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A Fetus with Hypertrophic Cardiomyopathy, Restrictive and Single Ventricle Physiology, and a β -Myosin Heavy Chain Mutation

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Abstract

Cardiomyopathy is a significant clinical problem associated with sudden death. A molecular taxonomy is emerging that is refining the clinical classification system. We describe a patient with a pathogenic familial β -myosin heavy chain mutation who was prenatally diagnosed with left ventricular hypoplasia and restrictive diastolic physiology.

Cardiomyopathy is a significant clinical problem associated with sudden death. Clinical taxonomy classifies various cardiomyopathy phenotypes as hypertrophic (HCM), dilated (DCM), restrictive (RCM), arrhythmogenic right ventricular cardiomyopathy or left ventricular noncompaction. Presentation in infancy is associated with a poor prognosis and can result from underlying metabolic or syndromic conditions. A molecular taxonomy is emerging that is refining the clinical classification system, and the genetic basis of many forms of cardiomyopathy has been elucidated¹. The presence of incomplete penetrance and variable expressivity suggests modifier effects in the context of apparently single gene defects. This may explain how identical mutations cause complex phenotypes that carry different prognoses, for example HCM with restrictive physiology and HCM that ultimately becomes DCM². Herein we describe a patient with a pathogenic familial β -myosin heavy chain mutation who was prenatally diagnosed with left ventricular hypoplasia and restrictive diastolic physiology.

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Case Report

A 29 year-old white G2P1 female was referred for fetal echocardiography at 22 weeks gestation due to an abnormal obstetric ultrasound, which demonstrated left ventricular hypoplasia, aortic valve atresia and a hypoplastic ascending aorta. The fetus was tentatively diagnosed with hypoplastic left heart syndrome, and the mother was referred for counseling and comprehensive fetal echocardiography. The family history was significant for RCM in the proband's cousin, caused by a mutation in β -myosin heavy chain, *MYH7* G768R (Figure 1, A). The cousin was diagnosed at 15 months of age by echocardiography and cardiac catheterization, and underwent orthotopic heart transplantation at 18 months. The *MYH7* G768R mutation has been reported as pathogenic previously in adults with HCM³. Interestingly, the proband's mother, a carrier of the mutation, was diagnosed with HCM one year after the pregnancy. Fetal echocardiography demonstrated marked left ventricular hypertrophy reminiscent of HCM and a hypoplastic left ventricular cavity. Hydrops was diagnosed. These findings were persistent and stable at 33 weeks gestation. Color flow Doppler imaging demonstrated nonrestrictive left to right interatrial shunting, retrograde filling (via the ductus arteriosus) of the transverse aortic arch, and minimal tricuspid regurgitation. Doppler interrogation revealed signs of restrictive physiology and high ventricular filling pressures (Figure 2, A). The right ventricular systolic function was hyperdynamic with reduced cavity size and rapid filling, characteristics of RCM. At birth, the nonsyndromic male infant was apneic and hypotensive, and the left ventricle was inadequate to support cardiac output; cyanosis and heart failure developed rapidly. Direct measurement of the central venous pressure was 15mmHg. The neonatal echocardiogram confirmed the fetal findings (Figure 2, E), and demonstrated no change in the severity of diastolic abnormalities. Genetic testing in the infant identified the familial β -myosin heavy chain mutation described above. To determine whether the severe presentation was related to additional abnormalities in other genes known to cause cardiomyopathy, further molecular testing was performed, but no additional abnormalities were identified (Figure 1, B). Hemodynamic instability continued with worsening oxygenation and anasarca despite aggressive management including inhaled nitric oxide, dopamine, epinephrine and vasopressin. Surgical palliation was deferred in light of a refined diagnosis of HCM with restrictive and single ventricle physiology, and the patient expired on day of life 1. Histopathology demonstrated tissue heterogeneity with areas of myocyte disorganization, hypertrophy, and replacement fibrosis including transmural scarring (Figure 1, C), consistent with classic infantile HCM⁴.

Discussion

The spectrum of phenotypes caused by sarcomeric gene mutations is expanding as exemplified by this case. Complex animal models of cardiomyopathy manipulating spatial and temporal gene expression will clarify both pathogenesis and taxonomy. The molecular diagnostic approach to disease has significant clinical implications. Early genetic diagnosis, including its application to the rare manifestation of cardiomyopathy during fetal life, will significantly enhance counseling efforts and inform treatment options after birth including transplantation and early intervention strategies.

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References

1. Ho CY, Seidman CE. A contemporary approach to hypertrophic cardiomyopathy. *Circulation* 2006;113:e858–862. [PubMed: 16785342]

2. Kubo T, Gimeno JR, Bahl A, Steffensen U, Steffensen M, Osman E, et al. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. *J Am Coll Cardiol* 2007;49:2419–2426. [PubMed: 17599605]
3. Ware SM, Quinn ME, Ballard ET, Miller E, Uzark K, Spicer RL. Pediatric restrictive cardiomyopathy associated with a mutation in beta-myosin heavy chain. *Clin Genet* 2008;73:165–170. [PubMed: 18076673]
4. Maron BJ, Tajik AJ, Ruttenberg HD, Graham TP, Atwood GF, Victorica BE, et al. Hypertrophic cardiomyopathy in infants: clinical features and natural history. *Circulation* 1982;65:7–17. [PubMed: 6458422]

Figure 1. The pedigree demonstrates the variable expressivity of cardiomyopathy, including HCM with restrictive physiology in the proband (arrowhead, A). The genes most commonly associated with HCM and RCM were screened (B). Histopathology of the left ventricular free wall of the proband using trichrome staining demonstrated tissue heterogeneity with areas of hypertrophy (asterisk, C), both subendocardial (arrowheads, C) and transmural (arrows, C) replacement fibrosis, and myocyte disorganization (arrowheads, C inset). Histopathology of an unrelated patient with left ventricular hypoplasia showing hypertrophy (asterisk, D) and subendocardial replacement fibrosis (arrowheads, D); in contrast to panel C, there is no myocyte disorganization (arrowheads, D inset) or transmural scarring. Panels C and D 1x; insets 20x.

Figure 2.

Fetal echocardiographic findings (A-D) demonstrating marked left ventricular hypertrophy and chamber hypoplasia (arrow, A), reduced right ventricular (RV) cavity size and enlarged right atrium (RA). Doppler interrogation showing severe flow reversal (arrows) during atrial contraction in the hepatic (B) and pulmonary (C) veins, and monophasic tricuspid valve inflow with short filling time (D) consistent with decreased ventricular compliance. Neonatal echocardiographic findings (E-H) confirming marked left ventricular hypertrophy and chamber hypoplasia (asterisk, E). Prominent hepatic venous flow reversals during atrial contraction (arrow, F), and monophasic tricuspid valve inflow (G) persist. Tissue Doppler demonstrating monophasic tricuspid valve annular motion in diastole (H) consistent with restrictive physiology. Asc, ascites.