone" was present in the midwall of the apex (Fig. 1). The patient's hypertrophic cardiomyopathy was treated with atenolol 25 mg as well as verapamil ER 120 mg, both twice daily, with improvement in symptoms.

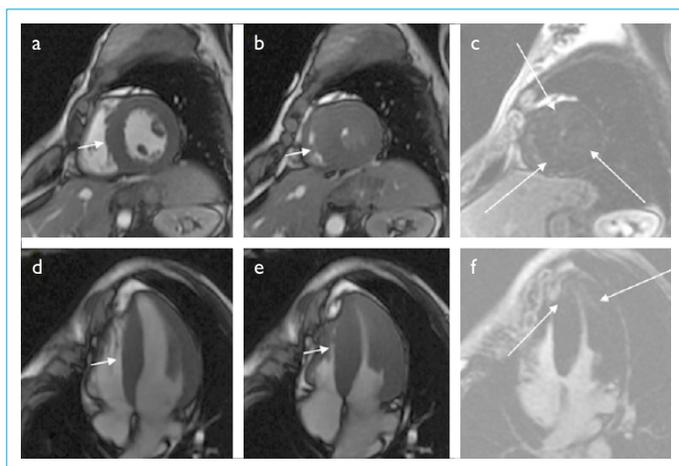
**Patient 2** is a 19-year-old male who presented with decreased exercise tolerance. At six months of age, he was diagnosed with hypotonia. A subsequent muscle biopsy found mitochondrial Complex 1 and Complex 4 deficiencies, indicating mitochondrial disease (MD) despite having no associated family history. An ECG showed the QTc interval to be 417ms. No cardiac arrhythmias detected on Holter monitoring performed in 2012. Echocardiography in 2013 demonstrated a dilated aortic root measuring 4.1cm and a left ventricular ejection fraction (LVEF) of 55-60%. A repeat echocardiogram was performed in 2015 and demonstrated an ejection fraction of 48%, no left

ventricular hypertrophy (LVH), and an aortic root measuring 4.0 cm with a Z-score of 3.9. He was treated with Co-Q10, carnitine, and vitamins B2, C, D3, and E. Cardiac MRI later that year showed dilation of the aortic root measuring 4.1 x 3.8 cm (Z-score of 4.11) and tricuspid aortic valve. The ascending thoracic aorta and LV chamber size were within normal limits and the LV ejection fraction was 55%. There was no left ventricular hypertrophy, noncompaction, or late gadolinium enhancement (Fig. 2).

**Patient 3** is a 20-year-old female who presented with intermittent palpitations. She had a known history of MD; however, the subtype was unknown as no records were available. Cardiac stress test findings were indeterminate for ischemia. Coronary CT angiogram showed normal coronary arteries, no LVH, and normal ventricular chamber size. However, mild left ventricular noncompaction was found with a ratio of 2.4 (Fig. 3). The aortic root measured 2.9 cm with a Z-score of 0.75. A small patent foramen ovale with left to right shunt was also identified.

## Discussion

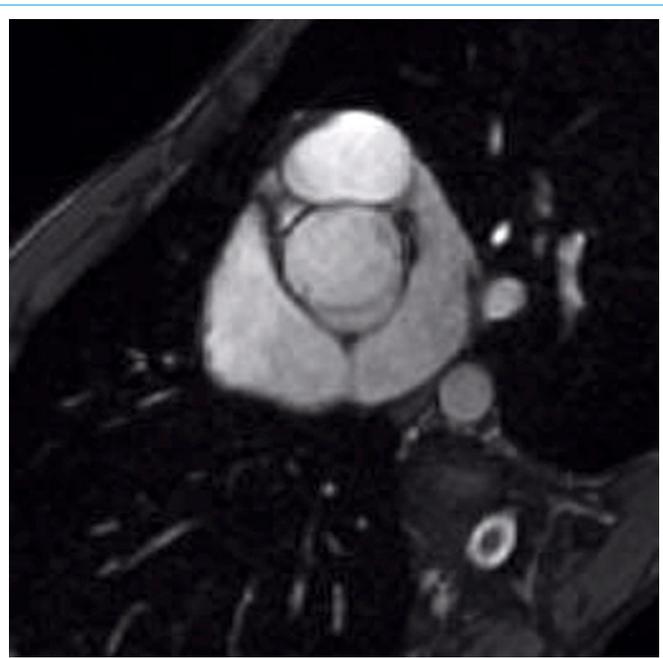
The patients discussed demonstrate how mitochondrial diseases can present with a variety of signs and symptoms. For this reason, MD can be difficult to diagnose, as varying genetic abnormalities may have distinct mutations which



