Initial Nutritional Status of Patients with Mitochondrial Disease: A Retrospective Study

Geum-ji Shin
Yonsei University College of Medicine
Ji-Hoon Na
Yonsei University College of Medicine
Hyunjoo Lee
Yonsei University College of Medicine
Young-Mock Lee (ymleemd@yuhs.ac)
Yonsei University College of Medicine

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Abstract

BACKGROUND:

Mitochondrial disease (MD) is a rare condition characterized by the dysfunction of mitochondrial DNA. Patients with MD are vulnerable to malnutrition due to adenosine triphosphate dysfunction, which disrupts gastrointestinal system function. Nutritional screening and assessment of these patients are important because malnutrition increases mortality and disease-related complications. This study aimed to investigate the nutritional status at the time of diagnosis and the need for targeted nutritional therapy in patients with MD according to subgroups.

METHODS:

We enrolled 91 patients diagnosed with clinical MD who were considered at high risk of malnutrition based on the Gangnam Severance Hospital's criteria. We divided them into three subgroups (Leigh syndrome; mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes [MELAS]; non-specific MD) and compared the nutritional status of the subgroups based on nutrition-related indices.

RESULTS:

Most of the patients with MD were classified as having a high risk of malnutrition. Lactic acidosis and vitamin D insufficiency and deficiency were the most common in patients with MELAS and non-specific MD. Among the subgroups, patients with obesity were more likely to have Leigh syndrome than the other two subtypes, whereas those who were underweight were more likely to have MELAS or non-specific MD than Leigh syndrome. Gastroesophageal reflux disease was the most common in the non-specific MD group.

CONCLUSIONS:

The nutritional status of patients with MD was poor at the time of diagnosis. As the nutritional status of patients belonging to different subgroups varied, each patient required individualized nutritional therapy.

Background

Mitochondrial disease (MD) is a rare condition in which mutations in mitochondrial DNA (mtDNA) cause dysfunction of oxidative phosphorylation, which is indispensable for energy production for cell functioning and maintenance, resulting in heterogeneous symptoms of multiorgan involvement [1, 2]. These metabolic errors result in the reduction of adenosine triphosphate (ATP) synthesis, thereby increasing reliance on non-aerobic metabolic pathways [3]. A reduction in ATP production leads to various manifestations of MD, including epilepsy, cognitive impairment, cardiac and skeletal myopathies, hepatopathies, and endocrinopathies [4–6]. Mitochondrial dysfunction has been implicated in pathophysiological processes related to glucose, lipid, and calcium metabolism [7].

Assessing the nutritional status of patients with neuromuscular disease is important because of the impact of suboptimal nutrition on function, quality of life, and life expectancy [8]. In particular, nutritional intervention is essential in patients with diseases such as MD, for which there are currently no specific drugs for treatment. However, a significant number of patients with MD have malnutrition and inadequate caloric intake because of feeding difficulties. Moreover, since MD is a heterogeneous condition, the nutritional status of affected individuals may vary depending on the type of MD [9]. Therefore, comprehensive nutritional evaluations and interventions are essential for patients with MD [10]. Early intervention with personalized nutritional plans to reach caloric goals can be effective in the increasing energy and protein intake of patients at nutritional risk [11].

In this study, we investigated the basis for providing targeted and focused nutritional intervention for patients with MD by evaluating their initial nutritional status. Our findings will be a valuable reference for clinicians caring for patients with MD.

Methods

Patients and study design

This study was performed retrospectively using the electronic medical records of patients diagnosed with clinical MD who visited our tertiary care center, Gangnam Severance Hospital, Seoul, Korea, between January 2010 and December 2020. The study design and enrollment of participants are shown in Fig. 1. First, 166 patients, highly suspected to have metabolic diseases, were referred for a nutritional consultation. Among them, 91 patients who were diagnosed with clinical MD were selected. The diagnosis of MD was made based on biochemical, pathological, and clinical data, as suggested by Bernier et al [12]. Clinical MD was classified into the following three subtypes: (1) Leigh syndrome; (2) mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); (3) non-specific MD. Among them, Leigh syndrome and MELAS were identified as pathogenic variants using genetic testing. The final study population consisted of 23 patients (25.3%) with genetically-confirmed Leigh syndrome, 17 patients (18.7%) with genetically-confirmed MELAS, and 51 patients with non-specific MD (56.0%). This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine.

