ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Clinical Characterization and Outcomes of Pediatric Mitochondrial Fatty Acid Oxidation Defects: Real-world Experience of a Single Tertiary Care Center in Türkiye

Pediatrik Mitokondriyal Yağ Asidi Oksidasyon Bozukluklarının Klinik Karakterizasyonu ve Sonuçları: Türkiye'den Bir Gerçek Yaşam Deneyimi

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Abstract

Introduction: This study evaluates the clinical, genetic, and prognostic landscapes of pediatric Mitochondrial Fatty Acid Oxidation Defects (mFAODs) in Türkiye. By characterizing the clinical spectrum and treatment outcomes, we aim to provide essential regional data to guide future newborn screening programs.

Materials and Methods: We retrospectively analyzed the clinical, biochemical, genetic, and imaging data of 45 pediatric patients followed at a tertiary metabolic center between 2015 and 2021. Longitudinal follow-up, therapeutic interventions, and clinical outcomes were evaluated.

Results: The median age of the cohort was 9.8 years (range: 2.3–19.4), and at diagnosis was 4.1 years (range: 8 days–16.7 years). Multiple acyl-CoA dehydrogenase deficiency (MADD) was the most frequent diagnosis (35.6%), followed by medium-chain (MCAD, 22.2%) and very long-chain acyl-CoA dehydrogenase deficiency (VLCAD, 17.8%). Major presenting features included myopathy (28.9%), developmental delay (26.7%), hypoglycemia (24.4%), and seizures (20%). Among the 32 patients with documented echocardiographic findings, cardiomyopathy was identified in two patients (6.3%), and structural cardiac defects were observed in five patients (15.6%). Six patients (13.3%) were lost to follow-up, and six deaths were recorded—four due to sudden cardiac arrest. Acute metabolic crises, triggered by infections, occurred in nine patients (20.0%). Conversely, 26 patients (57.8%) showed clinical improvement in neuromotor, muscular, and metabolic parameters, while four (8.9%) identified through screening remained asymptomatic.

Conclusion: This study delineates the clinical spectrum and outcomes of mFAODs in Türkiye, where these disorders are not yet included in the National Newborn Screening Program.

Keywords
Mitochondrial fatty acid oxidation defects, genetic, prognosis, pediatric

Anahtar kelimeler
Mitokondriyal yağ asidi oksidasyon bozuklukları, genetik, prognoz, pediatrik

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Öz

Giriş: Bu çalışma, Türkiye'deki pediatrik Mitokondriyal Yağ Asidi Oksidasyon Bozukluklarının (mFAOD'ler) klinik, genetik ve prognostik tablosunu değerlendirmektedir. Klinik spektrumu ve tedavi sonuçlarını karakterize ederek, gelecekteki yenidoğan tarama programlarına rehberlik edecek temel bölgesel verileri sağlamayı amaçlıyoruz.

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Gereç ve Yöntem: Üçüncü basamak bir metabolizma merkezinde 2015 ile 2021 yılları arasında takip edilen 45 pediatrik hastanın klinik, biyokimyasal, genetik ve görüntüleme verilerini geriye dönük (retrospektif) olarak analiz ettik. Boylamsal (longitudinal) takip, terapötik müdahaleler ve klinik sonuçlar değerlendirildi.
Bulgular: Hastaların medyan yaşı 9,8 yıl (aralık: 2,3–19,4) ve tanı anındaki yaşı 4,1 yıldı (aralık: 8 gün–16,7 yıl). Çoklu açil-CoA dehidrogenaz eksikliği (MADD) en sık konulan tanıydı (%35,6); bunu orta zincirli (MCAD, %22,2) ve çok uzun zincirli açil-CoA dehidrogenaz eksikliği (VLCAD, %17,8) izledi. Başlıca başvuru özellikleri arasında miyopati (%28,9), gelişimsel gerilik (%26,7), hipoglisemi (%24,4) ve nöbetler (%20) yer alıyordu. Ekokardiyografik bulguları belgelenmiş 32 hastadan ikisinde (%6,3) kardiyomiyopati saptandı ve beş hastada (%15,6) yapısal kalp kusurları gözlendi. Altı hasta (%13,3) takipten çıktı ve altısı ani kardiyak arrest nedeniyle olmak üzere altı ölüm kaydedildi. Enfeksiyonların tetiklediği akut metabolik krizler dokuz hastada (%20,0) meydana geldi. 26 hasta (%57,8) nöromotor, kas ve metabolik parametrelerde klinik iyileşme gösterirken, tarama yoluyla tespit edilen dört hasta (%8,9) asemptomatik kalmaya devam etti.
Sonuç: Bu çalışma, bu bozuklukların henüz Ulusal Yenidoğan Tarama Programına dahil edilmediği Türkiye'deki mFAOD'lerin klinik spektrumunu ve sonuçlarını tanımlamaktadır.

