

Mitochondrial Hypertrophic Cardiomyopathy Associated with Wolff-Parkinson-White Syndrome

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Today, several cardiac diseases are recognized as genetic in origin. Two examples of the genetic disease familial hypertrophic cardiomyopathy (HCM) are mutations in genes encoded with several sarcomere proteins with myocyte and myofibrillar disarray and one associated with Wolff-Parkinson-White syndrome (WPW). The latter has been identified in chromosome 7q3 as a result of a point mutation in the gene that encodes a regulatory subunit of AMP-activated protein kinase that expresses ventricular hypertrophy, ventricular pre-excitation, or both¹⁻³. Other inherited cardiac disorders in which hypertrophic or dilated cardiomyopathy and electrical disturbances may be present in about 20% to 30% of patients include some mitochondrial diseases⁴⁻⁶. We present the case of a newborn female with persistent tachycardia secondary to WPW, in which severe hypertrophy and other systemic abnormalities were attributed to a mitochondrial disease.

A female of 38-weeks gestation was born by Cesarean delivery because of a heart rate of 300 beats/min. At 25 days of age, she was transferred to a pediatric center because the tachycardia persisted even with the administration of digoxin and propranolol. In addition, the patient had a systemic hypertension of 140/80 mmHg. Digoxin was discontinued, but propranolol and propafenone, up to 400 mg/m²/day did not control the tachycardia. Hydralazine and furosemide gradually normalized the blood pressure. Surface electrocardiography and Holter monitoring revealed overt left-sided WPW, remarkable atrial and bi-ventricular enlargement, and abnormal ventricular repolarization (fig. 1). Chest X-rays showed moderate cardiomegaly and severe and universal wall thickness enlargement by echocardiography, with no obstruction to ventricular outflow tracts, diminished left ventricular ejection fraction (LVEF) 56%, and fractional shortening (FS) 24% (fig. 2).

Propafenone was replaced by amiodarone i.v., with the loading regimen increased to 36.8 mg/kg/day and adenosine boluses of 300 mcg/kg, which controlled the arrhythmia transiently. Plasma glucose and liver and thyroid function tests were normal, but serum enzymes were elevated: lactate dehydrogenase 687 U/L (normal <190); creatine kinase 1612 U/L (normal <232), and

aspartate aminotransferase 147 U/L (normal <37). Due to abnormal serum lactate determination (3.8 μmol/L, normal <2.0), a skeletal muscle biopsy was processed to search for enzymatic activity in the respiratory-chain complex.

The patient was transferred to our cardiology hospital at 71 days of age, with tachycardia of 300 beats/min, blood pressure of 90/60 mmHg, mild cyanosis and diaphoresis, and hepatomegaly 3 cm below the costal margin. Due to antiarrhythmic drug resistance (amiodarone maintenance doses 17 mg/kg/day and propranolol 1.5mg qid), clinical heart failure data, mild pericardial effusion, and ventricular dysfunction progression (LVEF ranged 45-54%, FS 21%), radiofrequency catheter ablation became mandatory.

She underwent an electrophysiological study 10 days later, under orotracheal intubation and use of midazolam, fentanyl, and propofol i.v. Three multipolar 5 French catheters were inserted by percutaneous femoral access. Groin hemorrhage, acidosis, and hypothermia, followed by ventricular tachycardia and fibrillation, and finally advanced atrio-ventricular block pace dependent, forced us to abandon the procedure. Earlier pacing on the right ventricular apex showed an extremely short ventricle-atrial interval on distal coronary sinus electrodes, compatible with a left atrio-ventricular accessory pathway (fig.1). The patient evolved to renal dysfunction, a mean blood pressure of 50 mmHg under dopamine-dobutamine infusion, besides intermittent sinus tachycardia and atrio-ventricular reentrant tachycardia that poorly responded to adenosine, either with amiodarone infusion or boluses. One prolonged seizure episode was registered, despite prophylactic phenytoin use, and the patient died 48 hours after the procedure.

Partial necropsy (lung and heart) findings included cardiomegaly (73 g; normal for age, 28 g), due to biventricular hypertrophy, with a mean wall thickness of 5 mm for the right ventricle and 14 mm for the left ventricle (normal for age, 1.80 mm and 4.43 mm, respectively). Hematoxylin-eosin and PAS staining revealed gross vacuolar myocyte changes, and discarded lipid or glycogen storage. Electron microscopy showed extensive loss of myofibrils, and augmented size and number of mitochondria, with severe morphological abnormalities and irregularity of the cristae, which were fragmented or had a concentric or peripheral array (fig.3). A spectrophotometric analysis from skeletal muscle biopsy revealed respiratory chain dysfunction due to a reduction in activity in complex III: NADH (nicotinamide adenine dinucleotide dehydrogenase)-cytochrome c reductase (3.81 nmol/min/mg, normal 36-68); complexes I through V were all normal.

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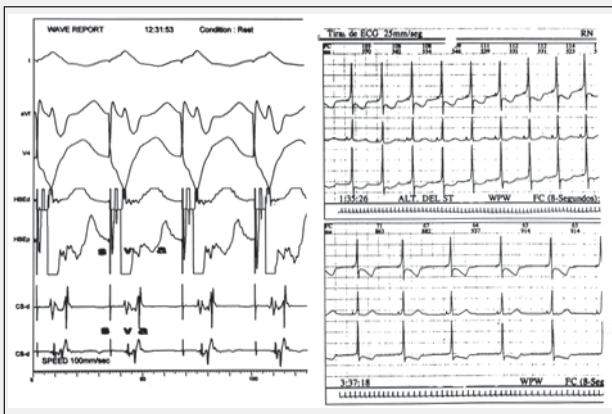


Fig. 1 - Intracardiac electrograms (left) showing under right ventricular pacing, atrial activation precocity in distal coronary sinus, followed by His bundle. Holter monitoring (right) showing a typical WPW syndrome. (s) spike, (V) ventricle, (a) atrial, (CSd) distal coronary sinus, (HB) His bundle.

