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Effective and safe diet therapies for Lennox-Gastaut syndrome with mitochondrial dysfunction

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Abstract

Background: Lennox-Gastaut syndrome (LGS) is a typical intractable form of epilepsy that most often occurs between the second and sixth year of life. This study aimed to evaluate the clinical efficacy and safety of ketogenic diet therapies (DTs) for LGS with mitochondrial dysfunction.

Methods: This was a retrospective study involving 20 LGS patients with mitochondrial dysfunction who received several DTs from 2004 to 2014 at a single tertiary care center. Seizure reduction rate, cognitive function, retention rate, electroencephalography (EEG) changes, and adverse effects were examined before and after DTs.

Results: The retention rates at 1 and 2 years after initiation of DTs were 45% and 40%, respectively. After 1-year follow up, we observed seizure freedom in two patients, 75% seizure reduction in two patients, 50% reduction in three patients, and 25% reduction in one patient. After 2-year follow up, the outcomes were seizure freedom in two patients, 90% seizure reduction in one patient, 75% reduction in two patients, and 50% reduction in two patients. EEG findings improved in nine patients. Nine patients were treated with DTs for 1 year; all patients demonstrated improved cognitive status. Eight patients were treated with DTs for 2 years, of whom seven had improved cognitive status. Poor tolerability of DTs was due to poor oral intake and gastrointestinal problems.

Conclusions: We demonstrate that, in LGS with mitochondrial dysfunction, improvement of seizures and cognitive function are not inferior to those in other patients treated with DTs. This study showed that DTs are efficacious and feasible for LGS patients with mitochondrial dysfunction and can significantly improve their prognosis.

Keywords: Lennox-Gastaut Syndrome, mitochondrial dysfunction, diet therapies, ketogenic diet, modified Atkins diet, efficacy, safety

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Introduction

Lennox-Gastaut syndrome (LGS) is a typical intractable form of epilepsy that most often appears between the 2nd and 6th year of life. Various etiologies underlie the onset of LGS.[1,2] Characteristic epileptic discharges known as generalized sharp and slow wave (GSSW) complexes and generalized paroxysmal fast activity (GPFA) in electroencephalography (EEG), multiple types of seizures, and severe intellectual impairment are the triad of LGS symptoms.[1–3] Pediatric neurologists prescribe several antiepileptic drugs (AEDs) for the treatment of LGS, but these are often ineffective. Therefore, alternative therapies such as ketogenic diet therapies (DTs) including the ketogenic diet (KD) and variants of KD, such as modified Atkins diet (MAD), and epileptic surgery have been attempted as treatments for LGS.[3]

Mitochondrial dysfunction with neurological manifestations may accompany several of the etiologies that can cause LGS.[4] Mutations in genes located in mitochondrial or nuclear DNA cause primary dysfunction of the mitochondrial respiratory chain

(MRC), which causes a heterogeneous group of disorders known as mitochondrial diseases.[5–7] The symptoms of mitochondrial dysfunction are diverse, and include neurologic, gastrointestinal (GI), endocrinological, and musculoskeletal symptoms. Among them, neurologic symptoms, mainly epilepsies, are an important factor that determines disease prognosis. Epilepsy with mitochondrial dysfunction is not well treated with conventional AEDs. In this regard, various other treatment methods are being attempted.[8–10]

There are reports of cases in which alternative treatments to AEDs have been applied in epilepsy patients with mitochondrial dysfunction. One such approach has been the use of DTs, which has been established since the mid-1990s as an effective treatment for intractable childhood-origin epilepsy.[4] DTs have produced beneficial effects in patients who do not respond well to conventional AEDs, such as patients with LGS, Ohtahara syndrome, and Dravet syndrome.[2] So far, the efficacy of DTs for treating mitochondrial dysfunction is unclear.[4,11,12] Previous studies have reported on the safe and effective use of DTs in patients with various epilepsies with mitochondrial dysfunction[4]; these studies also included cases of LGS. Nevertheless, due to the small number of LGS patients included, it was difficult to establish the characteristics of patients with LGS with mitochondrial dysfunction. Thus, it remains unclear whether DTs can be effectively administered as adjunctive therapy in patients with LGS with mitochondrial dysfunction.

Examination of the characteristics and treatment approaches for patients with LGS with mitochondrial dysfunction, the most severe form of epilepsy, is an important problem for pediatric neurologists in planning treatment. In this study, we prescribed DTs as adjunctive treatment for patients with LGS with mitochondrial dysfunction in a single tertiary hospital, and investigated their clinical efficacy, safety, and feasibility.

Materials and methods

Inclusion of patients and data collection

This was a retrospective study of patients with LGS with mitochondrial dysfunction who received DTs from 2004 to 2014 in a single tertiary care center: Severance Hospital, Seoul, Korea. As described earlier, LGS is characterized by a triad of symptoms: multiple types of seizures; EEG abnormalities: GSSW during wakefulness, and bursts of diffuse fast rhythmic waves and slow polyspikes and GPFA during sleep; and (3) severe intellectual impairment.[1–3] We first selected LGS patients based on this triad. The total number of patients with LGS with mitochondrial dysfunction included in this study was 20. Their epilepsy-related characteristics, mitochondrial dysfunction-related characteristics, and changes in clinical status after DTs were studied. This study was carried out in accordance with the recommendations of the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine, which approved the protocol, with written informed consent obtained from all subjects in accordance with the tenets of the Declaration of Helsinki (approval number 3-2017-0168).

Evaluation of epilepsy

The epileptic characteristics of the patients were evaluated based on intervals of age at first seizure, age at diagnosis of LGS, and age at initiation of DTs. History of infantile spasms, seizure type, seizure frequency, EEG findings, types of AEDs used before the DTs, and initial types of DTs, was collected.[3,4]

Evaluation of mitochondrial dysfunction

The mitochondrial dysfunction profiles of all patients, including the serum lactate/pyruvate ratio and severity of serum lactic acidosis, were graded as follows: normal, within the normal reference; mildly increased, $\geq$2-fold of the normal reference; moderately increased, $\geq$3-fold of the normal reference; severe, $\geq$4-fold of the normal reference values.[13] The serum lactate and pyruvate levels were measured in arterial blood samples, with a lactate to pyruvate ratio $>$20 being indicative of respiratory chain complex dysfunction.

Abnormalities of urine organic acids (UOAs), plasma amino acids (PAAs), magnetic resonance imaging (MRI), and MR spectroscopy (MRS) were examined. Muscle biopsies of patients were obtained, and samples of muscle biopsies were processed through routine morphological and histochemical staining that included periodic acid-Schiff, modified Gomori trichrome, ATPase 9.4, nicotinamide adenine dinucleotide tetrazolium reductase, and succinate dehydrogenase stains. All samples were examined for electron

microscopic changes, such as pleoconia and megaconia. Finally, MRC enzyme complex activities were evaluated by standard spectrophotometric assays to assess the activities of NADH–coenzyme Q (CoQ) reductase (complex I), succinate-CoQ reductase (complex II), succinate–cytochrome c reductase (complex II–III), cytochrome *c* reductase (complex III), cytochrome *c* oxidase (complex IV), and citrate synthase enzymes in isolated mitochondria from freshly prepared muscle tissue.[3,4,13,14] The activities of these complexes were assessed in isolated mitochondria obtained from muscle tissue using standard spectrophotometric assays, as described by Rustin and colleagues.[15] We defined MRC defects as a reduction of residual enzyme activity to below 10% of that of controls.[16]

Diet therapies

Most patients (16 patients) received a KD with a lipid:nonlipid ratio of 4:1. Some patients received a lipid:nonlipid ratio of 3:1 (two patients) or MAD (two patients) according to clinical tolerability. Plasma acyl carnitine profiles were used to screen for mitochondrial fatty acid disorders, and no abnormal findings were noted.[4] All patients were started on the DTs with a nonfasting protocol. On the first day of DT, the DT started with one-third of required calories, two-thirds on the second day, and full calories from the third day as tolerated, without any prior fasting or fluid restriction.[17,18] All patients receiving diet therapy screened initial lipid profile tests (cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride). We confirmed no abnormality in the lipid profile test in all patients. We also identified urine ketone and blood ketone during diet therapy, and confirmed that all patients established ketosis.

Efficacy and tolerability of diet therapies

To evaluate the efficacy of the DTs, seizure reduction rate, change in EEG findings, and cognitive progress were used as variables. Side effects and retention rate were used as variables to evaluate the tolerability of the DTs. To assess the seizure reduction rate after the DTs, the baseline seizure frequency of each patient was set as '0'. The effect of the DTs was evaluated every 3 months after starting the DTs. The higher the number, the greater the effect, with '100' indicating seizure freedom.[2,4] In addition, we examined the effect of DTs based on EEG findings and cognitive progress before and after DTs. The EEG findings were graded as follows: normalization; slow and disorganized background rhythm without focal or unilateral sharp wave discharges; slow and disorganized background rhythm with focal or unilateral sharp wave discharges; and slow and disorganized background rhythm with GSSW, GPFA, and multifocal sharp wave discharges.[4] Cognitive progress was expressed in two stages (Improved, Static) compared with baseline levels based on the results of interviews and simple questionnaire with careful examination of patents by more than two pediatric neurologists who directly treated the patients. The side effects of DTs, and clinical severity after the DTs, were evaluated in each patient.

Clinical severity after the DTs was graded as follows: normal, asymptomatic, or no apparent disability in cognition or mobility; mild, self-ambulatory, with or without independence for daily activities; moderate, full-time wheelchair-bound, or partially dependent for daily activities, with ability for brief communication; severe, bedridden, totally dependent for daily activities, or expired.[3,13] The retention rates at 1 year and 2 years after DT initiation were quantified to assess DT tolerabilitys.[19]

Results

Clinical characteristics of patients

Table 1 shows the clinical characteristics of the patients. The male to female ratio of the patients was the same. The median age at first clinical presentation was 13 months (range, 1–84 months). Seizure was the first symptom at disease onset in 80% of all patients. Based on the last visit to the clinic, it was determined that the patients presented with problems in various organs; symptoms in the central nervous system were observed in all patients. Perinatal history was documented in 15% of patients. Regression was observed in all patients.

Epilepsy profile of patients

Table 2 shows the epilepsy profiles of the patients. The median age at first seizure was 14 months (range, 1–88 months). The median age at diagnosis of LGS was 37 months (range, 12–132 months). The median value of the time interval from first seizure to diagnosis of LGS was 9 months (range, 1–120 months). The median age at initiation of

Table 1. Clinical characteristics of patients.

Characteristics	Total ($n = 20$)
Gender (male: female)	10 (50.0%): 10 (50.0%)
Age of first clinical presentation (months)	13 (1–84)
First symptom at disease onset, *n* (%)	
Seizure	16 (80.0%)
Delayed development	3 (15.0%)
CNS infection	1 (5.0%)
Organs involved at the last visit, *n* (%)	
CNS	20 (100.0%)
GI system	7 (35.0%)
Endocrinology	5 (25.0%)
Skeletal muscle	2 (10.0%)
Heart	1 (5.0%)
Perinatal history, *n* (%)	
NICU care	3 (15.0%)
IUGR	3 (15.0%)
Perinatal asphyxia	2 (10.0%)
Preterm	2 (10.0%)

CNS, central nervous system; GI, gastrointestinal; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit.

DTs was 4.6 years (range, 1.1–14.1 years). The median time interval from diagnosis of LGS to initiation of DT was 7 months (range, 0–93 months).

Nine patients (45.0%) had a history of infantile spasms. Patients had various types of seizures, most of which were daily seizures. Characteristic EEG findings of LGS, such as GSSW and GPFA, were observed in all patients at the point of LGS diagnosis. Several AEDs were used as first-line treatment. Zonisamide, valproic acid, clobazam, phenobarbital, and topiramate were the major AEDs used before DTs. When treatment with AEDs failed, DTs were prescribed. A total of 16 patients were prescribed a KD with a lipid:nonlipid ratio of 4:1. Two patients were prescribed a KD with a lipid:nonlipid ratio of 3:1, and two were prescribed the MAD.

Mitochondrial dysfunction profiles of patients

Table 3 indicates the mitochondrial dysfunction profiles of the patients. The median age of evaluation of mitochondrial dysfunction was 49 months (range, 7–138 months). The median time interval from first clinical presentation to diagnosis of mitochondrial disease was 31 months (range, 1–126 months).

Serum lactate and serum pyruvate were measured in initial laboratory assessments. The median value of lactic acidosis in patients was 2.13. The median value of the serum lactate: pyruvate ratio was 10.58 (range, 0.95–26.08). Based on grading of serum lactic acidosis diagnosis (%), patients were divided into four lactate levels, seven patients (35.0%) had normal lactate levels, eight patients (40.0%) had mildly increased levels (⩾2-fold), three patients (15.0%) had moderately increased levels (⩾3-fold), and two patients (10.0%) had severely increased levels (⩾4-fold).[13,14] UOA and PAA analyses were used as screening tools for mitochondrial dysfunction. Mitochondrial dysfunction was suspected in five patients based on UOA analysis, and in four patients based on PAA analysis.

Brain imaging was performed for all patients. Cerebral atrophy and cerebellar atrophy were detected in most patients on MRI. MRS revealed lactate peaks in four patients. Regarding the muscle biopsies, five (25.0%) patients had specific findings for mitochondrial diseases under light microscopy. Electron microscopy revealed seven (35.0%) patients with pleoconia and eight patients (40.0%) with megaconia. In the MRC complex enzyme assay, all patients had MRC complex I defects. All patients received mitochondrial cocktail treatment, such as coenzyme, L-carnitine, and multivitamins.

Outcomes of the DTs

Table 4 shows the outcomes of the DTs in patients with mitochondrial dysfunction with LGS. The median age at commencement of DTs was 4.6 years (range, 1.1–14.1 years). Most patients had daily seizures. Among the patients who received the 4:1 KD treatment, four switched to 3:1 KD as the 4:1 KD treatment was not tolerable. Patients who initially started with 3:1 KD or

Table 2. Epilepsy profiles of patients.

Characteristics	Total ($n = 20$)
Age of first seizure (months)	14 (1–88)[a]
Age of diagnosed as LGS (months)	37 (12–132)[a]
Time interval from first seizure to diagnosis of LGS (months)	9 (1–120)[a]
Age of initiation of DTs (years)	4.6 (1.1–14.1)[a]
Time interval from diagnosis of LGS to initiation of DTs (months)	7 (0–93)[a]
History of infantile spasm, *n* (%)	9 (45.0%)
Seizure type, *n* (%)	
Tonic	12 (60.0%)
Spasms	8 (40.0%)
Head-drop	6 (30.0%)
Atonic	6 (30.0%)
Absence	5 (25.0%)
Tonic-clonic	4 (20.0%)
Myoclonic	3 (15.0%)
Clonic	1 (5.0%)
Focal	1 (5.0%)
Seizure frequency	
Daily	16 (80.0%)
Weakly	4 (20.0%)
Monthly	0 (0%)
Electroencephalography (*n*, %)	
Abnormalities of background rhythm	
Generalized slowing	20 (100.0%)
Epileptiform discharges	
Multifocal sharp/spike waves	20 (100.0%)
Generalized epileptiform discharges (GSSW, GPFA)	20 (100.0%)
Number of AEDs, *n* (%)	
Zonisamide	15 (75.0%)
Valproic acid	14 (70.0%)
Clobazam	14 (70.0%)
Phenobarbital	12 (60.0%)
Topiramate	10 (50.0%)
Vigabatrin	9 (45.0%)
Levetiracetam	9 (45.0%)
Lamotrigine	9 (45.0%)
Steroid	7 (35.0%)
Clonazepam	4 (20.0%)
Oxcarbazepine	3 (15.0%)
Phenytoin	3 (15.0%)
Diazepam	3 (15.0%)
Initial type of diet therapy	
KD 4:1	16 (80.0%)
KD 3:1	2 (10.0%)
MAD	2 (10.0%)

[a]Median and range.
AED, antiepileptic drug; DT, diet therapy; GPFA, generalized paroxysmal fast activity; GSSW, generalized sharp and slow wave; KD, ketogenic diet; LGS, Lennox-Gastaut Syndrome; MAD, modified Atkins diet.

MAD were expected to have either GI trouble or poor oral intake at the onset of the DT, or were not expected to demonstrate clinical tolerability for 4:1 KD. The median of DT duration was 13.5 months (range, 1–24 months). The retention rates at 1 and 2 years after initiation of DTs were 45% and 40%, respectively.

At 3 months after the initiation of the DTs, the seizure reduction status was 75% reduction in one patient, 50% reduction in four patients, and 25% reduction in eight patients. At 12 months, there was 100% reduction (seizure freedom) in

Table 3. Mitochondrial dysfunction profiles of patients.

Characteristics	Total ($n = 20$)
Age at evaluation of mitochondrial disease (months)	49 (7–138)[a]
Time interval from first clinical presentation to the evaluation of mitochondrial disease (months)	31 (1–126)[a]
Serum lactic acidosis at diagnosis (mmol/l)	2.13 (0.75–5.50)[a]
	2.34 ± 1.29[b]
Serum lactate:pyruvate ratio	10.58 (0.95–26.08)[a]
	10.19 ± 7.81[b]
Grading of serum lactic acidosis, *n* (%)	
Normal	7 (35.0%)
Mildly increased (⩾2-fold)	8 (40.0%)
Moderately increased (⩾3-fold)	3 (15.0%)
Severely increased (⩾4-fold)	2 (10.0%)
Urine organic acid abnormalities, *n* (%)	
Compatible with/ suspicious of mitochondrial disease	5 (25.0%)
No specific findings	15 (75.0%)
Plasma amino acid abnormalities, *n* (%)	
Compatible with/ suspicious of mitochondrial disease	4 (20.0%)
No specific findings	16 (80.0%)
Magnetic resonance imaging obtained, *n* (%)	
Cerebral atrophy	16 (80.0%)
Cerebellar atrophy	10 (50.0%)
White matter signal abnormality	5 (25.0%)
Thalamus	4 (20.0%)
Basal ganglia	3 (15.0%)
Brain stem	3 (15.0%)
Midbrain	3 (15.0%)
Pons	0 (0.0%)
Medulla	1 (5.0%)
Magnetic resonance spectroscopy obtained, *n* (%, $n = 17$)	
Presence of lactate peak	4 (23.5%)
Decreased NAA peak	5 (29.4%)
Normal	9 (52.9%)
Muscle biopsy obtained, *n* (%)	
Light microscopic changes	
Specific findings for mitochondrial diseases	5 (25.0%)
Nonspecific findings	15 (75.0%)
Electron microscopic changes	
Pleoconia	7 (35.0%)
Megaconia	8 (40.0%)
MRC complex enzyme assay, *n* (%)	
MRC complex I defect	20 (100.0%)
Mitochondrial cocktail treatment	20 (100.0%)

[a]Median and range.
[b]Mean and standard deviation.
MRC, mitochondrial respiratory chain; NAA, N-acetylaspartate.

two patients, 75% reduction in two patients, 50% reduction in three patients, and 25% reduction in one patient. After 24 months from the onset of DTs, there was seizure freedom in two

Table 4. Outcomes of DT in 20 patients with LGS with mitochondrial dysfunction.

No. of Patients	Age at time of DT	Sex	Seizure frequency	Concomitant AEDs	Type of DT	Duration of DT	Reduction rate of seizures after DT						EEG before the DT	EEG after the DT	Cognitive progress[b] (baseline: before the DT)		Side effect	Clinical severity[c]
	(years)					(months)	Start	3 months	6 months	9 months	12 months	24 months	Grade[a]	Grade[a]	1 year f/u	2 year f/u		
1	1.1	M	Daily	ZNS, VGB	KD 4:1	5	0	25	50	–	–	–	4	4	N/A	N/A	POI, MA	Moderate
2	1.6	M	Daily	TPM, CLB, ZNS	KD 4:1	24	0	50	75	75	75	75	4	3	Improved	Improved	Not observed	Moderate
3	6.4	F	Weekly	ZNS, CLB, Steroid	KD 4:1 → 3:1	3	0	0	–	–	–	–	4	4	N/A	N/A	POI	Severe
4	9.4	M	Daily	PTH, ZNS, LEV, TPM, DZP	KD 4:1 → 3:1	24	0	50	50	75	75	75	4	3	Improved	Static	Moderate	Severe
5	14.1	F	Weekly	LEV, VPA	MAD	3	0	25	–	–	–	–	4	4	N/A	N/A	Osteopenia	Moderate
6	1.1	F	Daily	VGB, PB	KD 4:1	44	0	25	50	50	50	90	4	3	Improved	Improved	Not observed	Moderate
7	1.2	M	Daily	CLB, VGB, ZNS, VPA	KD 4:1	1	0	–	–	–	–	–	4	4	N/A	N/A	Aspiration	Severe
8	2.3	M	Daily	VGB, CLB	KD 4:1	24	0	25	50	50	50	50	4	3	Improved	Improved	Not observed	Moderate
9	4.9	F	Daily	CLB, TPM, VPA	KD 4:1	4	0	25	–	–	–	–	4	3	N/A	N/A	GI disturbance	Severe
10	7.7	M	Daily	LEV, CLB, VPA	KD 4:1	8	0	25	25	–	–	–	4	4	N/A	N/A	POI	Severe
11	1.1	F	Daily	VGB	KD 4:1 → 3:1	24	0	50	100	100	100	100	4	2	Improved	Improved	Not observed	Moderate
12	11.8	M	Weekly	LTZ, VGB, CLZ, PB, OXC	KD 3:1	24	0	75	50	100	100	100	4	2	Improved	Improved	Not observed	Moderate
13	4.3	M	Daily	LTZ, TPM	KD 4:1	3	0	0	–	–	–	–	4	4	N/A	N/A	POI, GI trouble	Moderate
14	11.1	F	Daily	LTZ, CLZ, TPM, VGB, VPA	KD 4:1 → 3:1	48	0	0	25	0	0	0	4	4	Improved	Improved	POI	Moderate

(Continued)

Table 4. (Continued)

No. of Patients	Age at time of DT (years)	Sex	Seizure frequency	Concomitant AEDs	Type of DT	Duration of DT (months)	Reduction rate of seizures after DT						EEG before the DT	EEG after the DT	Cognitive progress[b] (baseline: before the DT)		Side effect	Clinical severity[c]
							Start	3 months	6 months	9 months	12 months	24 months	Grade[a]	Grade[a]	1 year f/u	2 year f/u		
15	5.0	F	Daily	LEV, CLZ	MAD	3	0	0	–	–	–	–	4	4	N/A	N/A	POI, MA	Severe
16	8.3	F	Weekly	TPM, VPA ZNS, CLB	KD 4:1	34	0	0	0	25	25	50	4	3	Improved	Improved	MA	Moderate
17	1.2	F	Daily	PB, VGB, CLB, VPA	KD 4:1	8	0	50	50	–	–	–	4	4	N/A	N/A	UGI Bleeding	Severe
18	3.8	F	Daily	DZP, VPA	KD 3:1	19	0	25	50	–	–	–	4	3	N/A	N/A	GI trouble	Moderate
19	12.6	M	Daily	TPM, PB, LTZ, CLB, VPA	KD 4:1	44	0	25	25	50	50	–	4	4	Improved	N/A	Not observed	Moderate
20	2.4	M	Daily	LTZ, ZNS, CLB	KD 4:1	4	0	0	–	–	–	–	4	4	N/A	N/A	POI	Severe

[a]EEG grade, 1. Normalization, 2. Slow and disorganized, 3. Focal or unilateral sharp, 4. Multifocal sharp, GSSW, GPFA;
[b]The improvement of the cognitive function of patients was evaluated based on caregivers' answers to questionnaires and careful inspection by pediatric neurologists.
[c]The clinical severity of the patients was assessed at the end of the patients' diet therapies.
AEDs, anti-epileptic drugs; CLB, clobazam; CLZ, clonazepam; DT, diet therapy; DZP, diazepam; EEG, electroencephalography; F, female; GI trouble, gastrointestinal; KD, ketogenic diet; LEV, levetiracetam; LGS, Lennox-Gastaut syndrome; LTZ, lamotrigine; M, male; MA, metabolic acidosis; MAD, modified Atkins diet; N/A, Not available, OXC, oxcarbazepine; PB, phenobarbital; POI, Poor oral intake; PTH, phenytoin; TPM, topiramate; UGI, upper gastrointestinal; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

patients, 90% reduction in one patient, 75% reduction in two patients, and 50% reduction in two patients. EEG findings were altered before and after the DTs. EEG findings improved in nine patients. Notably, in two patients (Patients 11 and 12), epileptogenic discharges disappeared after the DTs.

Cognitive progress compared with cognitive status before starting DTs was examined at the 1- and 2-year follow up. Nine patients were followed up for 1 year, and all nine had improved cognitive status. Eight patients were followed up for 2 years, of which seven had improved cognitive status and one had regressed to the pre-DT cognitive status.

Various side effects were observed in 14 of the patients who received the DTs. The causes of poor tolerability of the DTs were due to poor oral intake (35%), followed by GI problems such as vomiting and diarrhea, and metabolic acidosis. The severity of clinical outcomes was assessed at the end of the DTs in each patient. All patients had a moderate-to-severe clinical course, with moderate status in 12 patients and severe status in 8 patients.

Discussion

Despite previous reports on the efficacy and tolerability of DTs in LGS patients, controversies regarding LGS associated with mitochondrial dysfunction exist.[4,12] In several reports, the application of DTs for metabolic diseases is not desirable, as it worsens metabolic acidosis, and DTs form reactive oxygen species (ROS), which can cause metabolic stress in patients with MRC enzyme defects.[11] Recently, ketosis achieved through DTs, such as KD, has been shown to reduce oxidative damage in the brain associated with various metabolic stresses, increase glutathione peroxidase in hippocampal cells, and decrease mitochondrial ROS production.[12] There is general consensus that DTs may improve mitochondrial function and have neuroprotective properties such as anticonvulsant effects, and this consensus forms the basis for the effective and safe application of DTs in patients with mitochondrial dysfunction.[20] We observed lactic acidosis and metabolic acidosis, but not life-threatening metabolic crises such as severe lactic acidosis, in several patients. Sodium valproic acid (VPA) therapy tends to reduce mitochondrial function, so it could be a potential danger to patients of mitochondrial dysfunction. But, according to Cross and colleagues, VPA therapy is an important first-line treatment for LGS patients.[21] Therefore, VPA therapy may be used effectively depending on the clinical situation in patients of LGS with mitochondrial function. In our study, some patients used VPA as an initial treatment before being diagnosed with mitochondrial dysfunction. After the patients were diagnosed with mitochondrial dysfunction, the VPA was gradually reduced, aiming to stop or remain at a low dose depending on the clinical situation in these patients. In this regard, DTs may have negative biochemical effects on, but not contraindications to, mitochondrial dysfunction. Thus, DTs are a viable treatment option for intractable epilepsy or mitochondrial dysfunction.

Studies on the efficacy of DTs for patients with either LGS or mitochondrial dysfunction reported that DTs can improve seizure frequency, EEG findings, and cognitive function.[1–4,10,13] However, as LGS with mitochondrial dysfunction is extremely rare, studies on the effects of DTs in LGS with mitochondrial dysfunction are lacking. In this study, we increased the sample size of patients with LGS with mitochondrial dysfunction to 20. We observed progressions of seizure frequency, EEG findings, and cognitive status at 1 year after initiation of DTs in 40–50% of patients with LGS with mitochondrial dysfunction. In previous studies, the application of DTs in intractable epilepsy such as West syndrome and LGS produced a seizure reduction rate of approximately 50–60% at the 6 months to 1 year follow up.[1,22–24] In our study, seizure reduction after DTs was approximately 40% at 1 year, a lower efficacy than in previous studies. However, at the 2-year follow up, we observed a higher efficacy (35% *versus* 28%).[24] Considering that LGS with mitochondrial dysfunction is a complex and combined disease, the efficacy of DTs in our study is not inferior to that reported by previous studies. Our results suggest that DTs can be applied to treat LGS with mitochondrial dysfunction as well as existing intractable epilepsies.

DTs increase seizure frequency and cognitive function in patients with refractory epilepsy. Van Berkel and colleagues reported that subjective cognitive improvements were observed in patients with epilepsy after KD treatment, primarily in the domains of alertness, attention, concentration, and global cognition.[25] Although it is difficult to establish firm conclusions due to confounding factors, the positive impact of DTs on cognition is