Diagnostic criteria for clinical MD

Clinical MD includes complete respiratory chain encephalomyopathy or mitochondrial cytopathy, defined as a suitable unexplained combination of multisystemic symptoms that is pathognomonic for a respiratory chain disorder, a progressive clinical course with episodes of exacerbations, or a family history that is strongly indicative of mtDNA mutation [12].

1) Leigh syndrome

Leigh syndrome is a neurogenerative disorder with an early onset, i.e., usually in infancy or childhood. Patients have signs of motor or intellectual retardation, usually with regression and brainstem

dysfunction, including respiratory abnormalities, nystagmus, and ophthalmoparesis. Leigh syndrome is clinically diagnosed based on the following characteristics: the presence of symmetrical brainstem and/or basal ganglia dysfunction on delayed intellectual and motor development and laboratory findings of elevated serum or cerebrospinal fluid (CSF) lactate levels [13, 14]. In this study, patients with Leigh syndrome were diagnosed with a pathogenic variant using genetic testing.

2) MELAS

MELAS is a syndrome with unique features of early-onset recurrent stroke-like episodes associated with epileptic conditions and migraine-like headaches.

In this study, MELAS was diagnosed based on clinical findings of stroke-like episodes (headache with vomiting, seizure, hemiplegia, cortical blindness or hemianopsia, and acute focal lesions on brain imaging) and evidence of mitochondrial dysfunction (elevated lactate levels in plasma and/or CSF, mitochondrial abnormalities on muscle biopsy, and definite gene mutations related to MELAS). We performed genetic testing for all study participants, and all patients were positive for mtDNA mutation (m.3243A > G) [15].

3) Non-specific MD

Clinical MD other than Leigh syndrome and MELAS was diagnosed as non-specific MD [12]. In addition, this group consisted of patients who showed clinically relevant findings for non-specific MD without finding a specific pathogenic variant in the genetic test.

General characteristics

We examined the disease-related clinical variables of 91 patients, including their clinical status at the first nutritional consultation, sex, mode of delivery, birth history, onset of symptoms, extent of organ involvement, functional status, feeding status, respiratory assistance, and serum lactic acid level.

Initial nutritional status

The initial nutritional status of the patients was evaluated based on their body mass index, laboratory findings (hemoglobin level, base excess, urine Ca/Cr ratio, etc.), imaging findings (abdominal radiography, abdominal ultrasonography, 24-h pH monitoring, esophagography, etc.). All baseline measurements were performed at the time of MD diagnosis and before the initial nutritional consultation.

Classification of patients as being at high risk of malnutrition and the nutritional interventions provided to them

We included patients at a high risk of malnutrition, i.e., those who met one or more of the following conditions: 1) weight for height < 90%; 2) diagnosed with diabetes mellitus, malnutrition, obesity, chronic renal failure, nephrotic syndrome, or intractable neurologic disorder; or 3) tube feeding or dysphagia diet. These conditions have been established by the Gangnam Severance Nutrition team. Nutritional

interventions were provided to patients who were referred for a nutritional consultation. There were seven interventions as follows: 1) education about nutrition; 2) tube feeding; 3) education about parenteral nutrition; 4) education about micronutrient intake; 5) education about obesity; 6) education about gastrointestinal problems; 7) education about diabetes mellitus.

Comparison of the initial nutritional status according to diagnosis

We compared the initial nutritional status of the three groups of MD. The variables compared were the ratio of failure to thrive, body mass index, and laboratory and imaging findings related to the patient's nutritional status. All baseline measurements were recorded before the initial nutritional consultation.

Statistical analysis

All analyses were conducted using SPSS version 20.0 for Windows (IBM Corp., Armonk, NY, USA). Descriptive statistics were used for analyzing the mean, standard deviation, median, and range. The chi-square test and Fisher's exact test were applied to evaluate differences between the groups. *p*-values < 0.05 were considered statistically significant.

