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Original Article

Cardiac involvement as a gateway to the diagnosis of inherited metabolic disorders: A 16-year pediatric experience from a tertiary metabolic center

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ABSTRACT

Objective: Cardiac involvement is a common but often underrecognized feature of inherited metabolic disorders (IMDs), particularly in pediatric populations. Early detection is crucial, since many IMDs have disease-specific treatments that can improve outcomes. This study aimed to evaluate the frequency and spectrum of inherited metabolic disorders among pediatric patients presenting with cardiomyopathy, and to emphasize the importance of early recognition for targeted management.

Material and Methods: We retrospectively analyzed the records of 71 pediatric patients referred to a tertiary metabolic center between 2004 and 2020 due to cardiomyopathy or other cardiac findings. Demographic, clinical, and diagnostic data were reviewed, with a focus on final diagnoses and metabolic etiology.

Results: The median age at presentation was 17 months (range, 15 days-17 years). Dilated cardiomyopathy was the most common phenotype (57.7%), followed by hypertrophic (21.1%) and non-compaction cardiomyopathy (15.4%). An inherited metabolic disorder was diagnosed in 12 patients (16.9%), most commonly Pompe disease, carnitine transporter deficiency, and very long-chain acyl-CoA dehydrogenase deficiency. Parental consanguinity was present in 50% of diagnosed cases. Despite therapy, four patients died due to cardiac failure.

Conclusion: Inherited metabolic disorders account for a substantial proportion of pediatric cardiomyopathy cases. Early metabolic screening should be considered in all children with cardiomyopathy, especially when suggestive features are present. Prompt diagnosis may allow for timely intervention, genetic counselling, and improved outcomes.

Keywords: Inherited metabolic disorders, cardiomyopathy, pompe disease, fatty acid oxidation defects, mitochondrial disorders

INTRODUCTION

Inherited metabolic disorders (IMDs) are a heterogeneous group of diseases caused by defects in biochemical pathways, most of which follow an autosomal recessive inheritance pattern. These disorders often present with multisystem involvement due to the accumulation of toxic metabolites or deficient energy production. The heart, being a metabolically active organ with high energy demands, is commonly affected in IMDs. Cardiac involvement may serve as an initial manifestation or may emerge during disease progression, significantly impacting prognosis (1).

Approximately 30% of pediatric cardiomyopathy cases are attributed to IMDs (2). The most common cardiac findings associated with metabolic disorders include hypertrophic, dilated, non-compaction, or restrictive cardiomyopathy, arrhythmias, conduction defects, valvular disease, and sudden cardiac death. The heart derives nearly 95% of its ATP from mitochondrial oxidative phosphorylation, and the remainder from glycolysis and the Krebs cycle. Thus, disruption of energy metabolism in IMDs can critically affect myocardial function (3, 4).

More than 200 metabolic disorders with cardiac involvement have been described to date, including fatty acid oxidation defects, glycogen storage diseases, lysosomal storage disorders, peroxisomal disorders, mitochondrial diseases, organic acidemias, aminoacidopathies, and congenital disorders of glycosylation (2, 5-7).

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The aim of this study was to retrospectively evaluate the frequency, clinical spectrum, and diagnostic yield of inherited metabolic disorders (IMDs) in pediatric patients presenting with cardiac findings who were referred to a tertiary metabolic center.

MATERIALS and METHODS

This retrospective study was conducted in the Division of Pediatric Nutrition and Metabolism, Department of Pediatrics, Ege University Faculty of Medicine. Medical records of pediatric patients referred between January 2004 and December 2020 for cardiac involvement suggestive of an IMD were reviewed. Inclusion criteria were: 1) presence of cardiomyopathy or arrhythmia identified by echocardiography or electrocardiography, and 2) referral for evaluation of a possible IMD. Patients with structural congenital heart disease or acquired causes of cardiomyopathy (e.g., viral myocarditis) were excluded.