Introduction

Mitochondrial fatty acid oxidation defects (mFAODs) constitute a heterogeneous group of autosomal recessive inherited metabolic disorders characterized by impaired energy production resulting from approximately 20 distinct enzymatic or transport defects affecting fatty acid transport and β-oxidation within the mitochondria (Figure 1). (1)

Since the introduction of newborn screening (NBS) programs, the overall incidence of MFAODs has been estimated at approximately 1 in 9.300 live births (2). Although mFAODs have not yet been included in the national newborn screening program in Türkiye, their estimated incidence is approximately 1 in 3.300 live births, which is higher than the global average (3).

MFAODs manifest with clinical features of energy deficiency, leading to hypoketotic hypoglycemia, metabolic lactic acidosis, myopathy, cardiomyopathy, and hepatic dysfunction. Depending on the specific enzymatic defect and underlying genetic mutation, additional manifestations such as peripheral neuropathy, seizures, neuromotor developmental delay, and ocular abnormalities may also occur (4). The onset of symptoms can vary widely, appearing at any stage of life, from prenatal manifestations such as the HELLP syndrome to variable degrees of severity during infancy, childhood, or adulthood. While certain cases present with severe congenital anomalies or may result in sudden infant death syndrome (SIDS), some others may remain asymptomatic until later in life. During catabolic stress — prolonged fasting, intense exercise, infections—organs with high energy demand, including skeletal muscle, the heart, and the liver, are primarily affected (5).

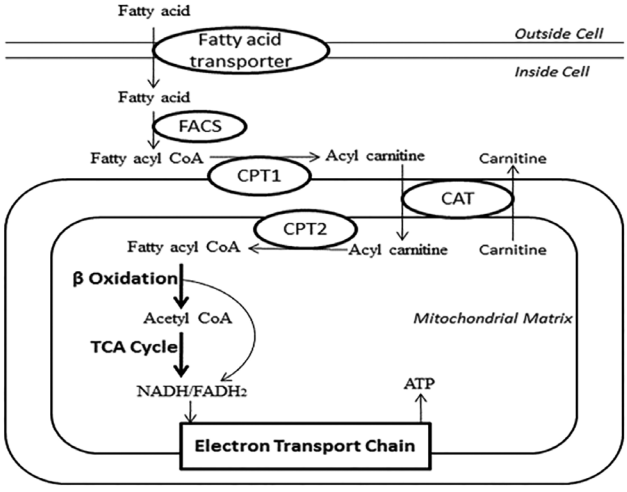

Figure 1. Fatty Acid Oxidation in the Mitochondria (1)
VLCFA: Very long-chain fatty acids, LCFA: Long-chain fatty acids, MCFA: Medium-chain fatty acids, SCFA: Short-chain fatty acids, CPT-I, II: Carnitine palmitoyltransferase I

The gold standard for MFAODs diagnosis is established through molecular characterization or enzyme activity assays. However, in the absence of molecular diagnosis, the combination of a characteristic acylcarnitine profile, and distinctive urinary organic acid excretion serves as a sufficient diagnostic criterion in patients with a typical clinical presentation (6,7). Riboflavin metabolism disorders, certain organic acidemias, and nutritional deficiencies are distinguished from MFAOD through differences in clinical presentation, recurrent laboratory findings, and specific treatment response (8).

MFAOD management focuses on individualized nutritional therapy, including Long-Chain Triglycerides (LCT) restriction and carnitine/cofactor supplementation, while avoiding fasting and exertion. Dietary focus shifts from Medium-Chain Triglycerides (MCT) supplementation in long-chain defects to MCT contraindication in medium-chain disorders and MADD. Treatment efficacy—defined by improved neuromotor, cardiac, and metabolic outcomes—varies by subtype and genotype. Ultimately, expanded

newborn screening is the most critical factor for improving prognosis and survival (9,10).

We aim to evaluate the clinical, laboratory, and genetic features, as well as the follow-up and prognosis of 45 Turkish patients with MFAODs, to provide a comprehensive perspective on the disease course.

Materials and Methods

The study included patients (n=45) aged 0–18 years diagnosed with mFAODs who were followed at the pediatric metabolic diseases outpatient clinic between January 1, 2015, and August 1, 2021.