Results

General characteristics

As shown in Table 1, the male to female patient ratio was 51:40. Most of the patients had no significant birth history. There were 14 patients (15.4%) who were small for gestational age, 5 patients (5.5%) who were born premature, 1 patient (1.1%) who was large for gestational age, and 1 patient (1.1%) who had perinatal asphyxia. In 4.4% of the patients, there was a family history of MD. More than half of the patients with MD initially experienced symptoms during infancy. Furthermore, 23 patients (25.3%) were diagnosed with Leigh syndrome, 17 patients (18.7%) with MELAS, and 51 patients (56.0%) were diagnosed with non-specific MD. Neuromuscular system involvement occurred in all the patients; it was the most common finding, followed by cardiological, respiratory, ophthalmological, endocrinological, nephrological, otological, gastroenterological, and psychological involvement.

Table 1
General characteristics of the 91 patients and their clinical status at the first nutritional consultation

Characteristics	Prevalence (n = 91)
Sex (M:F)	51(56.0):40(44.0)
Mode of delivery	
Cesarian section	38 (41.7)
NSVD	53 (58.2)
Birth history	
None	63 (69.2)
SGA	14 (15.4)
Prematurity	5 (5.5)
LGA	1 (1.1)
Perinatal asphyxia	1 (1.1)
Family history	4 (4.4)
Onset of symptoms (age)	
Neonatal period (< 1 month)	11 (12.9)
Infancy (1 month–1 year)	48 (52.7)
Toddler (1–3 year)	15 (16.5)
Preschool age (3–6 years)	4 (4.4)
School age (6–12 years)	7 (7.7)
Adolescence (12–20 years)	5 (5.5)
Adulthood (> 20 years)	1 (1.1)
Syndromic diagnosis	
Leigh syndrome	23 (25.3)
MELAS	17 (18.7)
Other mitochondrial diseases	51 (56.0)
Organ involvement	

Data are presented as mean ± standard deviation or number (percentage)

NSVD: normal spontaneous vaginal delivery, SGA: small for gestational age, LGA: large for gestational age, MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

Characteristics	Prevalence (n = 91)
Neuromuscular	91 (100)
Cardiology	18 (19.8)
Respiratory	14 (15.4)
Ophthalmology	10 (11.0)
Endocrinology	9 (9.9)
Nephrology	7 (7.7)
Otology	6 (6.6)
Gastroenterology	5 (5.5)
Psychology	3 (3.3)
Functional state	
Ambulatory	34 (37.4)
Wheelchair-bound	20 (22.0)
Bed-ridden	37 (40.7)
Feeding status	
Oral feeding	59 (64.8)
Temporary enteral tube feeding	23 (25.3)
Gastrostomy tube feeding	9 (9.9)
Respiratory assistance	
Tracheostomy	5 (5.5)
Endotracheal intubation status	8 (8.8)
Oxygen dependency	11 (12.1)
Serum lactic acidosis (0.7–2.1 mmol/L)	2.5 ± 1.7
Data are presented as mean ± standard deviation or number (percentage)	
NSVD: normal spontaneous vaginal delivery, SGA: small for gestational age, LGA: large for gestational age, MELAS: mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes	

At the time of the first nutritional consultation, 40% of the patients were bed-ridden, and the rest were able to move independently. Two-thirds of the patients could orally consume food, and the rest received temporary enteral tube feeding or gastronomical tube feeding. The mean serum lactate level of the patients was 2.8 mmol/L, with a standard deviation of 1.7 mmol/L.

Initial nutritional status

As shown in Table 2, the average age at the first nutritional consultation was 7 years and 5 months, with a standard deviation of 6 years. Patients with failure to thrive comprised 69.2% of the population. Moreover, 6.6% of the patients had a weight for age of < 5%, and 2.2% of the patients received intensive care.

