Aborted Sudden Cardiac Death and Severe Hypertrophic Cardiomyopathy in a 2-year-old

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ABSTRACT

Although hypertrophic cardiomyopathy has a reported prevalence of 1/500, compound, double, and triple mutations are infrequent. There is phenotypic variation between individuals with HCM, making disease course difficult to predict. There is some debate as to whether multiple mutations confer a worse prognosis and the extent to which the mutations affect an individual's prognosis. We report a case of homozygous MYBPC3 mutations in a 2-year-old presenting with aborted sudden cardiac death and a severe form of hypertrophic cardiomyopathy.

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a cardiac condition characterized by diastolic dysfunction and systolic outflow obstruction of the left ventricle. It is inherited in an autosomal dominant manner with beta-myosin heavy chain (MYH7) and myosin binding protein C (MYBPC3) being the most common sites of mutation[1]. Although HCM has a 1/500 reported prevalence, compound and double mutations for this condition are infrequent[2,3].

CASE REPORT

A 2-year-old presented to our pediatric intensive care unit as a transfer from an outside emergency department after an episode of aborted sudden cardiac death. Approximately 3 hours before arrival, she collapsed at home after clutching her chest. Her father began CPR and police arrived with an AED. The AED interpreted the rhythm as 'shockable', a single shock was delivered, and rhythm converted to sinus tachycardia. 12-lead electrocardiogram (ECG), obtained in our PICU, was significant for sinus rhythm, left ventricular hypertrophy, biventricular hypertrophy, and nonspecific ST and T wave abnormality.

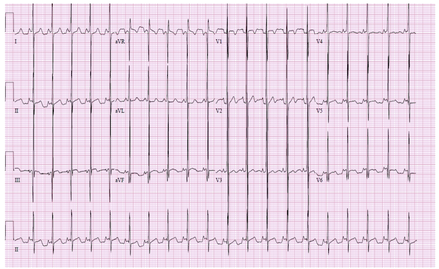

Figure 1. Electocardiography (ECG) on arrival to PICU. There are high voltage QRS complexes in the left precordial leads without T wave inversion indicating left ventricular hypertrophy. Prominent mid-precordial voltage indicates possible biventricular hypertrophy. There are also nonspecific ST and T wave abnormalities.

Echocardiography was completed and was significant for left ventricular hypertrophy without evidence of obstruction. The interventricular septum measured 1.1cm by direct measurement with a z-score of +3.65 by Detroit data.

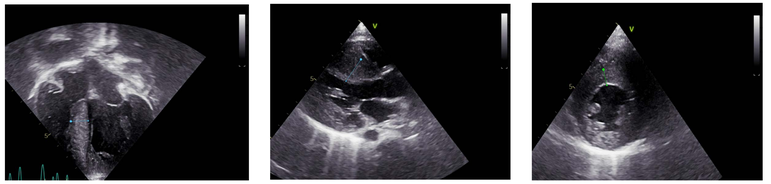

Figure 2. Echocardiographic images showing severe hypertrophic cardiomyopathy. The interventricular septum measures 1.2 cm, 1.8cm, and 1.0 cm in images 1, 2, and 3 respectively.

Upon questioning, the parents indicated there was no family history of sudden cardiac death, congenital heart defects, or hypertrophic cardiomyopathy. Propranolol therapy was initiated to decrease risk of arrhythmias and increase ventricular fill time. She was then transferred to a larger institution for surgical epicardial implantable cardioverter defibrillator (ICD) placement.

A cardiac MRI, with late gadolinium enhancement, was obtained prior to ICD placement, which was significant for severe septal hypertrophy with mild left ventricular free wall hypertrophy and increased trabeculation of the free wall and apex. The myocardium of the apex was noted to be thin. The interventricular septum was measured up to 16.9 mm on left ventricular outflow tract images. Short axis images revealed a septum measurement of 13-14mm (z-score +18, Boston) and a left ventricle free wall measurement of 6-7mm (z-score +2 to 3.8, Boston). There was scattered, delayed hyperenhancement of the mid-ventricular septum. A max noncompacted to compacted ratio of 2 was noted, which did not meet criteria for left ventricle noncompaction. There was no evidence of left ventricular outflow obstruction and a left ventricle ejection fraction of 57%.

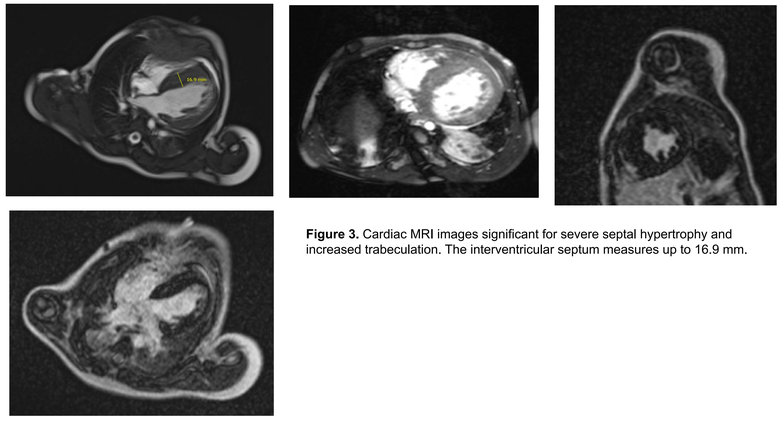

Figure 3. Cardiac MRI images significant for severe septal hypertrophy and increased trabeculation. The interventricular septum measures up to 16.9 mm.

