Unusual Cardiac “Masses” in a Newborn with Infantile Pompe Disease

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Abstract Glycogen storage disease type II (OMIM #232300), or Pompe disease, may present in the newborn period with moderate-to-severe biventricular hypertrophy with or without left ventricular outflow tract obstruction that typically leads to death from cardiorespiratory failure in the first year of life. Glycogen deposition tends to be uniform, and is only occasionally accompanied by patchy areas of fibrosis. Here, we present an infant identified with biventricular hypertrophy and cardiac masses by prenatal ultrasound. Postnatal molecular studies did not support the diagnosis of tuberous sclerosis in this case. Additional

evaluation for infantile hypertrophic cardiomyopathy confirmed the diagnosis of Pompe disease. We discuss whether the “cardiac masses,” which brought this infant to medical attention and facilitated an early diagnosis of Pompe disease, may represent an unusual manifestation of GSD type II or the coincidental occurrence of an unrelated disease process.

Introduction

Glycogen storage disease type II (OMIM #232300), also known as Pompe disease, is due to a deficiency of the lysosomal enzyme acid-alpha-glucosidase (GAA, E.C. 3.2.1.20). GAA is needed for the hydrolysis of both alpha-1,4- and alpha-1,6-glucosidic linkages within glycogen. Disease severity and age of onset are highly variable, with individuals presenting as early as birth or as late as the seventh decade of life. The classic infantile form is characterized by hypertrophic cardiomyopathy and hypotonia of the skeletal muscle, which results in cardiorespiratory failure and death at an average age of 8.7 months without treatment (Kishnani et al. 2006).

Echocardiography invariably reveals a hypertrophic cardiomyopathy with or without left ventricular outflow tract obstruction, which may progress to a dilated cardiomyopathy in advanced stages of the disease. To our knowledge, discrete masses within the myocardium have never been reported in infantile Pompe disease. We report a 1-month-old male with type II GSD and a discrete cardiac mass detected with routine prenatal ultrasound, which was confirmed with postnatal cardiac imaging. We briefly discuss cardiac imaging in Pompe disease, as well as the possibility that the abnormality may be related to abnormal glycogen storage rather than an incidental finding.

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Case Report

The patient first came to medical attention when a routine prenatal ultrasound at 30 weeks gestation identified an intracardiac “mass” and biventricular hypertrophy. Fetal echocardiography confirmed these findings, but no additional prenatal testing was performed before he was delivered at 38 and 0/7 week gestation via emergent cesarean section because of fetal distress. This pregnancy was otherwise uncomplicated and was the second for his 27-year-old mother. The couple’s first child is 15 months of age and healthy. No gestational diabetes was reported. His birth weight was 4,560 g (>95th percentile). He did well immediately after birth, and did not exhibit any cardiac, respiratory, or feeding difficulties despite close monitoring in an intensive care setting. No dysmorphic features were noted. Muscle tone was normal limits, and no other abnormal features were noted on neurologic exam. Family medical history was notable for tuberous sclerosis in the patient’s father’s first cousin. Additional information regarding this individual was unavailable. No intervening family members had been identified as affected, and the father exhibited no symptoms or outward signs of the disorder upon assessment in our clinic. There was no history of consanguinity in the family.

Echocardiography at 27 days of age demonstrated moderate biventricular hypertrophy, and a solitary echogenic mass within the left ventricle, measuring 1 cm $\times$ 0.5 cm (see Fig. 1 and supplementary Movie 1). Short-axis images revealed the possibility of an additional mass within the left ventricle adjacent to the papillary muscles, and

subcostal sagittal imaging revealed two additional areas of increased echogenicity within the right ventricular cavity on the septal surface, measuring 7 mm $\times$ 4.5 mm and 5 mm $\times$ 5 mm. A 12-lead electrocardiogram demonstrated right axis deviation and changes consistent with biventricular hypertrophy, but a normal PR-interval (see Fig. 2).