Table 2
Initial nutritional status of patients with mitochondrial disease

Evaluation	Findings (n = 91)
Age at first nutritional consultation	7 years, 5 months ± 6 years
Failure to thrive	63 (69.2%)
Body mass index category	
Normal	35 (38.5)
Underweight	35 (38.5)
Overweight	9 (9.9)
Obesity	12 (13.2)
Abdominal radiography findings	
Normal	28 (30.8)
Mild ileus	28 (30.8)
Moderate ileus	23 (25.3)
Severe ileus	6 (6.6)
Fecal impaction	9 (9.9)
Gasless bowel	1 (1.1)
Abdominal ultrasonography findings	
Normal	51 (56.4)
Fatty liver	8 (8.8)
Diffuse liver disease	9 (9.9)
Non-specific findings	6 (6.6)
Gastroesophageal reflux disease	27 (29.7)
Lactate level	
Normal (≤ 2.1mmol/L)	45 (49.5)
Abnormal (> 2.1mmol/L)	44 (48.4)
Base excess	
Normal	38 (41.8)
Metabolic acidosis	53 (58.2)

Data are presented as mean ± standard deviation or number (percentage)

Evaluation	Findings (n = 91)
Vitamin D status	
Sufficiency (20–100 ng/mL)	52 (57.1)
Insufficiency (12–20 ng/mL)	20 (22.0)
Deficiency (< 12 ng/mL)	19 (20.9)
Urine Ca/Cr ratio	
Normal	57 (62.6)
High	22 (24.2)
HbA1c level	
Normal (≤ 5.6%)	50 (55.0)
Prediabetes (5.7–6.4%)	5 (5.5)
Diabetes (≥ 6.5%)	4 (4.4)
C-peptide level	
Normal (0.5–3.0 ng/mL)	39 (42.9)
High (> 3.0 ng/mL)	19 (20.9)
Insulin level	
Normal (1.0–10.7 mcIU/mL)	36 (39.6)
High (> 10.7 mcIU/mL)	22 (24.2)
Reason for nutritional consultation	
High risk of malnutrition alone	83 (91.2)
High risk of malnutrition + weight for age < 5th percentile	6 (6.6)
High risk of malnutrition + intensive care unit admission	2 (2.2)
Results of nutritional consultation	
Appropriate nutrition	32 (35.2)
Malnutrition	59 (64.8)
Education on nutrition for overall malnutrition	30 (33.0)
Education on tube feeding	15 (16.5)
Education on parenteral nutrition	9 (9.9)

Data are presented as mean ± standard deviation or number (percentage)

Evaluation	Findings (n = 91)
Education on diabetes mellitus	4 (4.4)
Education on micronutrient intake	3 (3.3)
Education on obesity	3 (3.3)
Education on gastrointestinal issues	2 (2.2)
Data are presented as mean ± standard deviation or number (percentage)	

Eighty-three (64.8%) patients were classified as being at high risk of malnutrition. Among them, 30 (33.0%), 15 (16.5%), and 9 (9.9%) received education on nutrition, tube feeding, and parenteral nutrition, respectively. Four (4.4%), 3 (3.3%), 3 (3.3%), and 2 (2.2%) patients received education on diabetes mellitus, micronutrient intake, obesity, and gastrointestinal problems, respectively. Based on the body mass index, 35 patients (38.5%) had a normal weight, 35 (38.5%) were underweight, 9 (9.9%) were affected by overweight, and 12 (13.2%) had obesity. The most common abdominal radiography finding was ileus (62.6%). Based on the abdominal ultrasonography findings, 8.8% of patients had fatty liver and 9.9% had diffuse liver disease. One-third of the patients had gastroesophageal reflux disease, 55 patients were diagnosed with metabolic acidosis, and 44 patients showed an increase in the serum lactic acid levels. Vitamin D insufficiency or deficiency was seen in 42.9% of the patients. Diabetes mellitus and prediabetes were seen in 4.4% and 5.5% of the patients, respectively. The most common reason for nutritional consultation was the high risk of malnutrition. During the nutritional consultation for malnutrition, education on overall malnutrition was provided to 33% of the patients, while 16.5% and 9.9% of the patients received education on tube feeding and parenteral nutrition, respectively.

