의학석사 학위논문

소아 뇌전증 환자에서 식이 요법의 초기 반응을 이용한 치료 유지 결정

The early response to dietary therapy can predict the late outcome in children with intractable epilepsy

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이 논문을 의학석사 학위 논문으로 제출함

2021년 2월

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Abstract

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Title: The early response to dietary therapy can predict the late outcome in children with intractable epilepsy

Purpose: Dietary therapy (DT), including the ketogenic diet (KD), is one of the nonpharmacological treatment options for patient with drug-resistant epilepsy. However, maintaining DT in patients without seizure reduction is very difficult, so it is critical for clinicians to decide when to stop this intervention.

Methods: To determine the individualized effectiveness of DT during the initiation period, we retrospectively analyzed early clinical and laboratory findings in and the clinical characteristics of children who responded to DT for intractable epilepsy. We reviewed the medical records of intractable epileptic patients treated with DT. The maintenance of DT and the clinical seizure frequency were assessed at 1, 3, 6, 12, and 24 months after KD initiation. Responders were defined as patients showing an overall reduction in seizure frequency of >50% relative to the baseline. Clinical and laboratory findings were compared between responders and nonresponders at 6 months.

Results: We included 67 patients who received DT, but only 23 (34.3%) of these patients remained on DT at 6 months. Only 1 (5%) of the 20 responders at 1 month became a nonresponder at 6 months, while 11 (55%) remained responders and 8 (40%) had withdrawn. The response rate at 6 months was significantly higher among patients under 2 years of age (15/17, 88.2%) than older patients (2/6, 33.3%; $p = 0.021$). Moreover, the 6-month responders were significantly younger (29.4±38.6 months, mean±SD) than the nonresponders (98.9±84.6 months, $p = 0.012$) at the initiation of the diet. A high blood β-hydroxybutyrate (BHB) level at 1 month (with a cutoff of 3.9 mmol/L) predicted a good DT response at 6 months with a sensitivity and specificity of 80%.

Conclusion: This single-center cohort found that the long-term maintenance of DT was very difficult, but most 1-month responders remained on DT for up to 6 months. The blood BHB level at 1 month

was significantly correlated with the 6-month seizure outcome. Confirming clinical and laboratory biomarkers for the efficacy of DT requires further studies with larger cohorts.

Key Words: Diet, Ketogenic, Drug Resistant Epilepsy, Seizures, Biomarkers

차 례

표 및 그림 차례

Introduction

Refractory epilepsy is defined as "failure to achieve sustained seizure freedom with two appropriate and tolerated antiepileptic drugs" (AEDs) by the International League Against Epilepsy (ILAE).[1] Approximately one-third of children with epilepsy will be refractory to standard antiepileptic medication[2] despite the yearly expansion of AED availability. Among various alternative therapies for patients with refractory epilepsy, dietary therapy (DT) first reported as a treatment option in 1921.[3] The classic ketogenic diet (KD) consists of high fat, moderate protein, and low carbohydrate intakes, with a typical ratio of 3:1 or 4:1 for the ratio of fat to protein plus carbohydrate. The difficulty of maintaining the KD due to its unfamiliar taste and strict restrictions resulted in the introduction of the modified Atkins diet (MAD) and low-glycemic-index treatment.[4,5]

While the exact antiepileptic mechanisms of DT remain poorly understood, a KD has been known to influence neurotransmitters such as GABA and glutamate. Ketone bodies, such as β-hydroxybutyrate (BHB) has been considered as key mediators of antiepileptic effects of DT by reducing glucose consumption in the brain by regulating the activities of neurotransmitters and neuroprotective effects by modulation of the mitochondrial biogenesis of neurons.[6] DT also combines several mechanisms including the peroxisome proliferator activated receptors mediated anti-inflammatory or antioxidative modulation, control of K_{ATP} channels, and brain-derived neurotrophic factor (BDNF) signaling pathway, increased mitochondrial function, and epigenetic modification via DNA methylation that together reduce neuronal excitability.[7,8] A recent meta-analysis of five randomized controlled trials revealed that 35–56.1% of patients on a KD achieved a >50% reduction in seizures without severe adverse effects.[9]

Nevertheless, the use of DT for refractory epilepsy is restricted by its poor tolerability, insufficient feasibility for caregivers (due to diet complexity), and relatively poor compliance.[10] Diet maintenance is especially difficult in patients who do not experience definitive seizure reduction after DT. These characteristics indicate the need to determine the antiseizure efficacy of DT as early as possible.

Urine ketone (UK) levels have been used to monitor DT adherence due to their

noninvasiveness. However, some studies have shown that blood β-hydroxybutyrate levels are a more accurate indicator of seizure reduction.[11]

We hypothesized that early clinical and laboratory findings determine the final DT response in children with refractory epilepsy. We tested this hypothesis by examining DT-induced seizure reduction in a single-center cohort of children with refractory epilepsy. Furthermore, to identify early predictors of a DT-mediated response, clinical and laboratory data were compared between early responders and nonresponders.

