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ORIGINAL ARTICLE

Pediatric Mitochondrial Disease: Clinical and Genetic Insights From a Single-Center Cohort

Halil Tuna Akar*[1] Sabire Gökalp*[1] Abdullah Sezer[2] Asburçe Olgaç[1]

1 Ankara Etlik City Hospital, Department of Pediatrics, Division of Pediatric Metabolism, Ankara, Türkiye
2 Ankara Etlik City Hospital, Department of Medical Genetics, Ankara, Türkiye
* These authors contributed equally to this work.

Abstract

Background: Mitochondrial diseases are a heterogeneous group of inherited metabolic disorders characterized by dysfunction in oxidative phosphorylation, leading to impaired cellular energy metabolism. These disorders present with a broad clinical spectrum, often involving the nervous system, muscles, heart, and liver, making diagnosis complex.

Methods: This retrospective study evaluates the clinical, laboratory, and genetic characteristics of 19 pediatric patients diagnosed with mitochondrial diseases at the pediatric metabolism clinic.

Results: The most common clinical findings were hypotonia (52.6%), lactic acidosis (26.3%), and seizures (21.1%), followed by neuromotor delay (10.5%) and bilateral optic atrophy (10.5%). These findings reflect the multisystemic involvement and neurological predominance typical of mitochondrial disorders. Biochemical analyses frequently revealed abnormal metabolic profiles supportive of mitochondrial dysfunction.

Conclusions: Genetic analyses identified various mitochondrial DNA and nuclear DNA mutations, underscoring the importance of comprehensive molecular diagnostics. Molecular testing improved diagnostic accuracy and facilitated more tailored patient management, including early initiation of supportive treatments and genetic counselling.

Keywords: inborn errors of metabolism, mitochondrial disorders, NGS

Corresponding Author:
Halil Tuna Akar, MD, Ankara Etlik City Hospital
Department of Pediatrics, Division of Pediatric Metabolism, Yenimahalle, Ankara, TR06170, Türkiye
E-mail: akarhaliltuna@gmail.com

INTRODUCTION

Mitochondrial diseases are a heterogeneous group of inherited metabolic disorders characterized by dysfunctions in mitochondria, which are fundamental components of human physiology (1). Mitochondria play a central role in cellular energy production through the oxidative phosphorylation (OXPHOS) process and are critical for maintaining the homeostasis of energy-demanding tissues (2). During OXPHOS, energy is generated along the electron transport chain and converted into adenosine triphosphate (ATP), forming the cornerstone of cellular energy metabolism (3). However, the central role of mitochondria in energy production makes their functional impairments a key contributor to a wide spectrum of clinical manifestations.

The pathophysiology of mitochondrial diseases is rooted in genetic mutations affecting mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) (4). These mutations disrupt the energy production chain, leading to cellular dysfunction, damage, and clinical symptoms in energy-dependent tissues (5).

The clinical features of mitochondrial diseases are typically heterogeneous, complicating the diagnostic process. The most commonly affected systems are the central nervous system, heart, muscles, liver, and kidneys, which all have high energy demands (6). Clinical presentations range from life-threatening multisystem involvement in infancy to milder and isolated organ dysfunctions in adulthood. Common symptoms include hypotonia, epilepsy, cardiomyopathy, neuronal degeneration, and developmental delay (7). However, the nonspecific nature of initial symptoms often delays the diagnostic process.

