REVIEW ARTICLE

Cardiac Manifestations in Children with Inborn Errors of Metabolism

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Need and purpose: Cardiac involvement is a part of many inborn errors of metabolism, but has not been systematically studied. This review focuses on studies describing cardiac manifestations of inborn errors of metabolism in childhood.

Methods: Two independent reviewers searched the topic using PubMed database. Studies published within 20 years were considered, without applying any restrictions related to study design.Despite the small number of existing systematic studies on the topic, several case series/reports were identified.

Conclusions: Cardiomyopathy is the most frequent heart disorder in most metabolic defects. Heart rhythm disorders are mainly encountered in mitochondrial disorders and acidemias, whereas valvular dysfunction is a prominent finding in storage disorders. Cardiac involvement in mitochondrial disorders, congenital disorders of glycosylation and acidemias usually constitute an early symptom. On the contrary, in storage disorders, heart problems are revealed in later stages during routine multisystemic evaluation, with the exception of Pompe disease. As a variety of cardiac manifestations can be found in inborn errors of metabolism, these children should be systematically screened for heart problems during their follow-up.

Keywords: *Arrhythmia, Cardiomyopathy, Metabolic disorders.*

Inborn errors of metabolism consist of a heterogeneous group of disorders with multi-organ manifestations, including the heart. Although they are individually rare and incidence data is difficult to collect, they may be quite common collectively [1]. As the heart is a metabolically active organ,it can be adversely affected by metabolic defects [2]; the reported incidence of cardiac involvement varies from 15% to 60% [3-5]. To our knowledge there is no systemic review of the cardiovascular manifestations of inborn errors of metabolism so far. This narrative review aims to describe the cardiovascular manifestations, during childhood, of common congenital metabolic diseases.

A comprehensive literature review was conducted by two independent reviewers using Pubmed (*www.ncbi.nlm.nih.gov/pubmed*) as the medical database source and without applying any restrictions to study design. Papers published in the last 20 years (including citations of relevant articles found within) written in English, French, and German were considered.

The terms used were 'inborn errors of metabolism', 'metabolic defects', 'child', 'heart', 'cardiac', 'mitochondrial disorders', 'carnitine', 'fatty acid metabolism', 'acidemia', 'storage disorders', 'Pompe', 'Fabry', 'Barth syndrome', 'Smith-Lemli-Opitz', 'congenital disorders of glycosylation', 'cardiomyopathy', 'arrhythmia', 'heart rhythm disorders', 'valve', 'congenital heart disorders', and 'structural heart disorders'.

Our search initially identified 94 articles excluding studies conducted solely in adult populations, describing only vascular complications, or consisting of expert opinions or duplicate records. Overall, 17 original papers (clinical or experimental studies), 5 reviews and 28 case reports or case series were identified.

INBORN ERRORS OF METABOLISM

Inborn errors of metabolism are traditionally classified as urea cycle defects and disorders of carbohydrate metabolism, amino acid metabolism, organic acid metabolism, fatty acid oxidation, mitochondrial metabolism, peroxisomal function, porphyrine metabolism, purine and pyrimidine metabolism, steroid metabolism, lysosomal storage, and cholesterol biosynthesis [6].

In most cases, the underlying mechanism includes mutations in genes coding for proteins, which are involved in metabolic pathways. These changes may lead to abnormalities in synthesis or catabolism of various substances, as well as to accumulation of products, that are either toxic or interfere with normal body functions. Various types of inheritance are present, although the majority of inborn errors of metabolism are inherited in an autosomal recessive way [7].

PATHOPHYSIOLOGY OF CARDIAC INVOLVEMENT

Cardiac manifestations among these patients include cardiomyopathy (hypertrophic, dilated, restrictive), heart rhythm disorders, valvular defects, and congenital heart structure disorders. It should be noted; however, that more than one pattern of cardiac involvement may be present in some inborn errors of metabolism (***Table* I**) [4,5,8-22].