Method

Patients population and data collection

From April 2004 to April 2019, 81 patients with epilepsy started receiving DT at Asan Medical Center in Seoul, South Korea. We excluded patients with insufficient clinical data (n = 14).

We retrospectively reviewed clinical and laboratory data and collected information on (1) demographics (sex, weight, age at diagnosis, age at initiation of DT, number of AEDs prior to DT, and duration of DT), (2) epilepsy characteristics (etiology and baseline seizure frequency), (3) type of KD (KD formulation, classic KD, or MAD), (4) response rates to the diet at 1, 3, 6, 12, and 24 months, and (5) blood BHB levels. The ILAE classification divides the etiologies of epilepsy into structural-metabolic, genetic or presumed genetic, and unknown.[12] The clinical seizure frequency was obtained from caregivers' seizure diaries and evaluated at baseline (prior to DT) and at 1, 3, 6, 12, and 24 months after the initiation of DT. The blood BHB level was quantitatively measured using a test strip every other day during hospitalization and at 1, 3, 6, 12, and 24 months after the initiation of DT.

The study was approved by Institutional Review Board (IRB) 2018-0021 of Asan Medical Center.

KD protocol and outcome assessment

Patients were admitted to the hospital for 1 week to receive an introduction about DT. In general, patients were advised to begin consuming one-third of the target calories, followed by a gradual increased in caloric input over the first 3 days. The target calories and ketogenic ratio were established by the department of nutrition at the hospital.

The responders were defined as patients with a reduction of >50% reduction in the predominant seizure frequency relative to baseline. The effects of DT at 6 months were evaluated in the 1-month responder and nonresponder groups.

We compared clinical variables and blood BHB levels between 6-month responders and nonresponders in order to identify predictors of a DT-mediated response. Additionally, receiver operating characteristic curves with 95% confidence intervals for distinctions were calculated to determine the blood BHB cutoff for differentiating 6-month responders from nonresponders.

Statistical analyses

Categorical data were analyzed using Pearson's chi-square tests and numerical data were analyzed using independent Student's *t*-tests. Mann-Whitney *U*-tests were used to assess the relationships of urine and blood BHB levels with seizure reduction. Correlations with $p<0.05$ were considered significant in all tests.

Results

Patient demographics

The baseline demographics and epilepsy characteristics of the 67 patients included in the study are listed in Table 1. The mean age at diagnosis was 19.3 months, and most of the patients were diagnosed with West syndrome (*n* = 37) or Lennox-Gastaut syndrome (LGS) (*n* = 10). Most of the patients (*n* = 55, 82%) reported daily seizures. The mean age at the initiation of DT was 44.9 months and the mean duration on the diet was 6.6 months. Overall, 58 and 9 patients were initiated on the classic KD and MAD, respectively.

Efficacy and tolerability of DT

Figures 1 and 2 present the overall efficacy and tolerability of DT over time. At 3 and 6 months after DT initiation, 42 (62.7%) and 23 (34.3%) patients were able to remain on the diet, respectively. Moreover, at 1 and 2 years after DT initiation, only 8 (11.9%) and 4 (6.0%) patients continued the diet, respectively (Figure 1). Altogether, the data indicate that the DT retention rate had decreased to <50% after 6 months (Figure 2).

Among the patients who remained on DT, the overall rates of response to DT were 34.5% (20/58), 57.1% (24/42), 73.9% (17/23), 87.5% (7/8), and 50.0% (2/4) at 1, 3, 6, 12, and 24 months after diet initiation, respectively (Figure 1).

At 1 month, 58 of 67 patients remained on the diet, with the 9 patients discontinuing due to a lack of efficacy (*n* = 1), adverse effects (*n* = 7), or poor compliance (*n* = 1). Twenty (34.5%) of the patients who remained on the diet exhibited >50% seizure reduction, and five (8.6%) also achieved the electroencephalographic improvement: three patients with hypsarrhythmia and two LGS patients with generalized fast activities (Figures 1 and 3). At 6 months, 23 patients remained on DT, with 41 patients discontinuing due to a lack of efficacy (*n* = 12), adverse effects (*n* = 24), poor compliance (*n* = 4), or discontinued production (*n* = 1); 3 patients were lost to follow-up.

Only one of the 1-month responders became nonresponsive to DT after 6 months (Figure 3). Importantly, six of the 1-month nonresponders achieved seizure reductions of >50% at 6 months; their clinical characteristics are listed in Table 2. One of these six patients started on a 4:1 classic KD, but

their caregiver had difficulty making the diet properly, thereby inhibiting its effectiveness. The other five patients were on a 3:1 classic KD or the MAD, with two reporting poor tolerance or compliance. Moreover, 2 days after DT initiation, these two patients had blood BHB levels of 1.2 and 0.2 mmol/L. All these six patients achieved seizure reduction of >50% at 3 months.

