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Endocrine Disorders in Children with Primary Mitochondrial Diseases: Single Center Experience

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What is already known on this topic?

Primary mitochondrial diseases (MD) can manifest with endocrine abnormalities characterized by problems in hormone production and secretion. The initial clinical manifestation of primary MD may be a hormonal deficit.

What this study adds?

This study examined the genetics, phenotype, auxological data, and hormonal profiles of children and adolescent patients with MD. To the best of our understanding, this study represents the most extensive investigation conducted on this specific patient population in Türkiye.

Abstract

Objective: Endocrine abnormalities may be the only clinical manifestation of primary mitochondrial disorders. The aim of this study was to evaluate the endocrinological characteristics of mitochondrial disease (MD) in a cohort from a single center.

Methods: Pediatric patients diagnosed with MD were categorized on the basis of their specific genetic abnormalities. The auxologic data, pubertal development, and, based on their clinical symptoms, hormonal profiles were obtained.

Results: Twelve of the cohort of 26 patients (46%) were female. In 15 (57.6%), the MD was caused by nuclear DNA mutations (nDNA group). Four patients had Leigh syndrome, two patients had Leber's Hereditary Optic Neuropathy syndrome, two patients had Mitochondrial Encephalopathy Lactic Acidosis and Stroke Like episodes, and one patient had Kearns-Sayre syndrome clinical phenotype. The median age at diagnosis was 2.91 (0.59-16.8) years, and the median age at first endocrine evaluation was 4.62 (1.26-18) years. The mean height standard deviation score (SDS) was -1.34 ± 2.12, and the mean body mass index SDS was -0.82 ± 1.96 for all patients. Of the 26 patients, 6 (23%) had a range of hormonal deficits. Ovarian insufficiency, central adrenal insufficiency, central hypothyroidism, diabetes mellitus, and critical illness-related adrenal insufficiency were all observed. Three of the patients were initially monitored in the endocrine clinic for hormone deficiencies but it was later determined that the hormonal abnormalities were caused by underlying MD.

Conclusion: Individuals diagnosed with MD, particularly those with specific genetic abnormalities, are considered a high-risk group for developing hormonal deficits. Endocrine abnormalities may be one of the primary early warning symptoms for MD.

Keywords: Primary mitochondrial disease, genotype-phenotype, endocrine disorders, endocrin abnormalities

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Introduction

Primary mitochondrial diseases (PMDs) are multisystemic diseases that encompass a broad spectrum of conditions. The incidence of mitochondrial diseases (MDs) is estimated at 1/4,500-5,000 (1). These disorders are caused by point mutations or by large deletions in either the mitochondrial (mtDNA) or nuclear DNA (nDNA), which both alter the structure and function of the mitochondria. In addition to the well-known pattern of maternal inheritance of MD, mutations in two genes can result in autosomal dominant, autosomal recessive, and rare X-linked disorders. Occasionally, sporadic cases may occur (2). Clinical manifestations are extremely variable, and early symptoms of these disorders may manifest at any age. Mitochondrial inheritance patterns differ, in addition to being complex. A single cell may contain hundreds or thousands of mtDNA copies. Homoplasmy occurs when all cells' mtDNA copies are identical (mutant or wild type). Heteroplasmy refers to the presence of mutant or normal mtDNA in a cell. However, the ratio of mutant mtDNA heteroplasmy may not correlate with the patient's clinical symptoms. The precise reason for this is unknown (3). MDs are in the subgroup of inherited metabolic diseases that affected patients develop energy deficiencies. In the classification of MDs, specific clinical, radiological, biochemical findings and physiological analyzes are taken into consideration. However, since MDs has a wide spectrum of phenotypes and genotypes, it is the most difficult group of metabolic diseases to classify. Defects in respiratory chain function and oxidative phosphorylation affect mitochondrial energy metabolism, leading to multisystemic organ failure. PMDs are multisystemic diseases that primarily affect metabolically active tissues, such as the brain, kidney, heart, skeletal muscles, and endocrine organs. MDs constitute a large genetic group and are considered rare diseases or even, despite the prevalence of some types, a very rare disease. Therefore, due to the nature of the disease, it is almost impossible to create a single homogeneous genetic study group unless it is a multicenter, multinational study (4). Mitochondrial cocktails, which consist of antioxidant combinations, exhibit synergistic effects in enhancing final energy production and mitigating oxidative stress. This, in turn, contributes to slowing disease progression by decreasing both the frequency and severity of metabolic attacks (5). Endocrine abnormalities may be one of the early warning symptoms of PMDs (6). Although diabetes mellitus (DM) is a well-known illness resulting from mitochondrial dysfunction, PMDs can exhibit hormonal deficiencies, such as ovarian insufficiency, adrenal insufficiency, hypoparathyroidism, growth hormone deficiency, and hypopituitarism. In MDs such as Kearns-Sayre syndrome (KSS), which is characterized by extensive mtDNA rearrangements, endocrine abnormalities are prevalent (7). All steroid hormones are synthesized using energy supplied by the mitochondria, and poor oxidative phosphorylation results in mitochondrial dysfunction, which impairs the production of intracellular hormones and the secretion of extracellular hormones (8). When patients with multisystemic diseases have endocrine abnormalities, it should be kept in mind that this population may have PMD. Although endocrinological involvement in MDs has been recognized for a long time, publications describing genetic and phenotypic characteristics are quite limited.