The diagnosis of mFAODs was primarily established through a combination of pathognomonic biochemical signatures (distinctive acylcarnitine patterns on tandem mass spectrometry and characteristic urinary organic acid profiles) and consistent clinical phenotypes (10-12). Genetic testing was utilized as a confirmatory tool to support the biochemical diagnosis. In cases where genetic results were unavailable or inconclusive, patients were definitively classified based on their clear and recurrent biochemical markers and clinical presentation, as reviewed by independent metabolic specialists. Patients with secondary nutritional deficiencies, a history of drug or contaminated product ingestion, liver or kidney dysfunction, and other metabolic conditions, such as B2 metabolism disorders and mitochondrial diseases, were ruled out from the study.

Acylcarnitine profiles from dried blood spots (DBS) were analyzed via tandem mass spectrometry (Thermo Fisher TSQ Quantum Access Max) following standard extraction and derivatization protocols. Urinary organic acids were identified and quantified using GC/MS (Thermo Fisher Trace GC Ultra / ISQ) after organic solvent extraction and silylation. In both analyses, target analytes were quantified by calculating ion intensity or peak area ratios relative to their corresponding isotopically labeled internal standards.

The genetic diagnosis of the patients was initially performed using an MFAODs gene panel; whole-exome sequencing (WES) was subsequently conducted in patients whose findings could not be explained by the primary diagnosis. The clinical significance of the identified genetic variants was interpreted according to the standards and guidelines established by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP).

Clinical and laboratory data were recorded for all participants, with neuroimaging and cardiac findings documented only for accessible cases. Clinical findings, including hypotonia and developmental delay, were assessed through comprehensive physical and neurological examinations performed by pediatric metabolism specialists. Acute metabolic crisis was defined as sudden clinical deterioration characterized by metabolic acidosis, altered consciousness, or hypoglycemia. Hypoglycemia was defined as a blood glucose level <60 mg/dL across all age groups, in accordance with the Pediatric Endocrine Society (PES) guidelines for patients with fatty acid oxidation defects (13). Hepatic involvement was identified by the presence of hepatomegaly and/or elevated transaminases (ALT/AST >40 U/L). Cardiomyopathy and comprehensive anatomical cardiac evaluations were established based on standardized echocardiographic findings. Patients were categorized into eight groups according to their reasons for initial medical contact and predominant clinical presentation at the time of diagnosis. Since several patients exhibited more than one clinical feature, they were evaluated under multiple categories:

Myopathy – Elevated Muscle Enzymes: This group included patients with normal neurological development who gradually developed muscle pain, gait difficulties, or inability to squat. Diagnosis in these cases was established based on elevated serum muscle enzyme levels detected in laboratory analyses. Developmental Delay – Hypotonia: This category comprised patients exhibiting developmental delay or hypotonia, such as inability to achieve head control or delayed acquisition of walking skills. Hypoglycemia – Feeding Difficulties: Patients in this group were diagnosed with hypoglycemia either upon presentation to the pediatric emergency department with feeding difficulties and irritability, or following hospitalization for afebrile seizures where hypoglycemia was subsequently detected. Cardiac Involvement: This group included patients diagnosed during the evaluation of sudden cardiac arrest or cardiomyopathy. Seizures: Patients who were diagnosed with a fatty acid oxidation disorder following assessment for drug-resistant epilepsy or after presenting with afebrile or hypoglycemic seizures. Metabolic Acidosis: This group comprised patients presenting with drowsiness, irritability, or respiratory distress who were found to have metabolic acidosis at the time of admission. Hepatic Involvement: Patients diagnosed during evaluation for liver failure or those presenting with abdominal pain and found to have hepatomegaly on clinical examination or imaging. Family Screening: Asymptomatic individuals who were diagnosed as part of family screening due to a positive family history.

Laboratory findings at the time of diagnosis were classified into five categories: Presence of hypoglycemia, presence of dicarboxylic aciduria, elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, elevated creatine kinase (CK) levels, and abnormal carnitine/acylcarnitine profile.

While the study cohort initially comprised 45 patients, detailed clinical follow-up and treatment response analyses were focused on 41 patients (91.1%) for whom comprehensive longitudinal data were available. The remaining four patients, followed without specific intervention due to their clinical status or early diagnosis, were excluded from certain subgroup analyses to maintain the consistency of the clinical outcome data. The criteria for treatment efficacy were defined as follows: progression in neuromotor developmental milestones in patients with delayed neurological development, improvement of muscle weakness in those who presented with this symptom, and the absence of recurrent episodes in patients who initially presented with hypoglycemia or hypoglycemic seizures.

Statistical Analysis

Data were analyzed using NCSS 2007 Statistical Software. Descriptive statistics are presented as mean, standard deviation, frequency, and percentage.

Ethics

This study was conducted in accordance with the ethical guidelines outlined in the World Medical Association Declaration of Helsinki (2000) and Regulations in drug research Ministry of Health, Goverment of Türkiye, January 29,1993. Ethical approval was obtained from the local ethics committee (approval number: 2021/367) on 2021-14-08. Informed consent was obtained from the patient and/or their family for the sharing of clinical data.