In many cases, cardiac manifestations dominate the clinical phenotype, as they include one of the prominent symptoms (*e.g.,* Pompe disease or disorders of fatty acid oxidation). In other metabolic defects; however, heart problems consist of minor symptoms and are incidentally revealed during routine multisystem evaluation (*e.g.*, glycogen storage disorders, mucopolysaccharidoses). Lastly, there are cases of metabolic errors in which the heart may be the only affected organ (*e.g.,* some mitochondrial disorders) [2] (***Table* II**).

Pathophysiology includes three basic mechanisms: (*i*) impaired energy production due to enzyme deficiency, disturbed transport of molecules or cellular organelles dysfunction (*e.g.,* mitochondrial dysfunction), (*ii*) infiltration of cardiac myocytes with stored substrate and subsequent cellular damage, (*iii*) accumulation of intermediary metabolites, which exert a toxic effect on surrounding tissues and lead myocytes to apoptosis [2] (***Fig.* 1**). It is noteworthy that in many cases more than one mechanisms may be involved, especially in later stages of the disease course. ***Web Table* I** summarizes the main cardiac manifestations of inborn errors of metabolism found in the literature [3,5,13-19,22,23].

Impaired Energy Production

Disturbed energy production is the most prominent underlying mechanism of cardiac involvement in carnitine deficiency, fatty acid oxidation disorders, and other mitochondrial disorders. Cardiac manifestations typically appear early in the course of the disease, have an acute onset and dominate the clinical phenotype. Furthermore, their identification often leads to the diagnosis of the underlying defect [2].

It is estimated that inherited metabolic disorders account for approximately 30% of definable causes of cardiomyopathy in childhood [23]. More specifically, cardiomyopathy is the most common clinical manifestation in children with primary carnitine deficiency and includes dilated cardiomyopathy and hypertrophic cardio-myopathy. The average age of cardiomyopathy appearance is 2-4 years of age, indicating that it takes a long time for the changes in heart to manifest in severe carnitine deficiency. While the incidence of dilated cardiomyopathy seems to be higher than hypertrophic cardiomyopathy, a mild degree of ventricular hypertrophy may be present in some patients presenting with dilated cardiomyopathy [24,25].

Cardiomyopathy has also been reported in fatty acid metabolism disorders. Defects involving oxidation of long or very long chain fatty acids are more frequently associated with cardiomyopathy than those involving oxidation of the short chain fatty acids. In fact, most experimental and clinical studies have been conducted in this group of patients. Very-long-chain acyl-CoA dehydrogenase (VLCAD) catalyzes the first step in the beta-oxidation spiral of fatty acid metabolism with infantile hypertrophic cardiomyopathy being the most common clinical phenotype of its deficiency [8].

With regards to other energy production defects, MELAS syndrome (mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes) is associated with hypertrophic, dilated cardiomyopathy and even with cases of left ventricular non-compaction. However, very few cases of cardiomyopathy associated with MELAS in pediatric or adolescent populations are found in literature [26]. Hypertrophy of left ventricle is the dominant pattern of myocardial involvement in MERRF (myoclonic epilepsy with red-ragged fibers) syndrome, in Leigh disease, as well as in complex I-V deficiency [2]. The incidence of these cases in childhood is extremely low.

TABLE I MAJOR CARDIAC INVOLVEMENT IN COMMON METABOLIC ERRORS

Type of inborn error of metabolism	*Cardiomyopathy*	*Heart rhythm disorders*	*Valvular disease*
Carnitine deficiency [10-12,22]	+++	++	+
Fatty acid oxidation disorders [8,9]	+++	+++	-
Organic acidemias17-21]	+++	+	-
Storage disorders [5, 13-16]	+++	+++	+++
Congenital glycosylation disorders [4]	+++	-	-

+++: Retrospective/prospective studies, ++: Many case reports/series, +: Isolated case reports.

