Images and Case Reports in Heart Failure

Glycogen Storage Disease Because of a PRKAG2 Mutation Causing Severe Biventricular Hypertrophy and High-Grade Atrio-Ventricular Block

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A previously healthy 31-year-old man presented to the emergency department with a syncopal episode. He was otherwise asymptomatic. The patient had no known history of heart disease apart from a murmur, which was previously identified but not investigated. He did not take any medication and denied smoking, alcohol consumption, or illicit drug use. The patient did, however, endorse a significant family history of cardiac disease, including pacemaker placement in his father in his thirties and sudden cardiac death in his sixties, as well as sudden cardiac death in paternal aunts at ages 42 and 63 years (Figure 1A). Physical examination revealed hypotension and a systolic ejection murmur. The patient’s bloodwork was unremarkable. His 12-lead ECG revealed 5:1 high-grade AV block with severe bradycardia (heart rate = 20 beats per minute), left ventricular hypertrophy with strain, and the presence of delta waves (Figure 1B).

The patient had a further episode of asystole in the emergency department, requiring initiation of isoproterenol infusion. Transthoracic echocardiogram was performed and demonstrated dynamic biventricular outflow tract obstruction with a left ventricular outflow tract peak gradient of 55 mmHg and right ventricular outflow tract peak gradient of 38 mmHg, severe concentric left ventricular hypertrophy (left ventricular mass index, 222 g/m²), and a hyperdynamic left ventricle with ejection fraction of >70% (Figure 2A and 2B). The patient underwent dual-chamber pacemaker insertion without complication and was subsequently upgraded to a dual-chamber implantable cardioverter-defibrillator. The patient was also started on a β-blocker and was advised to refrain from high-intensity activity. Importantly, cardiac magnetic resonance imaging demonstrated severe concentric left ventricular hypertrophy and mild concentric right ventricular hypertrophy (Figure 2C and 2D) whereas gadolinium-based imaging revealed late phase moderate-to-severe ill-defined hyperenhancement throughout the myocardium with prominence in the periapical and apical regions (Figure 2E and 2F). Screening for amyloidosis, Fabry disease, and sarcoidosis were all negative. Endomyocardial biopsies were obtained and analyzed using light and electron microscopy, revealing hypertrophic cardiomyocytes overloaded with glycogen deposition without the evidence of any other metabolic abnormalities such as lysosomal storage disorders (Figure 3A through 3C). Electron microscopy demonstrated increased glycogen in the cytosol and mitochondrial changes in the absence of lysosomal involvement (Figure 3D and 3F). Genetic testing using a hypertrophic cardiomyopathy panel revealed that the patient was heterozygous for p.Arg302Gln (R302Q) missense mutation in the PRKAG2 gene (NM_016203.3).

Discussion

Hypertrophic cardiomyopathy is an autosomal dominant disorder characterized by increased cardiac mass because of cardiomyocyte hypertrophy and cardiac fibrosis, and it is associated with increased morbidity and mortality. Numerous mutations leading to hypertrophic cardiomyopathy have been identified, including those involving the PRKAG2 gene, which was initially noted to result in Wolf–Parkinson–White syndrome. The specific mutation of the PRKAG2 gene presented in this case, R302Q, results in a loss of function mutation in the γ-2 subunit of the AMP-activated protein kinase gene. The resulting metabolic defect is associated with a glycogen storage disorder resulting in advanced biventricular hypertrophy in the absence of valvular or systemic abnormalities. Indeed, expression of this mutation in transgenic mice induced severe pathological glycogen deposition in cardiomyocytes.

The R302Q genetic defect clearly affects the left and right ventricles resulting in biventricular hypertrophy and left ventricular outflow tract and right ventricular outflow tract outflow gradients that resulted in pressure overload, an additional stimulus for adverse hypertrophic remodeling. As illustrated by our pedigree analysis, PRKAG2 mutation–mediated cardiomyopathy is compatible with long-term survival although progressive conduction system disease and cardiomyopathy necessitates the use of device therapy. As such, early detection and treatment coupled with family screening are essential components in the management of this condition. Our case report also highlights that seminal findings of glycogen deposition are easily identifiable with histological analysis and electron microscopy and validates...
the importance of endomyocardial biopsy in the assessment of patients with undiagnosed hypertrophic cardiomyopathy with conduction disorders.4

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Disclosures
None.

References

Key Words: cardiomyopathies ■ genetics ■ heart diseases ■ hypertrophy ■ microscopy, electron ■ syncope
Figure 1. A, Family pedigree of the identified proband. Sudden cardiac death and relatively young permanent pacemaker implantation are key features across multiple generations. B, Twelve-lead ECG of 31-year-old male patient during his initial presentation for syncope showing 5:1 high-grade AV block with severe bradycardia (heart rate of 20 beats per minute), left ventricular hypertrophy, and delta waves.
Figure 3. The myocardial tissue showed hypertrophy of the myocardial fibers and interstitial fibrosis (A–C), as well as hyperglycogenated myocardial fibers as confirmed by periodic acid Schiff (B) staining and with previous diastase treatment (not shown). Electron microscopy showed increased glycogen in the cytosol without involving the lysosomal system. In particular, the lysosomal system did not show any evidence of abnormal dilatation or accumulation, whereas the mitochondria showed dilatation and loss of cristae (D and F). Magnification ×400 for A–C; ×10,000 for D, and ×25,000 for E and F.

Figure 2. Doppler images of the left ventricular outflow tract (A) and right ventricular outflow tract (B) gradients. Cine cardiac magnetic resonance images showing biventricular concentric hypertrophy and biatrial dilatation (C and D). In addition, a small pericardial effusion and a large right-sided pleural effusion were observed. Patchy, subepicardial, and midmyocardial late gadolinium enhancement consistent with nonischemic fibrosis (E and F).
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