In the present study pediatric patients with PMDs were assessed for any endocrinological abnormalities. All included patients had diagnoses confirmed genetically and phenotypically. Although three patients in the cohort had first been monitored in the endocrine clinic due to hormone deficiencies, it was later discovered that the cause of the hormone deficiencies was underlying MD.

Methods

Patients

Patients with confirmed PMD were evaluated in this cross-sectional, descriptive study. The auxological indices, clinical records, and hormonal profiles of patients when they were first admitted to the Bakırköy Dr. Sadi Konuk Training and Research Hospital Outpatient Pediatric Endocrinology and Metabolism Clinics were collected. All patients' clinical characteristics were reported, and they were categorized as having either nDNA or mtDNA mutations. These genetic changes were further categorized according to the areas affected, as previously described (9). The databases Mitocarta and Mitomap were used to improve the classification of the patients' genetic results. The study protocol was approved by Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Trials Ethical Committee (decision number: 2023-08-07, date: 17.04.2023).

Parameters for the Study

The metabolic features of the patients were documented from July 2016 to September 2023 and subsequently used to classify the identified mitochondrial disorders. The auxologic data, including height, weight, body mass index (BMI), and head circumference of patients were evaluated using the child metrics program and Turkish children's references (10). In addition, child metrics were used to assess the birth auxologic data for the patients, using Turkish neonatal reference data (11). Hormonal profiles were obtained based on individual patients' clinical symptoms. Anthropometric

parameters, nutritional status, vitamin supplements, and thyroid functions were monitored in the metabolism outpatient clinic, and in consultation with the endocrinology outpatient clinic when there were abnormalities in growth parameters and hormonal profiles. Bone metabolism and other enzyme and hormone profiles, including calcium, phosphorus, magnesium, alkaline phosphatase, parathyroid hormone (PTH) and 25-hydroxyvitamin D levels, were assessed using serum electrolytes. Vitamin D status was assessed by testing serum 25-hydroxyvitamin D. Vitamin D levels were classified as sufficient (20-100 ng/mL), insufficient (15-20 ng/mL), or deficient (< 15 ng/mL) (12). Glycated hemoglobin (HbA1c) was used to assess glucose metabolism. The blood glucose levels of hypoglycemic patients undergoing serial glucose monitoring were also assessed. Gonadotropin levels were acquired from patients whose secondary sex characteristics were considered clinically unusual. Girls older than 13 years and boys older than 14 years who had no pubertal signs were considered to have delayed puberty. The levels of thyroxine (fT4) and thyroid-stimulating hormone (TSH) were measured in every patient. Thyroid autoantibodies of patients whose thyroid function tests were abnormal were collected. Of note, none of the patients had goiters on physical examination. Serum triiodothyronine (fT3) levels were tested in 19 of the patients. In 19 patients with abnormal fT4 and TSH values in the initial evaluation, fT3 levels were also examined.

All patients' basal adrenocorticotropic hormone (ACTH) and cortisol levels were evaluated. Patients with low baseline cortisol levels and hypoglycemic symptoms were tested for adrenocortical insufficiency. A low-dose (1 µg) synthetic ACTH (Cosyntropin) (Alfasigma S.p.a. Via Ragazzi del '99 n.5 40133 Bologna, Italy) test was conducted on patients with basal cortisol levels below 15 µ/dL and with serum cortisol levels below 20 µ/dL during hypoglycemia. Serum cortisol levels were assessed at 10, 20, and 30 minutes. Adrenal insufficiency was indicated when cortisol levels fell below 20 µ/dL following an ACTH injection.

In patients whose growth continued, serum insulin like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) levels were evaluated. The standard deviation scores for IGF-1 and IGFBP-3 levels were calculated against the child metrics program (10).

Metabolic Medical Treatment

Cases were supported with medical treatment at the indicated doses: L-arginine 200 mg/kg/day, divided into three doses; coenzyme Q10 15 mg/kg/day, divided into two doses; vitamin B1 10 mg/kg/day, divided into two doses; vitamin B2 10 mg/kg/day, divided into two doses; vitamin B6 30 mg/kg/day, once a day; L-carnitine 50 mg/kg/day, divided into two doses; lipoic acid 10 mg/kg/day, once a day; dichloroacetate 25 mg/kg/day, divided into three doses; and vitamin C 100 mg/kg/day, divided into two doses.