The diagnostic process for mitochondrial diseases primarily relies on clinical findings, which are supplemented by specific biochemical and genetic analyses. Biochemical laboratory tests, such as elevated serum lactate levels, abnormal urinary organic acid profiles, and muscle biopsies showing characteristic mitochondrial changes under electron microscopy, are frequently used as initial diagnostic tools (8, 9). Assessments of OXPHOS enzyme activities in affected tissues provide additional diagnostic insights, particularly in cases with ambiguous clinical presentations. In recent years, the increasing availability of advanced genetic testing has significantly improved diagnostic precision (10). Next-generation sequencing (NGS) technologies have revolutionized the field by enabling rapid and accurate identification of pathogenic mutations in mitochondrial DNA (mtDNA) and nuclear DNA (nDNA), thus facilitating early diagnosis and tailored treatment approaches. Importantly, while mtDNA mutations are maternally inherited, nDNA mutations follow Mendelian inheritance patterns. This distinction has important implications for genetic counseling and risk assessment. Furthermore, because mtDNA heteroplasmy levels can vary significantly between tissues, molecular analyses may need to be performed on affected tissues (e.g., muscle or liver) in addition to peripheral blood in selected cases. (11-13). These advancements have significantly enhanced our understanding of the genetic heterogeneity and underlying molecular mechanisms of mitochondrial diseases.

In this study, we retrospectively evaluated the clinical, laboratory, and genetic data of patients diagnosed with mitochondrial diseases at the pediatric metabolism clinic. The aim of this study is to shed light on the clinical course of these diseases in our country, identify challenges in the diagnostic and therapeutic process, and provide new insights by comparing our findings with existing literature. Despite growing global awareness of mitochondrial diseases, there remains a lack of region-specific data, particularly in pediatric populations from our country. Our study provides one of the few institutional experiences in this area, offering insight into the genetic spectrum and clinical characteristics within a localized setting. Furthermore, the identification of rare or potentially novel mutations, such as those in NDUFAF5 and PDP1, highlights the evolving landscape of mitochondrial disease diagnostics and the necessity for inclusive molecular panels in routine practice.

MATERIALS AND METHODS

This study was approved by Ankara Etlik City Hospital Ethic Committee (Approval Date: 16.10.2024 Approval Number: AEŞH-BADEK-2024-934)

This retrospective study was conducted at the pediatric metabolism clinic and included 19 patients with a

confirmed molecular genetic diagnosis of mitochondrial disease. Only patients with a molecularly confirmed diagnosis were eligible for inclusion. The demographic data, clinical presentations, and laboratory findings of the patients were systematically analyzed. Ethical approval for the study was obtained from the local ethics committee. Patient records were reviewed retrospectively to gather comprehensive clinical and laboratory information. Descriptive statistical analyses included calculations of mean, standard deviation, median, minimum and maximum values, as well as frequencies and percentages for categorical variables

Genetic Analysis:

Next-generation sequencing (NGS) was performed using a targeted gene panel covering known genes associated with inborn errors of metabolism. Molecular analyses, including those targeting mitochondrial DNA (mtDNA), were conducted on peripheral blood samples. Detected variants were classified according to the 2015 guidelines of the American College of Medical Genetics and Genomics (ACMG). All pathogenic or likely pathogenic variants identified through NGS were confirmed by Sanger sequencing.

RESULTS

Study Population

This study included a total of 19 patients, of whom 12 (63.2%) were male and 7 (36.8%) were female. The mean ± SD age at the time of diagnosis was 33 ± 4 months, and the mean ± SD age at the time of data collection was 40 ± 7 months.

Clinical and laboratory finding of the patients

The most common clinical symptom was hypotonia, observed in 52.6% of the patients, followed by lactic acidosis (26.3%) and seizures (21.1%). Less frequent findings included neuromotor delay (10.5%) and bilateral optic atrophy (10.5%). These data reflect the predominant neurological involvement in mitochondrial disorders. The clinical characteristics of the patients are summarized in Table 1, while detailed laboratory and biochemical findings are presented separately in Table 2.

Genetic findings

Analysis of patient diagnoses revealed that five patients had mitochondrial DNA disorders, two patients had mitochondrial fusion defects, six patients had oxidative phosphorylation disorders, and three patients had mitochondrial depletion syndromes. Patients with PDP1, SLC19A3, and pyruvate carboxylase deficiencies were also identified (Table 3). The nuclear and mitochondrial gene mutations detected in our patients, along with their zygosity and plasmy levels (Table 3).

The most frequently detected laboratory abnormality was lactic acidosis. Urinary organic acid analysis often revealed the excretion of mitochondrial intermediates and end products, further supporting the diagnostic suspicion of mitochondrial dysfunction. The systemic evaluations reinforcing the mitochondrial disease diagnosis are presented in Table 4.

