Mitochondrial Cytopathies and Cardiac Disease

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Key Points

- The heart is metabolically very active, both in terms of energy production and of energy utilization. It is not surprising, therefore, that cardiac dysfunction often accompanies mitochondrial disorders and that several cardiac disorders have been associated with specific mitochondrial defects.

- Cardiac manifestations include arrhythmias as well as hypertrophic and, less commonly, dilated or non-compaction cardiomyopathies.

- There should be a high index of suspicion for potential cardiac involvement in any patient with a diagnosed mitochondrial cytopathy.

- Conversely, a possible mitochondrial basis should be suspected in patients presenting with isolated, unexplained cardiac disease, or a familial/genetic history of cardiac disease.

- Antenatal onset may occur.

Heart Metabolism

- The average (adult) heart weighs about 250-300 grams (7-10 ounces) and consumes about 27 ml (1 ounce) of oxygen per minute.

- To maintain myocardial contractility (keeping the heart beating), the mitochondria in the cardiac cells (myocytes) utilize oxygen to generate energy (ATP), through the process of oxidative phosphorylation.
o The myocytes contain high numbers of mitochondria (1000’s per cell), which account for about 20-40% of the cell volume.

o In the fetal heart, glucose and lactate are the primary fuel sources for energy production.

o After birth, fatty acids become the primary energy source and their metabolism accounts for about 60% of the oxygen consumed at rest and in the fasting state.

o The metabolism of glucose accounts for about 28% of oxygen consumption and that of lactate for about 11%.

o During exercise, the heart’s dependence on fatty acids to generate energy increases, whereas during myocardial ischemia (such as angina or a heart attack) glucose becomes the main fuel.

o Under hypoxic (low oxygen) conditions, the breakdown of glucose to pyruvate (through glycolysis) results in the formation of lactate instead of acetyl CoA, which would normally enter the citric acid cycle.

o Anaerobic glycolysis results in the production of two ATP molecules only, instead of the 36 molecules generated through the process of oxidative phosphorylation (under normal aerobic conditions).

o A normally contracting heart pumps oxygenated blood containing nutrients and metabolites to meet the other organs’ metabolic and energy requirements.
• The interplay between mitochondrial disease and cardiac disease can be considered at two levels. The heart may be involved as one component of a multisystem mitochondrial cytopathy or it may be the principal or even the only organ involved.

• Mitochondrial cardiopathies may manifest as structural alterations, such as dilated or hypertrophic cardiomyopathies or as a disturbance of heart rate and/or rhythm, such as ventricular tachycardia, Wolff-Parkinson-White syndrome, or heart block.

• The clinical manifestations include heart failure, reduced exercise tolerance, or death. Cardiac dysfunction may also give rise to failure of other organs.

• The frequency of cardiomyopathy in children with mitochondrial disease is approximately 20-25%\textsuperscript{1,2} although some series have reported incidences as high as 40%.\textsuperscript{14} Hypertrophic cardiomyopathy is more common than dilated cardiomyopathy.\textsuperscript{2,14} Left-ventricular non-compaction cardiomyopathy or left-ventricular hypertrabeculation cardiomyopathy is an unusual cardiomyopathy so-named for the trabeculated or spongiform appearance of the left ventricular wall. It is often associated with genetic cardiac, non-cardiac, metabolic and neuromuscular disease, most frequently mitochondrial cytopathies, especially Barth syndrome.\textsuperscript{14,15}

• Well-recognized mitochondrial cytopathies with distinct cardiac involvement include:
• Kearns-Sayre syndrome (KSS), which can cause third-degree heart block;

• Leber’s hereditary optic neuropathy (LHON), which is often accompanied by Wolff-Parkinson-White (WPW) syndrome (an aberrant conduction defect);

• Myoclonic epilepsy with ragged red fibers (MERRF) which may be associated with dilated cardiomyopathy and/or WPW syndrome.\textsuperscript{23}

• Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), frequently associated with hypertrophic cardiomyopathy,\textsuperscript{3,17} or