TABLE II CARDIAC MANIFESTATIONS IN INBORN ERRORS OF METABOLISM

Disease	*Prominent finding*	*Secondary finding(s)*	*Age at onset*
Carnitine deficiency	Cardiomyopathy	Heart rhythm/ valvular disorders	Neonatal to early childhood
Fatty acid oxidation disorder	Cardiomyopathy, heart rhythm disorders	–	Neonatal to early childhood
Acidemias	Cardiomyopathy	Heart rhythm disorders	Neonatal to childhood
Glycogen storage disorders*	Cardiomyopathy, valvular disorders	Heart rhythm disorders	Late infancy to childhood
Pompe	Cardiomyopathy, heart rhythm/ valvular disorders	–	Infancy to childhood
Gaucher*	Cardiomyopathy, valvular disorders	Heart rhythm disorders	Late infancy to childhood
Mucopolysaccharidoses*	Cardiomyopathy, valvular	Heart rhythm disorders disorders	Late infancy to childhood
Congenital glycosylation disorders	Cardiomyopathy	–	Neonatal to early childhood

**Cardiac manifestations ate usually not a presenting feature.*

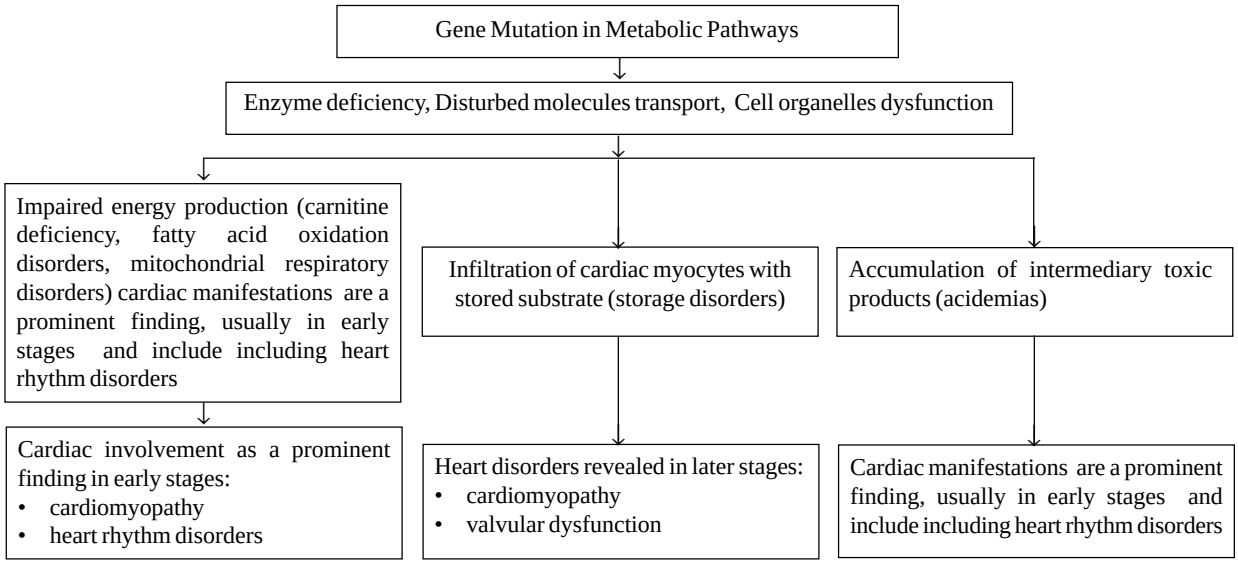

FIG. 1 *Pathophysiological mechanisms of cardiac involvement in metabolic disorders.*

Congenital disorders of glycosylation are also of special interest. They represent a group of recently described multisystem disorders characterized by defects in protein glycosylation. Hypertrophic cardiomyopathy contributes significantly to the high mortality of these patients, particularly those with subtype Ia (caused by mutations in *phosphomannomutase 2* gene). Cases of hypertrophic cardiomyopathy and other cardiac related adverse events (cardiac failure, tamponade, pericardial effusions) in this group have been reported from the prenatal period and neonatal age to late childhood [27,28]. On the other hand, dilated cardiomyopathy has been observed in few subtypes of glycosylation disorders. It usually results in lethal outcome and has been associated with mutations in *dolichol kinase 1* gene. Therefore, patients with congenital disorders of glycosylation type Ia

should be monitored regularly by echocardiography for cardiac complications. Furthermore, children with an undiagnosed cardiomyopathy should be screened for glycosylation disorders [28].

