Heart Diseases in Patients with Organic Acidemia

Organik Asidemi ile Takipli Hastalarda Kalp Hastalıkları

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ABSTRACT

Objective: Organic acidemias are intoxication-type inborn errors of the metabolism with multiple organ involvement. Patients with organic acidemia usually present in the neonatal or infantile period with high anion gap metabolic acidosis and hyperammonemia. The present study investigates the presence of congenital heart defects and secondary heart diseases in patients with organic acidemia.

Material and Methods: Included in the study were 31 patients of whom 14 were diagnosed with methylmalonic acidemia (MMA), 11 with propionic acidemia and six with isovaleric acidemia. The cardiac findings of all patients included in the study were evaluated.

Results: Of the sample, 63.64% were identified with accompanying congenital heart disease, with the most common diagnosis being propionic acidemia and the most common heart defects being atrial septal defects and mitral regurgitation.

Conclusion: The accumulation of toxic intermediate metabolites due to enzyme deficiency is thought to be the main mechanism behind the cardiac involvement noted in organic acidemias. In the presence of unexplained deterioration, the potential for organic acidemia to accompany congenital heart disease should be kept in mind, and so it is important to screen patients with organic acidemias by echocardiography.

Key Words: Echocardiography, Heart diseases, Organic acidemias

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ÖZ

Amaç: Organik asidemiler, çoklu organ tutulumu ile seyreden ciddi kalıtsal metabolik hastalıklardır. Pek çok organik asidemi neonatal veya infantil dönemde artmış anyon açıklığı, metabolik asidoz ve hiperamonyemi ile birlikte bulunur. Bu çalışmada; organik asidemi ile takipli hastalarda konjenital kalp defektleri ile sekonder kalp hastalıklarının araştırılması amaçlandı.

Gereç ve Yöntemler: Çalışmaya 14'ü metilmalonik asidemi, 11'i propionik asidemi ve 6'sı izovalerik asidemi tanılı toplam 31 hasta dahil edildi. Bu olguların kardiak bulguları değerlendirildi.

Bulgular: En sık propionik asidemi tanısı ile takipli hastalarda %63.6 oranında eşlik eden konjenital kalp hastalığı saptandı. Bunlar arasında en sık görülen kalp anomalisi ise atriyal septal defekt ve mitral yetmezlikti.

Sonuç: Organik asidemilerde kardiyak tutulumun ana mekanizmasının enzim eksikliğine bağlı toksik ara metabolitlerin birikimi olduğu düşünülmektedir. Klinikte açıklanamayan kötüleşme varlığında konjenital kalp hastalıklarına organik asideminin eşlik edebileceği akılda tutulmalıdır. Bu nedenle organik asidemilerde ekokardiyografi ile tarama yapılması önemlidir.

Anahtar Sözcükler: Ekokardiyografi, Kalp hastalıkları, Organik asidemiler

INTRODUCTION

Organic acidemias (OA) are congenital metabolic diseases with potential multiple organ involvement that result from an accumulation of toxic metabolites. Propionic acidemia (PA), methylmalonic academia (MMA) and isovaleric acidemia (IVA) are most frequently encountered in clinical practice.

In PA, propionate and other metabolites accumulate due to a deficiency in propionyl CoA carboxylase. At the culmination of the reaction in which propionyl-CoA carboxylase catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA, succinyl-CoA enters the tricarboxylic acid (TCA) cycle, and any problems in this enzyme results in an accumulation of propionyl-CoA and the formation of pathological metabolites such as 2-methylcitrate, 3-hydroxypropionate, tiglylglycine and propionylglycine. Propionyl-CoA and 2-methylcitrate are thought to be the major endogenous toxins of PA, inhibiting the pyruvate dehydrogenase complex and multiple enzymatic steps in the TCA cycle. In addition to metabolic decompensation, long-term complexes include such pathologies as myopathy, pancreatitis and cardiomyopathy, as well as such potentially long-term signs as acute cardiac dysfunction and acquired long QT syndrome occurring during metabolic crisis (1,2).