Among the 23 patients remaining on DT at 6 months, 17 (73.9%) showed >50% seizure reduction and 5 (21.7%) with infantile spasms also showed disappearance of hypsarrhythmia. When clinical characteristics were compared between responders and nonresponders after 6 months of DT (Table 3), there were significantly more responders under the age of 2 years (15/17, 88.2%) than older responders (2/6, 33.3%; $p = 0.021$). Moreover, 6-month responders were significantly younger (29.4±38.6 months, mean±SD) than the nonresponders (98.9±84.6 months, $p = 0.012$) at the initiation of the diet. Finally, there was no significant difference of diet types between 6-month responders and nonresponders ($p = 0.089$).

Table 1. Baseline demographics and clinical data for the study population

Variable	Value (*n* = 67)
Sex	
Male	39 (58)
Female	28 (42)
Weight	
>90th percentile	7 (10)
10–90th percentiles	37 (56)
<10th percentile	23 (34)
Age at diagnosis, months	19.3±31.5 (0–170)
Epilepsy etiology	
Structural or metabolic	38 (57)
Malformation of cortical development	11
Hypoxic ischemic encephalopathy	8
Sequelae of encephalitis	7
Tuberous sclerosis complex	6
Periventricular leukomalacia	4
Metabolic disease	2
Genetic or presumed genetic	5 (7)
Unknown	24 (36)
West syndrome	37 (55)
LGS	10 (15)
Baseline daily seizure frequency	
At least once	55 (82)
Less than once	12 (18)
Number of AEDs prior to DT	
Fewer than three	21 (31)
At least three	46 (69)
Initial blood BHB level, mmol/L	2.6±2.0 (0.1–5.8)
Age at initiation of DT, months	44.9±54.1 (1.8–253.3)
Duration of DT, months	6.6±11.4 (0–82)
Type of DT	
Classic KD	58 (87)
MAD	9 (13)

Data are mean±SD (range), *n*, or *n* (%) values

AED, antiepileptic drug; DT, dietary therapy; KD, ketogenic diet; LGS, Lennox-Gastaut syndrome; MAD, modified Atkins diet; BHB, β-hydroxybutyrate

Figure 1. Seizure outcomes of the patients on dietary therapy (DT) and dropouts at each time point