Nutritional Assessment of the Patients

The parents of the patients were trained to keep food records to evaluate the medical nutrition treatments, and three days of food records (two weekdays and a weekend day) were kept. A photographic food catalog was used to determine the amounts and portion sizes of the foods consumed (13). Based on these food records, daily mean energy and macronutrient intake were calculated using a nutrient database program (BeBis 8.2. software), based on the United States Department of Agriculture's FoodData Central and TurKomp National Food Composition Database (14,15,16,17). The energy requirements of patients were calculated according to age and gender according to Food and Agriculture Organization of the United Nations/World Health Organization/UNU equations (18,19).

Biochemical Analysis

Venous blood samples were obtained from the antecubital vein into vacutainer tubes, following an overnight fast by the participants. The plain tubes were centrifuged at 2000 g (10 min) to obtain serum for routine biochemical analyses. Blood samples were immediately centrifuged in EDTA tubes at 1000xg, at 4 °C (10 min) for the ACTH analyses. Another EDTA tube was used to measure HbA1c. Routine biochemical parameters were determined on a Roche Cobas C8000 modular auto-analyzer using commercial kits (Roche Diagnostics, CA, USA). Plasma ACTH was measured using a solid phase, two-site enzyme chemiluminescent system (Immulite 2000 XPi, Siemens Healthcare Diagnostics, USA). HbA1c levels were measured by an Arkray Adams HA-8160 analyzer, using reversed-phase cation exchange high performance liquid chromatography (Arkray KDK, Kyoto, Japan).

Genetic Analysis

Genomic DNA and mtDNA were isolated from peripheral blood lymphocytes. The initial test was for mtDNA sequencing using an in-house developed fragmentation-based methodology (20). The fragmentation process was performed using the Ion Xpress™ Plus Fragment Library Kit. Patients with unidentified genetic variation (no heteroplasmic or homoplasmic causative variant associations in mtDNA) were investigated with exome sequencing. They were examined by clinical exome sequencing (CES) using the Illumina Clinical-Exome Sequencing TruSight One Gene Panel. In the CES, the libraries generated were sequenced

using Illumina Nextseq500 next-generation sequencing platforms. The detected variants were then confirmed by conventional Sanger sequencing.

Statistical Analysis

All data were statistically analyzed using the GraphPad InStat program (v3.05; GraphPad Software Inc, San Diego, CA, USA). Parametrically distributed data were analyzed using descriptive statistics, including mean ± standard deviation, while non-parametric data were analyzed using median, minimum, and maximum. Categorical variables are given as count and percentage. The Kolmogorov-Smirnov test was used to test the normality of variable distribution and the homogeneity of the variance.

Results

The study included twenty-six pediatric patients. Twenty-three (88.5%) with PMD were monitored in a tertiary center pediatric metabolism unit. The remaining three patients were initially diagnosed in a tertiary center pediatric endocrinology unit with primary ovarian insufficiency, DM, and ACTH deficiency. Of the whole group, 12 patients (46%) were female and the MD of 15 patients (57.6%) was caused by nuclear DNA mutations (Tables 1, 2).

Patients' metabolic phenotype data were used to categorize recognized mitochondrial syndromes when the study was conducted. When the 26 patients in our study were evaluated in terms of the clinical findings, four (15.4%) patients had Leigh syndrome, two (7.7%) had Leber's Hereditary Optic Neuropathy (LHON) syndrome, two (7.7%) had Mitochondrial Encephalopathy Lactic Acidosis and Stroke-like episodes (MELAS), and one (3.85%) had a KSS clinical phenotype. Tables 1 and 2 summarize protein and complex deficiencies caused by mutations.

The median age of patients at MD diagnosis was 2.91 (0.59-16.8) years, and the median age at their first endocrinologic evaluation was 4.62 (1.26-18) years. The mean height SDS was -1.34 ± 2.12, with 38.4% (10/26) of all patients having a height SDS < -2 SDS. The mean BMI SDS was -0.82 ± 1.96 for all patients. Three individuals in our cohort had BMIs greater than 1.5 SDS, while eight had BMIs less than -1.5 SDS (Table 3).

The birth data included 13 (52%) with weight information, 12 (48%) with length measurements and 8 (38%) with head circumference measurements. The demographic data for the study group are presented in Table 3.

Twenty-two (84.6%) were prepubertal, and four were at pubertal stage 5. Three of the pubertal stage 5 patients were female (patients 5, 19, and 26) and one was male (patient 18). These female patients all had regular menstrual cycles. Patient 5 had ovarian insufficiency, but she had been given pubertal induction using hormone replacement therapy and had regular menstrual cycles (Table 3).

Serum calcium, phosphorus, and magnesium concentrations were in the normal range for all patients. The mean PTH level was 38.63 ± 23.59 pg/mL (Table 4). Of the cohort, 17 (65.4%) had 25-hydroxyvitamin D levels greater than 20 ng/mL but the median 25-hydroxyvitamin D level was 20 (4.71-94.2) ng/mL. Vitamin D deficiency and vitamin D insufficiency rates in the cohort were 19.2% and 15.4%, respectively.