DISCUSSION

Mitochondrial diseases represent a diverse group of inherited metabolic disorders characterized by dysfunctions in oxidative phosphorylation (OXPHOS), leading to impaired cellular energy metabolism (14). Given the central role of mitochondria in numerous cellular functions, mitochondrial diseases often exhibit significant heterogeneity in their clinical manifestations, ranging from isolated organ involvement to severe multisystem disorders (15). In our cohort, neurological symptoms such as hypotonia, epilepsy, and neuromotor developmental delay were among the most common clinical findings, consistent with the expected phenotypic variability of mitochondrial diseases. Additionally, biochemical abnormalities, particularly lactic acidosis, were frequently detected, reinforcing the role of metabolic disturbances in disease presentation. The genetic spectrum observed in our study, which includes mutations in MT-TL1, GTPBP3, OPA1, and NDUFS1, further highlights the complexity of mitochondrial disorders and the necessity of comprehensive molecular diagnostics.

One of the main challenges in diagnosing mitochondrial diseases is their broad and variable clinical presentation, which frequently overlaps with other metabolic and neurogenetic disorders. (16, 17). In our cohort, neurological symptoms such as developmental delay, hypotonia, epilepsy, and ataxia were among the most preva-

Table 1. Patient ages, mutant genes and clinical presentations

Patient number	Mutant gene	Age at diagnosis	Age at data curation	Gender	Clinical Presentation
1	*MT-TL1*	6 years	6 years	Male	Lactic acidosis, transient ischemic attack
2	*DNML1*	13 years	13 years	Male	Spasticity, neuromotor delay
3	*GTPBP3*	2 days	3 months	Male	Hypotonia, lactic acidosis
4	*MT-ATP6*	6 months	8 months	Female	Hypotonia, lower respiratory tract infection
5*	*OPA1*	8 years	1 year	Female	Bilateral optic atrophy, nystagmus
6*	*OPA1*	8 years	1 year	Male	Bilateral optic atrophy, nystagmus
7	*PDP1*	20 years	20 years	Male	Muscle weakness, lactic acidosis
8	*MSTO1*	16 years	16 years	Male	Diabetes mellitus, sudden cardiac arrest
9	*MT-RNR1*	4 months	1 year	Female	Hypotonia
10	*NDUFAF6*	6 days	1 year	Male	Hypotonia, ichthyosis
11	*SLC19A3*	1 month	6 months	Male	Hypotonia, general condition deterioration
12	*NDUFA1*	2 years	2 years	Male	Seizure, hypotonia
13	*NDUFV2*	6 years	10 years	Male	Seizure, intellectual disability
14	*NDUFS1*	1 year	1 year	Male	Joubert sydrome, hypotonia
15	*FBXL4*	1 year	6 years	Female	Hypotonia, epilepsy
16	*MT-ND3*	2 years	8 months	Female	Seizure, hearing loss
17	*PC*	6 months	1 month	Female	Lactic acidosis, hypotonia
18	*NDUFAF5*	4 years	3 years	Female	Hypotonia, neuromotor delay
19	*MT-CO1*	6 years	3 years	Male	Seizure, lactic acidosis

