TOPIC HIGHLIGHT

Infant with cardiomyopathy: When to suspect inborn errors of metabolism?

Stephanie L Byers, Can Ficicioglu

Stephanie L Byers, Can Ficicioglu, The Children's Hospital of Philadelphia, Section of Metabolic Disease, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, United States

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Correspondence to: Can Ficicioglu, MD, PhD, The Children's Hospital of Philadelphia, Section of Metabolic Disease, Perelman School of Medicine at the University of Pennsylvania, 3501 Civic Center blvd #9054, Philadelphia, PA 19104, United States. ficicioglu@email.chop.edu

Telephone: +1-215-5903376 Fax: +1-215-5904297
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Core tip: We highlight some very helpful red flags that, when present, should point physicians in the direction of doing a metabolic workup in patients with cardiomyopathy. Short case presentations will help readers to efficiently transfer metabolic diagnostic tools in their own practice. This article will be an essential reference for physicians as they evaluate patients with cardiomyopathy.

Abstract

Inborn errors of metabolism are identified in 5%-26% of infants and children with cardiomyopathy. Although fatty acid oxidation disorders, lysosomal and glycogen storage disorders and organic acidurias are well-known to be associated with cardiomyopathies, emerging reports suggest that mitochondrial dysfunction and congenital disorders of glycosylation may also account for a proportion of cardiomyopathies. This review article clarifies when primary care physicians and cardiologists should suspect inborn errors of metabolism in a patient with cardiomyopathy, and refer the patient to a metabolic specialist for a further metabolic work up, with specific discussions of "red flags" which should prompt additional evaluation.

INTRODUCTION

Cardiomyopathy is rare in children (1.13 cases annually per 100000) but it often has catastrophic consequences including heart failure and death[1]. While the etiology of cardiomyopathy in infancy and childhood is varied, inborn errors of metabolism cause a substantial percentage of pediatric cardiomyopathies. Determining the etiology of cardiomyopathy presenting in the first year of life is critical to ensure optimal treatment and management, provide appropriate genetic counseling, and anticipate additional medical complications which may arise.

Previously, it was reported that approximately 5% of pediatric cardiomyopathies are due to an inborn error of metabolism[2], however a more recent study found a substantially higher percentage, with 26% of hypertrophic and 16% of dilated cardiomyopathies having a metabolic etiology[3]. A separate study found five out of 35 infants (13.5%) diagnosed in the first year of life had a metabolic etiology to their cardiomyopathy[4]. Over 40

Disorder	Pathognomonic biochemical abnormalities	Red flags
Table 1 Red flags for inborn errors of metabolism associated with cardiomyopathy		
Mitochondrial disease	Elevated plasma lactate, elevated plasma alanine, proline	Hypotonia, developmental delays/ regression, other organ involvement
Barth syndrome	Urinary excretion of 3-Methylglutaconic acid	
VLCAD deficiency	Elevation of C14:1 acylcarnitine species	Hypoglycemia, elevated creatine kinase, liver dysfunction, metabolic decompensation with illness
LCHAD deficiency	Elevation of hydroxy compounds C14-OH, C16-OH, C18-OH	
Systemic primary carnitine deficiency	Very low plasma carnitine and elevated urinary carnitine extraction	
CPT2 deficiency	Elevation of C12 to C18 acylcarnitines, notably of C16 and C18:1	
GSD deficiency II (Pompe)	Decreased acid alpha-glucosidase enzyme activity	Hypotonia, enlarged tongue
MPS1 (Hurler, Hurler-Scheie, Scheie)	Elevated urine GAGs, decreased alpha-L-iduronidase enzyme activity	Dysmorphic features (coarse features), hepatomegaly, hernia, hearing loss, corneal clouding (MPS1) developmental delays/regression
MPS2 (Hunter)	Elevated urine GAGs, decreased iduronate-2-sulphatase enzyme activity	
Propionic aciduria	Urine organic acids: 3- hydroxypropionate, Methylcitrate, Tyglylglycine, Propionyl Glycine	Hypotonia, high anion gap acidosis, hyperammonemia, metabolic decompensation with illness
	Plasma acylcarnitines: Elevated C3 (propionylcarnitine)	
Malonic aciduria	Plasma acylcarnitines: Elevated C3-DC (Malonyl carnitine). Urine organic acids: elevated malonic acid	Developmental delay/regression, hypotonia, hypoglycemia
Congenital disorders of glycosylation	Abnormal carbohydrate deficient transferrin, abnormal N- and O-glycosylation profiles (qualitative and/or quantitative)	Hypotonia, developmental delays/ regression hypoglycemia, liver dysfunction

VLCAD: Very long-chain acyl-CoA dehydrogenase; GAGs: Glycosaminoglycan; CPT2: Carnitine-palmitoyl transferase deficiency; LCHAD: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency; GSD II: Glycogen storage disease type 2; MPS1: Mucopolysaccharidosis type 1.

different metabolic disorders are known to cause cardiomyopathy[2]. Most commonly, disturbances of fatty acid oxidation, organic acidurias and storage disorders are implicated; however congenital disorders of glycosylation and mitochondrial disorders have more recently been identified in infants with cardiomyopathy[2,3,5,6].