• Barth syndrome, which typically causes left ventricular non-compaction cardiomyopathy.\textsuperscript{4}

• In some instances, there may be more than one manifestation of cardiac disease in a specific syndrome: for example, His-ventricular (H-V) interval prolongation or dilated cardiomyopathy can be seen in Kearns-Sayre syndrome in addition to the “classical” heart block;\textsuperscript{5} or hypertrophic cardiomyopathy and/or, less commonly, WPW syndrome in MELAS.\textsuperscript{17,18}

**Cardiac Defects**

• Mitochondrial cardiopathies may be accompanied by alterations in mitochondrial numbers, shape, and function and can be primary or secondary.
• Primary cardiomyopathies are due to mutations either in mitochondrial DNA (mtDNA) or in nuclear DNA (nDNA). Except for 13 subunits encoded by mtDNA, all other components of the respiratory chain complexes are encoded for by nDNA.

• A mitochondrial cytopathy is secondary when the primary insult affects mitochondrial function either indirectly or through damage to the mitochondrial genome. For example, mitochondrial proliferate in myocytes as a result of mtDNA deletions induced by free radicals generated by altered oxidative phosphorylation in ischemic heart tissue (heart tissue that isn’t getting enough blood). Another example is the mtDNA depletion syndrome that may result from certain drug therapies, such as zidovudine (AZT) therapy for HIV/AIDS.

• Friedreich ataxia is a multisystemic genetic disorder (in this case due to a trinucleotide repeat) that causes accumulation of iron in cardiac myocytes. The result is hypertrophic cardiomyopathy.

• Barth syndrome perhaps requires special mention. Although this is a systemic disorder, cardiac involvement is a key feature and is somewhat specific due to the non-compaction or spongiform cardiomyopathy. Barth syndrome is an X-linked disorder due to a mutation in the G4.5 gene encoding the protein taffazin. Short stature and cyclic neutropenia are other associated features. Arrhythmias may also occur.

• Antenatal onset of cardiac disease (arrhythmias and/or cardiomyopathy) may occur and is increasingly being reported.\textsuperscript{19, 20, 21, 22}
• Defects of Mitochondrial DNA
  o Defects in mitochondrial DNA cause less than three percent of dilated and an even smaller percentage of hypertrophic cardiomyopathies.
  o The mtDNA-related cardiomyopathies usually result from mutations affecting transfer RNAs (tRNAs).[^6]^[15]
  o Some rare mutations involve ribosomal RNA (rRNA).[^7]
  o Rare mtDNA causes of cardiomyopathy are missense mutations in cytochrome b.[^6]
  o A recent report describes an apparently heart-specific mitochondrial DNA depletion syndrome, a problem usually associated with muscle or liver disease.[^9]

• Defects in Nuclear DNA
  o Nuclear DNA (nDNA) encodes for many proteins involved in mitochondrial function, including mtDNA replication and transcription factors, membrane proteins, and subunits of the electron transport chain respiratory complexes.
  o Defects in nDNA are likely to be more common causes of cardiac disorder than mtDNA defects.
  o Several defects in nDNA can cause infantile or early-onset hypertrophic cardiomyopathy by affecting complex I (mutations encoding for the NADH dehydrogenase ubiquinone flavorprotein—or NDUF—subunits),[^10] complex IV (mutations of the SCO2 or

[^6]: Reference 6[^15]: Reference 15[^7]: Reference 7[^9]: Reference 9[^10]: Reference 10
COX15 genes involved in the assembly of Complex IV),\textsuperscript{11,12,16} or the adenine nucleotide translocator (ANT1) protein—which has been demonstrated in mouse models.\textsuperscript{6} Nuclear subunits of Complex III have also been implicated.\textsuperscript{13}