For each patient, demographic data (age at presentation, sex), clinical findings, cardiac phenotype, and diagnostic work-up results were collected. Specific attention was paid to features associated with inherited conditions, including parental consanguinity, family history of sudden cardiac death or similarly affected siblings, and presence of multisystem involvement (e.g., developmental delay, hepatomegaly, hypotonia, dysmorphic features).

Cardiac evaluation included electrocardiogram (ECG) and transthoracic echocardiography (ECHO), both performed at the time of referral. Patients were classified into five categories based on cardiac phenotype: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), non-compaction cardiomyopathy (LVNC), restrictive cardiomyopathy (RCM), or arrhythmia without structural abnormality.

All patients underwent metabolic screening according to clinical suspicion, including serum lactate, ammonia, creatine kinase, acylcarnitine profile, urine organic acids, and plasma amino acids. In selected patients, enzyme assays or molecular genetic testing (e.g., next-generation sequencing, targeted gene panels, or Sanger sequencing) were performed to confirm a metabolic diagnosis. For those who underwent genetic testing, diagnoses were established based on the identified variants in accordance with ACMG (American College of Medical Genetics and Genomics) criteria.

The primary outcome was the proportion of patients who received a definitive diagnosis of an IMD. Descriptive statistics were used to summarize the distribution of clinical and diagnostic characteristics across the study population. No formal hypothesis was performed due to the observational nature of the study.

Statistical Analysis

Data were analyzed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were applied; continuous variables were expressed as median (range), and categorical variables as frequencies and percentages.

RESULTS

Seventy-one patients (36 males and 35 females) were included in the study. The age at presentation ranged from 15 days to 17 years, with a median of 17 months. Parental consanguinity was noted in 27 patients (38%), and 8 (11%) had a history of sibling death, often reported as sudden or unexplained.

Cardiac manifestations at presentation included dilated cardiomyopathy in 41 patients (57.7%), hypertrophic cardiomyopathy in 15 (21.1%), left ventricular non-compaction cardiomyopathy in 11 (15.4%), restrictive cardiomyopathy in 2 (2.8%), and arrhythmia without structural abnormalities in 2 (2.8%). The distribution of cardiac phenotypes observed in the study cohort is illustrated in Figure 1.

A confirmed diagnosis of an IMD was established in 12 patients (16.9%). Table I presents the demographic and clinical characteristics, cardiac phenotypes, specific diagnoses, administered treatments, and outcomes of these patients. Of the diagnosed cases, six (50%) had a history of parental consanguinity. Five patients with hypertrophic cardiomyopathy were diagnosed with infantile-onset Pompe disease. All five received enzyme replacement therapy with recombinant human acid α-glucosidase. Three patients died during follow-up. One patient with hypertrophic cardiomyopathy was diagnosed with very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency. Nutritional therapy including medium-chain triglyceride-enriched formula and feeding strategies to avoid catabolism was initiated. The patient died in early infancy. Four patients with dilated cardiomyopathy were diagnosed with carnitine transporter deficiency. Oral L-carnitine supplementation was

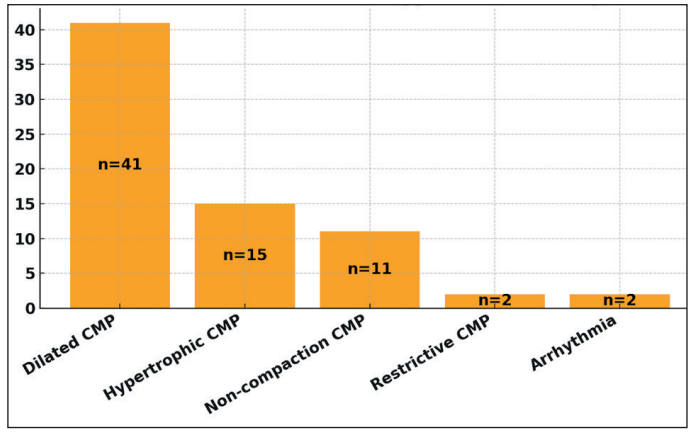

Figure 1: Distribution of cardiac phenotypes in the study cohort. CMP: cardiomyopathy

Table I: Patients diagnosed with inherited metabolic disorders presenting with cardiac involvement.