Of the patients, 16.7% currently followed a ketogenic diet (mean fat ratio of energy: 63.4%); 41.7% of the patients followed a diet rich in fat (mean fat ratio of energy: 44.1%), and 41.6% of the patients did not follow any specific diet. Furthermore, 16.6% were breastfed, and 38.5% of the patients used enteral nutrition products. The rate at which the energy requirement of the patients was met was 89.16 ± 20.20% (minimum-maximum: 58.9-123.6%). All patients met the recommended daily allowance values for protein. On average, 43.33 ± 10.69% of daily energy intake was provided from carbohydrates, 15.17 ± 7.22% from protein, and 43.33 ± 10.48% (minimum-maximum: 32.0-66.7%) from fat. A mean of 14.58 ± 4.48% of daily energy was obtained from saturated fats.

Six (23%) had a range of hormonal deficiencies. Four of these six patients were in the nDNA group. Half of individuals with proven PMD had received a diagnosis of hormonal deficiency and underwent their initial assessment in the endocrinology unit.

Patients with Hormonal Deficiencies in the nDNA Group

Critical Illness-related Adrenal Insufficiency

Patient 4 was a one-year-old female with neuromotor retardation, epilepsy, hypertrophic cardiomyopathy, cystic encephalomalasia, and growth retardation phenotype with autosomal recessive homozygous mutation in the *NDUFV1* gene. She had developed cathecolamine refractory shock and had persistent low blood glucose levels (< 50 mg/dL). She was in the pediatric intensive care unit during hospitalization with septic and metabolic shock. After initiation of 200 mg/m²/day hydrocortisone treatment, her blood pressure levels normalized, and normoglycemia was maintained. This patient was diagnosed with critical illness-related adrenal insufficiency. During periods of hypoglycemia and hypotension, her ACTH and cortisol levels were 96 (7.2-63.3) pg/mL and 68 (6.2-22.6), µg/dL (6.2-22.6), respectively.

Table 1. Characteristics of detected variants in 15/26 patients with proven mitochondrial disease

	Family number	Patient numbers	Gene; phenotype MIM number; inheritance	Variant in nucleotide	Variant in peptide	Associated region	Zygosity	Phenotypic features	Endocrine system findings
1. Mutations in genes encoding structural subunits of respiratory chain proteins	1	**1,2**	*FOXRED1;* # 618241; AR	c.473G > T	p.(G158V)	C I	Hom.	Epilepsy, NMR, strabismus, GR, autism, NMR Leigh syndrome	Vitamin D insufficiency (1), vitamin D deficiency (2)
	2	**3**	*NDUFS7;* # 618224; AR	c.511G > A	p.(D171N)	C I	Hom.	Myopathy, elevated CK	Normal
	3	**4**	*NDUFV1;* # 618225; AR	c.1018G > A	p.(D340N)	C I	Hom.	NMR, epilepsy, HCM, cystic encephalomalasia, GR Leigh syndrome	Criticall ilness related adrenal insufficiency Short stature
2. Mutations in genes encoding ancillary or assembly factors for the respiratory chain function	4	5	*COX15;* # 615119; AR	c.[1011dup]; [1030T > C]	p.([T338fs];[S344P])	C IV	CH	Myopathy, NMR	Ovarian insufficiency Short stature
	5	6	*MICU1;* # 615673; AR	c.330 + 1G > T	p.(?)	MCC	Hom.	Mild autism, mild NMR	Vitamin D deficiency
	6	7,8	*NNT* # 614736, AR	c.1225C > T	p.(Q409fs*)	IMM	Hom.	Dystonia, walking difficulty	Vitamin D insufficiency (8)
	7	9	*RMND1,* # 614922, AR	deletion in 6q25.1	p.(?)	COXPD	Hom.	SNHL, CRF, GR	Ovarian insufficiency Short stature Vitamin D deficiency
3. Mutations in genes encoding mtDNA translation factors	8	10	*ELAC2;* # 615440; AR	c.[85C > T]; [86G > T]	p.([R29C];.[R29L])	COXPD	CH	Epilepsy, hypotonia, NMR, GR	Slightly elevated anti-TPO antibodies Short stature
4. Mutations in genes encoding mitochondrial enzymes	9	11	*ECHS1D;* # 616277; AR	c.476A > G	p.(Q159R)	Mt Mrx	Hom.	Hypotonia, severe NMR, GR	Short stature
5. Defects of intergenomic signaling	10	12	*RRM2B;* # 612075; AR	c.462A > G	p.(Lys154 =)	MM	Hom.	SNHL, DM	DM
6. Other miscellaneous	11	13	*SERAC1;* # 614739; AR	c.1404-2A > G	p.(?)	MM	Hom.	MEGDEL, NMR, hypotonia, GR	Normal
	12	14		c.1396dupA	p.(M446Nfs*15)		Hom.		Short stature (14)
	13	15	*SLC19A3* # 607483; AR	c.597dupT	(p.H200Sfs*r25)	MM	Hom.	Epilepsy, NMR, blindness	Sightly elevated anti-TPO antibodies