Results

The mean current age of the patients was 10.4 ± 5.2 years (median: 9.8 years; range: 2.3–19.4 years), and the mean age at diagnosis was 5.3 ± 5.4 years (median: 4.1 years; range: 8 days–16.7 years). Of the total 45 patients**,** parental history was available for 42, of whom 57.1% (n = 24) had consanguineous parents. Similarly, data regarding sibling deaths could be obtained for 41 patients, of whom 14.6% (n = 6) reported sibling deaths. The mean and median follow-up durations of the patients were 31.87 ± 22.03 months and 30 months (range: 1–78), respectively. With respect to the subtypes of fatty acid oxidation disorders, the most frequent diagnosis was multiple acyl-CoA dehydrogenase deficiency (MADD), accounting for 35.56% (n = 16) of cases. This was followed by medium-chain acyl-CoA dehydrogenase deficiency (MCAD) in 22.22% (n = 10) and very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) in 17.78% (n = 8), respectively (Table 1). The molecular characteristics of patients who underwent genetic analysis (n=17) are presented in Table 2.

Comorbidities were present in 22% (n = 9) of 41 patients. Notably, atypical autism spectrum disorder was the most common comorbidity, observed in two patients (4.8%). The remaining conditions, including Friedreich's ataxia and hypoxic-ischemic encephalopathy, situs inversus totalis, Duchenne muscular dystrophy, trisomy 18, hypothyroidism, hyperexplexia, and ureteropelvic junction stenosis were each identified in only a single patient (2.4%).

The initial biochemical and clinical findings at the time of diagnosis were further categorized into three distinct clinical states to reflect the dynamic range of the metabolic

Table 1. Distribution of diagnostic subtypes and cohort characteristics in pediatric patients with MFAODs

Subtypes of fatty acid oxidation disorders	Number of Patients (n)	Percentage (%)
Multiple acyl-CoA dehydrogenase deficiency (MADD)	16	35.56
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	10	22.22
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	8	17.78
LCHAD / Mitochondrial trifunctional protein deficiency	3	6.67
Carnitine palmitoyltransferase type 2 (CPT-2) deficiency	2	4.44
Short-chain acyl-CoA dehydrogenase deficiency (SCAD)	3	6.67
Primary carnitine deficiency	2	4.44
Carnitine palmitoyltransferase type 1 (CPT-1) deficiency	1	2.22
Total	**45**	**100.0**

CPT-1 deficiency: Carnitine palmitoyltransferase type 1 deficiency, CPT-2 deficiency: Carnitine palmitoyltransferase type 2 deficiency, LCHAD: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, MADD: Multiple acyl-CoA dehydrogenase deficiency, MCAD: Medium-chain acyl-CoA dehydrogenase deficiency, SCAD: Short-chain acyl-CoA dehydrogenase deficiency, VLCAD: Long-chain acyl-CoA dehydrogenase deficiency

parameters: i)acute metabolic decompensation (n = 22, 48.9%), ii)organ-specific manifestation (n = 17, 38.8%), and iii)family screening (n = 6, 13.3%). Figure 2 summarizes the initial clinical presentations of the patients. Myopathy was the most frequent reason for hospitalization, reported in 28.9% (n = 13) of patients, followed by developmental delay (26.7%; n = 12), hypoglycemia (24.4%; n = 11), and seizures (20%; n = 9) (Table 3).

Bilateral optic atrophy was identified in a patient with medium-chain acyl-CoA dehydrogenase deficiency (MCADD) carrying a homozygous *ACADM* c.811G>A (p.Gly271Arg) variant, whereas retinitis pigmentosa was observed in

Table 2. Molecular characteristics of the subgroup of patients who underwent genetic testing (n=17)