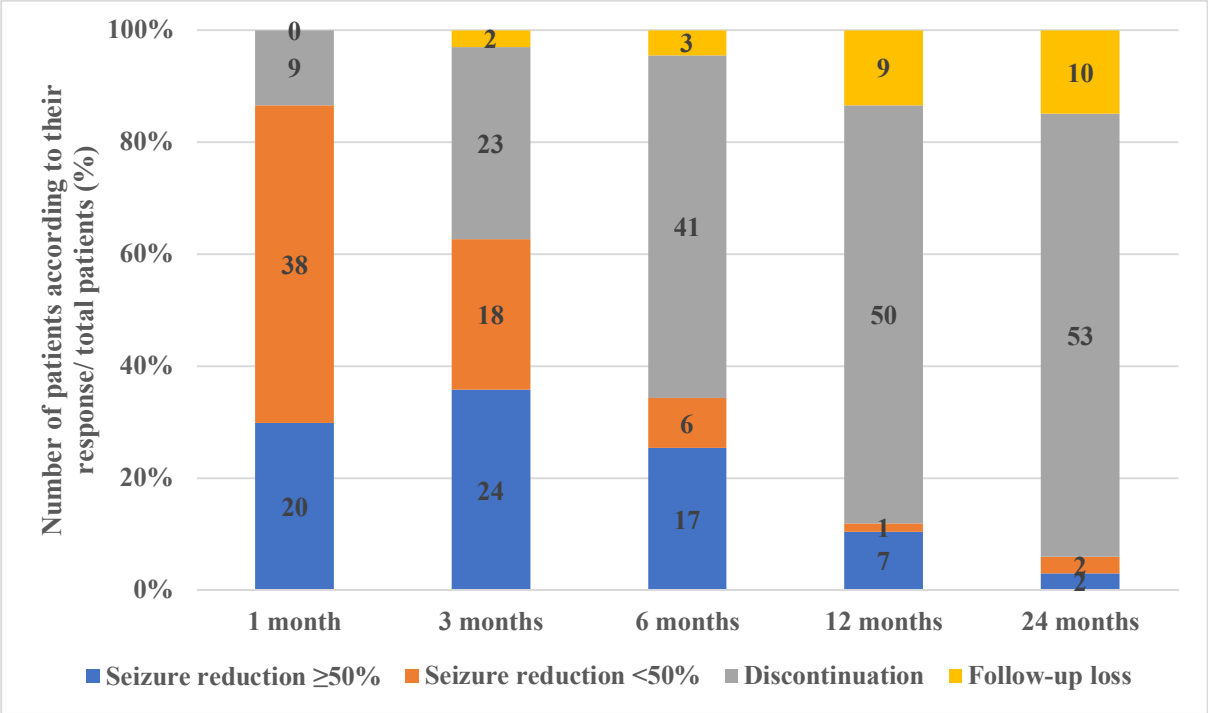


Figure 2. Kaplan-Meier curve showing the retention rate on DT

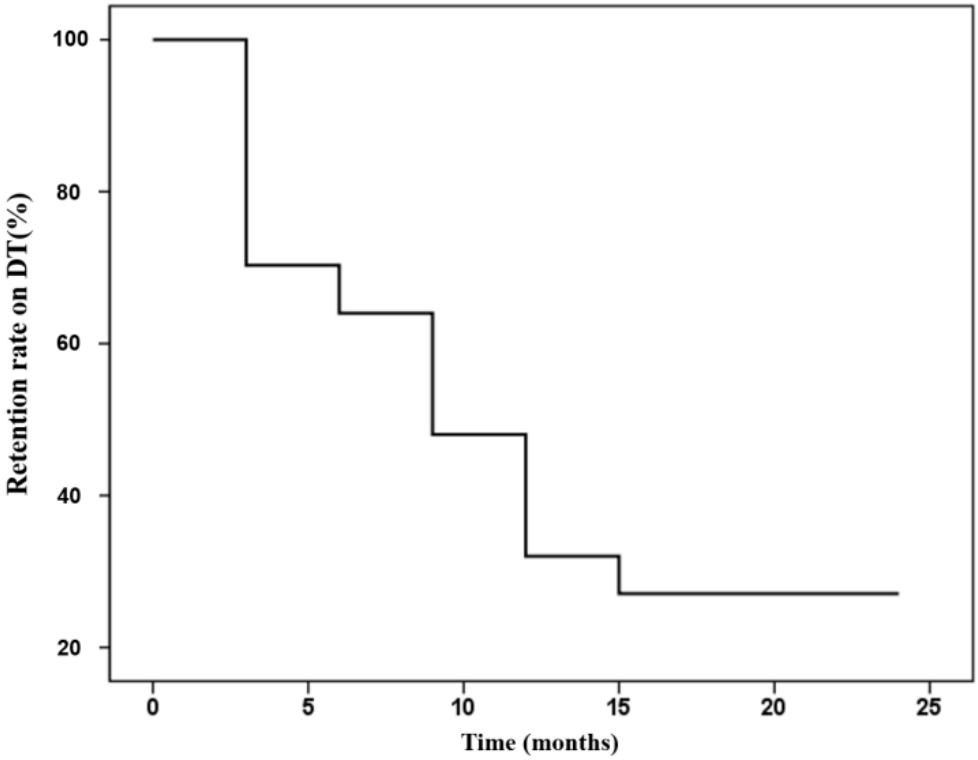


Figure 3. Flow chart of patients at 1 and 6 months after DT

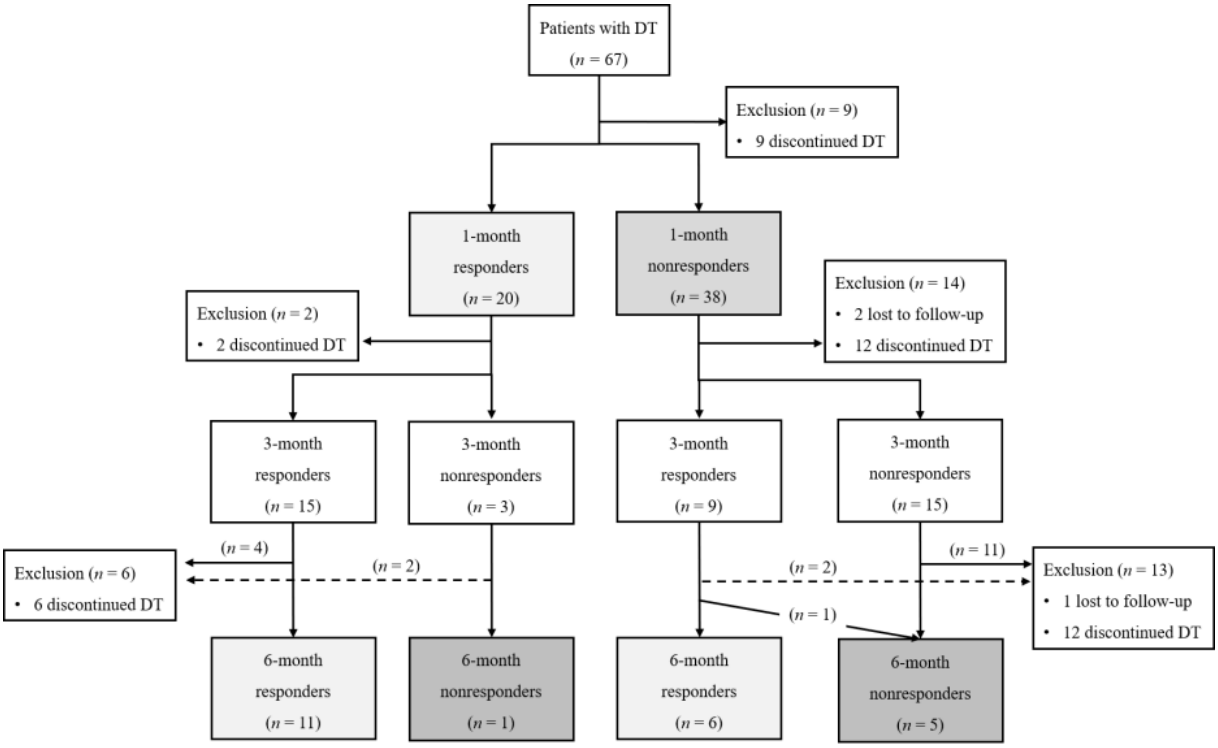


Table 2. Clinical characteristics of late responders who had no response at 1 month

Diagnosis	Age at diagnosis (months)	Age at initiation of DT (months)	Response at 3 months	DT type	Type of DT formula	Blood BHB level at 2 days after DT (mmol/L)	Daily seizure frequency	Seizure type	Number of AEDs	Adverse effects	Reasons for poor response at 1 month
Tuberous sclerosis, IS	10	16	+	Classic KD (4:1)	Homemade weaning food	-	Once+	Spasms	1	Vomiting, diarrhea	Poor parental education
Perinatal HIE, IS	0	10	+	Classic KD (3:1)	Homemade weaning food + ketogenic milk	-	Once+	Spasms	1	-	None
Perinatal HIE, IS	2	4	+	Classic KD (3:1)	Ketogenic milk	-	Once+	Spasms	3	Diarrhea	None
Encephalitis, focal seizures	135	140	+	MAD	Homemade Atkins diet	-	Once+	GTCS	5	-	None
Lissencephaly, IS, LGS	5	78	+	Classic KD (3:1)	Homemade DT	1.2	Once+	Head drops	3	Hypoglycemia	Poor tolerance
Dravet syndrome, generalized seizure	8	97	+	MAD	Homemade Atkins diet	0.2	<Once	GTCS	3	-	Poor compliance

IS, infantile spasms; GTCS, generalized tonic-clonic seizure; HIE, hypoxic-ischemic encephalopathy

Table 3. Responders versus nonresponders at 6 months after DT

