A 2-month-old girl with poor appetite and failure to thrive was admitted because of pallor, dyspnea, and tachycardia with periodic gallop rhythm. Chest x-ray (Figure 1) showed cardiomegaly, and echocardiography (Figure 2) revealed left ventricular dilation (diastolic diameter, 41.5 mm [normal, <23 mm]), decreased contractility, and mild to moderate mitral valve insufficiency. ECG (Figure 3) showed sinus rhythm with left bundle-branch block and repolarization abnormalities. These findings were compatible with severe dilated cardiomyopathy. Polymerase chain reaction of the serum failed to detect any cardiotropic virus genomes. There was lactic acidosis. On frozen striated muscle, the mitochondrial respiratory chain function was tested and found to have decreased activities of complexes I (NADH coenzyme Q reductase, 9.1 nmol/min per milligram [normal, 13 to 24]) and IV (cytochrome-c oxidase, 103 nmol/min per milligram [normal, 120 to 220]). Therapy with oxygen, digoxin, captopril, and furosemide was initiated. Despite this, her cardiovascular function continued to worsen; she was readmitted at 10 months of age for decompensated heart failure and died 8 days later. Her family history revealed 1 brother who had died suddenly at the age of 3 months (no autopsy was performed).

Autopsy confirmed cardiac enlargement with severe left ventricular chamber dilation (Figure 4A); the endocardium was whitish and extremely thickened (Figure 4B). Histopathologically, there was significant endocardial fibroelastosis (Figure 5A and 5B). The left ventricular subendocardial myocardium displayed diffuse myocyte vacuolization (Figure 5C) with foci of necrosis and fibrosis (Figure 5A). Ultrastructurally, the myocyte vacuoles corresponded to severe loss of sarcomeres (myolysis) with accumulation of abundant mitochondria (Figure 5D).
Endocardial fibroelastosis is a nonspecific reaction to endocardial stress and injury leading to elaboration of elastin-rich extracellular matrix, which is particularly prominent in the growing heart. Endocardial fibroelastosis often accompanies abnormal increases in mural tension (provoked by chamber dilation) or markedly elevated intracavitary pressure. Inadequate subendocardial blood flow and lymphatic obstruction are additional pathogenetic mechanisms that have been proposed in this process. In this patient, respiratory-chain enzyme analysis revealed deficiencies in oxidative phosphorylation complexes I and IV, which strongly suggest a pathogenic mitochondrial DNA (mtDNA) mutation. The progressive myolysis and growing number of nonfunctioning myocytes putatively induced left ventricular dilation. The resulting stresses placed on the endothelium had led to a dramatic increase in endocardial elastic fiber matrix, ostensibly in an attempt to hinder further chamber dilatation and allow for dynamic and reversible expansion during the cardiac cycle. Apart from 1 brother who had died prematurely of unknown causes, there were no family members with signs of metabolic disease.

Mitochondria possess their own DNA (mtDNA), which contains 37 different genes. Twenty-four of these are needed for transfer RNAs and ribosomal RNAs, and there are 13 for 4 respiratory chain multisubunit complexes (I, III, IV, V). Because in every organelle there are ∼900 different proteins, the great majority of these gene products are encoded by nuclear DNA. As a consequence, primary mitochondrial defects may be subdivided into disorders involving mtDNA (following the rules of mitochondrial genetics) and disorders due to nuclear DNA defects (which obey Mendel’s laws). In particular, mitochondrial genetics differs from the mendelian in 3 main peculiarities: (1) There is a maternal inheritance; (2) mutations affect only a fraction of mtDNAs (heteroplasmy); in addition to depending on the anatomic site, the clinical expression of these disorders will also depend on the proportion of mutated to wild-type mtDNAs within cells (threshold effect); and (3) the random subdivision of mitochondria during mitotic cell division can modify the proportion of mutated mtDNA within the daughter cells (mitotic segregation), and a “bottleneck” between egg-cell and embryo allows only a fraction of mtDNAs to become part of the fetal cells, very likely in order to filter out mutations and minimize heteroplasmy.

