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Case Report

Nonfatal Isolated Cardiac Nonlysosomal Glycogenosis: A Rare Cause of Infantile Hypertrophic Cardiomyopathy

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Metabolic diseases are common causes of infantile hypertrophic cardiomyopathy. Glycogen storage diseases with predominant cardiac involvement can be characterized as either lysosomal or nonlysosomal. Isolated cardiac nonlysosomal glycogenosis has been described as the result of *PRKAG2* or *PHK* gene mutations. Despite aggressive therapy, such diagnosis generally causes rapid demise. In this report, we outline the pathophysiology of infantile hypertrophic cardiomyopathy and describe a rare case of nonfatal isolated cardiac nonlysosomal glycogenosis of undetermined genetic cause.

History of Presentation

A 3-day-old baby girl was readmitted with poor feeding, lethargy, and syncope. Twelve hours after discharge, the patient started taking shorter and less frequent feeds. She was ultimately found unresponsive, pale, hypotonic, and barely breathing in her crib. Her parents immediately called emergency medical services and delivered rescue breaths, which triggered a cry. On arrival of the paramedics, the neonate appeared alert and active, displayed normal vital signs, and was in sinus rhythm.

Examination and Basic Investigations

In the emergency department, physical examination revealed a nondysmorphic neonate with a hyperdynamic precordium and harsh holosystolic murmur over the left upper sternal border. There was no blood pressure difference between extremities, cyanosis, or hepatomegaly. Laboratory investigations, including a serum glucose level, were unremarkable. A chest radiograph demonstrated moderate cardiomegaly with normal pulmonary vascular markings. Serial electrocardiograms displayed significant heart rate variations, high voltages, and a short PR interval with pre-excitation (Supplemental Fig. S1). A transthoracic echocardiography demonstrated severe hypertrophy of the interventricular septum with reverse curve morphology (interventricular septum thickness: 1.1 cm [z score: +7.4]), moderate hypertrophy of ventricular free walls (left ventricular posterior wall thickness: 0.5 cm [z score: +2.3]), and dynamic mid-cavitary left ventricular outflow tract (LVOT) obstruction (peak gradient: 64 mm Hg) with normal biventricular function (Videos 1-3, view video online).

Past Medical History

This baby girl was born at term from a healthy mother. She was delivered by caesarian section after labour arrest and failed forceps extraction. Besides a brief episode of noninvasive positive pressure ventilation, she had an uneventful fetal-to-neonatal transition. She was of South Asian descent. A detailed 3-generation pedigree ruled out the presence of consanguinity, intellectual disability, genetic syndromes, neuromuscular diseases, metabolic disorders, cardiomyopathies, arrhythmias, and premature or sudden cardiac deaths within the family.

Differential Diagnosis

Differential diagnosis of infantile hypertrophic cardiomyopathy (HCM) is presented in Table 1. In children <1 year, incidence of HCM is estimated between 2 and 3.5/100,000.[1,2] Approximately 70% of infantile cases are genetic, 15% metabolic, and 15% syndromic or associated with a neuromuscular disorder.[1] Although neonates are probably at higher risk of metabolic or syndromic presentation than older infants, there are limited data pertaining to this specific population.

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Novel Teaching Points

- Genetic syndromes and metabolic disea ses are the commonest causes of infantile hypertrophic cardiomyopathy (HCM).
- Isolated nonlysosomal cardiac glycogenosis is a very rare presentation of infantile HCM.
- Isolated nonlysosomal cardiac glycogenosis is usually caused by *PRKAG2* or *PHK* gene mutations and is rapidly fatal.
- However, a genetically elusive case of isolated nonlysosomal cardiac glycogenesis may result in a less malignant course treatable with standard medical and surgical therapies.

Advanced Investigations

Routine screening for inborn errors of metabolism, including disorders of carnitine transport and fatty acid oxidation, was negative. Additional metabolic testing, including an assessment of acid α-glucosidase enzyme activity, was also normal. Whole exome and mitochondrial genome sequencing were negative for a clear causative mutation but revealed a variant of uncertain significance in the cardiomyopathy-associated gene *TNNT2 (c.833G>A/p.R278H).* The mother shared the same variant but did not display the phenotype of cardiomyopathy on electrocardiography or transthoracic echocardiography.

Management and Follow-up

After her episode of syncope likely caused by an arrhythmia, the baby was admitted and started on propranolol, which was titrated up to the maximum tolerable dose, targeting a heart rate of 100-120 bpm. On this regimen, she remained free of arrhythmia and her peak LVOT gradient dropped below 50 mm Hg. On discharge, parents were provided with an automated external defibrillator and trained in basic life support.

The patient was then followed every 4-6 weeks with echocardiography (Fig. 1A). During the first 4 months, her peak LVOT gradient increased progressively for which disopyramide was added. She responded initially well to dual therapy. However, around 16 months of age, she developed again worsening fatigue and LVOT obstruction. A decision was then made to proceed with myectomy. Leading to surgery, no other malformations or systemic illnesses were detected. Her comprehensive neurodevelopmental assessment was normal.

At 20 months of age, the patient underwent extensive transaortic septal myectomy and placement of an implantable loop recorder. Coming off cardiopulmonary bypass, her peak LVOT gradient was only 10 mm Hg. Postoperatively, the patient experienced pulmonary oedema secondary to diastolic dysfunction requiring reintubation. Nevertheless, she recovered quickly and was discharged on postoperative day 9.

Surprisingly, the histologic examination of myocardial fragments resected at the time of surgery revealed extensive monoparticulate glycogen deposits within the cytosol of myocytes (Fig. 1B). In view of these findings pointing at a diagnosis of isolated cardiac nonlysosomal glycogenosis, genetic sequences were re-examined, but no pathologic mutation of the adenosine monophosphate (AMP)-activated protein kinase or phosphorylase kinase genes was identified.

Five months after surgery, the patient was more energetic and appeared to keep up better with her peers. Her peak LVOT gradient was <30 mm Hg on low-dose propranolol. She did not have documented arrhythmia on implantable loop recorder tracings. On last assessment, at the age of 5, more than 4 years after myectomy, she remains asymptomatic on 2 mg/kg per day of propranolol. To date, the patient has not expressed any extracardiac manifestations of glycogen storage diseases (GSDs).

Table 1. Differential diagnosis of hypertrophic cardiomyopathy

Genetic forms*
Mutations of calcium handling control mechanisms
Sarcomeric mutations
Z-disc mutations
Syndromic and neuromuscular diseases
Beckwith-Wiedemann syndrome
Cardiofaciocutaneous syndrome
Costello syndrome
Emery-Dreifuss muscular dystrophy
Familial amyloid
Friedreich ataxia
Leopard syndrome
Noonan syndrome
Swyer syndrome
Metabolic diseases
Carnitine transport disorders
Primary carnitine deficiency
Carnitine palmitoyl transferase-1 or -2 deficiency
Carnitine-acylcarnitine translocase deficiency
Fatty acid oxidation disorders
Medium-, long-, or very-long chain acyl-CoA dehydrogenase deficiency
Glycogenoses
Type 2: acid maltase deficiency (Pompe disease, Danon disease)
Type 3: debrancher enzyme deficiency (Cori disease)
Type 9: phosphorylase kinase deficiency
AMP-activated protein kinase deficiency
Glycoproteinoses
α-L-Fucosidase deficiency type 1
α-Mannosidase B deficiency
Glycosylation disorders
Mucolipidoses
Type 2: N-acetylglucosamine 1-phosphotransferase deficiency (I-cell disease)
Mucopolysaccharidoses
Type 1: α-L-iduronidase deficiency (Hurler syndrome)
Type 2: iduronate-2-sulfatase deficiency (Hunter syndrome)
Sphingolipidoses
α-Galactosidase A deficiency (Fabry disease)

*Also termed idiopathic or nonsyndromic.

Discussion

There are many enzymes and receptors involved in glucose metabolism within the myocyte (Fig. 1C). Although there are 15 distinct types of GSD, only 5 can trigger symptomatic HCM: type II (Pompe), type IIb (Danon), type III (Cori), GSD due to γ2-subunit of AMP-activated protein kinase deficiency (PRKAG2), and GSD due to phosphorylase kinase (PHK) deficiency. At a cellular level, Pompe and Danon diseases cause lysosomal glycogen deposits, whereas Cori

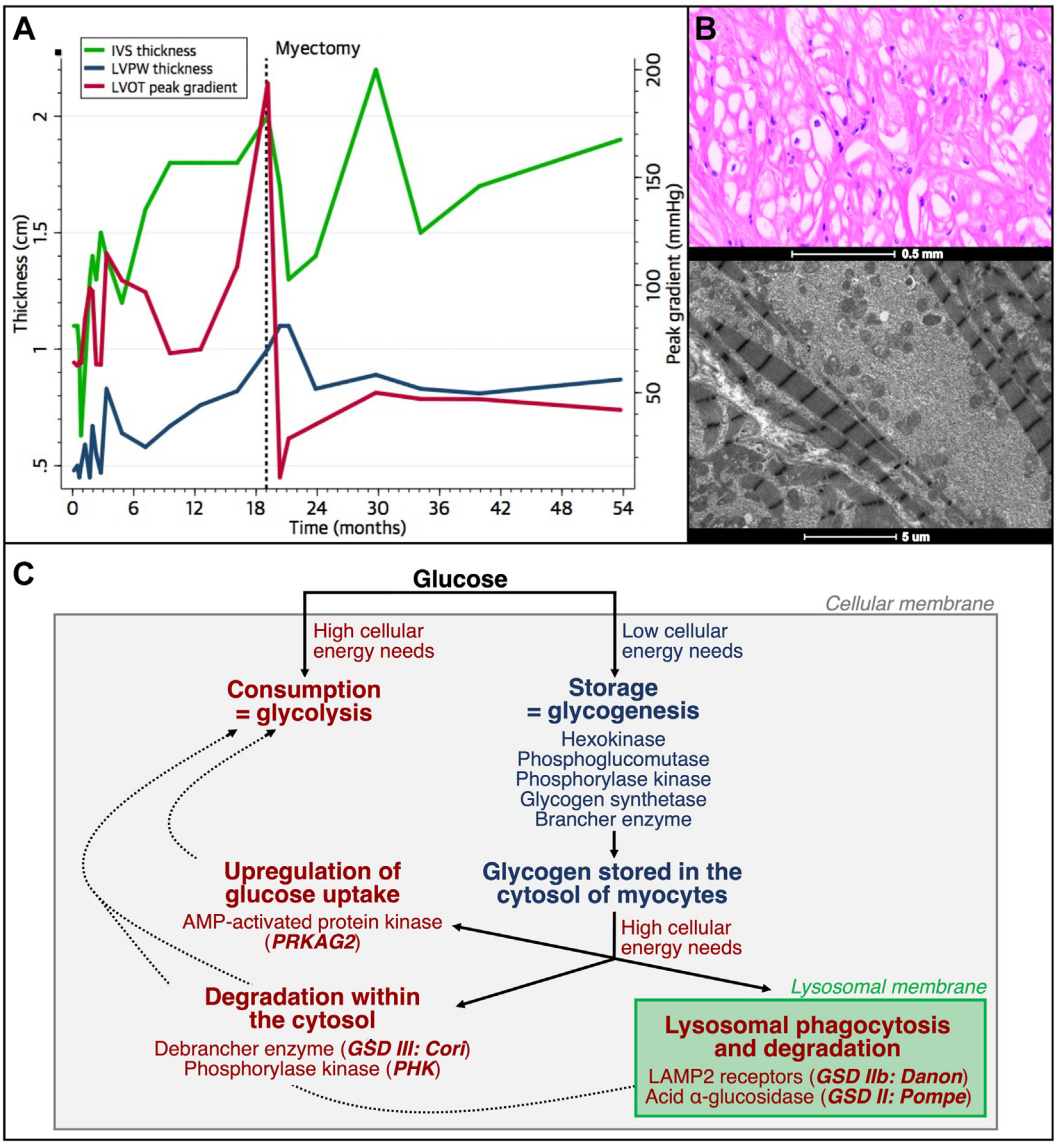

Figure 1. Diagnosis and echocardiographic monitoring. (**A**) Evolution of echocardiographic findings over time. The **dashed line** separates pre- and postoperative data. (**B**) Pathologic evaluation of operative specimen. The superior haematoxylin and eosin stain displays hypertrophied myocytes with cytoplasmic vacuoles. The inferior transmission electron microscopy shows myocyte cytoplasms filled with monoparticulate glycogen displacing normal sarcomeres. (**C**) Summary of the main enzymes and receptors involved in glycogen metabolism within myocardial cells with common glycogen storage diseases causing hypertrophic cardiomyopathy listed in parentheses. GSD, glycogen storage disease; IVS, interventricular septum; LVOT, left ventricular outflow tract; LVPW, left ventricular posterior wall; PHK, phosphorylase kinase.

disease and GSD due to kinase deficiencies lead to the accumulation of cytosolic, or nonlysosomal, deposits.[3,4]

In newborns with predominant cardiac involvement, the most common GSD is Pompe disease. A handful of cases of *PRKAG2* and *PHK* gene mutations were also described in the literature.[5] In contrast, Cori and Danon diseases are usually diagnosed based on extracardiac manifestations, and cardiomyopathy does not emerge before the second or third decade of life.[6]

Early-onset Pompe disease is associated with hepatomegaly, macroglossia, and severe myopathy. Infants with the disease live a few years before dying from respiratory failure. Cardiomyopathy may be treated with enzyme replacement. However, as penetration of the recombinant enzyme into skeletal muscle is poor, targeted treatment does not generally impact survival.[7]

Kinase deficiencies causing GSD are cardiospecific. Babies diagnosed with such conditions usually experience a fulminant course of illness with rapid demise within the first few days of life. Consequently, many diagnoses of *PRKAG2* and *PHK* gene mutations in infants are made post-mortem.[5] To this date, there is still no specific therapy targeting GSD due to kinase deficiencies.

There are many unusual characteristics about the presented case. First, nonlysosomal cardiac glycogenosis in the absence of any other organ involvement is very rare. Second, such presentation is usually lethal with poor survival beyond the first year of life. In contrast, our patient was medically

stabilized for months before undergoing myectomy, and she has been thriving since. Lastly, our patient remains genetically elusive with no evidence of *PRKAG2* or *PHK* gene mutations, the 2 causes of nonlysosomal cardiac glycogenosis so far reported in the literature.

Conclusions

We described a unique presentation of isolated cardiac nonlysosomal glycogenolysis diagnosed as infantile HCM without any known causative genetic mutation. Our report emphasizes an instance when such a pathology does not necessarily result in a malignant course and can be successfully treated with a combination of medical therapy and timely surgical myectomy in the face of refractory ventricular obstructive symptoms.

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Ethics Statement

The reported research article has adhered to IWK Health Center ethical guidelines.

Patient Consent

The authors confirm that a patient consent form has been obtained for this article.

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Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Pediatric and Congenital Heart Disease* at https://www.cjcpc.ca// and at https://doi.org/10.1016/j.cjcpc.2024.02.003