Variable	Responders at 6 months (*n* = 17)	Nonresponders at 6 months (*n* = 6)	*p*
Sex			
Male	8 (47)	4 (67)	0.408
Female	9 (53)	2 (33)	
Weight			0.134
<10th percentile	4 (24)	4 (67)	
Age at diagnosis			
<24 months	15 (88)	2 (33)	0.021*
≥24 months	2 (12)	4 (67)	
Epilepsy etiology			
Structural/metabolic	9 (53)	3 (50)	0.715
Genetic or presumed genetic	1 (6)	1 (17)	
Unknown	7 (41)	2 (33)	
Baseline daily seizure frequency			
At least once	14 (82)	4 (67)	0.576
Less than once	3 (18)	2 (33)	
Number of AEDs prior to DT			
Fewer than three	8 (47)	0 (0)	0.058
At least three	9 (53)	6 (100)	
Age at initiation of DT, months	29.4±38.6	98.9±84.6	0.012*
Type of DT			
Classic KD	15 (88)	3 (50)	0.089
MAD	2 (12)	3 (50)	
Blood BHB level, mmol/L			
2 days	3.2 ± 2.2	1.4 ± 1.4	0.257
1 month	4.8 ± 1.0	1.2 ± 1.0	0.016*
3 months	5.2 ± 1.3	1.7 ± 1.7	0.036*

Data are mean±SD or *n* (%) values

* $p<0.05$

Adverse events of DT

Several adverse events were reported while receiving DT (Table 4). During DT initiation, 40 (60%) of the 67 patients experienced adverse events, including food refusal (n = 14), vomiting (n =12), and hypoglycemia (<50 mg/dL, n = 10). After discharge, anorexia (n = 17) and vomiting (n = 15) were the most frequent difficulties, and hypertriglyceridemia (≥200 mg/dL, n = 46) was the most common abnormal laboratory finding.