In the presence of a respiratory chain defect, complex I isolated deficiency is the most frequent one, followed by a combined deficiency of complexes I, III, or IV. A mtDNA mutation may affect either specific proteins belonging to the respiratory chain apparatus or the entire mitochondrial protein synthesis (when involving transfer RNA, ribosomal RNA, or as a result of giant deletions).

Mitochondrial cardiomyopathies can genetically be subdivided into sporadic, mendelian-inherited, and maternally inherited disorders. Sporadic cardiomyopathy may be encountered in the Kearns-Sayre syndrome, which is caused by mtDNA deletions or duplication. It is invariably characterized by early onset (before age 20 years), external ophthalmoplegia, and pigmentary retinopathy; ataxia, short stature, and hearing loss may be additional symptoms. When present, cardiac involvement consists of conduction defects (prolonged intraventricular conduction and atrioventricular blocks, probably as a result of preferential accumulation of mutated mtDNA in the conduction system myocytes) and, only as a later event, impaired myocardial contractility.

![Figure 3](image1.png)

**Figure 3.** ECG obtained at first admission to the hospital showing left bundle-branch block and repolarization abnormalities.

![Figure 4](image2.png)

**Figure 4.** A, Autopsy heart specimen, cut along a midventricular short-axis plane, showing severe left ventricular chamber (LV) dilation with right ventricular (RV) compression. Bar=4.5 cm. B, A higher-magnification view of the left ventricular wall, with significant whitish endocardial thickening (asterisk) with partial obliteration of the trabeculae. Bar=2 cm.
Mendelian inheritance in mitochondrial cardiomyopathies is an infrequent event in which the genetic change affects the nuclear DNA and, only secondarily, the mtDNA as multiple deletions. An example of this is the reported autosomal dominant chronic progressive external ophthalmoplegia associated with dilated cardiomyopathy and multiple mtDNA deletions.\(^5\)

Maternally inherited mutations represent the most frequent category of mitochondrial cardiomyopathies whose cause is an mtDNA point mutation in almost all the cases. More than 50 different point mutations have been associated with various clinical disorders (mainly affecting heart, brain, and skeletal muscle).\(^5\) MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) can become manifest with cardiac involvement (as hypertrophic cardiomyopathy or, less frequently, Wolf-Parkinson-White syndrome) in 20\% to 30\% of cases. Another well-known maternally inherited disorder is the MERRF syndrome (myoclonic epilepsy with ragged red fibers), in which, in addition to presenting with myopathy, ataxia, and deafness, approximately one third of the patients show cardiomegaly and ventricular arrhythmic episodes.\(^5\)

From the pathological standpoint, very frequently, mitochondrial cardiomyopathy becomes manifest as a left ventricular concentric hypertrophy with, in isolated cases, an evolution into a dilated form that is only rarely associated with endocardial fibroelastosis.\(^1\)\(^,\)\(^2\) Unfortunately, preclinical specific signatures of mitochondrial cardiomyopathy are scarce. In general, clinical suspicion for neonatal mitochondrial disorders with cardiomyopathy should arise in the presence of deafness, failure to thrive, lactic acidosis, and cardiomegaly with increasing signs of failure and/or arrhythmia, all of these sometimes within the spectrum of a multisystem presentation (mainly nervous system or skeletal muscle) and often with a clear maternal inheritance.\(^8\) In the presence of nonspecific signs of dilated cardiomyopathy in children, a large spectrum of tests must be performed to narrow the differential diagnosis between mitochondrial and other metabolic diseases (eg, fatty acid oxidation defects). Blood and muscle samples should also be kept for genetic tests and biochemical/morphological studies including those for mitochondrial diseases. In addition, clinical gene-based screening is strongly recommended in patients’ family members to provide either early cardiomyopathy diagnosis or personalized evaluation of risk assessment.\(^4\)

**Disclosures**

None.

**References**


Dilated Form of Endocardial Fibroelastosis as a Result of Deficiency in Respiratory-Chain Complexes I and IV

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