Case Report

Neonatal cardiac hypertrophy: A rare case of clinically suspected and genetically confirmed mitochondrial disorder presenting as hypertrophic cardiomyopathy

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ABSTRACT

Infants presenting with ventricular hypertrophy in the absence of structural heart disease causes can be either genetic, metabolic, or storage disorders. Familial hypertrophic cardiomyopathy is very rare in the neonate. We present a rare case of infantile cardiomyopathy with clinical suspicion of mitochondrial disorder confirmed genetically to have a disorder of mitochondrial oxidative phosphorylation with both parents as a carrier of the recessive gene to highlight the importance of detail genetic evaluation of all neonates presenting with ventricular hypertrophy.

Key words: Cardiomyopathy, Mitochondrial disorder, Neonate

Cardiomyopathy is a heterogeneous group of diseases of the myocardium. The annual incidence of cardiomyopathy is 1.2/100,000 children [1]. In hypertrophic cardiomyopathy, there is a disorderly arrangement of the myocardium resulting in the left ventricular hypertrophy. Infantile cardiomyopathy occurring as a result of disorders of mitochondrial oxidative phosphorylation is very rare disorders with wide variation in clinical presentation ranging from fetal presentation to adult-onset disease manifestation [2]. Neonatal presentation is often severe and can present as isolated cardiomyopathy or as a part of multiorgan involvement involving either the brain, liver, musculoskeletal system, or kidney [3].

We present a rare case of infantile cardiomyopathy with clinical suspicion of mitochondrial disorder confirmed genetically to have a disorder of mitochondrial oxidative phosphorylation and also discussed in brief, the evaluation and possible differential of a neonate with ventricular hypertrophy in the absence of structural heart disease to highlight the importance of proper genetic evaluation of neonates with the left ventricular hypertrophy.

CASE REPORT

A 3.5-month-old female child second in birth order, born of a non-consanguineous marriage with premature normal delivery presented with complaints of poor weight gain and fast breathing. The child had an APGAR score of 9 and a birth weight of 2.2 kg.

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The mother was 28-year-old, non-diabetic, euthyroid, and not on any medication. All routine investigations done were normal except one laboratory value of high serum lactate level of 45 mg/dl (normal range 6–16 mg/dl). She was referred for cardiac evaluation.

At presentation, she had a failure to thrive with a weight of 3.2 kg, mildly tachypnoeic with a respiratory rate of 56/min. Cardiac auscultation revealed an ejection systolic murmur grade 2/4 in the left lower sternal border. She had a significant developmental delay.

Chest X-ray showed cardiomegaly. Electrocardiogram was normal. Echocardiography showed features of the left ventricular hypertrophy with minimal mid-cavity left ventricular outflow gradient of 20 mmHg (Fig. 1). At this time with clinical features of failure to thrive, raised lactate levels, cardiomegaly, and echocardiographic features of the left ventricular hypertrophy, a possibility of mitochondrial disorder was kept with other differential diagnosis being familial hypertrophic cardiomyopathy and storage disorders.

The genetic evaluation was done which confirmed mitochondrial oxidative phosphorylation disorder (Complex I deficiency). The parents were also genetically screened and found to have a recessive mutant gene. Optimal medical management including diuretics, angiotensin-converting enzymes inhibitors were started, and the family was prognosticated regarding the poor outcomes.

DISCUSSION

Neonates with left ventricular hypertrophy can be associated with a syndrome, metabolic disorder, fatty acid oxidation disorder, or mitochondrial defect. Familial hypertrophic cardiomyopathy as

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a result of a mutation in sarcomere proteins are rarely diagnosed in a neonate (Table 1) [4,5]. Evaluation is usually dependent on clinical suspicion. If the child is syndromic, then evaluation is done accordingly or else all neonates should be evaluated for the mitochondrial or metabolic cause for ventricular hypertrophy (Table 2). In our case, the neonate had features of prematurity, low-birth weight, poor feeding, failure to thrive with raised serum lactate levels, and echocardiographic evidence of the left ventricular hypertrophy pointing to the disorder of mitochondrial oxidative phosphorylation disorder (Complex I deficiency). The incidence of neonatal mitochondrial cardiomyopathy as described in the published literature ranges from 5.2% to 29% [5,6].

Table 1: Neonatal ventricular hypertrophy in absence of structural heart disease causes

1. Syndromes	a. Noonan syndrome b. Beckwith-Weidman syndrome c. Trisomy 21 d. Costello syndrome e. Eagle Barrett syndrome f. Friedrich's ataxia
2. Metabolic disorders	a. Pompe's disease
3. Fatty acid oxidation disorder	a. Carnitine deficiency b. Carnitine palmitoyltransferase deficiency c. Medium chain acyl- coenzyme A dehydrogenase deficiency d. Long chain acyl- coenzyme A dehydrogenase deficiency
4. Mitochondrial defects	a. Complexes I, II, and IV deficiency b. MELAs syndrome c. Adenine nucleotide translocator abnormalities
5. Other causes	a. Infant of diabetic mother b. ACTH administration c. Hypothyroidism d. Dexamethasone administration

Table 2: Evaluation of a neonatal ventricular hypertrophy in the absence of structural heart disease

1. Laboratory evaluation	a. Electrolytes b. Serum glucose c. Liver function test d. Serum lactate e. Serum pyruvate f. Complete metabolic panel g. Genetic evaluation – cytogenetics (if syndromic), gene sequencing analysis h. Urine analysis for amino acids, lactate and organic acids
2. Biopsy	a. Skin – Pompe's disease b. Skeletal muscle- mitochondrial disorders c. Cardiac – mitochondrial disorders

In a normal cell, mitochondria have an important function to provide energy through oxidative phosphorylation. Mitochondrial oxidative phosphorylation system usually comprises four respiratory chain (complexes I-IV) and adenosine triphosphate complex. Any disorder in the oxidative phosphorylation system can have wide variety of clinical manifestations depending on the involvement of organs or systems. The presentation of the disease is usually severe and can lead to early death in the neonatal period or in adulthood [6].

The manifestation of disorder of oxidative phosphorylation can be non-specific as poor feeding, recurrent vomiting, and failure to thrive. Specific clinical manifestation can be cardiac form, hepato-intestinal form, encephalomyopathy form, and rarely nephropathic form. This characterization is more helpful in specific enzymatic diagnosis clinically [7]. Complex I deficiency usually presents with prematurity and growth retardation. Increased lactate levels can result in cerebral atrophy and are associated with hypertrophic cardiomyopathy and encephalopathy [8]. Infants with mitochondrial disorders usually present with hypertrophy and rarely as dilated cardiomyopathy.

Cardiac muscle biopsy is usually diagnostic with a typical appearance of swollen and cleared cardiac myocyte which can be further confirmed by histochemical staining to differentiate between subtypes of mitochondrial oxidative phosphorylation disorder (Complex I-IV) [9]. Cardiac biopsy in a neonate has its own limitation so routinely not done. The application of next-generation gene sequencing (NGS) is particularly effective in such condition. Sanger sequencing was previously the preferred method, but NGS-based testing is becoming more prevalent; this testing not only identifies a primary mitochondrial DNA defect but also provides an accurate measure of heteroplasmy [10].

In our case, there was a clinically strong suspicion of mitochondrial disorder which was confirmed on genetic sequencing and moreover, familial screening revealed both parents as a carrier of the recessive mutant gene.

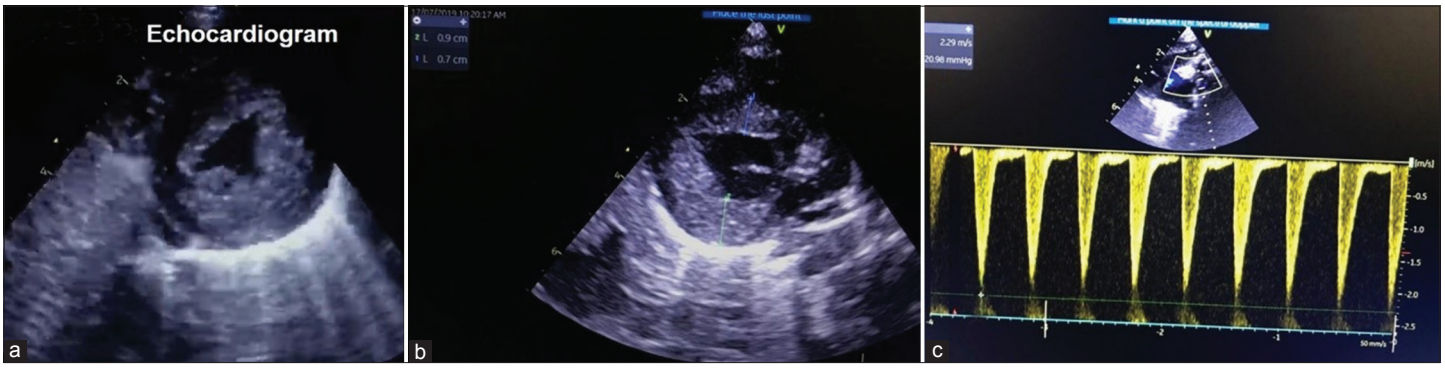

Figure 1: (a and b) Parasternal short axis and long axis showing the left ventricular hypertrophy; (c) Doppler interrogation in the left ventricular mid-cavity showing mid-cavity gradient

CONCLUSION

Infants presenting with ventricular hypertrophy in the absence of structural heart disease can have either genetic, metabolic, or storage disorders as etiology. Familial hypertrophic cardiomyopathy due to mutation in sarcomere protein is very rare in neonate so an attempt should be made to look for other possible etiologies. Mitochondrial disorders are very rare and those with cardiac involvement have a poor prognosis as compared to the non-cardiac forms. Neonates with mitochondrial oxidative phosphorylation disorders can have perinatal complications leading to early neonatal death thus missed in the initial period. Increased awareness about all possible differentials in neonates with hypertrophic cardiomyopathy with the availability of genetic testing may lead to correct diagnosis and proper prognostication of these neonates.

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