Number	Diagnosis	Gender	Consanguinity	History of Sibling Death	Age at diagnosis (months)	Cardiac Phenotype	Treatment	Outcome
1	Carnitine transporter deficiency	Female	No	No	24	Dilated cardiomyopathy	Oral L-carnitine	Alive
2	Carnitine transporter deficiency	Male	Yes	No	60	Dilated cardiomyopathy	Oral L-carnitine	Alive
3	Carnitine transporter deficiency	Male	No	No	72	Dilated cardiomyopathy	Oral L-carnitine	Alive
4	Carnitine transporter deficiency	Female	Yes	No	168	Dilated cardiomyopathy	Oral L-carnitine	Alive
5	Complex I deficiency	Female	No	Yes	10	Left ventricular non-compaction	MCS	Alive
6	Pompe disease	Female	No	No	2	Hypertrophic cardiomyopathy	ERT	Alive
7	Pompe disease	Male	No	No	3	Hypertrophic cardiomyopathy	ERT	Alive
8	Pompe disease	Female	No	No	3	Hypertrophic cardiomyopathy	ERT	Deceased
9	Pompe disease	Male	Yes	No	5	Hypertrophic cardiomyopathy	ERT	Deceased
10	Pompe disease	Female	Yes	No	7	Hypertrophic cardiomyopathy	ERT	Deceased
11	VLCAD deficiency	Female	Yes	Yes	1	Dilated cardiomyopathy	DM	Deceased
12	VLCAD deficiency	Male	Yes	Yes	3	Hypertrophic cardiomyopathy	DM	Deceased

MCS: *Mitochondrial cofactor supplementation,* ***ERT:*** *Enzyme replacement therapy,* ***VLCAD:*** *very long-chain acyl-CoA dehydrogenase,* ***DM:*** *Dietary management (MCT (medium-chain triglyceride), fasting avoidance)*

administered. Clinical follow-up indicated stable cardiac status without progression to heart failure. One patient with dilated cardiomyopathy was diagnosed with VLCAD deficiency. Nutritional management was initiated. The patient died in early infancy. One patient with left ventricular non-compaction cardiomyopathy was diagnosed with mitochondrial complex I deficiency. Supportive therapy with cofactor supplementation (carnitine, coenzyme Q10, riboflavin) was provided. Cardiac function remained unchanged during follow-up.

The median age at diagnosis among patients with confirmed IMDs was 6 months (range, 1 month-14 years). Pompe disease was diagnosed at a mean age of 4 months, and carnitine transporter deficiency at a mean age of 6.7 years. In total, five patients (three with Pompe disease and two with VLCAD deficiency) died during the follow-up period.

Fifty-nine patients (83%) remained without a confirmed metabolic diagnosis despite metabolic investigations. Earlier diagnosis was more frequently observed in cases presenting with early-onset cardiomyopathy and multisystem involvement.

DISCUSSION

Cardiac involvement is a well-recognized yet frequently underdiagnosed manifestation of IMDs, especially in pediatric populations. The myocardium's high energy requirements make it particularly vulnerable to metabolic derangements, including mitochondrial dysfunction, impaired fatty acid oxidation, and toxic substrate accumulation (8). Cardiomyopathy may be the initial or even sole presenting feature in some IMDs, early recognition of a metabolic etiology is critical (9). Timely diagnosis not only enables disease-specific interventions that may improve cardiac outcomes but also allows for family counseling and screening (2).

IMDs represent an essential and often overlooked cause of pediatric cardiomyopathies. In our cohort, 16.9% of patients presenting with cardiac findings were ultimately diagnosed with an IMD. This prevalence is comparable to rates reported in previous studies, such as 8.7% in the Pediatric Cardiomyopathy Registry (n=855 with hypertrophic cardiomyopathy) and 22.4% in the cohort reported by Bonnet et al. (n=58) (10,11).