- Cardiac involvement with mutations of the Twinkle (PEO1) gene, an essential mitochondrion-specific helicase important in mtDNA maintenance and mtDNA copy number is increasingly being recognized.\textsuperscript{24}
- Mutations resulting in enzyme deficiencies in the beta-oxidation pathway of lipid metabolism (e.g. VLCAD, LCAD, MCAD and SCAD) and in the transport of carnitine often cause cardiomyopathies. In this case, in addition to the reduced energy production, the accumulation of fatty acids is also toxic to the cardiac myocytes.
- Defects in the mitochondrial trifunctional protein (MTP), another component of the beta-oxidation pathway, may result in dilated cardiomyopathy.
- A recent animal study has shown the first gene mutation (Dnm1L) involved in mitochondrial fission and remodeling to result in a dilated cardiomyopathy in the mouse mutant Python phenotype.\textsuperscript{25} No human disease involving this gene or mechanism has yet been described.
Clinical Manifestations

- The clinical manifestations of cardiac involvement in mitochondrial disease may be either “pure” cardiopathies or, more commonly, part of multi-systemic mitochondrial cytopathies – which may include: short stature, sensorineural hearing loss, diabetes mellitus, peripheral neuropathies, and many more symptoms and signs.
- The cardiac manifestations are similar to those caused by any other medical or primary cardiac condition.
- There are three main clinical groups – asymptomatic, arrhythmias, and cardiomyopathies.
  1. Asymptomatic – cardiac dysfunction is detected as part of a screening evaluation of a patient with mitochondrial disease, or is found in an asymptomatic family member.
  2. Arrhythmias
     a. Symptoms: palpitations - tachycardia, bradycardia, or irregular heart rate, syncope or pre-syncope, dizziness, pallor, shortness of breath, chest pain or sudden death.
     b. Signs: Irregular pulse rate, pallor, and/or sweating.
  3. Congestive heart failure
     a. Symptoms:
        i. Arrhythmia (as above)
        ii. Shortness of breath, dyspnea with effort, orthopnea, easy fatigability.
iii. Failure-to-thrive, loss of appetite

iv. Swelling of feet and ankles

v. Chronic cough

b. Signs: Irregular pulse rate, weight loss or alternatively excessive weight gain, elevated jugular venous pressure, edema, hepatomegaly, displaced cardiac apex, and/or murmur.

Evaluation of Cardiac Disease

• Evaluation:

  1. Clinical

  2. Fractionated creatine kinase (CK): elevation of the MM fraction may indicate a concomitant underlying skeletal myopathy providing an additional clue to a possible mitochondrial cytopathy (or other primary genetic neuromuscular disorder).

  3. Special Investigations: will vary according to the nature of the suspected underlying problem, but includes –

     a. Electrocardiogram (ECG) – should be done in all patients

     b. Echocardiogram (Echo) – should be done in all patients

     c. Chest X-ray

     d. Holter monitor

     e. Stress test

     f. Chest computed tomography (CT) scan or cardiac magnetic resonant imaging (MRI) scan
g. Nuclear heart scans - radionuclide ventriculography (RNV) or multiple gate acquisition scan (MUGA)

h. Heart catheterization

i. Electrophysiological studies (EPS) may be necessary for further evaluation of some cases of arrhythmias

4. Cardiac biopsy: in select instances, cardiac biopsy may be helpful for the diagnosis of a mitochondrial cardiomyopathy. Electron microscopy may identify abnormalities in mitochondrial number, shape or size.

5. Screening of family members: first degree relatives of the index case should be screened by ECG and echocardiogram for potential sub-clinical involvement. This should include female carriers in the case of X-linked inheritance and matrilinear relatives if mtDNA mutations are suspected.

Treatment of Cardiac Disease

- The treatment of cardiac disease is unrelated to its possible mitochondrial nature, and is directed towards the underlying etiology and symptoms.

1. Arrhythmias: treatment options will vary based on the type of arrhythmia but may include -
   a. Medication: anti-arrhythmic drugs
   b. Defibrillation or cardioversion
c. Radiofrequency ablation

d. Pacemaker

e. Implantable cardioverter-defibrillator (ICD) device

2. Congestive heart failure: treatment options will vary but may include

   a. Limitation of sodium intake

   b. Medications: anti-arrhythmic drugs, diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and/or angiotensin receptor blockers (ARB)

   c. Heart transplantation

References:


