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미토콘드리아 질환에서 웨스트 증후군 환자의 경련 발생 연령에 따른 임상 양상 비교

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Age-Based Characteristics of West Syndrome in Patients with Mitochondrial Disease

Purpose: West syndrome is a severe form of age-specific epilepsy that typically affects infants younger than 2 years of age with mitochondrial disease. We aimed to examine age-specific characteristics of the syndrome in these patients.
Methods: We retrospectively analyzed 54 patients with West syndrome diagnosed with mitochondrial disease between March 2006 and March 2016. We compared treatment strategies and diagnostic and clinical variables between patients with early-onset (<6 months of age) and late-onset (≥6 months of age) seizures.
Results: Seizure was the first symptom in 30 (90.9%) and 13 (65%) patients of the early-onset and late-onset groups, respectively (*P*=0.046). Delayed development was observed in 3 (9.1%) and 7 (35%) patients of the early-onset and late-onset groups, respectively (*P*=0.023). Lactate levels were normal in 17 patients (55%) of the early-onset group and 5 (25%) of the late-onset group (*P*=0.036), while initial brain magnetic resonance imaging (MRI) findings were normal in 23 (67.6%) and 8 (40%) patients of the early-onset and late-onset groups, respectively. Final MRI findings were abnormal in 32 patients (94.1%) of the early-onset group and 18 (90%) of the late-onset group (*P*=0.036). Although ketogenic diets reduced seizure frequency in both groups, the difference was not significant.
Conclusion: There is no significant difference in epilepsy-related variables when patients are divided based on a cut-off age of 6 months. However, differences in the first symptom at onset and MRI findings were observed. Although lactate levels were not of significant diagnostic value in the early-onset group, they may be in the late-onset group.

Key Words: Mitochondrial disease, West syndrome, Epilepsy, Lactic acidosis, Spasm

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Introduction

Mitochondrial disease is characterized by defects in mitochondrial energy metabolism (e.g., insufficient production of adenosine triphosphate (ATP) via the respiratory chain) as well as abnormal oxidative phosphorylation[1,2]. Mitochondrial disease is a clinically heterogeneous, multisystem disorder that represents a major cause of neurometabolic disorders during childhood[3]. Many patients with mitochondrial disease exhibit central nervous system (CNS) dysfunction, particularly

in the form of epilepsy[4].

West syndrome is a severe form of encephalopathy/age-specific epilepsy that typically affects infants under 2 years of age. It is characterized by spasms, hypsarrhythmia on electroencephalography (EEG), and delayed development. The incidence of West syndrome is 2 to 5 cases per 10,000 live births, with a prevalence rate of 1.5–2 per 10,000 children[5-7]. First-line treatment options include adrenocorticotropic hormone, high-dose prednisolone and vigabatrin; second-line options include the adoption of a ketogenic diet or the use of other antiepileptic drugs (AEDs)[8-10]. Patients with West syndrome diagnosed with mitochondrial disease show poor prognosis; 75–90% of these patients present with neurologic and developmental regression, and 50–60% present with recurrent seizures.

While several studies have investigated mitochondrial disease and West syndrome individually, few studies have examined these two together in children[1,2,11]. Previous studies have revealed that the proportion of patients with West syndrome is high among patients with mitochondrial disease who experience seizures, and that prognosis is poor in this population[11]. In the present study, we aimed to examine age-specific characteristics of West syndrome in patients with mitochondrial disease. We also reviewed clinical/diagnostic features and treatment options based on age.

Materials and Methods

1. Patients and inclusion criteria

We conducted a retrospective analysis of 54 patients with West syndrome diagnosed with mitochondrial disease at the Department of Pediatrics of Gangnam Severance Hospital between March 2006 and March 2016. Among 372 patients who met the modified criteria for mitochondrial disease proposed by Bernier et al.[12], 248 patients with diagnoses of epilepsy were selected. A total of 54 selected patients were diagnosed with West syndrome based on the following three features, in accordance with criteria outlined by the International League Against Epilepsy (ILAE): epileptic spasms, developmental delay, and characteristic EEG patterns (i.e., hypsarrhythmia)[13]. We then compared diagnostic and clinical variables between patients with early-onset (<6 months of age) and late-onset (≥6 months of age) seizures. Leigh syndrome (LS) that fulfilled the following criteria were included: 1) characteristic features of LS on neuroimaging, i.e., symmetrical hyperintense lesions in the basal ganglia and/or brainstem on T2-weighted magnetic resonance imaging; 2) abnormal energy metabolism indicated by a severe defect in oxidative phosphorylation or pyruvate dehydrogenase complex activity, and 3) genetic analysis of whole mtDNA performed at a diagnostic workup[14]. The study was approved by the Institutional Review Board of the Yonsei University Gangnam Severance Hospital (4-2011-0463).

2. Data collection for mitochondrial disease

Diagnostic evaluations for mitochondrial disease were performed based on detailed clinical features, laboratory studies, imaging studies, histology studies, and enzymatic analyses. Laboratory studies included serum lactic acid level. The degree of serum lactic acidosis was defined as mild, moderate, or severe if the increase relative to the normal reference values that is 0 to 2.0 mmol/L was at least two-, three-, or more than three-fold, respectively. Imaging studies included brain magnetic resonance imaging (MRI) and magnetic resonance spectroscopy. Histological and enzymatic analyses were performed using muscle biopsy specimens obtained from the quadriceps femoris muscle. Histological findings associated with mitochondrial disease were categorized as either specific (e.g., the presence of ragged red fibers or succinate dehydrogenase (SDH) staining) or non-specific (e.g., percentages of muscle fiber types and sizes on light microscopy). Biochemical enzyme analysis was performed to evaluate mitochondrial respiratory chain enzyme activity, which was regarded as defective when residual enzyme activity was less than 10% of the reference value. In the present study, the clinical status of mitochondrial disease was classified according to severity, as follows: 0, mild (i.e., the patient is independently ambulatory, but may or may not be dependent on others during daily activities); 1, moderate (i.e., the patient is confined to a wheelchair full-time or partially dependent on others during daily activities, with limited communication abilities); 2, severe (i.e., the patient is bedridden and totally dependent on others during daily activities; 3, expired.

3. Data collection regarding epileptic features of West syndrome

We investigated features of West syndrome, including seizure type, EEG pattern, and treatment strategies. Seizure type was classified based on the first symptom (head drop, spasms, generalized seizures), in accordance with ILAE criteria[13]. EEG studies were graded based on the presence of generalized slowing or focal slowing of background rhythms, focal sharp waves, multifocal sharp waves, generalized epileptiform discharge, and classic/modified hypsarrhythmic background activity. Treatment strategies included antiepileptic drugs, ketogenic diets, and surgery. Patients were evaluated for resistance to antiepileptic drugs based on the number of drugs utilized[15]. Ketogenic diets were assessed based on the frequency of seizures 6 months after initiation of the diet.

2. Statistical analysis

To assess the impact of age at the onset of the first seizure, patients were divided into early-onset (<6 months of age) and late-onset (≥ 6 months of age) groups. We then compared variables associated with mitochondrial disease and West syndrome between the two groups. All data were coded and analyzed using SPSS Statistics 22.0 (SPSS Inc, Chicago, IL, USA). Data were analyzed using descriptive statistics, including the mean, standard deviation, median, and range. Bivariate analyses were performed using t-tests and chi-square tests to evaluate differences between the groups. The level of statistical significance was set at $P<0.05$.

Results

1. Patient characteristics

A total of 54 pediatric patients with West syndrome were diagnosed with mitochondrial disease between January 2006 and January 2016, among whom 25 were male (46.3%) and 29 were female (53.7%) (Table 1). Prenatal asphyxia and hypoxic-ischemic encephalopathy (HIE) injuries at birth were noted in 14.8% and 9.3% of patients, respectively. Family history of mitochondrial disease was absent in 96.0% of patients. Initial symptoms included seizures (81.1%) and delayed development (18.9%). Mean age at first seizure onset was 6.3±6.0 months (range: 1 to 17 months). Most patients (92.6%) exhibited CNS involvement, although various organ involvement was also noted. Functional state at the

Table 1. Clinical Characteristics of the 54 Included Patients

Characteristics	Prevalence (n=54)	Subgroup based on age at first seizure		*P*-value
		<6 months (n=34)	≥6 months (n=20)	
Sex (male: female)	25 (46.3%):29 (53.7%)	17 (50%):17 (50%)	12 (60%):8 (40%)	0.477
Birth history				
Prematurity (<37 wks)	5 (9.3%)	3 (8.8%)	2 (10%)	0.619
SGA (<2,500 g)	4 (7.4%)	3 (8.8%)	1 (5%)	0.525
Prenatal asphyxia	8 (14.8%)	7 (20.6%)	1 (5%)	0.121
HIE	5 (9.3%)	4 (11.8%)	1 (5%)	0.381
Family history				
None	52 (96.3%)	33 (97.1%)	19 (95%)	0.608
Mitochondrial disease	0 (0%)	0 (0%)	0 (0%)	-
Seizure	2 (3.7%)	1 (2.9%)	1 (5%)	0.608
First presenting symptoms (n, %)				
Seizure	43/53 (79.6%)	30/33 (90.9%)	13/20 (65%)	0.046
Delayed development	10/53 (18.5%)	3/33 (9.1%)	7/20 (35%)	0.023
Age at first symptoms (months)	5.1±4.2 (1–17)	2.7±1.4 (1–5)	9.3±4.2 (3–17)	<0.001
Age at first seizure (months)	6.3±6.0 (1–29)	2.9±1.5 (1–5)	12.2±6.4 (6–29)	<0.001
Organs involvement (n, %)				
Central nervous system	50 (92.6%)	32 (94.1%)	18 (90%)	0.475
Gastrointestinal system	17 (31.5%)	12 (35.3%)	5 (25%)	0.318
Respiratory system	9 (16.7%)	7 (20.6%)	2 (10%)	0.270
Musculoskeletal system	6 (11.1%)	2 (5.9%)	4 (20%)	0.127
Renal system	6 (11.1%)	5 (14.7%)	1 (5%)	0.268
Cardiologic system	5 (9.3%)	4 (11.8%)	1 (5%)	0.381
Eye	2 (3.7%)	1 (2.9%)	1 (5%)	0.608
Endocrine system	2 (3.7%)	2 (5.9%)	0 (0%)	0.392
Hematologic system	1 (1.9%)	0 (0%)	1 (5%)	0.370
Functional state				
Mild*	2 (3.7%)	2 (5.9%)	0 (0%)	0.392
Moderate†	14 (25.9%)	8 (23.5%)	6 (30%)	0.600
Severec‡	33 (61.1%)	21 (61.8%)	12 (60%)	0.898
Expired§	5 (9.3%)	3 (8.8%)	2 (10%)	0.475

SGA, Small for gestational age; HIE, Hypoxic-ischemic encephalopathy.
*The patient is independently ambulatory, but may or may not be dependent on others during daily activities.
†The patient is confined to a wheelchair full-time or partially dependent on others during daily activities, with limited communication abilities.
‡The patient is bedridden and totally dependent on others during daily activitie.
§Expired.

final follow-up visit was classified as mild, moderate, and severe in 3.7%, 25.9%, and 61.1% of patients, respectively.

2. Diagnostic evaluations for mitochondrial disease

The results of diagnostic evaluations for mitochondrial disease are presented in Table 2. Twenty-nine patients exhibited increases in serum lactic acid levels. Serum levels of lactic acid were normal, mildly increased, moderately increased, and severely increased in 22 (43.1%), 17 (33.3%), 9 (17.6%), and 3 (5.9%) patients, respectively. Muscle biopsy findings and mitochondrial respiratory chain enzyme activity are also shown in Table 2. Mitochondrial respiratory chain (MRC) complex I, II, and IV defects were noted in 42 (89.4%), 1 (2.1%), and 4 (8.5%) patients, respectively. Specific findings for mitochondrial disease were noted 13 patients (24.5 %) based on light microscopy analyses. Electron microscopy analyses revealed megaconia and pleioconia in 29 (55.8%) and 26 (50.0%) patients, respectively. Initial MRI findings were normal in 31 patients (57.4%) and abnormal in 23 patients (42.6%). MRI findings at the last visit were normal in 5 patients (9.3%) and abnormal in 49 (90.7%). Abnormalities included abnormal signals in different areas of the brain or atrophy. Specifically, abnormal signals were observed in the basal ganglia in 6 patients (11.1%), in the thalamus in 8 patients (14.8%), and in the brainstem in 9 patients (16.7%). Atrophy of the cerebellum and cortex was observed in 28 patients (51.8%), while diffuse cerebral atrophy was observed in 47 patients (87.1%).