This review article clarifies when primary care physicians and cardiologists should suspect inborn errors of metabolism in a patient with cardiomyopathy, and refer the patient to a metabolic specialist for a further metabolic work up. Short case presentations are designed to help readers efficiently transfer metabolic diagnostic tools into their clinical practice.

WHEN TO SUSPECT A METABOLIC DIAGNOSIS IN A CHILD PRESENTING WITH CARDIOMYOPATHY

Table 1 includes a summary of some of the more common metabolic disorders associated with cardiomyopathy along with pathognomonic biochemical abnormalities. Several "red flags" may be evident in the medical history and on initial physical examination. Identification of the following "red flags" should warrant a consultation with a metabolic specialist.

Medical history
A thorough medical history, including prenatal history, may give evidence of metabolic disease. Maternal history of acute fatty liver or hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome during pregnancy may indicate that the fetus was affected with a fatty acid oxidation disorder. Newborn metabolic screening result should be obtained. A normal newborn screening is re-

assuring; however, many inborn errors of metabolism (IEM) such as storage disorders, mitochondrial disorders and congenital disorders of glycosylation are not included in the newborn screening panels; they could present with cardiomyopathy. Episodes of vomiting, lethargy, hypoglycemia, and metabolic decompensation in the context of poor feeding or illness are important clues of the potential presence of IEMs. A history of multisystem involvement, delayed developmental milestones, low muscle tone, developmental regression, coarse facial features, enlarged tongue, feeding difficulties and failure to thrive, recurrent ear and/or upper respiratory infections, rhabdomyolysis, muscle pain or spasms warrant consultation with a metabolic specialist.

Cardiomyopathy with hypoglycemia: Episodes of hypoglycemia, particularly nonketotic hypoglycemia, can be a red flag that there is a disturbance of energy production. In conjunction with cardiomyopathy, disorders of fatty acid oxidation are high on the list of differential diagnoses. Although some glycogen storage disorders may also be associated with episodic hypoglycemia, the hepatic glycogenoses are not generally associated with cardiomyopathy.

Family history
Family history of other closely related individuals with cardiomyopathy of unexplained etiology warrants further genetics evaluation. As most inborn errors of metabolism are inherited in an autosomal recessive manner, affected siblings and siblings who died at a young age from uncertain etiology should raise the suspicion for a metabolic etiology. X-linked disorders and many mitochondrial disorders are often inherited from the mother, thus family history should include second and third degree relatives,

Table 2 Biochemical testing recommendations for metabolic evaluation

Tier 1
    Creatine kinase
    Plasma acylcarnitine profile
    Urine organic acids
    Plasma lactate/pyruvate
    Plasma amino acids
    Enzyme analysis[1]
Tier 2
    Carbohydrate deficient transferrin analysis
    Urine glycosaminoglycans
    Lysosomal storage disease enzyme panel (large panels are available through many laboratories)
Tier 3
    Specific gene sequencing

[1]If there is a high suspicion for a single metabolic disease, for example Pompe disease.

particularly on the maternal side. Mitochondrial disorders may show considerable inter-individual variation, thus focus on maternal family history for other features of mitochondrial disorders, such as migraines, seizures, stroke-like episodes, developmental disabilities/regression, movement disorders, and exercise intolerance, may provide additional indication of mitochondrial dysfunction. Information regarding parental consanguinity and ethnic origins may also increase the suspicion of a metabolic etiology.

Cardiomyopathy with hypotonia: Hypotonia can be a key indicator of systemic muscle disease not limited to the heart. In an infant, hypotonia often results in the failure to meet developmental milestones on time. Hypotonia can also manifest as difficulty feeding and respiratory distress in an infant. For an infant with severe hypotonia and cardiomyopathy, Pompe disease should be excluded from the differentials. Congenital disorders of glycosylation and mitochondrial disorders may also present with cardiomyopathy and hypotonia due to an inability to produce and utilize energy in muscle. Lastly, due to the build-up of toxic waste products, organic acidurias may present in this manner.