VUS: variant of unknown significance, Hom.: homozygous, AR: autosomal recessive, C-I: complex-1, C-IV: complex-4, CK: creatinine kinase, CH: compound heterozygous, COXPD: combined oxidative phosphorylation deficiency, CRF: chronic renal failure, DM: diabetes mellitus, GR: growth retardation, HCM: hypertrophic cardiomyopathy, IMM: inner mitochondrial membrane, MM: mitochondrial membrane, MCC: mitochondrial calcium channel, MMrx: mitochondrial matrix, MEGDEL: 3-methylglutaconic aciduria with deafness-encephalopathy Leigh-like syndrome, NMR: neuromotor retardation, SNHL: sensorineural hearing loss, TPO: thyroid peroxidase

Table 2. Genotype and phenotype characteristics and endocrine dysfunctions in patients with mitochondrial DNA mutations

	Patient no	Gene; locus MIM number; inheritance	Nucleotide change	Amino acid change	Associated region	Zygosity	Phenotypic features	Endocrine system findings
1. Large-scale rearrengements								
2. Single-nucleotide variants (point mutation) in genes encoding structural proteins	16	*MT-ATP6;* * 516060; Mt-in	m.8993T > C	p.L156P	C-V	Heteroplasmy (89%)	Dystonia, hypotonia, contractures, walking difficulty, GR	Normal
	17	MT-ND4 * 516003 Mt-in	m.11467A > G	p.L236L	C-1	Homoplasmy (99%)	Hypoglycemia, encephalopaty, liver failure	Vitamin D insufficiency
	18	*MT-ND5;* * 516005; Mt-in	m.12372G > A	p.L12L	C-I	Homoplasmy (99%)	LHON, epilepsy, NMR	Vitamin D insufficiency
	19		m.12706T > C	p.F124L	C-I	Homoplasmy (97%)	MELAS, cortical blindness, epilepsy	Vitamin D deficiency
	20	*MT-ND1;* * 516000; Mt-in	m.4216T > C	p.Y304H	C-I	Homoplasmy (99%)	LA, nystagmus, NMR, GR Leigh syndrome	Central adrenal insufficiency Vitamin D insufficiency Short stature
	21	*MT-ND3;* * 516002; Mt-in	m.10398A > G	p.T114A	C-I	Homoplasmy (99%)	Microcephaly, contractures, LHON, NMR, GR	Central hypothyroidism Vitamin D deficiency Short stature
3. Mutation in genes encoding tRNA	22	*MT-TA;* * 590000; Mt-in	m.5631G > A	tRNA Ala	Mitochondrial-nuclear crosstalk	Homoplasmy (100%)	HCM, SNHL, GR, myopathy, lactate and CK elevation	Normal
	23	*MT-TN;* * 590010; Mt-in	m.5667G > A	tRNA Asn	Mitochondrial-nuclear crosstalk	Heteroplasmy (88%)	Strabismus, epilepsy, NMR	Vitamin D insufficiency
	24	*MT-TL1;* * 590050; Mt-in	m.3243A > G	tRNA Leu	Mitochondrial-nuclear crosstalk	Heteroplasmy (87%)	MELAS, ptosis, LA, myopathy	Normal
	25	*MT-TL2;* * 590055; Mt-in	m.12308A > G	tRNA Leu	Mitochondrial-nuclear crosstalk	Homoplasmy (97%)	NMR, autism	Normal
4. Mutation in genes encoding rRNA								
5. Other miscellaneous	26	MT-CR	16519T > C	(non-coding)	Entire Control Region	Homoplasmy (100%)	KSS, hypotonia, NMR, GR	Vitamin D deficiency Short stature

C-I: complex-1, C-V: complex-5, CK: creatinine kinase, GR: growth retardation, HCM: hypertrophic cardiomyopathy, MCR: mitochondrial control region, Mt-in: mitochondrial inheritance, KSS: Kearns-Sayre syndrome, LA: lactic acidemia, LHON: Leber hereditary optic neuropathy, MELAS: mitochondrial encephalopathy with lactic acidosis and stroke like episodes, NMR: neuromotor retardation, SNHL: sensorineural hearing loss

Table 3. Demographic and clinical characteristics of the whole cohort

	Number of patients (%)	Mean ± SDS or Median (min-max)
Age (years) at mitochondrial diagnosis* (median)	26 (100)	2.91 (0.59-16.8)
Age (years) at endocrine system evaluation* (median)	26 (100)	4.62 (1.26-18)
Sex		
Female	12 (46.2)	
Male	14 (53.8)	
Gestational age	13 (52)	38.77 ± 1.54
Birth weight SDS	13 (52)	-0.43 ± 2.22
Birth height SDS	12 (48)	-0.20 ± 1.64
Birth head circumference SDS	8 (32)	0.42 ± 1.89
Height SDS	26 (100)	-1.34 ± 2.12
Weight SDS	26 (100)	-1.36 ± 2.26 [(-7.04)-2.33]
BMI SDS	26 (100)	-0.82 ± 1.96
Head circumference SDS	11 (42.3)	-3.51 ± 2.35
Pubertal stage		
1	22 (84.6)	
2		
3		
4		
5	4 (15.4)	