3. Diagnosis and treatment of West syndrome

In patients with West syndrome diagnosed with mitochondrial disease, seizure was the first symptom in 34 (63%) patients before the age of 6 months and in 20 (37.1%) patients after age of 6 months. The latest age for seizure onset was 29 months (Table 3). The first seizure type was spasm in 43 patients (79.6%), head drop in 4 patients (7.4%), and generalized seizure in 7 patients (13%). EEG revealed classic hypsarrhythmia in 37 patients (68.5 %), generalized slowing of background rhythms in all patients, and focal slowing in 10 patients (18.9%). The epileptiform discharge was multifocal in 49 patients (92.5%). Within the first 3 months after diagnosis, the mean number of AEDs used was 1.7±0.9, although this value increased to more than 2 AEDs after the age of 6 months, which indicates drug resistance. Patients whose seizures remained uncontrolled despite the use of more than 2 AEDs were started on a ketogenic diet, which was effective in reducing seizures by 50% in 22 patients (71%). In addition, 20 patients (64.5%) experienced sustained reductions in the incidence of spasms for more than 6 months. Of the two patients who received surgery, one underwent total callostomy, while the other underwent right frontal lobectomy with temporal disconnection.

4. Analysis of clinical characteristics by subgroup

Clinical characteristics according to subgroup are presented in Table 1. The age at first symptom onset was 2.7±1.4 months in the early-onset group and 9.3±4.2 months in the late-onset group.

Table 2. Results of Diagnostic Evaluations for Mitochondrial Disease

Evaluation	Findings	Prevalence (n=54)	Subgroup based on age at first seizure		*P*-value
			<6 months (n=34)	≥6 months (n=20)	
Serum lactic acidosis	Normal	22/51 (43.1%)	17/31 (54.8%)	5/20 (25%)	0.036
	Mildly increased (1- to 2-fold)	17/51 (33.3%)	7/31 (22.6%)	10/20 (50%)	0.043
	Moderately increased (2- to 3-fold)	9/51 (17.6%)	5/31 (16.1%)	4/20 (20%)	0.723
	Severely increased (≥3-fold)	3/51 (5.9%)	2/31 (6.5%)	1/20 (5%)	0.830
Syndromic Diagnosis	Leigh syndrome	11/54 (20.4%)	7 (20.6%)	4 (20%)	0.623
	Nonspecific mitochondrial disease	43/54 (79.6%)	27 (79.4%)	16 (80%)	0.623
Biochemical enzyme assay	MRC complex I defect	42/47 (89.4%)	26/29 (89.7%)	16/18 (94.1%)	0.644
	MRC complex II defect	1/47 (2.1%)	0/29 (0%)	1/18 (5.9%)	0.383
	MRC complex IV defect	4/47 (8.5%)	3/29 (10.3%)	1/18 (5.9%)	0.502
Histopathologic assay under LM	Normal	33/53 (62.3%)	18/34 (52.9%)	15/19 (78.9%)	0.061
	Specific findings for mitochondrial diseases	13/53 (24.5%)	10/34 (29.4%)	3/19 (15.8%)	0.223
	Nonspecific abnormalities	7/53 (13.2%)	6/34 (17.6%)	1/19 (5.3%)	0.201
Histopathologic assay under EM	Normal	23/52 (44.2%)	13/33 (39.4%)	10/19 (52.6%)	0.355
	Megaconia	29/52 (55.8%)	20/33 (60.6%)	9/19 (47.4%)	0.773
	Pleioconia	26/52 (50%)	17/33 (51.5%)	9/19 (47.4%)	0.355
MRI at initial diagnosis	Normal	31/54 (57.4%)	23/34 (67.6%)	8/20 (40%)	0.047
	Abnormal	23/54 (42.6%)	11/34 (32.4%)	12/20 (60%)	0.047
MRI at last visit	Normal	5/54 (9.3%)	2/34 (5.9%)	2/20 (10%)	0.475
	Abnormal	49/54 (90.7%)	32/34(94.1%)	18/20 (90%)	0.475

MRC, mitochondrial respiratory chain; LM, light microscopy; EM, electron microscopy; MRI, magnetic resonance imaging.