**Figure 1.** 24-year-old female with Friedreich ataxia.

**Findings:** **a-d** demonstrates balanced steady-state free precession sequences in short axis at end-diastole and end-systole (**a,b**) and horizontal long axis (**c,d**). Note asymmetric thickening of the mid interventricular septum as well as obliteration of the mid and apical LV chamber during systole (short arrows). **e,f** demonstrates inversion recovery prepared late gadolinium enhanced sequences showing patchy "grey-zone" enhancement in the midmyocardium of the apex (long arrows).

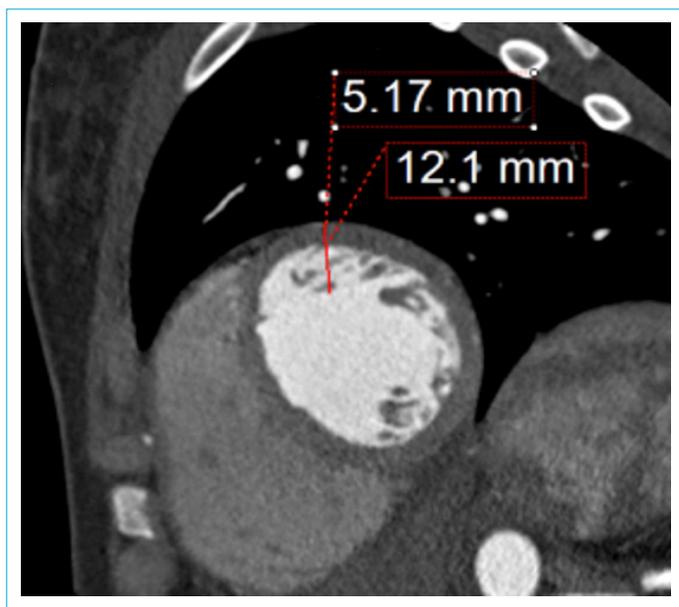
**Technique:** Multiplanar cardiac MR performed on a 1.5T Siemens Aera with a dedicated 18-channel cardiac surface coil. Postcontrast imaging was performed after IV administration of 10mL of Gadovist.



**Figure 2.** 19-year-old male with Complex 1 and Complex 4 deficiency.

**Findings:** Orthogonal projection of the aortic root during systole using a balanced steady state free precession sequence. The aortic root measured 4.1x3.8 cm.

**Technique:** Orthogonal plane of the aortic root. Cardiac MR performed on a 1.5T Siemens Aera with a dedicated 18-channel cardiac surface coil.



**Figure 3.** 20-year-old female with mitochondrial disease.

**Findings:** Reformatted, contrast-enhanced cardiac CT in short axis at end-diastole showing increased number and thickness of LV trabeculations along the anterior and lateral walls with a noncompaction ratio of 2.4.

**Technique:** Short axis reformatted image. Siemens SOMATOM Definition Flash dual source scanner. Images acquired after injection of 75mL of IsoVue 370 at 5mL/sec followed by a saline chaser.

lead to unique manifestations in each case. Diagnosis of MD is based on clinical, imaging, biochemical, histopathological, and genetic criteria. MD should be considered in patients with a constellation of symptoms involving three or more organ systems. Other red flags include early onset diabetes, muscle weakness, alopecia, deafness, and ptosis. A detailed three-generation pedigree may reveal either a maternal (mtDNA mutation) or Mendelian (nDNA mutation) inheritance pattern.