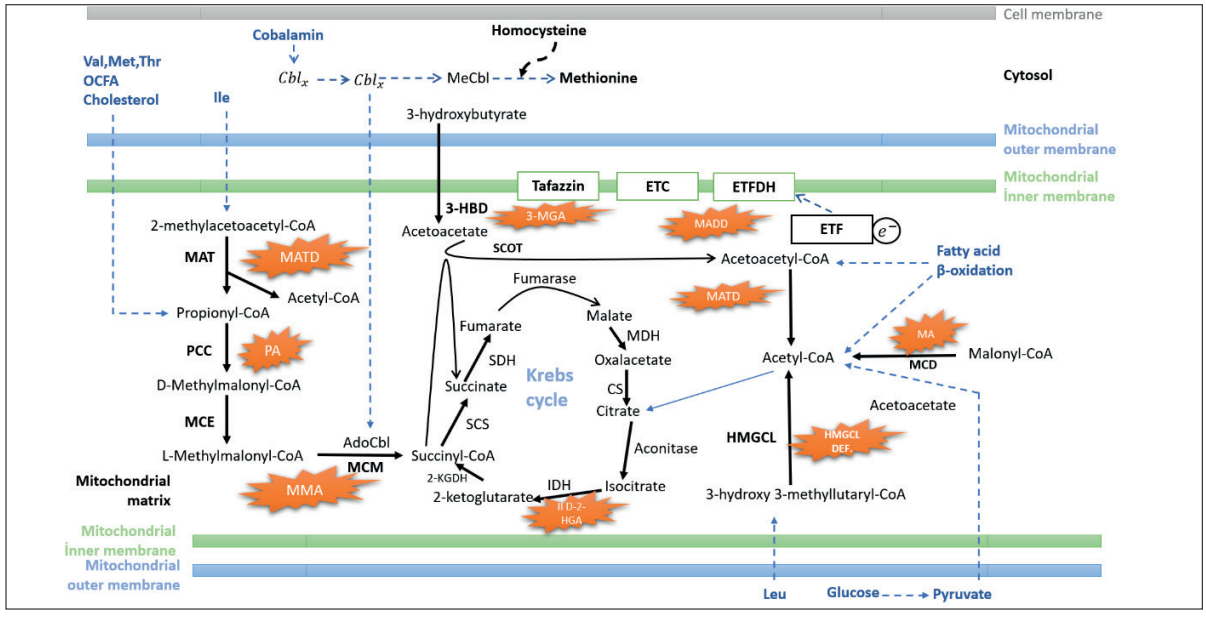

Figure 1: Schematic diagram of selected metabolic pathways in the heart that are affected and implicated in organic acidemias. AdoCbl: adenosylcobalamin; Cbl: cobalamin; 2-KGDH: 2-ketoglutarate dehydrogenase; CS: citrate synthase; ETC: electron transport chain; ETF: electron-transfer flavoprotein; ETFDH, electron-transfer flavoprotein dehydrogenase; II D-2-HGA, type II D-2-hydroxyglutaric aciduria; 3-HBD: 3-hydroxybutyrate dehydrogenase; HMGCL: 3-hydroxy-3-methylglutaryl-CoA lyase; IDH,: isocitrate dehydrogenase; Ile, isoleucine; Leu: Leucine; MA: malonic acidemia; MADD: multiple acyl-CoA dehydrogenase deficiency; MATD: mitochondrial acetoacetyl-CoA thiolase deficiency; MCD: malonyl-CoA decarboxylase; MCE: methylmalonyl-CoA epimerase (methylmalonyl-CoA racemase); MCM: methylmalonyl-CoA mutase; MDH: malate dehydrogenase; MeCbl: methylcobalamin; Met: methionine; 3-MGA: 3-methylglutaconic aciduria; MMA: methylmalonic acidemia; PA: propionic acidemia; PCC: propionyl-CoA carboxylase; SCOT: succinyl-CoA:3-ketoacid CoA transferase; SCS: succinyl-CoA synthetase (succinyl-CoA ligase); SDH: succinate dehydrogenase; Thr: threonine; Val: valine. Cblx refers to different oxidation states of the central cobalt ion in cobalamin. Blue dashed lines indicate the several metabolic steps.