Type of fatty acid oxidation disorder	Mutant Gene Transcript ID	Nucleotide Change	Amino Acid Change	Zygosity	Germline classification
MADD	*ETFDH* NM_004453.4	c.1130T>C	p.Leu377Pro	homozygous	pathogenic
MADD	*ETFDH* NM_004453.4	c.1130T>C	p.Leu377Pro	homozygous	pathogenic
MADD	*FLAD1* NM_025207.5	c.745C>T	p.Arg249Ter	homozygous	pathogenic
MADD	*ETFB* NM_001985.3	c.614_616del	p.Lys205del	homozygous	variant of uncertain significance (VUS)
MADD	*ETFDH* NM_004453.4.2	c.814G>A	p.Gly272Arg	homozygous	pathogenic
VLCAD	*ACADVL* NM_000018.4	c.1269+1G>A	p.(?)splice_donor_+1	homozygous	likely pathogenic
VLCAD	*ACADVL* NM_000018.4	c.1269+1G>A	p.(?)splice_donor_+1	homozygous	likely pathogenic
VLCAD	*ACADVL* NM_000018.4	c.602dup	p.Tyr201*	homozygous	likely pathogenic
LCHAD	*HADHA* NM_000182.5	c.1528G>C	p.Glu510Gln	homozygous	pathogenic
MCAD	*ACADM* NM_001127328.3	c.811G>A	p.Gly271Arg	homozygous	pathogenic
MCAD	*ACADM* NM_001127328.3	c.811G>A	p.Gly271Arg	homozygous	pathogenic
MCAD	*ACADM* NM_000016.6/ NM_001127328.3	c.985A>G c.811G>A	p.Lys329Glu p.Gly271Arg	compound heterozygous	pathogenic/ pathogenic
SCAD	*ACADS* NM_000017.4	c.988C>T	p.ARG330Cys +	homozygous	pathogenic
SCAD	*ACADS* NM_000017.3	c.625G>A	p.Gly209Ser	homozygous	likely pathogenic
PCD	*SLC22A5* NM_003060.4	c.254_264dup	p.I89GfsX45	homozygous	pathogenic
PCD	*SLC22A5* NM_003060.4	c.1088T>C	p.Leu363Pro	homozygous	likely pathogenic
CPT-2	*CPT2* NM_000098.3	c.338C>T	p.Ser113Leu	homozygous	pathogenic

MADD: Multiple acyl-CoA dehydrogenase deficiency, MCAD: Medium-chain acyl-CoA dehydrogenase deficiency, VLCAD: Long-chain acyl-CoA dehydrogenase deficiency, SCAD: Short-chain acyl-CoA dehydrogenase deficiency, CPT-2 deficiency: Carnitine palmitoyltransferase type 2 deficiency, LCHAD: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, PCD: Primary carnitine deficiency

another patient with carnitine palmitoyltransferase II (CPT-II) deficiency harboring the *CPT2* c.338C>T (p.Ser113Leu) mutation. Whole-exome sequencing of the MCADD patient additionally revealed a heterozygous *OTX2* c.97+3_97+6del variant, which was considered to be responsible for the optic nerve atrophy. Therefore, this ocular finding was interpreted as a comorbidity associated with the pathogenic OTX2 variant rather than a feature of the MCADD clinical spectrum.

Biochemical analysis showed hypoglycemia in 23.3% (n = 10), elevated serum transaminases in 53.7% (n = 22), and increased creatine kinase levels in 56.1% (n = 23) of patients. Metabolic screening revealed dicarboxylic aciduria in 82.9% (n = 34) and abnormal carnitine–acylcarnitine profiles in 93.0% (n = 40) of cases (Figure 3).

Echocardiography was performed in 32 patients, revealing normal findings in 68.7% (n = 22). Hypertrophic and dilated cardiomyopathy was observed in one patient with primary carnitine deficiency carrying the *SLC22A5* c.254_264dup (p.I89GfsX45) variant, whereas another patient with a homozygous *SLC22A5* c.1247G>A (p.Gly416Glu) variant exhibited dilated cardiomyopathy. Additionally, isolated left ventricular dysfunction was detected in one patient with very long-chain acyl-CoA dehydrogenase deficiency (VLCAD) (Table 4). Structural closure defects—including atrial septal defect (ASD) secundum, perimembranous ventricular septal defect (VSD), patent ductus arteriosus (PDA), and patent foramen ovale (PFO)—were identified in 15.6% (n = 5) of cases (Table 4).

Table 3. Categorization of patients based on predominant presenting symptoms and reasons for clinical referral

	n	%
Myopathy / Elevation of muscle enzymes	13	28.9
Developmental delay / Hypotonicity	12	26.7
Hypoglycemia symptoms	11	24.4
Seizure	9	20.0
Asymptomatic / Family history	6	13.3
Cardiac involvement	5	11.1
Metabolic acidosis	4	8.9
Liver involvement	2	4.4

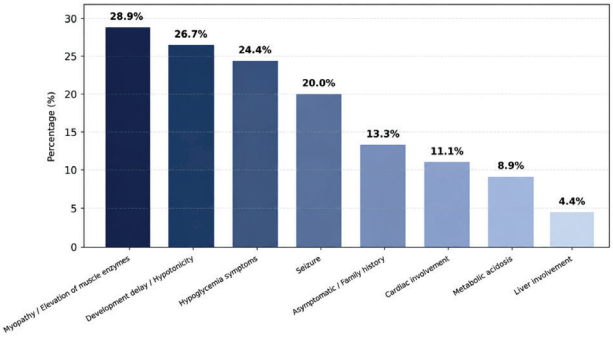

Figure 2. Distribution of clinical presentation patterns and reasons for initial medical contact at the time of diagnosis