The age at first seizure was 2.9±1.5 months in the early-onset group and 12.2±6.4 months in the late-onset group. As classification criteria were based on age, significant differences in these criteria were observed between the groups. There were 30 patients (90.9%) with earlier seizure onset who experienced seizure as the first symptom, relative to 13 patients (65%) with late-onset seizures (P=0.046). Delayed development was observed in 3 patients (9.1%) with early-onset seizures and 7 patients with late-onset seizures (35%) (P=0.023). No significant differences in organ involvement, functional state, respiration, or feeding status were observed. The duration between the first diagnosis of West syndrome and the final follow-up was 8.0±5.1 years in the early-onset group and 9.8±5.1 years in the late-onset group.

5. Diagnostic analysis of mitochondrial disease by subgroup

We evaluated serum levels of lactic acid based on the age at the onset of the first seizure (Table 2). Serum levels of lactic acid were normal in 17 patients (54.8%) of the early-onset group and 5 patients (25%) of the late-onset group (P=0.036). Significant differences in these abnormalities were observed only among patients with mild increases in serum lactic acid levels (early-onset group: 22.6% (n=7) vs. late-onset group: 50% (n=10) (P=0.043)). Initial MRI findings were normal in 23 patients (67.6%) of the early-onset group and 8 patients (40%) of the late-onset group (P=0.047). There was a statistically significant difference in the initial MRI findings between the two groups according to the age at onset. MRI findings at the last visit were abnormal in 32 patients (94.1%) of the early-onset group and 18 patients (90%) of the late-onset group, with no significant differences between the two groups (P=0.475).

6. Diagnosis and treatment of West syndrome

Because we classified first seizure onset based on age, significant differences in this variable were observed between the two groups (P<0.001). No significant differences in seizure type or EEG findings (i.e., hypsarrhythmia, background rhythm, epileptiform

Table 3. Diagnosis and Treatment of Infantile Spasms

Clinical Feature	Specification	Prevalence (n=54)	Subgroup based on age at first seizure		P-value
			<6 months (n=34)	≥6 months (n=20)	
First Seizure Type	Head drop	4/54 (7.4%)	1/34 (2.9%)	3/20 (15%)	0.138
	Spasm				
	Flexor dominant	18/54 (33.3%)	12/34 (35.3%)	6/20 (30%)	0.690
	Extensor dominant	9/54 (16.7%)	5/34 (14.7%)	4/20 (20%)	0.441
	Indeterminant	16/54 (29.6%)	9/34 (26.5%)	7/20 (35%)	0.507
	Generalized seizure				
	GTC	4/54 (7.4%)	4/34 (11.8%)	0/20 (0%)	0.147
	GT	3/54 (5.6%)	3/34 (8.8%)	0/20 (0%)	0.241
EEG					
Background rhythm	Generalized slowing	53/53 (100%)	34/34 (100%)	19/19 (100%)	-
	Focal slowing	10/53 (18.9%)	8/34 (23.5%)	2/19 (10.5%)	0.217
Epileptiform	Focal sharp/spike waves	4/53 (7.5%)	3/34 (8.8%)	1/19 (5.3%)	0.547
	Multifocal sharp waves	49/53 (92.5%)	31/34 (91.2%)	18/19 (94.7%)	0.547
	Generalized epileptiform discharge	36/53 (67.9%)	22/34 (64.7%)	14/19 (73.7%)	0.502
Hypsarrhythmia	Classic	37/53 (68.5%)	22/34 (64.7%)	15/20 (75%)	0.432
	Atypical	17/53 (31.5%)	12/34 (35.3%)	5/20 (25%)	0.432
Treatment options					
Antiepileptic drugs	3 months after diagnosis	1.7±0.9 (1–4)	1.8±0.8 (1–3)	1.7±1.1 (1–4)	0.916
	6 months after diagnosis	2.6±0.9 (1–4)	2.7±0.9 (1–4)	2.4±0.9 (1–4)	0.282
	1 year after diagnosis	2.6±1.0 (1–5)	2.6±1.0 (1–5)	2.5±1.1 (1–4)	0.614
	2 years after diagnosis	2.6±1.3 (0–6)	2.7±1.4 (0–6)	2.6±1.1 (1–5)	0.942
Ketogenic diet	Seizure reduction rate				
	Reduction >50%	22/31 (71.0%)	13/18 (72.2%)	9/12 (69.2%)	0.583
	Reduction <50%	2/31 (6.5%)	0/18 (0%)	2/13 (15.4%)	0.168
	No effect	7/31 (22.6%)	5/18 (27.8%)	2/12 (16.7%)	0.358
	Retention rate				
	Retention >6 months	20/31 (64.5%)	13/18 (72.2%)	7/12 (53.8%)	0.334
	Retention <6 months	11/31 (35.5%)	5/18 (27.8%)	6/12 (46.2%)	0.263
Epilepsy surgery	Yes	2/54 (3.7%)	1/34 (2.9%)	1/20 (5%)	0.400