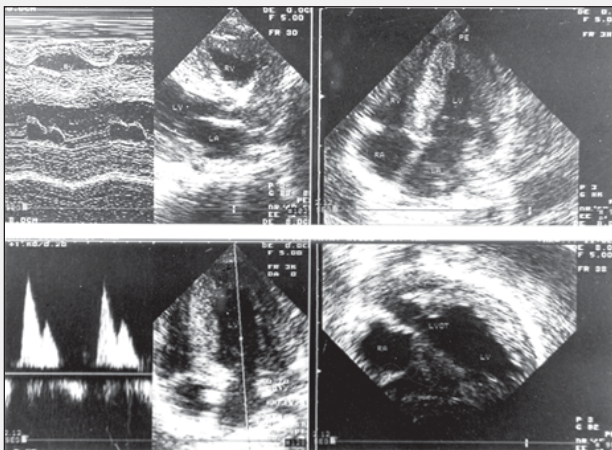


Fig. 2 - Transthoracic echocardiogram showing severe hypertrophied septal and biventricular wall, mode M, and BD 4-chamber view (upper panels). Restrictive Doppler pattern (left bottom) and left ventricle outflow tract (LVOT) without obstruction (right bottom).

Discussion

Traditionally, patients with WPW have no other structural heart abnormalities; however, HCM has been described in association with WPW as a well-recognized inheritable entity^{1,2}. Because relevant hypertrophy is not usually recognized before 1 year of age, a differential diagnosis of familial HCM in infancy must be made, and includes the following: diabetes history, Noonan syndrome in which right outflow tract obstruction is predominant; and metabolic disorders like Pompe's disease⁷. None was present in our newborn patient.

Today, several major mitochondrial disorders have been described in which those organs rich in mitochondria (brain, heart, and skeletal muscle) are predominantly involved, secondary to mitochondrial DNA (mtDNA) mutations.^{4,5} HCM associated with mitochondrial proliferation is known to be common in MELAS disease, a mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes^{6,8,9}. Moreover, in 2 large series of patients with MELAS disease, WPW has also been associated^{6,8}.

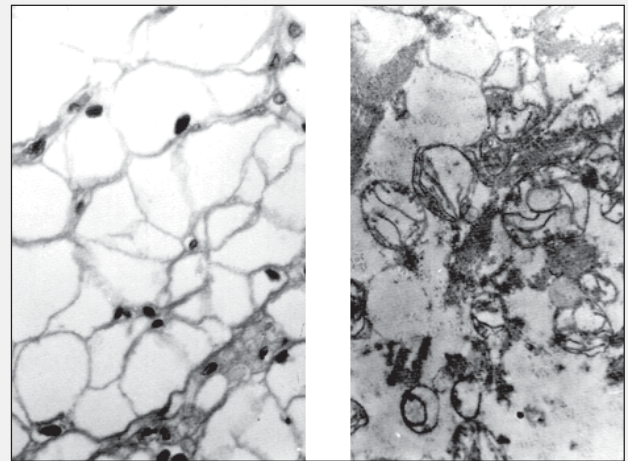


Fig. 3 - Light microscopy showing extensive vacuolar changes (left). Electron microscopy showing mitochondrial abnormalities in size and structure and severe morphologic alterations of the cristae (right).

Although we have not identified a DNA mutation, high levels of serum lactate; seizures; reduced activity of complex III of the mitochondrial oxidative phosphorylation pathway on skeletal muscle specimens; and abnormal serum myocardial enzyme elevation, probably related to advanced myocardial tissue damage attributed to remarkable mitochondrial abnormalities, support this condition. The early hypertrophic cardiac manifestation observed in our case could be an expression of a high level of mutant mtDNA, as has been described in other cases, in which predominant or exclusive heart or skeletal muscle abnormalities are present^{4,5,9,10}.

Furthermore, electrophysiological study represents a true challenge for diagnosis and treatment, although it supports the existence of an accessory pathway. Unfortunately, a mandatory radiofrequency catheter ablation attempt due to drug-refractoriness and progression of cardiac dysfunction could not be done; otherwise, we probably could have modified the clinical outcome considering that persistent tachycardia aggravated the myocardial dysfunction, which constitutes the survival milestone problem in these patients⁶.

Two other major mitochondrial syndromes associated with mtDNA mutations may have cardiac involvement: MERRF, the acronym for myoclonus epilepsy with ragged red fibers, and Kearns-Sayre. The former may clinically express HCM or dilated cardiomyopathy, and the latter involves almost exclusively permanent heart block, although cardiomyopathy is unusual. Interestingly, WPW has not been related to these syndromes^{5,8}. In contrast, transient atrio-ventricular block registered in the present case was attributed to anesthetic drugs and other critical conditions that influence the cardiac conduction system.

In summary, this is an unusual newborn female case of severe HCM and uncontrollable atrio-ventricular reentrant tachycardia secondary to WPW, in whom myocardial mitochondria abnormalities and associated multiorgan dysfunction suggest a mitochondrial disease. An integral clinical evaluation of atypical HCM must include biochemical and molecular analysis searching for a genetic background.

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