widely acknowledged.[25–27] In patients with LGS with mitochondrial dysfunction, cognitive decline and seizures are important factors for treatment. In general, the cognitive status of LGS with mitochondrial dysfunction is too low to be evaluated, and cognitive status is difficult to quantify as a prognostic method due to the rarity of this pediatric condition. Therefore, serial evaluation by close caregivers and qualified pediatric neurologists will be crucial for evaluating the cognitive function of LGS with mitochondrial dysfunction. In the future, study enrolling more mitochondrial dysfunction patients may suggest a good methodology for evaluating cognitive function of patients with mitochondrial dysfunction. In our study, there were improvements in subjective cognitive functions in most patients at the 1- and 2-year follow up after DTs, with 100% at the 1-year follow up and 87.5% at the 2-year follow up. Cognitive evaluation in patients with LGS with mitochondrial dysfunction should be considered an important parameter in future studies, as using seizure reduction alone to evaluate treatment efficacy in intractable epilepsy patients has limitations.

Pediatric neurologists are cognizant of tolerability when prescribing DTs to patients. Although DTs may be efficacious, efforts to improve DT tolerability are critical, as poorly tolerated DTs cannot be sustained. We evaluated tolerability of DTs with retention rate, as also performed in previous studies.[19,28,29] In this study, the retention rate after 1 year of DTs was 45%, and, after 2 years, 40%. Indeed, patients who tolerated DTs for 1 year were more likely to receive DTs successfully without significant changes in tolerability. Cai and colleagues performed a systematic review of 45 studies, including seven randomized controlled trials, examining the application of DTs in intractable epilepsy. The study reported total retention rates of 45.7% and 29.2% at 1 year and 2 years, respectively.[29,30] The retention rate in our study was similar to those reported by previous studies at the 1-year follow up, but higher at the 2-year follow up (45% *versus* 45.7% and 40% *versus* 29.2%, respectively), suggesting that DTs for LGS with mitochondrial dysfunction are safe and tolerable.

Another way to assess tolerability for DTs is to evaluate side effects. A major side effect of DTs is GI problems.[4,31] In patients with mitochondrial dysfunction, GI problems can be life-threatening. This is because the lack of buffering of energy metabolism due to mitochondrial dysfunction can have adverse effects on major organs. Since overcoming GI troubles can influence the success or failure of DTs, overcoming GI troubles in patients with LGS with mitochondrial dysfunction is critical. Poor oral intake and GI troubles were major side effects of DTs in our study. To overcome this, we altered the fat:(carbohydrate + protein) ratio of DTs in some patients and considered establishing a stable feeding route. Some studies recommend methods that supplement energy metabolism before DTs to increase tolerability. These methods include application of enteral tube feeding such as percutaneous endoscopic gastrostomy (PEG) tubes, increasing the carbohydrate ratio of DTs, skipping fasting during the early ketosis period, and mitochondrial cocktail treatment as mitochondrial supportive care. These methods may stabilize nutrition and energy metabolism in LGS with mitochondrial dysfunction, and may reduce GI problems.[4,18,31–34]

Conclusion

In conclusion, mitochondrial dysfunction is often accompanied by intractable epilepsy. It is therefore important to consider and establish the management of patients with LGS with mitochondrial dysfunction. Although the effects of DTs on mitochondrial dysfunction and its stability are controversial due to potential negative effects on energy metabolism, we have shown that in patients with LGS with mitochondrial dysfunction, improvement of seizures and cognitive function are not inferior to those in other patients who receive DTs. GI trouble was the most prominent side effect of the DTs. Active GI interventions such as PEG tubes may be required for DTs in patients with LGS with mitochondrial dysfunction. In our study, we attempted DTs in a rare patient group of LGS with mitochondrial dysfunction, with a larger sample size than those of previous studies. Notably, we evaluated cognitive function and changes in seizure frequency to assess the effects of DTs. However, the number of patients in this study was low ($n = 20$) and was insufficient to draw definitive conclusions. More research is needed in the future to address this limitation. This study shows that DTs are efficacious and feasible for treating LGS with mitochondrial dysfunction, and can significantly improve disease prognosis. As LGS with mitochondrial dysfunction is rare, definitive conclusions cannot be drawn, but studies that provide more conclusive evidence should be performed to optimize individualized treatment of this disease.

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Author contribution statement

Young-Mock Lee conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed and revised the manuscript. Ji-Hoon Na designed the data collection instruments, collected data, carried out the initial analyses, drafted the initial manuscript, and revised the manuscript. Heung-Dong Kim critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted, and agree to be accountable for the content of the work.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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