* Two twin sibling patients

Table 2. Biochemical findings of patients at diagnosis

Patient number	Mutant gene	Urinary Organic Acid Analysis	Acylcarnitine Analysis	Urinary Amino Acid Analysis	Plasma Amino Acid Analysis	Plasma Lactate (mmol/L)	AST/ALT (µmol/L)	Ammonia (µmol/L)	Creatine Kinase (mg/dL)
1	*MTTL1*	Lactate, pyruvate, 3OH-butyrate	Normal	Normal	Elevated alanine	10	78/55	46	110
2	*DNM1L*	Normal	Normal	Normal	Normal	1.7	20/16	77	126
3	*GTPBP3*	Normal	Normal	Normal	Normal	9.9	104/137	112	532
4	*MT-ATP6*	Normal	Normal	Normal	Elevated alanine	16	53/21	80	109
5	*OPA1*	Normal	Normal	Normal	Normal	3.1	28/20	28	99
6	*OPA1*	Methylglutaconic acid	Normal	Normal	Mild ornithine elevation	2.7	31/34	45	44
7	*PDP1*	Lactate, pyruvate	Normal	Normal	Elevated alanine	8	21/19	78	71
8	*MSTO1*	Normal	Normal	Normal	Normal	4	18/19	36	51
9	*MT-RNR1*	Ethylmalonic acid, succinic acid	Normal	Normal	Normal	1.6	48/19	67	226
10	*NDUFAF6*	Normal	Normal	Normal	Normal	1.7	71/101	49	180
11	*SLC19A3*	Normal	Mild C3 elevation	Normal	Normal	1.2	35/21	43	128
12	*NDUFA1*	3OH-butyrate, ethylmalonic acid	Normal	Normal	Normal	3.8	24/14	21	65
13	*NDUFV2*	Normal	Normal	Normal	Normal	1.6	14/27	47	52
14	*NDUFS1*	Normal	Normal	Normal	Normal	3.5	44/51	58	115
15	*FBXL4*	Lactate, pyruvate	Normal	Normal	Elevated alanine	10	76/65	104	78
16	*MT-ND3*	Lactate	Normal	Normal	Normal	5	34/46	86	89
17	*PC*	Lactate, pyruvate	Normal	Normal	Mild citrulline elevation	16	128/145	130	128
18	*NDUFAF5*	Normal	Normal	Normal	Normal	1.55	25/20	NA	103
19	*MT-CO1*	Normal	Normal	Normal	Normal	2.09	25/40	NA	52

Table 3. Genetic Findings of Patients Diagnosed with Mitochondrial Disease

Patient number	Mutated Gene	Nucleotide Change	Protein Change	Zygosity/ Plasmy	Disease group	Novelty	ACMG Classification
mtDNA variants							
1	*MT-TL1*	m.3243A>G (rs199474657)		Heteroplasmic (72%)	Mitochondrial DNA Disorders	Reported	Pathogenic
4	*MT-ATP6*	m.8993T>G (c.467T>G)	p.(Leu156Arg)	Homoplasmic (100%)	Mitochondrial DNA Disorders	Reported	Pathogenic
9	*MT-RNR1*	m.1530A>G		Heteroplasmic (99.9%)	Mitochondrial DNA Disorders	Novel	VUS
16	*MT-ND3*	m.10158T>C	p.(Ser34Pro)	Heteroplasmic (83%)	Mitochondrial DNA Disorders	Reported	Pathogenic
19	*MT-CO1*	m.6060A>C	p.(Ile53Leu)	Homoplasmic (100%)	Mitochondrial DNA Disorders	Novel	VUS
nDNA variants							
2	*DNM1L*	c.179G>C	p.(Arg60Pro)	Heterozygous	Mitochondrial Fusion Disorders	Novel	Likely pathogenic
3	*GTPBP3*	c.1133T>C	p.(Leu378Pro)	Homozygous	Oxidative Phosphorylation Disorders	Reported	VUS
5	*OPA1**	c.1609-5A>G		Homozygous	Mitochondrial Depletion Syndromes	Novel	VUS
6	*OPA1**	c.1609-5A>G		Homozygous	Mitochondrial Depletion Syndromes	Novel	VUS
7	*PDP1*	c.1534C>T	p.(Arg512*)	Homozygous	Pyruvate metabolism defects	Novel	Likely pathogenic
8	*MSTO1*	c.161del	p.(Asn54Thrfs Ter5)	Homozygous	Mitochondrial Fusion Disorders	Novel	Likely pathogenic
10	*NDUFAF6*	c.35C>G	p.(Pro12Arg)	Homozygous	Oxidative Phosphorylation Disorders	Novel	VUS
11	*SLC19A3*	c.894T>G	p.(Tyr298Ter)	Homozygous	Thiamine transport defects	Reported	Pathogenic
12	*NDUFA1*	c.894T>G	p.(Tyr298Ter)	Homozygous	Oxidative Phosphorylation Disorders	Novel	Pathogenic
13	*NDUFV2*	c.664C>T	p.(Arg222Cys)	Homozygous	Oxidative Phosphorylation Disorders	Reported	VUS
14	*NDUFS1*	c.1012G>A	p.(Val338Met)	Homozygous	Oxidative Phosphorylation Disorders	Reported	VUS
15	*FBXL4*	c.1777T>C	p.(Ser593Pro)	Homozygous	Mitochondrial Depletion Syndromes	Novel	VUS
17	*PC*	c.2493_2494del	p.(Phe832*)	Homozygous	Gluconeogenesis defects	Reported	Pathogenic
18	*NDUFAF5*	c.441C>A	p.(Phe147Leu)	Homozygous	Oxidative Phosphorylation Disorders	Novel	VUS