*Non-parametric distribution according to Kolmogorov-Smirnov test.
BMI: body mass index, SDS: standard deviation score, min-max: minimum-maximum

Table 4. Biochemical and hormonal profiles of study population

	Number of patients (%)	Mean ± SDS or Median (min-max)
TSH (mIU/mL)	26 (100)	2.49 ± 1.27
Free T4 (ng/dL)*	26 (100)	1.25 (0.85-4.09)
Free T3 (pg/mL)	19 (73)	3.97 ± 0.95
ACTH (pg/mL)*	26 (100)	35 (4-365)
Cortisol (µg/dL)*	26 (100)	14.95 (5-68)
Calcium (mg/dL)	26 (100)	9.79 ± 0.56
Phosphorus (mg/dL)	26 (100)	4.57 ± 0.91
Magnesium (mg/dL)	26 (100)	2.1 ± 0.18
ALP (U/L)	26 (100)	203.5 ± 71.52
PTH (pg/mL)	26 (100)	38.63 ± 23.59
25 OH vitamin D (ng/mL)*	26 (100)	20 (4.71-94.2)
HbA1c %*	26 (100)	5.2 (4.7-7.25)
FSH (mIU/mL)*	6 (23)	9.5 (3.05-280)
LH (mIU/mL)*	7 (26.9)	8.3 (0.85-66)
IGF-1 (ng/mL) SDS*	23 (88.5)	0.6 (-2.1-9.03)
IGFBP-3 (mg/L) SDS*	22 (84.6)	-0.25 (-2.38-7.07)

*Non-parametric distribution according to Kolmogorov-Smirnov test.
TSH: thyroid stimulation hormone, T4: thyroxine, T3: tri-iodothyronine, ACTH: adrenocorticotrophic hormone, ALP: alkaline phosphatase, PTH: parathyroid hormone, 25 OH vitamin D: 25-hydroxyvitamin D, HbA1c: glycolysated haemoglobin A1c, FSH: follicle stimulating hormone, LH: luteinising hormone, IGF-1: insulin like growth factor-1, IGFBP-3: IGF binding protein-3, min-max: minimum-maximum

Ovarian Insufficiency

Two patients (patients 5 and 9) had ovarian insufficiency. Both were 46,XX karyotypes and had elevated gonodotropin levels after 13 years of age. Patient 5 was initially followed in the metabolism unit with mild myopathy and neuromotor retardation. Her baseline follicle stimulating hormone (FSH), luteinising hormone (LH), and estradiol levels were 61.99 mIU/mL, LH 19.76 mU/mL, and estradiol 5 pg/mL, respectively.

Patient 9 had sensorineural hearing loss (SNHL), chronic renal failure (CRF), and growth retardation. This patient was admitted to the pediatric endocrinology unit due to the absence of breast development. Her baseline FSH, LH, and estradiol levels were 280 mIU/mL, 66.34 mU/mL, and < 20 pg/mL, respectively. Investigation for MD was initiated because of her multisystemic involvement.

Diabetes Mellitus

Patient 12 was a nine-year-old female diagnosed with insulin-dependent DM when she was 4.8 years old. At the time of diagnosis, her glucose level was 299 mg/dL, c-peptide was 0.415 µg/L (0.9-7.1), HbA1c was 9.1%, islet cell antibodies (ICA) were positive at 1/10 (< 1/4), insulin antibodies were positive at 13% (NR 4-10%), glutamic acid decarboxylase antibodies were very high at 1803 IU/L (NR 0-5). This patient had SNHL. Her hearing loss was diagnosed when she was 13 months old. Her parents were first-degree cousins. Four years after the diagnosis of diabetes, her growth was normal, her mean HBA1c was 7% during the follow-up period, her mean daily insulin dose was 0.5 unit/kg/day, and her c-peptide level was low at 0.296 µg/L (0.9-7.1). This patient was evaluated for unusual causes of DM and a mutation was identified in the *RRM2B* gene.

Patients with Hormonal Deficiencies in the mtDNA Group

Central Adrenal Insufficiency

Patient 20 was an eighteen-month-old hypotonic boy admitted to the pediatric endocrinology outpatient clinic for hypoglycemic attacks. During hypoglycemia, when his blood glucose level reached 28 mg/dL, his ACTH and cortisol levels were 12 pg/mL and 5 µg/dL, respectively. A 1 µg ACTH stimulation test was performed, and his peak cortisol was 11.85 µg/dL. The patient was diagnosed with central adrenal insufficiency; no additional pituitary hormone deficiencies were present. The patient's neurological development was retarded. He was unable to walk or sit without support. Magnetic resonance imaging of the pituitary showed that it was normal. The patient also had lactic acidemia, nystagmus, and neuromotor and growth retardation phenotypes, and a mutation was identified in the *MT-ND1* gene.