Comparison of the initial nutritional status according to diagnosis

As shown in Table 3, among the three MD groups, the age at the first nutritional consultation was the lowest in the Leigh syndrome group and the highest in the MELAS group. The proportion of patients with failure to thrive was high in the MELAS and non-specific MD groups ($p = 0.006$). The proportion of underweight patients was also higher in the MELAS and non-specific MD groups than in the Leigh syndrome group, and a higher number of patients with obesity were present in the Leigh syndrome group than in the other two groups. Lactic acid levels were higher in patients with MELAS ($p < 0.001$) than in patients with the other two subtypes, and vitamin D deficiency was more common in patients with MELAS and non-specific MD ($p = 0.017$) than in patients with Leigh syndrome. Patients with MELAS (88.2%) were highly likely to be prediabetic or diabetic. Gastroesophageal reflux disease was most commonly seen in patients in the non-specific MD group. The most common nutritional consultation received by patients with Leigh syndrome was an education on obesity. Education on diabetes mellitus was mainly provided to patients with MELAS.

Table 3
Comparison of initial nutritional status among the three subgroups of patients with mitochondrial disease

Characteristics	Leigh syndrome (n = 23)	MELAS (n = 17)	Non-specific MD (n = 51)	*p-value*
Age at first nutritional consultation	3 years, 6 months ± 3 years, 2 months	12 years, 7 months ± 7 years, 4 months	7 years, 5 months ± 5 years, 3 months	**< 0.001**
Failure to thrive	10 (43.5)	12 (70.6)	41 (80.4)	**0.006**
Body mass index category				
Normal	8 (34.8)	6 (35.3)	21 (41.2)	0.834
Underweight	3 (13.0)	8 (47.1)	24 (47.1)	0.015
Overweight	4 (17.4)	1 (5.9)	4 (7.8)	0.368
Obesity	8 (34.8)	2 (11.8)	2 (3.9)	**0.001**
Lactate level				
Normal (≤ 2.1 mmol/L)	8 (34.8)	2 (11.8)	35 (68.6)	**< 0.001**
Abnormal (> 2.1 mmol/L)	15 (65.2)	15 (88.2)	16 (31.4)	
Base excess				
Normal	11 (47.8)	2 (11.8)	25 (49.0)	**0.021**
Metabolic acidosis	12 (52.2)	15 (88.2)	26 (51.0)	
Hemoglobin level				
Normal	19 (82.6)	13 (76.5)	42 (82.4)	0.850
Low	4 (17.4)	4 (23.5)	9 (17.6)	
Serum iron level				
Normal (≥ 22 mcg/dL)	23 (100)	16 (94.1)	42 (82.4)	0.125
Low (< 22 mcg/dL)	0 (0)	1 (5.9)	7 (13.7)	
Iron saturation				
Normal (≥ 16%)	8 (34.8)	11 (64.7)	23 (45.1)	0.172

MD: mitochondrial disease, MELAS: Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

*p values < 0.05 were considered statistically significant.

Characteristics	Leigh syndrome (n = 23)	MELAS (n = 17)	Non-specific MD (n = 51)	*p-value*
Low (< 16%)	15 (65.2)	6 (35.3)	26 (51.0)	
Vitamin D status				
Sufficiency(20–100 ng/mL)	19 (82.6)	8 (47.1)	25 (49.0)	**0.017**
Insufficiency(12–20 ng/mL)	3 (13.0)	4 (23.5)	13 (25.5)	0.482
Deficiency(< 12 ng/mL)	1 (4.3)	5 (29.4)	13 (25.5)	0.074
Urine Ca/Cr ratio				
Normal	16 (69.6)	12 (70.6)	29 (56.9)	0.575
High	5 (21.7)	3 (17.6)	14 (27.5)	
HbA1c level				
Normal (≤ 5.6%)	13 (56.5)	9 (52.9)	28 (55.0)	0.975
Prediabetes (5.7–6.4%)	1 (4.3)	3 (17.6)	1 (2.0)	**0.047**
Diabetes (≥ 6.5%)	0 (0)	4 (23.5)	0 (0)	**< 0.001**
C-peptide level				
Normal (0.5–3.0 ng/mL)	9 (39.1)	10 (58.8)	20 (39.2)	0.802
High (> 3.0 ng/mL)	5 (21.7)	6 (35.3)	8 (15.7)	
Insulin level				
Normal (1.0–10.7 mcIU/mL)	9 (39.1)	8 (47.1)	19 (37.3)	0.492
High (> 10.7 mcIU/mL)	5 (21.7)	8 (47.1)	9 (17.6)	
Abdominal radiography findings				
Normal	7 (30.4)	8 (47.1)	13 (25.5)	0.248
Mild ileus	6 (26.1)	3 (17.6)	19 (37.3)	0.270
Moderate ileus	6 (26.1)	3 (17.6)	14 (27.5)	0.719
Severe ileus	1 (4.3)	1 (5.9)	4 (7.8)	0.847
Fecal impaction	3 (13.0)	3 (17.6)	0 (0)	**0.014**

MD: mitochondrial disease, MELAS: Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

*p values < 0.05 were considered statistically significant.

Characteristics	Leigh syndrome (n = 23)	MELAS (n = 17)	Non-specific MD (n = 51)	*p-value*
Gasless bowel	0 (0)	0 (0)	1 (2.0)	0.673
Abdominal ultrasonography findings				
Normal	15 (65.2)	8 (47.1)	28 (54.9)	0.504
Fatty liver	1 (4.3)	4 (23.5)	3 (5.9)	0.058
Diffuse liver disease	1 (4.3)	0 (0)	8 (15.7)	0.101
Non-specific findings	0 (0)	1 (5.9)	5 (9.8)	0.288
Gastroesophageal reflux disease	5 (21.7)	1 (5.9)	21 (41.2)	**0.014**
Reason for nutritional consultation				
High risk of malnutrition only	22 (95.7)	16 (94.1)	45 (88.2)	0.520
High risk of malnutrition + weight for age < 5th percentile	0 (0)	1 (5.9)	5 (9.8)	0.288
High risk of malnutrition + intensive care unit admission	1 (4.3)	0 (0)	1 (2.0)	0.641
Results of nutritional consultation				
Appropriate nutrition	8 (34.8)	7 (41.2)	17 (33.3)	0.841
Malnutrition	15 (65.2)	10 (58.8)	34 (66.7)	
Education on nutrition for overall malnutrition	8 (34.8)	6 (35.3)	16 (31.4)	0.935
Education on tube feeding	3 (13.0)	1 (5.9)	11 (21.6)	0.280
Education on parenteral nutrition	3 (13.0%)	0 (0)	6 (11.8%)	0.313
Education on micronutrient intake	2 (8.7)	0 (0)	1 (2.0)	0.227
Education on obesity	12 (52.2)	2 (11.8)	0 (0)	**< 0.001**
Education on gastrointestinal issues	0 (0)	0 (0)	2 (3.9)	0.448
Education on diabetes mellitus	0 (0)	4 (23.5)	0 (0)	**0.01**

MD: mitochondrial disease, MELAS: Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes

*p values < 0.05 were considered statistically significant.

Discussion

MD comprises a diverse group of disorders characterized by the disruption of ATP production [16]. Neurons and skeletal and cardiac muscles that require a high amount of energy are especially susceptible to impairment due to a limited ATP supply. In addition to neuromuscular system dysfunction, mitochondrial dysfunction causes gastrointestinal system-related malnutrition problems. A suboptimal nutritional status due to diverse factors causes various complications in patients with MD and adversely affects their quality of life and survival [17]. This study investigated the initial nutritional status of patients with MD, and we found that most of the patients were at a high risk of malnutrition based on the initial laboratory findings. Currently, as the key conservative treatment for MD is to improve mitochondrial energy and metabolic pathways, nutritional intervention may be as important as medication, such as mitochondrial cocktail therapy [18].