Disturbed energy production is also involved in heart rhythm disorders. Case reports describing prolonged QTc and ventricular tachycardia in neonates and infants with fatty acid metabolism disorders (very long and medium chain acyl-CoA dehydrogenase deficiency) have been found. In many of these cases, heart rhythm disorder is the major presenting symptom leading to the diagnosis of the underlying inborn error [9,29,30] (***Table* II**). Similarly, cases of QTc prolongation and heart rhythm disorders in children with carnitine deficiency have been identified in literature [10,11,31]. Studies have also shown that specific mutations in mitochondrial DNA (*e.g.*, G13513A mutation) are associated with increased risk for Wolff-Parkinson-White syndrome in patients with MELAS syndrome or Leigh disease [12].

With regards to other heart-related manifestations, Trivellato, *et al*. [32] had described low plasma and urinary carnitine levels in adult patients with idiopathic mitral valve prolapse, but no further information on this topic is available. Mitral valve regurgitation has been reported in a case of mitochondrial cardiomyopathy [33]. Although dysfunction of mitochondria in patients with valvular disorders has been histopathologically confirmed and associated with aging, no correlation between specific mitochondrial diseases and valvular defects has been reported [34].

Infiltration of Cardiac Myocytes With Stored Substrate

Progressive infiltration of cardiac myocytes with stored substrate is the basic pathophysiological mechanism in storage disorders. Although hypertrophic cardiomyopathy is a well-recognized manifestation in these disorders, there is poor literature documentation related to cases specific to various subforms [2] (***Table* I**). In the vast majority of the published cases, cardiac hypertrophy is an echocardiographic finding in asymptomatic patients and is related to the natural course of the disease. Pompe disease and Anderson-Fabry disease, in which cardiac hypertrophy usually occurs in the late childhood period, present the only exceptions to the above [2] (***Table* II**).

Most infants with Pompe disease develop cardiomyopathy (massive hypertrophy of both ventricles) before the age of 6 months and often present symptoms of congestive heart failure [35]. On the other hand, children with late-onset Pompe disease experience slower progression of muscle involvement and do not usually have significant cardiac manifestations [13]. In Fabry disease, left ventricular hypertrophy is the most common pattern of cardiac involvement in childhood and can appear at an early age in both genders [2,14].

Symmetrical hypertrophy of the left ventricle is the most frequent echocardiographic finding in glycogen storage disease type III [15]. However, according to Mogahed, *et al*. [15], there is no relation between skeletal myopathy and cardiomyopathy.

Arrhythmias can also appear in later stages of storage disorders secondary to progressive heart dysfunction, and do not usually consist a prominent clinical finding in early childhood with the exemptions of Pompe and Danon disease [2] (***Table* II**). Children with Pompe disease can develop significant ectopy (mainly premature ventricular contractions) or even ventricular tachycardia in ambulatory electrocardiograms [16]. The co-existence of Danon disease and Wolff-Parkinson-White syndrome, along with concentric hypertrophy of left ventricle, has also been reported in literature for young patients [36,37].

Valvular dysfunction is an additional significant finding with the mitral valve being the most commonly affected valve. Cases of valvular defects in childhood (from infancy to adolescence) have been identified in literature and are related to Pompe disease, Gaucher disease and mucopolysaccharidoses [38,39]. According to Bigg, *et al*. [40], mitral valve disease in mucopolysaccharidosis can be associated with upregulation of enzymes (that degrade collagen or collagen-associated proteins), as well as with accumulation of glycosaminoglycans (that compete with proteoglycans to bind with collagen). Macrophage infiltration seems to be the cause of mitral valve pathology in mucopolysaccharidosis VI [41].