*2 twin siblings

Table 4. Cranial, cardiac, and abdominal imaging findings of the patients

Patient number	Mutant gene	Central Nervous System Findings	Cardiac Findings	Abdominal Ultrasound Findings
1	*MT-TL1*	Arachnoid cyst	Normal	Normal
2	*DNM1L*	Normal	Aortic sheath dilatation	Normal
3	*GTPBP3*	Normal	Patent foramen ovale	Normal
4	*MT-ATP6*	Basal ganglion involvement	Dilated cardiomyopathy	Perihepatic free fluid
5*	*OPA1*	Normal	Mild mitral regurgitation	Normal
6*	*OPA1*	Normal	Mild mitral regurgitation	NA
7	*PDP1*	NA	NA	NA
8	*MSTO1*	Mild encephalomalacia	Normal	Normal
9	*MT-RNR1*	NA	Patent foramen ovale	Normal
10	*NDUFAF6*	Mild ventricular dilatation	Tricuspid regurgitation	Normal
11	*SLC19A3*	Basal ganglia involvement	Thin patent ductus arteriosus	Normal
12	*NDUFA1*	Leigh syndrome findings	Normal	Normal
13	*NDUFV2*	Leigh syndrome findings	NA	Normal
14	*NDUFS1*	Normal	Normal	Normal
15	*FBXL4*	Cytotoxic edema	Normal	Normal
16	*MT-ND3*	Leigh syndrome findings	Normal	Normal
17	*PC*	Intraventricular hemorrhage	Atrial septal defect	Bile sludge
18	*NDUFAF5*	Leigh syndrome findings, hydrocephalus	NA	NA
19	*MT-CO1*		Perimembranous ventricular septal defect	Mild prominence of the intrahepatic bile ducts. Increased echogenicity of the right renal parenchyma

NA: Not Available, *Twin sibling patients

lent clinical features, consistent with previous literature indicating the central nervous system as a primary target of mitochondrial dysfunction(18). Additionally, systemic manifestations such as cardiomyopathy, myopathy, and metabolic abnormalities highlight the multisystem involvement frequently observed in mitochondrial disorders(8).

Biochemical and genetic investigations play a crucial role in confirming mitochondrial disease diagnoses While serum lactate measurements and metabolic screening were historically relied upon as initial indicators of mitochondrial dysfunction, their diagnostic utility is now increasingly complemented by advanced molecular techniques. Muscle biopsies remain an important diagnostic tool, particularly in cases with ambiguous clinical and biochemical findings, as they can reveal characteristic mitochondrial abnormalities under electron microscopy (10). However, the advent of NGS has revolutionized the diagnostic approach, enabling the rapid identification of pathogenic variants in mtDNA and nDNA (11). The genetic heterogeneity observed in our cohort underscores the importance of comprehensive molecular analyses to establish a definitive diagnosis and inform disease prognosis and management (16, 19). Our findings highlight this shift, with NGS allowing the rapid identification of pathogenic variants in both mtDNA and nDNA, facilitating precise diagnoses and guiding patient management. The increasing reliance on genetic testing, as demonstrated in our study, underscores its pivotal role in modern mitochondrial disease diagnostics, aligning with the broader trend toward molecular-based approaches.