GTC, generalized tonic clonic; GT, generalized tonic; EEG, electroencephalography.

discharge) were observed between the groups. In addition, we observed no significant differences in surgery rates or the use of AEDs or ketogenic diets between the two groups (Table 3).

Discussion

In the present study, we examined the age-specific characteristics of West syndrome in 54 pediatric patients who were diagnosed with mitochondrial disease. West syndrome is usually classified as either cryptogenic or symptomatic, although approximately 60–80% of cases are symptomatic[16,17] . While some studies have indicated that spasm is typically the first major symptom, followed by developmental delay, others have indicated the reverse[18,19]. These differences are considered to be due to differences in the criteria for categorizing symptoms, as well as differences among patient groups and observers. In the present study, most patients in the early-onset group experienced spasm as the first symptom, while most patients in the late-onset group experienced developmental delay as the first symptom. These findings suggest that West syndrome should be considered when patients with mitochondrial disease present with developmental delay after the age of 6 months, and that patients prior to this age should be evaluated for spasms, since developmental assessments may be ambiguous.

West syndrome is an epilepsy syndrome characterized by early onset, usually presenting between the ages of 4 and 7 months[20]. Bednarek et al. studied West syndrome by dividing patients into groups of those younger or older than 1 year . While there were similar characteristics, such as developmental delay and hypsarrhythmia, the etiology and EEG findings were different in each group[21,22]. The late-onset group was characterized by less-prominent slow waves, more-numerous multifocal spikes, and more-marked interhemispheric synchronization on interictal EEG. The treatment responses to vigabatrin and steroids are lower in patients with late-onset[23,24]. Gul Mert et al. reported that neurodevelopmental outcomes are worse in patients with early-onset infantile spasms[25]. In the present study, patients were categorized based on the cut-off age of 6 months, which was the highest incidence. Although we observed no significant differences in seizure type, EEG findings, or treatment based on age, further studies are required to determine whether our findings were due to variables associated with mitochondrial disease or to West syndrome.

Lactic acidosis is the most recognized laboratory abnormality in patients with mitochondrial disease[26,27]. In patients with primary mitochondrial disease, true elevations in lactate levels exhibit a sensitivity between 34–62%, and a specificity between 83–100%[28,29]. Previous studies have also indicated that increases in lactate levels are more significant in children than in adults[30]. In the present study, lactate levels were not of significant diagnostic value in the early-onset group. However, significant changes were observed in patients of the late-onset group, indicative of greater diagnostic value in this group. These findings suggest that, even though lactate levels are more sensitive in children than adults, these levels are less useful prior to the age of 6 months.

MRI abnormalities are reported in approximately 70–80% of patients with West syndrome[31,32]. The duration of spasms tends to be shorter in patients with normal MRI findings than in those with abnormal MRI findings. Developmental outcomes are also better for patients with normal MRI findings and worse for patients with perinatal injuries[33,34]. In the present study, MRI findings were normal in 67.6% of patients with early-onset seizures but only 40% of patients with late-onset seizures. However, at the last visit, findings were normal in 5.9% and 10% of patients with early- and late-onset seizures, respectively. These findings suggest that the timing of the MRI evaluation is important, and that continued MRI evaluations are necessary as brain development progresses.