Cardiac magnetic resonance imaging (MRI) at 1 month of age demonstrated moderate global cardiomegaly with moderate concentric biventricular hypertrophy. Three areas of increased signal intensity on T2- and T1-weighted imaging suggestive of mass-like lesions were visualized in the anteroseptal wall at the mid-short-axis level, the inferoseptal wall near the apex, and within the papillary muscles. The increased signal intensity in the anteroseptal region corresponded to the “mass” visualized by echocardiography. This mass was hyperintense on T1- and T2-weighted imaging, and isointense on steady-state free precession, HASTE, and gradient-echo imaging (see Fig. 3a–c). Applying fat saturation did not affect signal intensity of the mass, and there did not appear to be perfusion to this region on perfusion imaging. On myocardial tagging, the mass did appear to contract. On delayed enhancement imaging, no increased signal intensity was noted.

Additional evaluation was done to exclude other genetic causes of infantile hypertrophic cardiomyopathy, especially those amenable to treatment. The serum creatine kinase was elevated (478 U/L; normal 60–305 U/L). Normal results were noted for levels of plasma amino acids, lactate and pyruvate, total and free carnitine, and acylcarnitine compounds. Urine organic acid quantitation was normal.

Fig. 1 Echocardiography at 27 days of age demonstrates moderate biventricular hypertrophy and a 1 cm $\times$ 0.5 cm discrete echogenic mass within the left ventricle

Fig. 2 Electrocardiography demonstrates right axis deviation and changes consistent with biventricular hypertrophy, but a normal PR interval

Fig. 3 The mass appears hyperintense on both T1- (a) and T2-weighted (b) magnetic resonance imaging, and as a “filling defect” on perfusion-weighted imaging (c)

GAA activity in whole blood from a blood spot (Duke University metabolic lab; Durham, NC) was 1.8 pmol/punch/hour (control 10–49 pmol/punch/hour), consistent with a diagnosis of infantile Pompe disease. Sequencing of the GAA gene identified two mutations: c.525delT and c.1927 G > A (p.Gly643Arg). Cross-Reactive-Immunological Material (CRIM) testing by western blot analysis of the patient’s fibroblasts was positive. Due to the presence of an intracardiac mass and a remote family history of tuberous sclerosis, blood was sent for *TSC1* and *TSC2* gene sequencing and deletion/duplication analysis. MRI of brain was normal, as was analysis of the *TSC1* and *TSC2* genes.

Clinical follow-up at 6 weeks of age demonstrated the interval development of mild hepatomegaly, decreased muscle tone, “hypotonic facies,” and brisk reflexes in the lower extremities with bilateral ankle clonus. His cardiac function remained stable, both clinically and by echocardiography.

Discussion

Cardiac imaging in Pompe disease typically reveals uniform hypertrophy due to abnormal glycogen accumulation.

In some cases, there may also be left ventricular outflow tract obstruction due to severe hypertrophy. (Ehlers et al. 1962; Hohn et al. 1965; Rees et al. 1976; Shapir and Roguin 1985) However, discrete or patchy abnormalities within the myocardium are rarely seen, and to our knowledge, discrete cardiac masses have never been reported in an infant with Pompe disease, either by echocardiogram or cardiac MRI.

Only recently has the use of cardiac MRI been described for the assessment of cardiac structure and function in infants with Pompe disease. Barker et al. were able to quantitate biventricular hypertrophy and measure hemodynamics parameters in these infants ($n = 10$). They also identified areas of fibrosis through delayed enhancement with gadolinium (Barker et al. 2010). Myocardial fibrosis, that may be patchy, has been reported in other lysosomal storage disorders, including Fabry disease (De Cobelli et al. 2009). However, it was seen in only one of ten patients in the study of Barker et al., and can be excluded as the cause of the “masses” in our patient based on their overall general appearance and lack of delay in gadolinium enhancement.

The imaging characteristics of this infant’s cardiac masses were felt to be most consistent with rhabdomyomas.

This raises the possibility of the concurrence of tuberous sclerosis with infantile Pompe disease. To our knowledge, these two disorders have never been reported in association with one another. Sequencing and duplication/deletion analysis of both *TSC1* and *TSC2*, as well as a chromosomal microarray analysis did now show any deleterious genetic changes. This does not completely exclude the diagnosis, as the estimated sensitivity of combined testing is 70–80% (Au et al. 2007; Dabora et al. 2001; Jones et al. 1999; Sancak et al. 2005). Moreover, somatic mosaicism has been well described in the tuberous sclerosis complex, and if limited to the cardiac tissue in this patient, could account for the multiple cardiac masses with negative DNA sequencing performed on peripheral leukocytes (Verhoef et al. 1999). This infant had no other clinical stigmata of TS, such as ashleaf macules, nor any MRI features.