Blood BHB levels according to responsiveness to DT

A blood BHB test was performed in 21 of the 58 patients receiving DT at 1 month (Figure 4). After the initiation of DT, blood BHB levels of 1-month responders were significantly higher than those of nonresponders at both 2 days (4.4±1.3 vs. 2.0±1.7 mmol/L, p = 0.031) and 1 month (5.1±0.9 vs. 2.2±1.7 mmol/L, p = 0.011) (Figure 4). For 1-month responders, a blood BHB cutoff at DT initiation of 3.1mmol/L yielded a sensitivity of 100% and a specificity of 70.6% (Figure 5-A). Blood BHB levels were measured in 10 of the 23 patients who were still receiving DT at 6 months (Table 3, Figure 4). The blood BHB level was significantly higher in 6-month responders than in nonresponders at both 1 month (4.8±1.0 vs. 1.2±1.0 mmol/L, p = 0.016) and 3 months (5.2±1.3 vs. 1.7±1.7 mmol/L, p = 0.036) (Table 3, Figure 4). Additionally, for 6-month responders, a blood BHB cutoff at 1 month after DT of 3.9 mmol/L yielded a sensitivity and specificity of 80% (Figure 5-B). Overall, the blood BHB levels of patients on a 4:1 and 3:1 classic KD were higher than those on the MAD (Supplementary Table 1 and Figure 4).

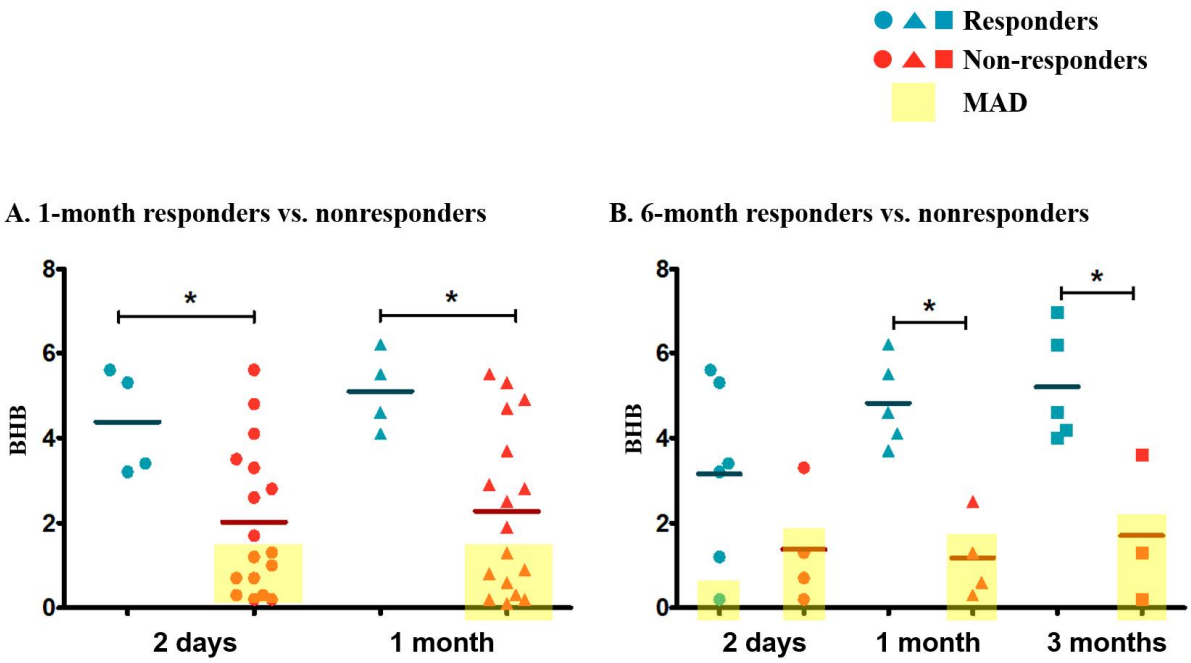
Table 4. Adverse events of DT

Variable	Value (*n* = 67)
Adverse events during DT initiation	
Food refusal	14 (21)
Vomiting	12 (18)
Hypoglycemia (BST <50 mg/dL)	10 (15)
Diarrhea	7 (10)
Constipation	4 (6)
Fever	4 (6)
Adverse clinical events after discharge	
Anorexia	17 (25)
Vomiting	15 (22)
Seizure aggravation	11 (16)
Infection	9 (13)
Weight loss	6 (9)
Constipation	4 (6)
Adverse chemical events after discharge	
Hypertriglyceridemia (triglyceride ≥200 mg/dL)	46 (69)
Hyperuricemia (uric acid >7 mg/dL)	41 (61)
Hypercholesterolemia (total cholesterol ≥200 mg/dL)	30 (45)
Metabolic acidosis	21 (31)
Hypoglycemia (BST <50 mg/dL)	18 (27)
Hypomagnesemia (magnesium <1.8 mg/dL)	13 (19)
Hypercalcemia (total calcium >10.2 mg/dL)	11 (16)
Hypocalcemia (total calcium <8.6 mg/dL)	6 (9)