Cranial magnetic resonance imaging (MRI) was performed in nine patients who exhibited neurological manifestations, with abnormalities detected in seven (77.8%). Among these, five patients (1 SCAD, 1 LCHAD, 2 MCAD, and 1 MADD deficiency) exhibited symmetrical T2-weighted hyperintensities in the parieto-occipital periventricular white matter, consistent with hypoglycemic sequelae. Additionally, one patient with MCADD showed a mild signal increase in the globus pallidus, and another with CPT-II deficiency presented with corpus callosum thinning and diffuse bilateral white matter loss (Table 4).

Regarding the clinical outcomes of the 45 patients, six (13.3% — diagnosed with SCAD, CPT-I, PCD, MADD, LCHAD, and VLCAD) died—four from sudden cardiac arrest and two from unknown causes. Acute metabolic crises, primarily triggered by intercurrent infections, were documented in nine patients (20.0%). In contrast, 26 patients (57.8%) demonstrated clinical improvement, characterized by advancements in neuromotor milestones, increased muscle strength, and enhanced metabolic stability with better seizure and glycemic control. Finally, four patients (8.9%) identified through screening remained asymptomatic and were followed without specific intervention (Table 5).

Discussion

This study provides a comprehensive analysis of the diagnostic, clinical, laboratory, and genetic landscapes, alongside the clinical trajectories, of 45 patients with

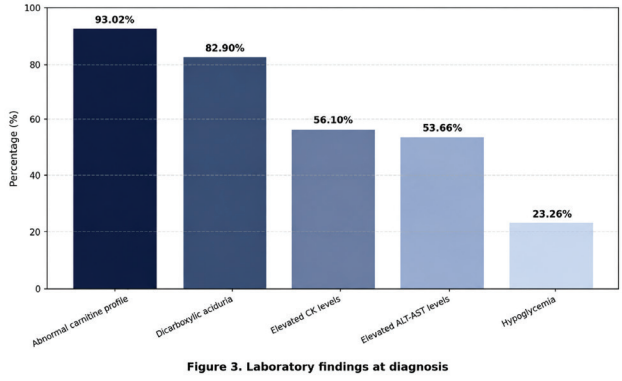

Figure 3. Laboratory findings at diagnosis

mitochondrial fatty acid oxidation defects (mFAODs) followed at a tertiary reference center.

The incidence of fatty acid oxidation disorders (FAODs) exhibits significant geographical and ethnic variability, largely dictated by regional genetic backgrounds and the implementation of Newborn Screening (NBS) programs. Globally, the overall incidence is estimated at approximately 1 in 9,300 live births following the widespread adoption of NBS (2). Although FAODs have yet to be integrated into the National NBS Program in Türkiye, primary data from an extended newborn screening pilot study (n=78,850) conducted in Istanbul reported an incidence as high as 1 in 3,285, likely influenced by high consanguinity rates (14). In our cohort, Multiple Acyl-CoA Dehydrogenase Deficiency (MADD) emerged as the predominant subtype, accounting for 35.56% of cases, followed by MCAD (22.22%) and VLCAD (17.78%) deficiencies. This distribution pattern aligns with data from China, where MADD is reported as the most frequent FAOD subtype (53.7%) (9). Conversely, European studies consistently identify MCAD deficiency as the most prevalent subtype (15,16). These disparate findings underscore the influence of founder effects and population-specific genetic architectures, while also reflecting potential selection biases in regions where universal screening is absent. In our clinical cohort, the higher detection of MADD may be attributed to its more pronounced clinical manifestations, whereas asymptomatic or 'non-disease' MCAD phenotypes often remain clinically silent without NBS detection (17,18).

The clinical spectrum and prognosis of fatty acid oxidation disorders (FAODs) exhibit significant phenotypic heterogeneity, ranging from paucisymptomatic presentations triggered only by fasting or metabolic stress to fulminant, life-threatening metabolic crises, depending largely on the residual enzyme activity and the patient's age (12). The age at

Table 4. Central nervous system and cardiac imaging abnormalities in the study cohort