Toxic Intermediary Metabolites

The production of toxic intermediary products secondary to enzymatic deficiencies is the dominating mechanism of myocardial involvement in acidemias. The most frequent cardiac complication in children with propionic acidemia is dilated cardiomyopathy [2]. Romano, *et al*. [42] presented a series of five neonates who developed dilated cardiomyopathy and were later diagnosed with propionic acidemia. Furthermore, acute onset of dilated cardiomyopathy has been reported as the only symptom of propionic acidemia in infants and adolescents [43]. The co-existence of myocardial involvement with methylmalonic acidemia has also been reported for both adults and children [44]. Cardiomyopathy is of special interest in cases of X-linked Barth syndrome (3-Methylglutaconic aciduria type II), as it may be one of the presenting symptoms and is related with poor prognosis.

It may include hypertrophic or dilated cardiomyopathy, although left ventricular non-compaction is the most frequent type [17,18,45].

Isolated cases of prolonged QTc have been reported among children with propionic acidemia, either as a presenting symptom or as an additional finding in children already diagnosed with this defect [19,20]. Arrhythmias have also been revealed in patients with methylmalonic acidemia, as well as in patients with Barth syndrome [21,46]. Few sporadic case reports in literature describe a co-existence of congenital heart structure disorders and organic acidemias. Ebstein cardiac anomaly and functional pulmonary atresia has been reported in a newborn with isovaleric acidemia, while coexistence of both propionic acidemia and cyanotic congenital heart disease has been reported in another child [47,48]. Despite the above case reports, a clear pathophysiological association between structural heart disorders and metabolic defects has not yet been identified.

CLINICAL FEATURES

Metabolic disorders have varying and overlapping clinical picture [49,50]. Symptoms and signs from the cardiovascular system are often non-specific and include shortness of breath, hepatomegaly, edema, pathologic murmurs, failure to thrive, heart failure and even sudden death [2]. The aforementioned symptomatology is related to a variety of cardiac diseases (cardiomyopathy, heart rhythm disorders, valvular dysfunction), as described above (***Fig.* 1**). It is noteworthy that in some cases cardiac symptoms may arise after specific precipitating factors, such as stress, febrile illness, fasting, dietary change and intensive exercise [50].

DIAGNOSTIC APPROACH

The wide variety of multisystemic presentation of inborn errors of metabolism constitutes a diagnostic challenge for most physicians. A systematic approach is required for the early detection of these entities, primarily guided by a detailed medical and family history and physical examination [2,49]. In most cases, characteristic biochemical findings are observed, such as metabolic acidosis, hypoglycemia, elevated creatine phospho-kinase, lactate or ammonia. However, the definite diagnosis usually requires a more specialized work-up based on advanced laboratory techniques. These include assessment of plasma amino acids and acyl caritines, urine organic acids profile, carnitine analysis, enzymatic assays or even molecular testing [49]. The knowledge of the genetic background at an early age allows an individualized approach to each patient, according to predicted clinical phenotype, and promotes genetic counseling of patients and their families [2].

The diagnosis of cardiac manifestations is usually based on electrocardiographic and echocardiographic findings. Conduction abnormalities and heart rhythm disorders are easily diagnosed with the electrocardiogram, whilst echocardiography is the most easily applicable imagining tool for the diagnosis of defects of cardiac morphology. Simple imaging techniques (*e.g.*, *X*-rays) may reveal cardiac dilatation, while cardiac magnetic resonance imaging and endomyocardial biopsy can exclude other morbidities (*e.g.*, infectious myocarditis) [2].

Until now few "genotype-phenotype correlations" have been described with regards to heart disorders due to inborn metabolic errors. The deeper understanding of the genotype-phenotype correlation provides the opportunity for more appropriate therapeutic interventions and allows better understanding of disease expression [25].

MANAGEMENT OF CARDIAC ABNORMALITIES

Significant progress has been made for the treatment of metabolic diseases, especially during the last decade. A large number of studies are still being conducted aiming for better and more targeted therapies. Early diagnosis is crucial for the initiation of early treatment in these patients.