The ketogenic diet is accepted as a potent antiepileptic treatment for intractable childhood epilepsy[35,36]. Eun et al. reported that ketogenic diets exhibit dramatic efficacy even among patients with intractable infantile spasms[37]. However, some studies have suggested that ketogenic diets can be lethal in patients with underlying metabolic diseases[38]. The ketogenic diet is also known to promote metabolic stress in patients with MRC complex defects, and its use is typically avoided in such cases[39,40]. However, Kang et al. reported that patients with such defects can tolerate the ketogenic diet when supplementary mitochondrial cocktail therapy is administered[41]. In the present study, we observed that ketogenic diets were effective in treating patients with West syndrome and mitochondrial disease, although there was no statistically significant difference between the two age groups. Nonetheless, clinicians should remain aware of the potential complications associated with their use in this patient population.

The present study is limited in that prospective randomization was not used to select participants or set other research parameters, as mitochondrial disease is incredibly rare. Despite these limitations, our analyses provide valuable data regarding a homogenous group of patients with West syndrome and mitochondrial disease. Our study is also advantageous in that patients were compared and analyzed according to the age at symptom onset. Previous studies have revealed that the proportion of patients with West syndrome is high among patients with mitochondrial

disease who experience seizures.

In conclusion, our findings indicated that there was no significant difference in epilepsy-related variables when patients with West syndrome and mitochondrial disease were divided based on a cut-off age of 6 months. However, differences in the first symptom at onset and MRI findings were observed according to age at onset. In addition, MRI findings were more specific in the late-onset group. Although our findings indicate that lactate levels were not of significant diagnostic value in the early-onset group, they were of diagnostic value in the late-onset group. Our findings also indicated that ketogenic diets are effective in reducing symptoms in patients with West syndrome and mitochondrial disease. Taken together, our results can be applied to the diagnosis and treatment of West syndrome based on the age at disease onset. Future large-scale studies are required to develop a clinical protocol for age-related diagnosis and treatment.

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요약

목적: 미토콘드리아 질환은 산화적 인산화의 결함으로 인한 세포 에너지의 부족으로 발생하는 이질적인 질환이다. 이 질환은 소아에서 대사질환의 중요한 원인이며 임상증상으로는 경련이 대표적이다. 웨스트 증후군은 영아기에 특징적으로 보이는 뇌전증 증후군이다. 우리는 미토콘드리아 질환에서 웨스트 증후군 환자의 임상 양상을 비교분석하였다.

방법: 본 연구는 2006년부터 2016년까지의 의무기록을 통해 후향적 연구를 진행하였다. 미토콘드리아 질환으로 진단 된 환자 중 웨스트 증후군으로 확인 된 54명의 소아를 대상으로 하였다. 환자군을 경련 발생 연령 6개월을 기준으로 조기 발병 그룹과 후기 발병 그룹으로 나누었고 이들의 임상 양상을 비교분석하였다.

결과: 첫 임상증상으로 경련을 보이는 경우가 조기 발병 그룹에서 90.9%, 후기 발병 그룹에서는 65% 였으며(P=0.046) , 발달 지연은 조기 발병 그룹에서는 9.1%, 후기 발병 그룹에서는 35% 였다(P=0.023). 또한 조기 발병 그룹에서 젖산 혈증은 45%, 초기 MRI 이상 소견은 67.6%, 마지막 MRI 이상 소견은 94.1%에서 나타났고 후기 발병 그룹에서 젖산 혈증은 75%, 초기 MRI 이상 소견은 40%, 마지막 MRI 이상 소견은 90%에서 나타났다. 케톤생성 식이요법은 미토콘드리아 질환을 가진 웨스트 증후군 환자 31명에서 시행하였고 22명의 환자에서 경련 횟수가 50% 이상 감소하는 효과가 있었다.

결론: 미토콘드리아 질환에서 웨스트 증후군 환자들을 경련 발생 연령을 기준으로 비교분석 했을 때 경련 관련 요인에 대해서는 큰 차이를 보이지 않았다. 하지만 미토콘드리아 질환 관련 요인과 MRI에 대해서는 일부 의미 있는 차이가 있었다. 또한 케톤생성 식이요법은 미토콘드리아 질환을 가진 웨스트 증후군 환자에서도 효과가 있었다.

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