Another potential autosomal recessive metabolism disorder is methylmalonic acidemia (MMA), which is caused by a deficiency in methylmalonyl-CoA mutase activity or the impaired transport and synthesis of its cofactor, cobalamin. MMA's clinical spectrum is broad, with phenotypes ranging from a relatively benign condition to fatal neonatal disease. Isovaleric acidemia (IVA) is an inborn error of leucine catabolism, caused by mutations in the isovaleryl-CoA dehydrogenase (IVD) gene and resulting in an accumulation of derivatives of isovaleryl-CoA, including isovaleryl (C5)-carnitine (3). It is rarer than other organic acidemias and the incidence of cardiac defects is less. Cardiac defects have been reported in several OA, among which cardiomyopathy and arrhythmia are the most common, although heart diseases may also be seen due to carnitine deficiency. The metabolic pathways of OAs are depicted schematically in Figure 1 (4). PA and MMA in particular can develop in the presence of cardiac dysfunction. Isovaleryl CoA rarely can be accompanied by cardiac pathologies (5). The association with congenital heart defect in the early period was remarkable in the patients in the present study who were diagnosed with organic acidemia, and so cardiac dysfunction should be kept in mind in such cases. The present study investigates the congenital heart diseases seen in patients with organic acidemia (6).

MATERIAL and METHODS

Included in the study were 31 patients with organic acidemias, all of whom were screened for congenital heart disease and possible cardiac pathologies by electrocardiogram (ECG) at a paper speed of 50 mm/sec. The echocardiographic parameters and ECG recordings were subsequently analyzed. The study was approved by Ankara Bilkent City Hospital, Clinical Research Ethics Committee No. 2 (E2-22-2950/07.12.2022).

Statistical Analyses

The study data were evaluated with IBM SPSS Statistics for Windows (Version 22.0. Armonk, NY: IBM Corp.). Descriptive statistics were presented as mean±standard deviation (mean±SD) and as minimum-maximum values, while distribution information was presented as numbers (n) and percentages (%).

RESULTS

The median age of the patients was 76±17 months (minimum 7 days; maximum 27 years). All of the patients had been diagnosed with organic acidemia during the neonatal or infantile periods. The clinical, cardiological and molecular features of the sample are presented in Table I. Of the total, 16 (52%) participants were male and 15 (48%) were female; and 14 (45%) had MMA, 11 (36%) had propionic acidemia and six (19%) had isovaleric acidemia. Accompanying congenital heart disease was identified in 63.6 % of the patients, the most common diagnosis of which was propionic acidemia, and among these, the most common heart defects were ASD and mitral valve insufficiency. Cardiac defects were detected in 50 percent of the patients with MMA, with the most encountered congenital heart defects being atrial septal defects, ventricular septal defects, aortic valve insufficiency, mitral valve insufficiency and left ventricular hypertrophy. Heart disease was rare in the patients followed up with isovaleric acidemia. ASD was detected in 25% of patients with isovaleric acidemia (Table II).

DISCUSSION

Then clinical presentation of organic acidemias can be very complicated, including the effects of the metabolites associated with the defect. The mechanism of cardiomyopathy is not clear, although it is thought to be caused by lactic acidosis and metabolic decompensation, while another known complication is arrhythmia.

The limitations of the study include the retrospective collection of data and the small number of patients in the sample. Studies reporting on the presence of cardiac defects in organic acidemia are rare (7). The accumulation of toxic intermediate metabolites due to enzyme deficiency is thought to be the main mechanism behind cardiac involvement in cases of organic acidemia. A recent study reported a reduction in reactive oxygen production, the presence of various respiratory chain deficiencies, and decreased detoxification in the tissues and fibroblast cultures taken from children with OA (8). Low levels of free carnitine as well as biotin deficiency have been suggested as potential risk factors for the development of cardiomyopathy in patients (9). Propionyl CoA has been reported to cause mitochondrial dysfunction and to impair adenosine triphosphate generation through oxidative phosphorylation, resulting in cardiotoxicity. Toxic metabolites such as propionate, propionyl-CoA and 2-methylcitrate cause cardiac pathologies. Previous studies have voiced a need for routine cardiac evaluations of patients with organic acidemias (10). Although cardiomyopathies are most seen in PA, they may also develop in MMA (11). Dilated cardiomyopathy is among the most frequent cardiac complications identified a long side PA, while there have been few studies to date reporting cases with isovaleric acidemia with congenital heart disease (12). To date, no specific marker of cardiomyopathy has been identified. While the major mechanism behind cardiac alterations in PA remains unclear, it is likely to be multifactorial. Metabolic decompensation and lactic acidosis are known to trigger cardiomyopathy, while other factors include myocarditis, carnitine deficiency and rhythm abnormalities. Cardiac diseases are complications of other known organic acidemias, although the causative pathophysiology has yet to be clarified. Identifying the molecular targets in the hearts of OA patients will provide a better understanding of the processes and may steer the development of new treatments in the future.