Therapeutic strategies for mitochondrial diseases remain largely supportive, focusing on symptom management and metabolic stabilization. In our patient group, the administration of coenzyme Q10, riboflavin, and other mitochondrial cofactors was commonly employed as part of the therapeutic regimen (20, 21). Despite these interventions, the progressive nature of mitochondrial diseases poses significant challenges, necessitating a multidisciplinary approach involving neurologists, geneticists, metabolic specialists, and rehabilitation teams to optimize patient outcomes (13).

Another critical aspect highlighted by our findings is the importance of early recognition and intervention. Delayed diagnosis can result in irreversible neurological damage and worsening clinical outcomes. Given the increasing availability of genetic testing, integrating whole-exome sequencing (WES) and whole-genome sequencing (WGS) into routine clinical practice may facilitate earlier and more precise diagnoses, thereby enabling timely therapeutic interventions and genetic counselling for affected families(6).

Our study provides institution-specific data on the clinical, biochemical, and genetic characteristics of pediatric patients with mitochondrial diseases. As demonstrated in our study, genetic testing plays a pivotal role in modern mitochondrial disease diagnostics; however, accurate interpretation and diagnosis depend on the enlightening clinical information provided by the clinician. A purely genetic approach, without clinical context, may lead to incomplete or misleading conclusions.s. The findings underscore the importance of comprehensive molecular diagnostics, as all patients in our cohort were genetically confirmed, reflecting the shift from traditional biochemical assessments to NGS-based approaches in routine clinical practice.

Furthermore, the application of next-generation sequencing (NGS) played a critical role in the timely and accurate diagnosis of mitochondrial disorders in our cohort. Early molecular confirmation enabled prompt initiation of supportive therapies, including coenzyme Q10 and vitamin supplementation, which may help stabilize or delay disease progression in selected patients. Moreover, genetic diagnosis provided families with essential information for genetic counselling and reproductive planning, emphasizing the broader impact of precise diagnosis beyond individual patient care.

This study has several limitations. First, the retrospective design may have led to incomplete or variable data collection, particularly regarding early clinical signs. Second, the relatively small sample size reduces the statistical power and limits the generalizability of our findings. Finally, as a single-center study, the patient population may reflect center-specific diagnostic or referral patterns. Therefore, while our findings offer valuable insight into pediatric mitochondrial diseases in a specific setting, broader multicenter studies are needed to validate and expand upon these results.

Mitochondrial diseases have a broad clinical spectrum, highlighting the critical importance of increased clinical awareness during the diagnostic process. Supportive therapies (e.g., coenzyme Q10, riboflavin) can benefit some patients, but definitive treatments remain unavailable. Integrating next-generation sequencing (NGS) into routine diagnostic algorithms is essential for timely and accurate diagnosis, enabling early interventions and informed family counselling. Future research should focus on prospective, longitudinal studies to assess treatment efficacy and long-term outcomes in genetically characterized cohorts.

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Abbreviations list

mtDNA: mitochondrial DNA
nDNA: nuclear DNA
NGS: next-generation sequencing
OXPHOS: oxidative phosphorylation
ATP: adenosine triphosphate
ACMG: American College of Medical Genetics and Genomics
NA: not available
SD: standart deviation
VUS: variant of uncertain significance

Ethics approval and consent to participate

This study was approved by Ankara Etlik City Hospital Ethic Committee (Approval Date: 16.10.2024 Approval Number: AEŞH-BADEK-2024-934)

Consent for publication

It does not contain any personal data.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

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Authors' contributions

Idea/Concept: HTA,SG. Design: HTA,SG. Control/Supervision AS,AO. Data Collection and/or Processing: HTA,SG.AS. Analysis and/or Interpretation HTA,SG. Literature Review: HTA,SG,AS,AO. Writing the Article: HTA,SG,AS,AO. Critical Review: HTA,SG,AS,AO. References and Fundings: HTA,SG,AS,AO.

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