Central Hypothyroidism

Patient 21 had a mutation in the *MT-ND3* gene, was phenotypically LHON, and had microcephaly, neuromotor and growth retardation, and contractures. This patient was diagnosed with MD at the age of 1.16 years and with central hypothyroidism at the age of 2.34 years. TSH was 1.3 mIU/mL, fT4 was 0.87 ng/dL, and fT3 was 3.7 pg/mL (2.41-5.5) in her first assessment with no other acute illnesses. Her thyroid function tests were TSH 0.8 mIU/mL, fT4 0.81 ng/dL, and fT3 2.2 pg/mL (2.41-5.5) at the baseline time of the ACTH stimulation test. Her basal ACTH level was 22 pg/mL, and her cortisol level was 8.26 mg/dL. 1 mcg ACTH stimulation test was performed, and her peak cortisol level was found to be 22 mcg/dL, and L-thyroxine treatment started at 10 mcg/kg/daily. There were no other pituitary hormone deficiencies. Magnetic resonance imaging of the pituitary showed it to be normal.

In addition to the six MD patients who had endocrinological hormone secretion deficiency, two patients in the nDNA group had anti-thyroid peroxidase antibody (ATPO) positivity, despite their normal thyroid function tests and normal thyroid gland ultrasonography. The ATPO levels for patient 10 and patient 15 were 16 IU/mL and 22.6 IU/mL, respectively. Anti-TPO levels below 13 IU/mL are considered normal in our laboratory references.

The classification of the genotype-phenotype and endocrinological characteristics of patients with nDNA and mtDNA mutations are presented in Tables 1 and 2, respectively. The study population characteristics, and hormonal profiles can be seen in Tables 3 and 4, respectively.

Discussion

Hormone synthesis and secretion are both energy-dependent processes, dependent on the energy generating systems of the cellular mitochondria. This dependency makes the endocrine glands sensitive to mitochondrial dysfunction. PMDs may result in one or more hormone deficiencies, depending on the severity of the mitochondrial disorder. In addition, due to the random distribution of mitochondria during embryogenesis, patients with affected endocrine glands may present with unpredictable clinical characteristics (9). It is known that findings may be very different, depending on whether the pathogenic variation is inherited in the nDNA or the mtDNA, together with its type. Even within the same family, clinical findings of varying severity may develop depending on penetrance and on the inherent variability of these conditions (1). In this paper, the pattern of endocrinological involvement in patients with MDs, as diagnosed in our single tertiary center, are presented.

MD prevalence is estimated as 1/5000 in the adult age group (2/3 of whom are mtDNA), and as 5-10/100,000 in the pediatric age group (80% of whom are nDNA) (3). In the North American Mitochondrial Disease Consortium (NAMDC) Patient Registry study, 60% of pediatric patients had mtDNA mutations (9), which was similar in our cohort. The explanation for this is that patients with nDNA mutations are diagnosed earlier as more severe clinical findings develop at an earlier stage of life.

The Mitochondrial Society 2017 guideline recommends annual or biannual endocrinological evaluation for these patients, even if they have no hormonal dysfunction at the time of diagnosis (21). An Australian cohort with a mean age of 5.09 years at diagnosis was considerably older than our cohort at diagnosis (22). In contrast to our study, in a large cohort that consisted of patients of any age, female dominance was observed (9). However, in our cohort, there were more male than female patients (Table 3). This may be related to the fact that our group included a relatively limited number of patients.

Twenty-three percent of our patients (two with mtDNA and four with nDNA mutations) had already recognized endocrinological abnormalities. It is difficult to estimate the prevalence of endocrinological disorders in all MDs. Theoretically, in all cases of MD, the endocrine glands are sensitive to energy deficiency and oxidative stress. However, it has been shown that some well-known mutations can cause distinct endocrine findings (23,24). While endocrinological follow-up is recommended for all patients with MDs, patients with these identified mutations should be evaluated more closely. MD patients are known to show poor growth, quite apart from any growth hormone insufficiency. There are many factors affecting growth in this group of patients. Most patients show prenatal and postnatal growth failure. Von Kleist-Retzow et al. (25) observed that 22.7% of 300 mitochondrial respiratory chain deficiency patients had intrauterine developmental retardation. Feeding difficulties, restriction of energy production, frequent infections, and multiple organ system failure all have negative effects on normal growth patterns. Skeletal changes, such as joint contractures, scoliosis, or kyphosis, also have negative effects on MD patients. Growth hormone deficiency may be the first symptom of MD (26,27). The majority of our patients were close to normal height but, within our group, there were ten (38.5%) with SDS values below -2 at the time of first endocrine assesment. None was growth hormone deficient. In this respect, supportive treatment is found to be valuable in MD patients, even without growth hormone deficiency. Despite the fact that not all of our patients had completed their growth, the mean height was slightly greater than that of an adult MD cohort from the United Kingdom published in 2009 (27).

Hypo- or hyper-gonadotropic hypogonadism are both well-known entities in MD patients. Ovarian insufficiency alone, with or without SNHL, is frequently seen in MDs (28). Recently, some studies have reported that the *RMND-1* gene is a candidate for premature ovarian insufficiency. Our patients had phenotypic features similar to those of these studies, including SNHL and CRF (29,30,31,32,33,34).