Table I: Clinical, laboratory and molecular genetic features of patients with organic acidemia

Patient	Diagnosis	Age	Sex	Genetic Analyses	Ecg	Age At Diagnosis	Ecocardiogrphy	Ecocardiographic Evaluation	Follow-Up Time
1	PA	5 Years	M	PCCB c.370C>G (p. Gln124Glu) Homozygous	Normal	2 Years	Secundum ASD	2 Years	3 Years
2	PA	6 Years	M	PCCB c.1369G>A (p. Gly457Ser) Homozygous	Normal	17 Days	Secundum ASD	4 Years	6 Years
3	MMA	5 Years	F	MMUT c.325C>T (p. Q109*) (p. Gln109Ter) Homozygous	Normal	2 Months	Normal	2 Years	5 Years
4	MMA	4.5 Years	M	MUT 0 : p. Leu674Phe c.2020c>T Homozygous	Normal	2 Years	VSD, PFO	2.5 Years	2.5 Years
5	MMA	7 Days	F	MMAB : c.571 C>T p. (Arg191Trp) Homozygous	Normal	3 Days	Hypoplastic left heart	3 Days	7 Days
6	PA	5 Years	M	PCCB c.1373C>T (p. Ala458Val) (p.A458v) Homozygous	Normal	9 Months	Normal	12 Months	4 Years
7	PA	6 Years	M	PCCB : c.1540C>t p.Arg 514*rs749908889 Homozygous	Normal	12 Months	Normal	2 Years	5 Years
8	MMA	9 Years	M	MUT : c.2020C>T p. Leu674Phe rs1164271240 : Homozygous	Normal	18 Months	VSD, ASD, MVI, TVI	5 Years	8 Years
9	MMA	2.5 Years	F	MMUT: c.1106G>A: Compound Heterozygous	Normal	1 Month	Normal	1 Month	2.5 Years
10	MMA	2 Years	F	MMAA: c.1104G>A p. Trp368Ter rs1131692023 Homozygous	Normal	32 Days	Secundum ASD	1 Month	2 Years
11	MMA	20 Years	F	MMADHC: c .211_212dupAG (p. Phe72fs*8) Homozygous	Long -QT	3 Years	Normal	18 Years	17 Years
12	MMA	3.5 Years	M		Normal	4 Months	Normal	2 Years	3 Years
13	PA	10 Years	F		Normal	2.5 Years	Normal	6 Years	10 Years
14	IVA	27 Years	F	IVD: c.158G>A/p. Arg53His and c.535A>G p. Met179Val Compound Heterozygous	Sinus Tachycardia	7 Years			20 Years
15	PA	11 Years	M		Normal	7 Years	Normal	7 Years	4 Years
16	IVA	4 Years	M		Normal	1 Years	Normal	1 Years	4 Years
17	IVA	5.5 Years	F	İVD: c.941C>T (p. Ala314Val) Homozygous	Normal	2 Years	Secundum ASD	4 Years	3 Years
18	IVA	19 Years	M		Normal	3 Years	LVH	17 Years	16 Years
19	MMA	5 Years	F	MUT: c.309_327del19; p. Arg103Ser Homozygous	Normal	4 Years			5 Years
20	IVA	4.5 Years	M		Normal	1 Month			4.5 Years
21	PA	2.5 Years	F	PCCA:c. I629delT (p.Q544Kfs*13) (p.Gln544LysfsTerl3) Homozygous	Normal	2.5 Months	MVI, LVH	6 Months	2.5 Years
22	MMA	3 Years	M	MUT (0): p. Val438serfsTer3(c.1311_1312insA) Homozygous	Normal	1 Years	Normal	1 Years	3 Years
23	MMA	3.5 Years	M			4 Days			3.5 Years
24	MMA	7 Years	M		Normal	2 Months	LVH, AF	4 Years	7 Years
25	MMA	28 Years	M	MMA: c.904A>T: Homozygous	Normal	12 Years	Normal	12 Years	28 Years
26	MMA	6 Years	F		Normal	1 Month	LVH, MVI, AF	3 Years	7 Years
27	IVA	7 Years	F	IVD: p.R398Q (c.1193G>A)/ p.E411K (c.1231G>A) Compound Heterozygous	Normal	2 Years	Normal	2 Years	5 Years
28	PA	4 Months	M	PCCA: c.2171T>A (p. L724H) (p. Leu724His) Homozygous	Normal	2 Months	BAV, AORT STENOZU(AS), AF, MVI, ASD	2 Months	4 Months