Physical examination
Thorough examination of the patient should be performed and focused on the following: (1) Detection of hepatosplenomegaly, hypertrophic tonsils, joint contractures (indicative of lysosomal storage disorders); (2) Assessment of a neurologic function (may be abnormal in mitochondrial disorders, storage disorders, malonic aciduria); and (3) Identification of dysmorphic features such as coarsened facial features (pathognomonic for mucopolysaccharidosis).

Hearing and vision should always be included in the exam. Involvement of multiple organ systems in a child with cardiomyopathy should increase the suspicion for an IEM.

Cardiomyopathy with hepatomegaly: Hepatomegaly is a characteristic feature of storage disorders due to accumulation of waste materials in the liver. Liver biopsy may show characteristic storage materials. These waste materials may accumulate in other areas of the body, including soft tissues, joints and bones, which may be identified on physical examination. Coarse facial features in an infant with hepatomegaly should highly increase the suspicion of a storage disorder.

Laboratory studies
Confirmation of IEMs often relies on measuring the enzyme activity and/or identifying the genetic mutations responsible, but gene sequencing and copy number analysis may take weeks to months prior to having results. In an experienced laboratory, biochemical analysis can expeditiously determine whether a metabolic etiology warrants further investigation for some IEMs. In the absence of an obvious syndromic etiology, we recommend a biochemical evaluation as a standard of care for all infants with cardiomyopathy. Specifically, we recommend an acylcarnitine profile, plasma lactate/pyruvate, creatine kinanse and urine organic acids that could help in the diagnosis of fatty acid oxidation defects or malonic acidemia, which can be treated. Additional laboratory studies such as urine glycosaminoglycan quantification (for lysosomal storage disorders), N and O-glycans with carbohydrate deficient transferrin analysis (for congenital disorders of glycosylation) and specific enzyme analysis (for glycogen storage disorders and lysosomal storage disorders) may need to be performed to rule out some IEMs (Table 2).

MAJOR ETIOLOGICAL CATEGORIES
The major categories of inborn errors of metabolism associated with cardiomyopathy in infants are fatty acid oxidation disorders, lysosomal storage disorders, glycogen storage disorders, mitochondrial disorders and organic acidurias.

Fatty acids are used by the body as an alternative energy source when glucose is not available. Disorders of almost every step of the beta oxidation pathway, as well as disorders of fatty acid uptake and transport, have been identified and associated with cardiomyopathy. Carnitine-acylcarnitine translocase deficiency, carnitine palmitoyl-transferase II (CPT2) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency, trifunctional protein deficiency and glutaric acidemia type 2 are well known to be associated with cardiomyopathy[7]; however others such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency have also rarely been identified in infants with cardiomyopathy[8].

Lysosomal storage disorders (LSD) are an individually rare, but collectively common group of disorders in which waste materials accumulate in the lysosome. The accumulation of these materials in various organs and

tissues throughout the body is the main mode of pathogenesis for these disorders; however the exact mechanisms are unknown. Of the lysosomal storage disorders, Hurler syndrome (mucopolysaccharidosis type I) and Hunter syndrome (mucopolysaccharidosis type II) are the most well-known to be associated with cardiomyopathy in infancy and childhood. Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI) has also been reported as presenting with cardiomyopathy in the infant period[9]. Inheritance is autosomal recessive, with the notable exception of Hunter syndrome and Fabry syndrome, which are both X-linked. LSDs are also notable in that enzyme replacement therapies (ERTs) are available for many of these disorders. ERTs halt the further accumulation of additional waste materials in the heart, but may not fully reverse the damage already done, further stressing the importance of early diagnosis.

Caused by many enzymes involved in the synthesis and breakdown of glycogen, glycogen storage disorders have primarily either hepatic or muscle involvement. Generally, muscle glycogenoses do not have symptoms of hypoglycemia. Pompe disease, a disorder which falls into both categories of lysosomal storage disorders and glycogen storage disorders, is one of the most common metabolic disorders associated with cardiomyopathy in infants. Infantile onset is associated with extreme hypotonia, failure to thrive, respiratory distress and cardiomyopathy. Although there are juvenile and adult-onset forms of Pompe disease, cardiomyopathy is not a feature of the later onset disorder. A similar disorder, Danon disease, is X-linked and affected males exhibit cardiomyopathy, intellectual disability and myopathy. ERT is available for Pompe disease, but not Danon disease at this time. Other glycogen storage disorders, which rarely present with cardiomyopathy in the infant period, include type III (debranching enzyme deficiency)[10] and type IV (Andersen disease)[11].