	Findings	n	%
ECHO	**Normal**	**22**	**68.75**
	Presence of pathological findings	**10**	**31.25**
	Closure defects (PDA, PFO, VSD, ASD secundum)	5	15.63
	Hypertrophic and/or dilated CMP	2	6.25
	Pulmonary hypertension	2	6.25
	Mitral valve insufficiency	2	6.25
	Isolated decrease in left ventricular functions	1	3.13
	Pulmonary stenosis	1	3.13
	Dextrocardia	1	3.13
MRI	**Normal**	**2**	**22.22**
	Abnormal MRI findings	**7**	**77.78**
	Hypoglycemia sequelae (1 SCAD, 1 LCHAD, 2 MCAD, 1 MADD)	5	55.55
	Signal increase in globus pallidus (MCAD)	1	14.29
	Corpus callosum thinness and white matter deficiency at both cerebral hemispheres (CPT-II)	1	14.29

ECHO: Echocardiography, MRI: Magnetic resonance imaging, CMP: Cardiomyopathy, PDA: Patent ductus arteriosus, PFO: Patent foramen ovale, VSD: Ventricular septal defect, ASD: Atrial septal defect, CPT-2 deficiency: Carnitine palmitoyltransferase type 2 deficiency, LCHAD: Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, MADD: Multiple acyl-CoA dehydrogenase deficiency, MCAD: Medium-chain acyl-CoA dehydrogenase deficiency, SCAD: Short-chain acyl-CoA dehydrogenase deficiency

Table 5. Summary of clinical outcomes and prognostic characteristics (n=45)

Clinical Outcome	n (%)	Key Characteristics / Triggers
Mortality	6 (13.3)	Sudden cardiac arrest (n=4), Unknown (n=2)
Acute metabolic crises	9 (20.0)	Primarily triggered by intercurrent infections
Clinical improvement	26 (57.8)	Patients demonstrating clinical improvement during follow-up
Asymptomatic	4 (8.9)	Identified via screening; followed without specific intervention
Total	**45 (100)**	

diagnosis varies in parallel with the specific disorder subtype and the severity of clinical manifestations. Current literature underscores that the primary determinant of diagnostic age is the implementation and scope of Newborn Screening (NBS) programs. While approximately 80% of cases globally are diagnosed within the first two years of life, structured screening protocols enable detection within the initial postnatal days (19). In Türkiye, the absence of mFAODs in NBS Program remains a significant diagnostic challenge. While expanded screening is available in select centers, it often depends on individual institutional protocols and parental consent, leading to a late-symptomatic diagnosis rather than early-neonatal detection. Consequently, the mean age at diagnosis in our cohort (5.3 ± 5.4 years) is notably higher than in regions with universal NBS, aligning instead with reports from other countries where diagnosis relies primarily on clinical presentation.

In our cohort, additional comorbidities or clinical findings were documented in 22% (n=9) of the screened patients, the majority of which were attributed to other underlying genetic conditions. Notably, atypical autism spectrum disorder was the most recurring finding, identified in two patients (4.4%). This potential association between atypical autism and fatty acid oxidation disorders (FAODs) has recently gained scholarly attention. For instance, a case report previously described a possible link between LCAD deficiency and autism spectrum disorder (ASD), and a study by Ersoy et al. (20) identified MCAD deficiency in one of 239 individuals with ASD (21). While current evidence remains insufficient to establish a definitive causal relationship, the identification of two cases in our relatively small group suggests that metabolic dysregulation may play a role in certain neurodevelopmental phenotypes. These observations emphasize the necessity for more extensive, large-scale metabolic screenings in patients presenting with ASD to clarify potential pathophysiological links and to determine whether these findings are coincidental or representative of a shared metabolic pathway.

Myopathy (28.9%; n = 13) and hypoglycemia (24.4%; n = 11) emerged as the most predominant initial clinical manifestations in the present cohort, presenting at comparable frequencies. These observations align with literature identifying muscle involvement as a hallmark feature in approximately half of all cases (22). The prevalence of hypoglycemia in our cohort (24.4%) aligns with the established literature, which characterizes hypoketotic hypoglycemia as a classic hallmark of mFAODs during periods of increased metabolic demand, such as fasting or infection (23). Consistent with the findings of Saudubray et al. (12), who reported hypoglycemia as a primary presenting feature in various FAOD subtypes, our results underscore the critical inability of these patients to maintain energy homeostasis when fatty acid oxidation is required to spare glucose. While some European cohorts reported higher rates of hypoglycemia in MCAD deficiency, the relatively balanced distribution in our study reflects the broad clinical spectrum of mFAODs in non-screened populations where clinical crises often serve as the primary diagnostic trigger.

Comprehensive cardiac evaluation identified pathological findings in 31.25% (10/32) of patients at the time of diagnosis. Notably, the prevalence of cardiomyopathy (6.25%; 2/32) was significantly lower than the 20-30% observed in international cohorts (24). This discrepancy likely reflects the temporal evolution of mFAOD-related cardiac injury; the relatively low rate suggests that at the point of initial diagnosis, many patients had not yet reached the threshold of irreversible hypertrophic remodeling. Conversely, the high prevalence of structural cardiac anomalies may be attributed to the predominance of MADD cases, which are frequently associated with congenital malformations due to impaired organogenesis during energy-deficient states.