The treatment approaches for inborn errors of metabolism can be divided in two main topics: acute and chronic treatment. The same strategy is followed for cardiac abnormalities; treatment of acute complications and long-term management. The emergency treatment is very important for preventing morbidity and mortality and has to be planned even when the diagnosis is suspected. Treatment of acute complications is based on conventional drugs (inotropes, diuretics, antiarrhythmic drugs) and supportive measures [2].

It is important; however, to note that cardiac complications are resistant to conventional therapies in some metabolic defects. More specifically, cardiac function responds poorly to treatment with diuretics and inotropes in patients with primary carnitine deficiency. On the contrary, continued therapy with oral L-carnitine supplements can alter the natural course of the disease and efficiently alleviate the signs of cardiomyopathy [22]. Positive outcomes have also been reported about the effect of carnitine administration on heart rhythm disorders in these patients [10,11].

Long-term management strongly depends on the underlying pathophysiology. New enzyme replacement therapies seem to exert a beneficial effect on cardiac

symptoms of patients with specific storage disorders (*e.g*., Pompe and Anderson-Fabry disease) [13,14] (***Web Table* I)** Furthermore, liver transplantation represents definite and curative intervention for some metabolic errors, such as organic acidemias. In these cases, cardiomyopathy too may reverse totally after liver transplantation [42].

CONCLUSIONS

Heart disorders are increasingly being recognized as comorbidity in children with inborn errors of metabolism. Although there is a lack of systematic prospective studies on this topic, the potential adverse effect of cardiac disorders on the natural course of metabolic defects cannot be overlooked. At a clinical level, children with metabolic diseases should be systematically screened for cardiac involvement during their follow-up. Furthermore, the recognition of heart disease (especially cardiomyopathy and heart rhythm disorders) in young patients may indicate a possible underlying metabolic defect and promote appropriate diagnostic work-up. The correlation of cardiac complications with specific mutations will also permit the genetic counseling of patients and their families. On the other hand, associating specific cardiac manifestations with specific inborn errors of metabolism can narrow the spectrum of differential diagnosis and contribute to a more cost-effective investigation.

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WEB TABLE I STUDIES REPORTING MAIN CARDIAC MANIFESTATIONS OF INBORN ERRORS OF METABOLISM

Study [Ref.]	*Type*	*Population*	*Outcome(s)*
Mogahed, *et al.* [15]	Retrospective	28 children with glycogen storage disease type III	9 cases with left ventricular hypertrophy
Rigaud, *et al.* [17]	Retrospective	22 patients with Barth syndrome	Cardiomyopathy documented in 20 patients
Fu, *et al*. [22]	Retrospective	75 children with unexplained cardiomyopathy	6 diagnosed with carnitine deficiency; L-carnitine has a good therapeutic effect on cardiomyopathy
Leal, *et al.* [5]	Retrospective	28 children with muco-polysaccharidosis	Echocardiographic abnormalities in 26 patients
Hughes, *et al*. [14]	Prospective (double blind randomized controlled trial)	15 patients with Anderson-Fabry disease	Regression of hypertrophic cardiomyopathy by enzyme replacement therapy
Baumgartner, *et al*. [19]	Retrospective	10 patients with propionic acidemia	QTc prolongation in 70%, rhythm disorders in 20%, ↓left ventricular contractility in 30%
Evangeliou, *et al.* [3]	Retrospective	287 patients with inborn errors of metabolism	Cardiac manifestations in 41 patients
Cook, *et al.* [16]	Retrospective	12 infants with Pompe disease	Significant ectopy in the ECG of 2 patients
Spencer, *et al*. [18]	Retrospective	34 patients with Barth syndrome	Clinical history of cardiomyopathy in 90%
Wang, *et al.* [23]	Retrospective	58 children with unexplained cardiomyopathy	31% diagnosed with inborn errors of metabolism
Winkel, *et al.* [13]	Retrospective (Analysis of case records)	225 patients with Pompe disease	Cardiac symptoms in 25 patients