In patients with known MD, the determination of cardiac involvement is critical, since the associated cardiac abnormalities can be fatal if left untreated. Therefore, cardiac testing is especially important when MD is suspected. Imaging often plays an integral role, with variable cardiac findings depending on the particular mitochondrial gene defect and function. ECG, echocardiography and CMR can be used for cardiac testing, which can later reveal MD as the cause if cardiac disease is found.<sup>[4]</sup>

Patient 1 was found to have hypertrophic cardiomyopathy on cardiac MR. This is the most common cardiac abnormality seen across the spectrum of mitochondrial diseases and can be found in more than 50% of patients with mitochondrial disease related cardiomyopathy.<sup>[5]</sup> Patient 1 also had a history of Friedreich ataxia, which is a mitochondrial disease and the most common inherited ataxia. It is inherited in an autosomal recessive pattern and usually results from

a GAA triplet expansion in the FRDA gene, which encodes a protein named frataxin. Frataxin is located in mitochondria and is involved in mitochondrial iron homeostasis. Trinucleotide expansion within the gene leads to decreased frataxin synthesis, thereby causing impairment of mitochondrial respiration in skeletal and cardiac muscle.<sup>[6]</sup> Patients with Friedreich ataxia typically present with progressive gait ataxia with mortality most commonly attributed to hypertrophic cardiomyopathy.<sup>[7]</sup>

Another cardiac finding associated with mitochondrial diseases is dilation of the aortic root. This was found with the use of echocardiography and CMR in patient 2 who had a history of mitochondrial complex 1 and complex 4 deficiencies. CMR and cardiac CT are effective tools for diagnosing aortic root dilation. Brunetti-Pierrri et al.<sup>[8]</sup> reported a mean Z-score for the aortic root of 3.1 in a group of 10 patients with MD and aortic root dilation. They further reported a statistically significant enlargement of the aortic root, annulus, sinotubular junction, and main pulmonary artery in a group of 48 patients with MD. A majority of those with MD and aortic root dilation had no other known cardiac disease. The underlying cause of aortic root dilation in MD is unknown.

Patient 3 was found to have left ventricular noncompaction after coronary CT angiography was performed. Left ventricular noncompaction has been seen to resolve on its own sporadically in these patients, and is more prevalent in males. Cardiac CT has been shown to be useful in making the diagnosis.<sup>[9]</sup> Dilated cardiomyopathy is another common finding associated with MD, although it was not seen in these patients. It can be primary or secondary, usually as a result of hypertrophic cardiomyopathy.<sup>[5]</sup>

While a major role of cardiac imaging is to rule out other causes of cardiac disease, CMR is also useful for characterization of cardiac manifestations of MD. In these patients, CMR has been shown to reveal perfusion defects despite a normal coronary angiogram.<sup>[10]</sup> More specifically, findings may include focal perfusion defects on first pass perfusion imaging with associated delayed myocardial enhancement on contrast-enhanced imaging.<sup>[10]</sup> The pattern of delayed enhancement can provide soft tissue characterization, in addition to the use of T1 and T2 mapping and extracellular volume fraction analysis. Typically, there will be increased T2 signal diffusely throughout the myocardium without T1 shortening.

## Conclusion

In summary, mitochondrial disease can result in detrimental effects on the heart, most commonly hypertrophic cardiomyopathy, left ventricular noncompaction, and dilated car-

diomyopathy. In the appropriate clinical setting, identification of one of these cardiac disorders may prompt further investigation to exclude mitochondrial disease. Cardiovascular imaging using MRI and CT can effectively reveal cardiac disease associated with mitochondrial disease.

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### Disclosures

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