In contrast to previous studies focusing predominantly on hypertrophic cardiomyopathy, the most common phenotype in our cohort was dilated cardiomyopathy (57.7%), followed by hypertrophic and left ventricular non-compaction types. However, among the IMD-positive cases, hypertrophic cardiomyopathy was more frequent, largely due to infantile-onset Pompe disease. This reinforces prior observations that specific metabolic disorders preferentially affect certain myocardial patterns (12, 13).

Pompe disease accounted for five out of twelve IMD diagnoses in our study. All cases manifested as early-onset hypertrophic cardiomyopathy and were treated with enzyme replacement therapy. Despite intervention, three patients died, underscoring the aggressive disease course and the limited reversibility of advanced cardiac involvement. These outcomes align with international data suggesting that prognosis in classic infantile Pompe disease is closely tied to the timing of diagnosis and treatment initiation (12, 14).

Carnitine transporter deficiency was exclusively seen in patients with dilated cardiomyopathy in our cohort. All affected individuals responded positively to L-carnitine therapy, with stabilization of cardiac function and no heart failure progression. These findings are consistent with previous reports highlighting the treatable nature of this disorder and the potential for complete reversal of cardiac symptoms when diagnosed early (15, 16).

Conversely, VLCAD deficiency was associated with a fulminant disease course in both affected patients, despite the initiation of dietary management protocols that included medium-chain triglyceride enriched formulas and avoidance of fasting. The poor outcomes highlight the high mortality risk associated with the neonatal-onset phenotype, which is known to present with early cardiac decompensation, arrhythmias, and hepatomegaly. In such cases, the window for therapeutic intervention is often narrow, and even with appropriate nutritional support, cardiomyopathy may progress rapidly to intractable heart failure (17, 18). These findings underscore the need for prenatal or newborn screening strategies in high-risk populations, especially where consanguinity is common.

Similarly, the patient with mitochondrial complex I deficiency presenting with LVNC cardiomyopathy exhibited only a modest clinical response to mitochondrial cofactor therapy, including carnitine, riboflavin, and coenzyme Q10. While such supportive regimens are widely used in clinical practice, evidence for their efficacy remains limited, particularly in cases with significant myocardial structural abnormalities. LVNC is increasingly recognized in mitochondrial disorders, likely reflecting the underlying disruption in myocardial development due to impaired oxidative phosphorylation. Given the multisystemic and progressive nature of mitochondrial diseases, early diagnosis and prognostication remain challenging, and cardiac involvement is often a significant determinant of survival (19-21).

Despite a thorough workup, 83% of patients remained undiagnosed, which reflects both the limitations of current diagnostic methods and the possibility of unrecognized or ultra-rare disorders. This highlights the potential future role of advanced tools such as whole-exome or genome sequencing in uncovering hidden etiologies.

It is important to note that the relatively high proportion of IMD diagnoses in our cohort may reflect a referral bias. Our study population consisted exclusively of patients referred to the metabolic clinic due to cardiomyopathy or unexplained cardiac findings. As such, these children represent a preselected group with an increased likelihood of having an underlying metabolic etiology. Therefore, while our findings underscore the diagnostic importance of metabolic evaluation, the reported prevalence rates should not be directly extrapolated to the general pediatric cardiomyopathy population.

Taken together, our findings support the integration of metabolic screening into the routine evaluation of pediatric cardiomyopathy. In cases with suggestive features, such as consanguinity, early-onset symptoms, or multisystem involvement, metabolic causes should be actively investigated, as early diagnosis can lead to targeted and potentially life-saving interventions. A collaborative approach between pediatric cardiologists and metabolic specialists is essential to ensure timely diagnosis, personalized treatment, and improved long-term outcomes.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ege University (02.01.2023, reference number: 22-12.2T/34).

Contribution of the authors

M.Y.Ç and ***S.K.U***; data collection: ***M.Y.Ç, E.C., H.Y., F.E.K., A.Y.Y., Z.Ü.T., R.E.L, S.K.U, M.Ç.***; analysis and interpretation of results: ***M.Y.Ç***; draft manuscript preparation: ***M.Y.Ç*** and ***S.K.U*** All authors reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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