Data are *n* (%) values

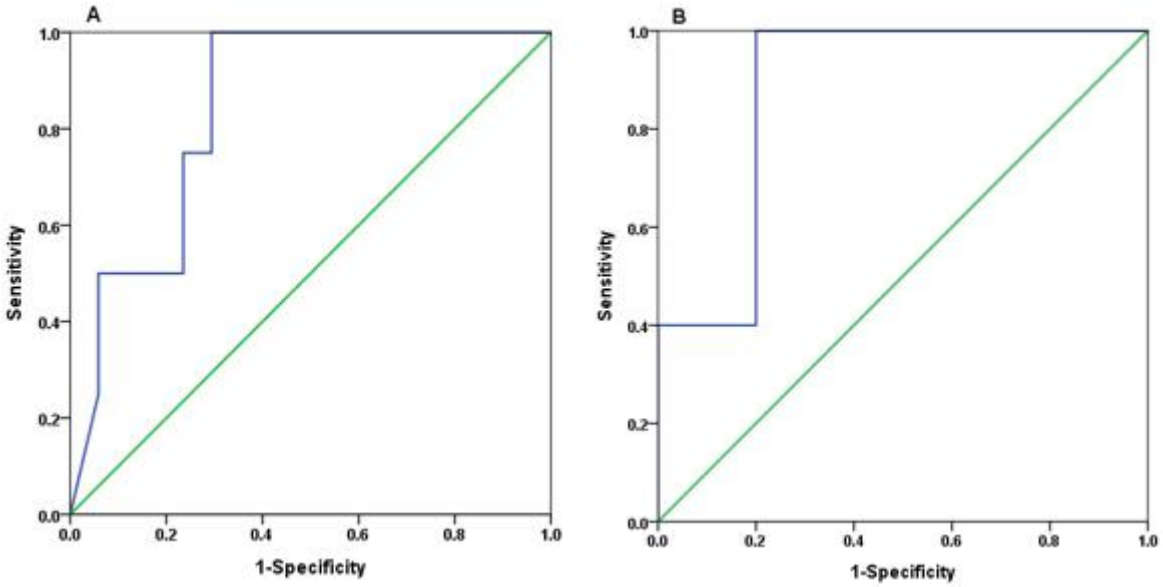
BST, blood sugar test

Figure 4. Scatter plots of β-hydroxybutyrate (BHB) level in responders and nonresponders at each time point



*p<0.05

Figure 5. ROC curve for predilection of DT efficacy



A. BHB cutoff value at DT initiation for predilection of 1 month-responder is 3.1 with 100% sensitivity and 70.6% specificity, AUC = 0.846, p = 0.035

B. BHB cutoff value at 1 month after DT for predilection of 6 month-responder is 3.9 with sensitivity and specificity of 80%, AUC = 0.880, p = 0.013

Supplementary Table 1. Blood β-hydroxybutyrate (BHB) level according to the type of dietary therapy (DT)

	Type of DT	Number of patients	BHB at 2 days (mmol/L)	BHB at 1 month (mmol/L)	BHB at 3 months (mmol/L)
1-month responders and nonresponders	4:1 KD	6	4.4±1.6	3.8±2.3	*
	3:1 KD	7	3.0±0.9	3.8±1.1	*
	MAD	8	0.6±0.4	0.6±0.4	*
6-month responders and nonresponders	4:1 KD	3	4.8±1.2	5.3±1.1	5.8±1.4
	3:1 KD	3	2.6±1.2	3.6±1.1	4.1±0.5
	MAD	4	0.6±0.5	0.7±0.5	0.8±0.8

Data are *n* or mean±SD values

KD, ketogenic diet; MAD, modified Atkins diet

Discussion

This study has demonstrated the difficulty of maintaining DT in children with epilepsy, as evidenced by the low retention rate of 34.3% after 6 months. The mean duration of DT was 6.6 months, which was shorter than those described in other reports.[13-15] Many epileptic patients have difficulty remaining on DT due to side effects, lack of efficacy, or poor compliance. However, the overall efficacy of DT was 73.9% at 6 months, with most of the 6-month responders also showing responsiveness after 1 month. A few 1-month nonresponders became 6-month responders, but those patients failed to benefit from the full strength of the classic KD and ketosis, since they had difficulty remaining on DT during the first month and only reported seizure reduction 2–3 months later. This illustrates the importance of the successful induction of early ketosis and strict DT for achieving the effective control of seizures. Considering the poor DT retention rate, an early decision about DT maintenance can be made since the efficacy can be predicted during the initiation period of DT.

To identify other clinical factors affecting DT responses, the clinical characteristics of 6-month responders and nonresponders were compared. Six-month responders were diagnosed with epilepsy and initiated DT at a significantly lower age than did nonresponders. This group also showed significantly higher blood BHB levels at 1 and 3 months after DT initiation. The DT efficacy did not vary with sex, weight, epilepsy etiology, baseline seizure frequency, or number of AEDs. In line with our findings, previous studies have suggested that initiating DT at a lower age results in better outcomes.[16,17] It seems that young children, especially those younger than 2 years, can tolerate DT better, which is probably due to their eating habits being more flexible. Although not statistically significant, the classic KD seemed to be more effective than the MAD. However, this result is inconsistent with recent findings,[18,19] which is probably due to the younger age and higher seizure burden of our patient group, as well as the inclusion of fewer patients on the MAD.