Determining the mortality rate of mFAODs is complex due to their association with sudden infant death and undiagnosed cases (25). While Baruteau et al. (15) reported an overall mortality rate of 48% in their series, the mortality rate in our cohort was 13.3% (n=6). Among the six deaths, four resulted from sudden cardiac arrest, likely triggered by the pro-arrhythmic effects of accumulated long-chain fatty acids rather than chronic energy failure (16,17,24). The impact of diagnostic timing is further illustrated by Spiekerkoetter et al. (26) who found a mortality rate of 12.5% among patients identified through NBS, compared to 27.6% in those diagnosed clinically. While the lower mortality in our clinically diagnosed cohort may reflect the presence of milder phenotypes or effective symptomatic management, the global discrepancy between screening-detected and clinically-presenting cases is significant (27,28).

The most critical diagnostic biomarkers for mFAODs remain carnitine and acylcarnitine profiles. However, their diagnostic yield is significantly influenced by the patient's metabolic state; levels may normalize during asymptomatic intercritical periods, potentially leading to false-negative results. While Wang et al. (29) reported 100% sensitivity for tandem mass spectrometry (MS/MS) in their cohort, abnormalities were detected in 93.02% of our evaluated patients. This slight discrepancy likely reflects sampling

during stable periods when metabolites return to baseline, a phenomenon well-documented in milder phenotypes or certain subtypes like MCAD deficiency. Therefore, a single normal profile during clinical stability cannot exclude an mFAOD diagnosis, and repeated testing during acute crises remains vital for clinical accuracy while awaiting definitive genetic confirmation.

The literature lacks large-scale studies evaluating cranial imaging in mFAODs, making our findings particularly noteworthy. In our cohort, MRI abnormalities were not uniform but reflected specific clinical trajectories. For instance, the diffuse T2-hyperintensities observed in the periventricular white matter and basal ganglia of our SCAD patient (presenting with refractory seizures) align with cases described by Chiplunkar et al. (30). Furthermore, while findings resembling hypoxic-ischemic encephalopathy (HIE) sequelae have been reported in severe cases (31), they remain non-specific. Distinctly, our CPT-II patient exhibited corpus callosum thinning and bilateral white matter loss at 5 months of age. The absence of the 'boomerang sign'—typically associated with acute hypoglycemia—suggests these structural anomalies represent a primary manifestation of CPT-II deficiency rather than secondary metabolic injury, consistent with the known association between early-onset CPT-II and brain malformations (32).

Our genetic analysis further highlights significant regional differences; the c.811G>A (p.Gly271Arg) variant was the predominant mutation in our MCAD cohort, whereas the common European c.985A>G (p.Lys329Glu) variant was notably rare. This underlines the unique mutational landscape in Türkiye compared to Western populations. In accordance with previous research evaluating treatment outcomes, our cohort also demonstrated a high rate of therapeutic success following appropriate intervention (33,34). However, a significant difference in clinical outcomes remains between patients diagnosed symptomatically and those identified through screening. These findings collectively emphasize that early identification through NBS is the most critical factor for optimizing treatment response and preventing irreversible sequelae (35,36).

Study Limitations

The primary limitations of this study are its retrospective, single-center design and the relatively small sample size inherent to these rare disorders. Additionally, a minor portion of the cohort was lost to follow-up, which may limit the comprehensiveness of the long-term prognostic outcomes.

Conclusion

Fatty acid oxidation disorders represent a relatively prevalent subgroup of rare inherited metabolic diseases, generally characterized by favorable outcomes when identified early and managed with appropriate therapeutic interventions. In the absence of a universal National Newborn Screening Program in Türkiye, the present study provides a critical clinical perspective for evaluating the clinical course and long-term management of symptomatic patients under treatment. Although a definitive genotype-phenotype correlation was not identified in our cohort, the occurrence of autistic features as a notable comorbidity in MCAD deficiency and the novel identification of corpus callosum thinning in CPT II deficiency significantly expand the known clinical and structural spectrum of these disorders.

Ethics

Ethical Approval: This study was conducted in accordance with the ethical guidelines outlined in the World Medical Association Declaration of Helsinki (2000) and Regulations in drug research Ministry of Health, Goverment of Türkiye, January 29,1993. Ethical approval was obtained from the local ethics committee (approval number: 2021/367) on 2021-14-08. Informed consent was obtained from the patient and/or their family for the sharing of clinical data.

Data availability statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Footnotes

Conflict of Interest: No conflict of interest was declared by the authors.

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