Mitochondria are involved in the utilization of nutrients through various metabolic pathways. Mitochondria generate most of the energy through aerobic mechanisms from macronutrients such as glucose, fatty acids, and amino acids. These energy sources are imported from the cytoplasm and enter metabolic pathways (citric acid cycle, b-oxidation, and amino acid oxidation), which produce nicotinamide adenine dinucleotide hydrogen and flavin adenine dinucleotide, transferring electrons into the mitochondrial respiratory chain via complexes I–IV. The passage of electrons, O_2, and H + ions across the inner mitochondrial membrane creates an electrochemical proton gradient between the matrix and the intermembrane space, thereby generating ATP [3]. Patients with MD show defects in oxidative phosphorylation, which reduces ATP synthesis and increases dependency on non-aerobic metabolic pathways for energy. These pathways may produce reactive oxygen species, causing oxidative cell damage [3]. Coenzyme Q10 deficiency may cause MD [18]. This biochemical defect may not only lead to malnutrition in these patients but may also cause weakness in the muscles of the gastrointestinal tract and severe gastroesophageal reflux disease, which may require temporary or permanent tube feeding [19].

Several studies have indicated that dietary interventions help correct the malnutritional status of patients with MD [3, 19]. Such patients may have inadequate caloric intake due to feeding difficulties caused by dysphagia or vomiting, which are the major gastrointestinal problems of patients with MD [20]. Because they are very susceptible to malnutrition, increasing the caloric quality and supply may help to increase the oxidative phosphorylation capacity [20]. Vitamin D supplementation is beneficial for patients with MD who have muscular weakness and fatigue, and it prevents the progression of osteoporosis [21]. Percutaneous endoscopic gastrostomy may be a good option for patients with insufficient nutritional intake due to difficulty in swallowing [20]. Ketogenic diets have been proposed as a nutritional therapeutic approach for patients with MD who have epilepsy [22]. A high-lipid and low-carbohydrate diet is known to be beneficial for patients with MD because it has neuroprotective and anti-inflammatory effects as it reduces excitotoxicity and oxidative stress. Ketogenic diets can be helpful in patients with pyruvate dehydrogenase deficiency. As per reports, affected individuals who were placed on a high carbohydrate restriction diet early in life showed increased longevity and improved mental development [23]. A

combination of coenzyme Q10, creatinine monohydrate, and lipoic acid, which is called antioxidant supplementation, reportedly led to a statistically significant improvement in biochemical markers [24].

Recently, studies focused on the malnutritional status of patients with neurological or metabolic diseases are being conducted, and active nutrition-based evaluation and intervention in patients with neuro-metabolic diseases are emphasized along with medication. Approximately 45% of patients with neurologic disease, except for vascular disease, in European hospitals are at a high risk of malnutrition [25]. Patients with malnutrition have a decreased quality of life and increased incidence of disease-related complications. Few patients with MD can be specifically treated, and most treatments are experimental or mainly symptomatic. Therefore, the early evaluation of malnutrition and active intervention to improve the nutritional status are relatively important for these patients. Generally, treatments for MD are mainly focused on increasing energy production. Probable therapies can include simple dietary management, micronutrient supplementation, and administration of antioxidants and cofactors. Thus far, there are relatively few studies that describe the nutritional status and quality of life of patients with MD. Particularly, there are almost no studies elucidating the nutritional status and treatment depending on the exact diagnosis of MD based on its subtypes [26]. In our study, we measured the initial nutritional status at the time of diagnosis of MD through various indicators and investigated the characteristics of malnutrition that appear according to the subgroup of MD. As mentioned above, the proportions of failure to thrive and underweight were higher in patients with MELAS and non-specific MD. Obesity was more commonly seen in the Leigh syndrome group than in the other two groups. There were many patients with gastroesophageal reflux disease in the non-specific MD group. Therefore, the need for nutritional intervention could be different among patients with MD as the nutritional status of each subgroup was different. As seen in our study, patients with Leigh syndrome were the youngest at the time of diagnosis among the three subgroups. Thus, they were able to receive more support and care, such as nutritional intervention, from the medical staff and their parents than the patients with the other subtypes of MD. Conversely, patients with MELAS had relatively less time to receive support because they were diagnosed later in life.