Recent studies have shown that blood BHB levels are more strongly correlated with seizure reduction than are UK levels.[11] Van Delft et al. reported that UK levels were merely indicative of the compliance with DT, rather than accurately reflecting treatment efficacy.[11] For this reason, the present study measured blood BHB levels rather than UK levels. We found that the blood BHB levels at 1-

month after DT initiation were higher in 6-month responders than in nonresponders. Moreover, high blood BHB levels were significantly correlated with reductions in DT-mediated seizures. These data suggest that the 6-month response can be predicted by measuring the blood BHB level at 1 month, allowing direct decisions to be made regarding the continuance of the diet as early as 1 month after initiating DT.

Overall, DT was found to be safe with no severe effects on mortality or ICU admissions during the study period, which may have been due to the flexible DT applied at our center and the low retention rate. During the initiation of DT, 60% of the patients displayed side effects, the most common of which were food refusal and vomiting.

Our study was subject to some limitations, including its retrospective design with the seizure frequencies being reported by caregivers, the relatively short duration of DT maintenance, and the lack of data on blood BHB levels for patients who began DT before 2015. However, since the DT protocol remained consistent, it is unlikely that the blood BHB levels of patients would have differed between before and after 2015.

Notwithstanding these limitations, this study has revealed the critical value of the early prediction of DT efficacy in reducing DT-related side effects, which can help medical professionals to make decisions regarding DT for children with refractory epilepsy. Moreover, our data illustrate the usefulness of blood BHB levels as an early biomarker for DT efficacy.

Conclusion

Maintaining DT is very difficult in children with refractory epilepsy. Moreover, most patients with DT-mediated clinical responses exhibited effects at 1 month or at least until 3 months after initiating DT. Blood BHB levels at 1 month are reliably predictive of the 6-month seizure outcome in patients on DT for a cutoff of 3.9 mmol/L. Further studies are needed to confirm clinical and laboratory biomarkers for the efficacy of DT.

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국문요약

제목: 소아 뇌전증 환자에서 식이 요법의 초기 반응을 이용한 치료 유지 결정

목적: 약물 난치성 소아 뇌전증 환자에서 비약물 치료 방법으로 케톤 생성 식이를 비롯한 식이 요법이 시행되고 있다. 하지만 경련 빈도의 감소 없이 치료를 유지하는 것은 어렵기 때문에 임상에서 식이 요법의 중단 시점을 결정하는 것은 중요하다. 따라서 식이 요법의 초기 반응과 혈액 검사 결과를 통해 장기적인 효과를 예측할 수 있는 지 확인하고자 하였다.

방법: 2004년 4월부터 2019년 4월까지 서울아산병원에서 식이 요법을 시행한 약물 난치성 소아 뇌전증 환자의 차트를 통해 식이 요법에 대한 초기 반응과 혈액 검사 결과를 후향적으로 분석하였다. 식이 요법의 유지와 경련 빈도의 감소 여부는 치료 시작 1, 3, 6, 12, 그리고 24개월 째에 평가하였다. 치료 시작 전과 비교하여 50% 이상의 경련 빈도 감소를 보인 환자들을 반응군으로 정의하였고, 반응군과 비반응군 간의 임상적 특성과 혈액 검사 결과를 비교하였다.

결과: 식이 요법을 시행 받은 67명의 환자들 중 23명 만이 6개월 이상 해당 식이 요법을 유지하였다. 1개월째 반응군은 20명이었고 그 중 1명만이 6개월째 비반응군이 되었으며, 11명은 반응을 유지하였고, 8명이 치료를 중단하였다. 6개월째 반응율은 2세 미만에서 식이 요법을 시행한 경우가 88.2%로 2세 이상에서 시행한 경우 33.3%에 비하여 통계적으로 유의하게 높았다. 식이 요법 시작 당시 나이는 6개월째 반응군이 29.4개월로 비반응군의 98.9개월보다 통계적으로 유의하게 어렸다. 혈액 검사 결과에서 1개월째 혈중 베타수산화부티레이트 수치가 높을수록 식이 요법 6개월째 반응율이 더 높았다.

결론: 소아 뇌전증 환자에서 식이 요법을 장기간 유지하는 것은 어렵지만 대부분의 1개월째 반응군은 6개월까지 반응을 유지하며 치료를 지속하였다. 식이 요법 1개월째 혈중 베타수산화부티레이트 수치는 6개월째 경련 빈도 감소와 유의한 상관관계를 보였다. 식이 요법의 효과를 평가할 수 있는 임상적, 그리고 혈액 검사 지표에 대한 대규모의 코호트 연구가 필요하겠다.

중심단어: 식이 요법, 케톤 생성 식이, 약물 난치성 뇌전증, 경련, 혈액 검사 지표