DISCUSSION

Studies have reported an upwards of 6% of patients with HCM have more than 1 mutation[2-5]. One study reported a prevalence of 0.8% of HCM patients with triple mutations[4]. Homozygous mutations are presumably rare with few case reports and one study reporting 3 patients having homozygous mutations out of 197 patients with HCM[1,6-8].

Although MYBPC3 is one of the most common mutations seen in HCM, only a few cases of homozygous MYBPC3 mutations have been reported. In these accounts, patients are described as having severe HCM with symptoms occurring in infancy resulting in early death or heart transplant[6-9]. Two studies described homozygous MYBPC3 mutations among an Amish community[6,8]. Affected children presented with symptoms of heart failure shortly after birth and resulted in either death before 1 year of age or heart transplant despite treatment[6-8]. All children described from this Amish community had splice site mutations in intron 30 (3330+2T>G), which were traced to an ancestral founder mutation[8].

There is pronounced phenotypic variation between individuals with HCM, even with the same mutation or within the same family, making disease course difficult to predict[1, 9-10]. Multiple mutations for HCM within the same individual could have significant implications in genetic counseling and patient management.

CONCLUSION

Studies suggest that multiple HCM mutations tend to confer a worse prognosis with a more severe phenotype[1,3-4,9]. Patients with multiple mutations tend to demonstrate increased incidence of sudden cardiac death, risk of end-stage progression and ventricular arrhythmias[3-4]. Our patient having a significantly worse disease course, and much earlier onset, than both parents supports this notion. Cardiac MRI showed advanced fibrosis at an early age, further supporting more severe pathology due to homozygosity.

REFERENCES

1. Richard P, Charron P, Carrier L, Ledeuil C, Cheav T, Pichereau C, Benaiche A, Isnard R, Dubourg O, Burban M, Gueffet JP, Millaire A, Desnos M, Schwartz K, Hainque B, Komajda M; EUROGENE Heart Failure Project. Hypertrophic cardiomyopathy: distribution of disease genes, spectrum of mutations, and implications for a molecular diagnosis strategy. Circulation. 2003 May 6;107(17):2227-32. doi: 10.1161/01.CIR.0000066323.15244.54. Epub 2003 Apr 21. Erratum in: Circulation. 2004 Jun 29;109(25):3258. PMID: 12707239.

2. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE. Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. Circulation. 1995 Aug 15;92(4):785-9. doi: 10.1161/01.cir.92.4.785. PMID: 7641357.

3. Ingles J, Doolan A, Chiu C, Seidman J, Seidman C, Semsarian C. Compound and double mutations in patients with hypertrophic cardiomyopathy: implications for genetic testing and counselling. J Med Genet. 2005 Oct;42(10):e59. doi: 10.1136/jmg.2005.033886. PMID: 16199542; PMCID: PMC1735926.

4. Girolami F, Ho CY, Semsarian C, Baldi M, Will ML, Baldini K, Torricelli F, Yeates L, Cecchi F, Ackerman MJ, Olivotto I. Clinical features and outcome of hypertrophic cardiomyopathy associated with triple sarcomere protein gene mutations. J Am Coll Cardiol. 2010 Apr 6;55(14):1444-53. doi: 10.1016/j.jacc.2009.11.062. PMID: 20359594.

5. Van Driest SL, Vasile VC, Ommen SR, Will ML, Tajik AJ, Gersh BJ, Ackerman MJ. Myosin binding protein C mutations and compound heterozygosity in hypertrophic cardiomyopathy. J Am Coll Cardiol. 2004 Nov 2;44(9):1903-10. doi: 10.1016/j.jacc.2004.07.045. PMID: 15519027.

6. Xin B, Puffenberger E, Tumbush J, Bockoven JR, Wang H. Homozygosity for a novel splice site mutation in the cardiac myosin-binding protein C gene causes severe neonatal hypertrophic cardiomyopathy. Am J Med Genet A. 2007 Nov 15;143A(22):2662-7. doi: 10.1002/ajmg.a.31981. PMID: 17937428.

7. Wessels MW, Herkert JC, Frohn-Mulder IM, Dalinghaus M, van den Wijngaard A, de Krijger RR, Michels M, de Coo IF, Hoedemaekers YM, Dooijes D. Compound heterozygous or homozygous truncating MYBPC3 mutations cause lethal cardiomyopathy with features of noncompaction and septal defects. Eur J Hum Genet. 2015 Jul;23(7):922-8. doi: 10.1038/ejhg.2014.211. Epub 2014 Oct 22. PMID: 25335496; PMCID: PMC4463499.

8. Zahka K, Kalidas K, Simpson MA, Cross H, Keller BB, Galambos C, Gurtz K, Patton MA, Crosby AH. Homozygous mutation of MYBPC3 associated with severe infantile hypertrophic cardiomyopathy at high frequency among the Amish. Heart. 2008 Oct;94(10):1326-30. doi: 10.1136/hrt.2007.127241. Epub 2008 May 8. PMID: 18467358.

9. Kelly M, Semsarian C. Multiple mutations in genetic cardiovascular disease: a marker of disease severity? Circ Cardiovasc Genet. 2009 Apr;2(2):182-90. doi: 10.1161/CIRCGENETICS.108.836478. PMID: 20031583.

10. Maron BJ. Risk stratification and prevention of sudden death in hypertrophic cardiomyopathy. Cardiol Rev. 2002 May-Jun;10(3):173-81. doi: 10.1097/00045415-200205000-00006. PMID: 12047795.