This study has several limitations. First, it had a retrospective design; therefore, selection bias might have occurred and data on the variables studied might be missing. Second, we confirmed the difference in initial nutritional status according to the subtypes of MD but could not completely define this difference physiologically. Therefore, there is a need for further studies to elucidate the exact mechanism underlying differences in nutritional status between MD subtypes. However, even though MD is a rare, incurable disease, this study included a relatively large number of patients and data from a single institution with a homogeneous treatment protocol followed over a period of 10 years. Till now, very few studies have examined the initial nutritional status of patients with MD and studied the need for different therapeutic interventions based on the nutritional status of patients with different subtypes of MD. Therefore, this study provides valuable insights into the need for nutritional intervention in patients with MD and shows the potential benefits of targeted nutritional intervention according to the MD subtype.

Conclusions

Through this study, we found that the nutritional status of patients with MD at the time of diagnosis is poor. Patients with malnutrition have a lower quality of life and more disease-related complications than patients with a good nutritional status. Very few studies have focused on the need for different nutritional interventions according to the clinical characteristics of patients with MD. The clinical course of MD is chronic and progressive, and a long-term follow-up of large cohorts is necessary for better understanding the severity of these conditions [27]. It is necessary to evaluate whether the nutritional status of the patients improves after appropriate nutritional interventions have been implemented. Accordingly, follow-up studies of patients with MD who are malnourished and continued research to track the progress of their nutritional status after implementing interventions are needed. In addition, in-depth studies are required to examine the exact mechanisms that contribute to the nutritional differences between patients with different subtypes of MD.

List Of Abbreviations

MD
mitochondrial disease
mtDNA
mitochondrial DNA
ATP
adenosine triphosphate
MELAS
mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
CSF
cerebrospinal fluid
NSVD
normal spontaneous vaginal delivery
SGA
small for gestational age
LGA
large for gestational age

Declarations

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

Y.L. and J.N. contributed in the concept, design and drafting of this study. G.J. and J.N. performed the acquisition, analysis, and interpretation of data. J.N and H.L. critically revised the manuscript. All authors approved the final version of the manuscript.

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Figures

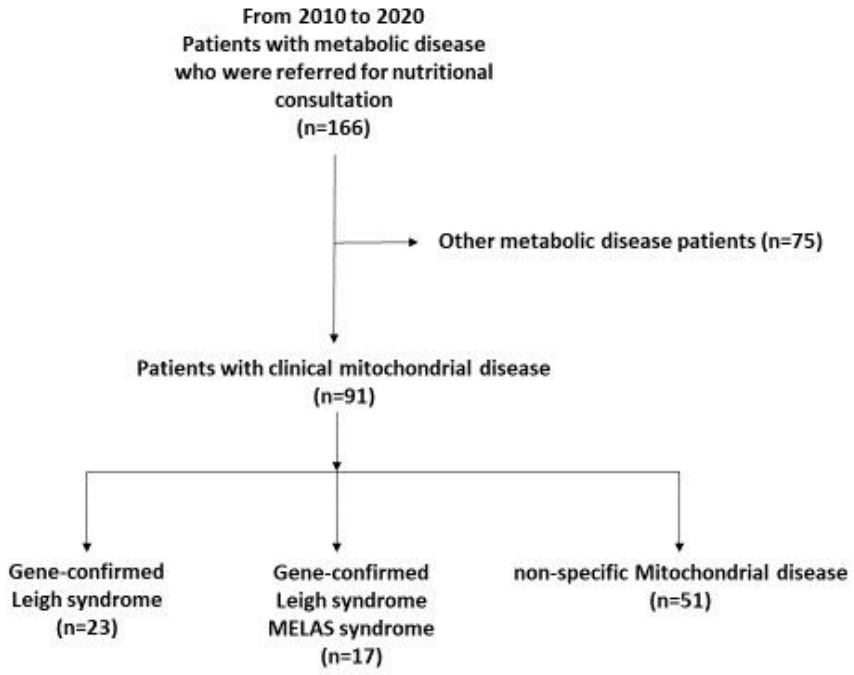

Figure 1. Summary of subjects and study design

Figure 1

See image above for figure legend.