Primary adrenal insufficiency is the main cause of adrenal insufficiency in MDs. To the best of our knowledge, secondary adrenal insufficiency has been reported only in a Japanese woman at fifty years of age (35). In another report including 18 patients with single, large-scale mitochondrial DNA deletions, 39% of patients had impaired basal adrenocortical function (36). In our cohort there were two patients with adrenal insufficiency, and only one of them had a critical illness related adrenal insufficiency. This patient had elevated cortisol levels, despite having clinical adrenal insufficiency. Under conditions of critical stress, the elevation of the cortisol level is explained by the adrenal gland's subacute response to the insult, decreasing cortisol clearance, and shifting to increased cortisol receptor activation (37). None of our patients had primary adrenal insufficiency, including two siblings with *NNT* mutations. Both of these had dystonia and difficulty walking, although neither had hypoglycemia, fatigue, or hyperpigmentation, and their reactions to the 1 µg ACTH test were normal (peak cortisol responses were 19 and 22 µg/dL, respectively). This mutation is a well-known cause of familial glucocorticoid deficiency (38).

DM is a common occurrence in MDs. Decreased sensitivity and insulin production are both seen in some pathophysiologies. The *MT-TL-1* gene m.3243A > G mutation is the most prevalent mutation in diabetes-associated MD (39). Patient 23 had this genetic abnormality, but no clinical or biochemical signs of diabetes. This genotype is associated with the MELAS phenotype, as was the case in our patient. In the general population, the prevalence of this genotype is 1/400 and the mean age for diagnosis of diabetes is thirty-eight years. This mutation is suggested to be responsible for ~0.5-2.9% of all diabetes (28,39,40). In our cohort there was only one female patient with DM who had a mutation in *RRM2B* gene. Mutations in *RRM2B* have been reported as a cause of MD (28). In a Japanese diabetic cohort with m.3243A > G mutations, one patient had high positivity for anti-GAD and ICA antibodies, and the authors suggested the coexistence of MD with autoimmunity in this patient. In this Japanese study, another 12 patients had slightly elevated ICA antibodies. It is suggested that this may be due to an autoimmune response to mitochondrial cell injury (39).

In the NAMDC study mentioned earlier, the prevalence of hypothyroidism in their MD cohort was 4.3%. This percentage was considered close to that of the general population (6.3%) in the USA (9). It has also been reported that hypothyroidism is more prevalent with nDNA deletions than with mtDNA variants (28). In our relatively small cohort there was only one patient with central hypothyroidism, and no one in our cohort had primary hypothyroidism. However, we did have two patients with slightly elevated anti-TPO antibodies. Some studies report that MD patients frequently have autoimmune disorders, but we have no proof that autoimmunity is more prevalent in MD patients than in the general population (41). One study reported KSS in a patient with autoimmune thyroid disease (42). There hasn't been an objective evaluation of mitochondrial cocktails' effectiveness in terms of the endocrine and other involved systems. Unfortunately, it is not easy to evaluate its effectiveness.

Study Limitations

This study was a cross-sectional observational study in which we analyzed 26 patients' auxological data and endocrinological parameters at the time of the study. We were unable to access some of these patients' birth auxologic data. Furthermore, we evaluated the auxologic data of the patients at a specific time only, and were unable to document their growth velocity. In future, prospective follow-up studies conducted with patients with PMD should provide more comprehensive data on growth patterns and the development of other endocrine disorders in this specific patient population. Furthermore, PMDs are rare diseases, and our study focused on data from a single center only, so the study group consisted of a limited number of cases. However, this work does present an extensive preliminary endocrinological assessment of children with mitochondrial disorders.

Conclusion

Individuals diagnosed with MD, particularly those with specific genetic abnormalities, are considered a high-risk group for developing hormonal deficits. Endocrine abnormalities may serve as an early warning sign for PMDs. Timely identification and treatment of hormonal insufficiency can significantly influence the course of clinical development. Conducting further research in this area will provide additional positive outcomes for evidence-based guidelines regarding the endocrinological assessment of patients with PMD.

Ethics

Ethics Committee Approval: The study protocol was approved by Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Trials Ethical Committee (decision number: 2023-08-07, date: 17.04.2023).

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Esra Deniz Papatya Çakır, Melike Ersoy, Nihan Çakır Biçer, Concept: Esra Deniz Papatya Çakır, Melike Ersoy, Asuman Gedikbaşı, Design: Esra Deniz Papatya Çakır, Melike Ersoy, Asuman Gedikbaşı, Data Collection or Processing: Esra Deniz Papatya Çakır, Melike Ersoy, Nihan Çakır Biçer, Analysis or Interpretation: Esra Deniz Papatya Çakır, Melike Ersoy, Nihan Çakır Biçer, Asuman Gedikbaşı, Literature Search: Esra Deniz Papatya Çakır, Melike Ersoy, Nihan Çakır Biçer, Writing: Esra Deniz Papatya Çakır, Melike Ersoy, Nihan Çakır Biçer.

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