Alternatively, these cardiac masses may represent uneven and irregular areas of glycogen deposition within the cardiac tissue, simulating the appearance of multiple masses. A third possibility is that these cardiac masses are neither rhabdomyomas, nor abnormal glycogen deposits, but are merely another, incidentally discovered, tumor type. Only cardiac catheterization with biopsy of the mass for histopathologic analysis and *TSC1/TSC2* gene sequencing on tumor tissue would be able to make this distinction, an invasive procedure that is not currently indicated in this infant.

Cardiac masses in the fetus and neonate are rare, and have previously never been reported in association with infantile Pompe disease. In this instance, cardiac masses and biventricular hypertrophy were detected by routine prenatal ultrasound. The case highlights not only a potentially unusual manifestation infantile Pompe, but also the importance of including Pompe disease in the differential diagnosis of an infant or fetus with biventricular cardiac hypertrophy. It remains to be seen whether the masses in this case are an unusual manifestation of infantile Pompe, or represent the concurrence of tuberous sclerosis complex, or an otherwise isolated benign cardiac tumor.

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One-Sentence Take-Home Message

Cardiac masses may be an unusual presenting feature of the infantile form of glycogen storage disease type II, and may be identifiable on prenatal ultrasound evaluation.

References

- Au KS, Williams AT, Roach ES et al (2007) Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. *Genet Med* 9:88–100
- Barker PC, Pasquali SK, Darty S et al (2010) Use of cardiac magnetic resonance imaging to evaluate cardiac structure, function and fibrosis in children with infantile Pompe disease on enzyme replacement therapy. *Mol Genet Metab* 101:332–337
- Dabora SL, Jozwiak S, Franz DN et al (2001) Mutational analysis in a cohort of 224 tuberous sclerosis patients indicates increased severity of *TSC2*, compared with *TSC1*, disease in multiple organs. *Am J Hum Genet* 68:64–80
- De Cobelli F, Esposito A, Belloni E et al (2009) Delayed-enhanced cardiac MRI for differentiation of Fabry's disease from symmetric hypertrophic cardiomyopathy. *AJR Am J Roentgenol* 192: W97–W102
- Ehlers KH, Hagstrom JW, Lukas DS, Redo SF, Engle MA (1962) Glycogen-storage disease of the myocardium with obstruction to left ventricular outflow. *Circulation* 25:96–109
- Hohn AR, Lowe CU, Sokal JE, Lambert EC (1965) cardiac problems in the glycogenoses with specific reference to Pompe's disease. *Pediatrics* 35:313–321
- Jones AC, Shyamsundar MM, Thomas MW et al (1999) Comprehensive mutation analysis of *TSC1* and *TSC2*-and phenotypic correlations in 150 families with tuberous sclerosis. *Am J Hum Genet* 64:1305–1315
- Kishnani PS, Hwu WL, Mandel H, Nicolino M, Yong F, Corzo D (2006) A retrospective, multinational, multicenter study on the natural history of infantile-onset Pompe disease. *J Pediatr* 148:671–676
- Rees A, Elbl F, Minhas K, Solinger R (1976) Echocardiographic evidence of outflow tract obstruction in Pompe's disease (glycogen storage disease of the heart). *Am J Cardiol* 37:1103–1106
- Sancak O, Nellist M, Goedbloed M et al (2005) Mutational analysis of the *TSC1* and *TSC2* genes in a diagnostic setting: genotype-phenotype correlations and comparison of diagnostic DNA techniques in tuberous sclerosis complex. *Eur J Hum Genet* 13:731–741
- Shapir Y, Roguin N (1985) Echocardiographic findings in Pompe's disease with left ventricular obstruction. *Clin Cardiol* 8:181–185
- Verhoef S, Bakker L, Tempelaars AM et al (1999) High rate of mosaicism in tuberous sclerosis complex. *Am J Hum Genet* 64:1632–1637