Mitochondrial disorders typically have multisystem involvement, which can include hypertrophic or dilated cardiomyopathy, as well as left ventricular non-compaction[6]. Although mitochondrial disorders are estimated to have an incidence of 1 in 5000 births, these disorders are likely under diagnosed. Many of the well characterized mitochondrial disorders, including Leigh syndrome, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) and myoclonic epilepsy with ragged-red fibers (MERRF), are known to include cardiomyopathy[6].

Congenital disorders of glycosylation (CDGs) are a heterogeneous group of disorders caused by enzymatic disturbances in the synthesis of glycoproteins. The spectrum of CDGs is ever expanding. Several case reports in the literature suggest that CDGs should be considered in infants with cardiomyopathy and multisystem disorders. Infants with CDG I a (phosphomannomutase 2 deficiency) are have been most often been reported to have hypertrophic cardiomyopathy[12-16] and infants with dolichol kinase deficiency have been reported to have dilated cardiomyopathy[17,18]. Case reports exist for cardiomyopathy associated with other CDGs[12,19].

Organic acidurias are the result of enzyme deficiencies characterized by the excretion of specific organic acids in the urine. Although this group is large, only a few have been associated with cardiomyopathy. Barth syndrome, characterized by urinary excretion of 3-methylglutaconic acid due to defects in the mitochondrial protein tafazzin, causes dilated cardiomyopathy in infant males, which is often severe[20]. Propionic acidemia is the most well known; however, individuals with propionic acidemia generally do not develop cardiomyopathy in the newborn period. Cardiomyopathy has rarely been reported in infants with methylmalonic acidemia[21].

NEWBORN SCREENING

With the advent and standardization of neonatal screening in the United States, many metabolic disorders associated with cardiomyopathy are identified within the first days of life. Fatty acid oxidation disorders, including VLCAD deficiency, LCHAD deficiency and carnitine uptake deficiency, as well as propionic acidemia are included in the disorders recommended by the American College of Medical Genetics as part of the core panel of disorders included on the newborn screen[22]. Despite the inclusion of several inborn errors of metabolism, this should not lead to a false sense of comprehensiveness. False negatives have been reported[23] and individuals with fatty acid oxidation disorders may have normal acylcarnitine profiles when they are not in a state of metabolic decompensation. Lysosomal storage disorders, congenital glycosylation defects, glycogen storage disorders and mitochondrial disorders are not screened. Although many states are moving towards screening for lysosomal storage disorders, it is uncertain whether there will be universal acceptance of neonatal screening for these disorders.

CASE PRESENTATIONS

The following cases represent several infants who presented in the newborn period with cardiomyopathy and a metabolic etiology was determined.

Patient 1

He is a male infant of Puerto Rican ethnicity. He presented to an emergency department in the setting of respiratory distress. Upon evaluation, the patient was found to have pneumonia. An echocardiogram was performed, which revealed dilated cardiomyopathy with severe dysfunction. The ejection fraction was estimated at 20%. The patient was transferred to our medical center for further evaluation and management of his cardiac dysfunction.

Physical examination of the patient showed an interactive male, with frontal bossing and dysmorphic features, including depressed nasal bridge, and low set, posteriorly rotated ears. He had developmental delays and had a history of failing his newborn hearing screen. Family history was significant for consanguinity, as the patient's parents are first cousins. Family history was also remarkable for a

sister who died at age 3 years 5 mo from unspecified cardiac dysfunction.

Red flags for IEM and final diagnosis: Patient 1

Red flags: (1) Family history of sibling death due to unspecified cardiac dysfunction. Further investigation revealed that she had coarse facial features and developmental delays as well; (2) Consanguinity; and (3) Coarse facial features, dysmorphic features, hearing loss, and developmental delay.

The deceased sibling had the same signs and symptoms as this patient, and the parents are consanguineous. This suggests autosomal recessive inheritance. The patient had many other clinical findings besides dilated cardiomyopathy so this was not simply an isolated cardiomyopathy. Based on coarse facial features, hearing loss, developmental delay, and cardiomyopathy, lysosomal storage disorders such as mucopolysaccharidosis were suspected first in the differential diagnosis. Leukocyte enzyme analysis showed alpha-iduronidase activity of 0 nmol substrate per hours per milligram per protein (normal 6-71.4). This was consistent with a diagnosis of Mucopolysaccharidosis type 1, or Hurler syndrome. Genetic testing confirmed this diagnosis with homozygous c.208C > T (p.Q70X) mutations in the *IDUA* gene. Urinary glycosaminoglycan quantitation showed elevation at 163.51 mg/nmol creatinine.