Patient	Diagnosis	Age	Sex	Genetic Analyses	Ecg	Age At Diagnosis	Ecocardiogrphy	Ecocardiographic Evaluation	Follow-Up Time
29	PA	13 Months	F	PCCB Homozygous	Sinus Tachycardia	1 Month	PDA, PFO, TVI	1 Years	1 Years
30	PA	3 Months	F	PCCB Homozygous	Normal	3 Months	PFO	3 Months	3 Months
31	PA	7 Months	F	PCCB: c.395_408delGTCTGTCAGGAGCA p. Ser132ThrfsTer24 Homozygous	Normal	1 Month	MVI, PFO, LVH	1 Month	7 Months

ASD: *Atrial septal defect,* ***AF:*** *Aortic failure,* ***BAV:*** *Bicuspid aortic valve,* ***F:*** *Female,* ***HLF:*** *Hypoplastic left heart,* ***IVA:*** *Isovaleric Acidemia,* ***LVH:*** *Left ventricle hypertrophy,* ***M:*** *Male,* ***MMA:*** *Methylmalonic Acidemia,* ***MVI:*** *Mitral valve insufficiency,* ***PA:*** *Propionic acidemia,* ***PDA:*** *Patent ductus arteriosus,* ***PFO:*** *Patent foramen ovale,* ***TVI:*** *Tricuspid valve insufficiency,* ***VSD:*** *Ventricular septal defect*

Table II: Distribution of organic acidemias according to echocardiography findings

Echo Findings	Methyl Malonic Acidemia (%)	Isovaleric Acidemia (%)	Propionic Acidemia (%)
NORMAL	50.00	75.00	36.36
ASD	16.67	25.00	27.27
AF	16.67	0.00	9.09
BAV	8.33	0.00	9.09
HLF	8.33	0.00	0.00
LVH	16.67	0.00	18.18
MVI	16.67	0.00	27.27
PDA	0.00	0.00	9.09
PFO	8.33	0.00	27.27
TVI	8.33	0.00	9.09
VSD	16.67	0.00	0.00
TOTAL	100.00	100.00	100.00

ASD: *Atrial septal defect,* ***AF:*** *Aortic failure,* ***BAV:*** *Bicuspid aortic valve,* ***HLF:*** *Hypoplastic left heart,* ***LVH:*** *Left ventricle hypertrophy,* ***MVI:*** *Mitral valve insufficiency,* ***PDA:*** *Patent ductus arteriosus,* ***PFO:*** *Patent foramen ovale,* ***TVI:*** *Tricuspid valve insufficiency,* ***VSD:*** *Ventricular septal defect*

The association between cardiomyopathies and organic acidemia is well known, as well as such inborn metabolism errors as mitochondrial disorders, fatty acid oxidation defects, carnitine transport defects and glycogen storage diseases (13). There have been few studies to date, however, reporting an association between cardiomyopathy and organic acidemia. In cases of PA, cardiac complications a leading factor in major morbidity and mortality. Besides cardiomyopathy, long QT syndrome is also an important ECG finding in PA (14,15). Cardiomyopathies appear mostly during childhood (mean age 7 years), while long QT syndrome emerges over time in patients with PA (16). Similar to the rates reported in previous studies, only one patient among the 31 cases reported in the present study was identified with long QT syndrome (Case 11).

In the present study, congenital heart defects were most associated with propionic acidemia and were most rarely seen in patients with isovaleric acidemia. In contrast to previous studies in literature, an important finding of the study was the detection of ASD at a rate of 25% in patients diagnosed with IVA, revealing the potential of cardiac defects to occur as a complication of organic acidemias, or congenital heart disease to accompany the pathology Such an association is rare, and so further studies are needed to clarify the relationship between heart defects and organic acidemia. Cardiac defects can cause sudden death or rapid clinical deterioration, and so clinicians should keep an eye out for cardiac pathologies in the presence of an unexpected sudden clinical deterioration or acute respiratory stress with organic acidemia, and cases of organic acidemia should thus undergo echocardiographic examinations. Further studies of organic acidemia are necessary with an increased number of patients in the sample.

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