Following the diagnosis of mucopolysaccharidosis type 1, this patient started enzyme replacement therapy (Aldurazyme). The patient's cardiac function has stabilized at one year of age and he will continue to be followed for signs of cardiac dysfunction.

Patient 2

He is an 8-mo-old ex-full term male born to a 32-year-old G1P0 Haitian mother and Dominican father. Pregnancy was unremarkable except for hypertrophic cardiomyopathy noted on second trimester ultrasounds that was confirmed by fetal echocardiogram. He was initially asymptomatic, but echocardiogram at birth confirmed the presence of biventricular hypertrophy with increased trabeculation and decreased left ventricular function. Cardiac catheterization and endomyocardial muscle biopsy at three weeks of life revealed non-specific findings of cardiomyopathy with muscle disarray, and there was no evidence of glycogen accumulation. Additional metabolic evaluations were unremarkable, including acylcarnitine profile, urine and plasma amino acids, ammonia, cholesterol, urine and plasma carnitine and creatine kinase. Although the lactate level was normal, pyruvate was slightly low, which caused the lactate/pyruvate ratio to be elevated at 53 (normal 10-20). Pompe disease was ruled out based on normal enzyme activity.

Red flags for IEM and final diagnosis: Patient 2

Red flags: There was no clear explanation for this patient's hypertrophic cardiomyopathy. It appeared to be an isolated cardiomyopathy without significant neurologic or other organ involvement. Elevated lactate/pyruvate ratio was a red flag for mitochondrial disorders. This warranted further mitochondrial work up.

The patient had genetic testing for mutations in genes associated with mitochondrial disorders. The patient was found to have two predicted pathogenic variants in the *SLC25A3* gene, c.599T > G (p.L200W) and c.886-898delins7 (p.G296-S300delinsQIP). Parental testing indicated that the *SLC25A3* variants were in trans.

Mutations in *SLC25A3* are associated with mitochondrial phosphate carrier deficiency. There are only two papers in the literature describing five children from two families with mutations in this gene. Of the five children reported, three died in early infancy[24]. Two of the other children had difficult neonatal courses, but were living at age 9 and 17 as of 2011[25]. Mitochondrial phosphate carrier deficiency is characterized by hypertrophic cardiomyopathy, skeletal myopathy and lactic acidosis.

Patient 2 was listed for a cardiac transplant and received a heart at 8 mo of age. Following the surgery, this patient was observed to have new-onset seizures. Patient 2 continues to be followed by Cardiology, Metabolism, and Neurology at 10 mo of age.

Patient 3

He was previously reported[26] and is included with permission of the original author. A full term male of African American ethnicity presented at 5 mo of age in the setting of decreased oral intake, fatigue with feeds, cough and fever. His prenatal history was unremarkable. His first months were significant for poor head control and gross motor delays. Echocardiogram demonstrated left ventricular dilation, spongiform appearance of the left ventricular free wall and poor ventricular functioning. The ejection fraction was shortened at 21%.

Red flags for IEM and final diagnosis: Patient 3

Red flags: Hypotonia and developmental delay, in addition to cardiomyopathy, warrant additional testing to rule out an IEM. The metabolic tests such as plasma acylcarnitine profile, blood and urine carnitine levels, creatine kinase and urine organic acid analysis should be ordered as the first step tests.

Biochemical evaluation included urine organic acids [increased excretion of malonic acid (1060 mg/g creatinine) and methylmalonate (59 mg/g creatinine)], plasma acylcarnitine profile (elevated malonyl carnitine of 0.13 nmol/mL), lactate/pyruvate (normal), and creatine kinase (normal). The patient was neither acidotic nor hypoglycemic.

Malonyl-CoA decarboxylase enzyme assay showed 12% of normal activity. Retrospective analysis of the patient's newborn screening showed an elevated malonyl carnitine of 0.39 nmol/mL, which was not reported due to lack of routine screening for this compound and lack of established standards.

This patient was treated with carnitine supplementation, medium-chain triglyceride supplementation and a high-carbohydrate diet. After one year of treatment, the

patient did not have any further episodes of metabolic decompensation, but developmental delays persisted. Follow-up cardiac surveillance continued to show left ventricle dilation with a shortening fraction of 41%.

CONCLUSION

In conclusion, determining the etiology of cardiomyopathy in the infant is critical for determination of a treatment plan, accurate genetic counseling and discussion of prognosis. A significant proportion of infants with cardiomyopathy may have a metabolic etiology and some of these benefit greatly from diagnosis and follow up treatment. The efficacy of such treatments makes it important to exclude metabolic causes for all infants presenting with cardiomyopathy.

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