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Short- and long-term seizure-free outcomes of dietary treatment in infants according to etiology

Igam Riantarini[a,1], Heung Dong Kim[b,1], Ara Ko[b], Se Hee Kim[b], Hoon-Chul Kang[b], Joon Soo Lee[b], Da Eun Jung[c,*]

[a] Department of Neurology, Siloam Hospitals Bali, Indonesia
[b] Division of Pediatric Neurology, Epilepsy Research Institute, Severance Children's Hospital, Department of Pediatrics, Yonsei University College of Medicine, Seoul, South Korea
[c] Department of Pediatrics, Ajou University School of Medicine, Suwon, South Korea

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ABSTRACT

Purpose: It is important to determine whether specific etiology is more effective to dietary treatment so that the diet can be started earlier for infants. We evaluated etiology-specific, seizure-free outcomes of dietary treatment in infants < 1 year of age.

Methods: We conducted a 10-year, retrospective, longitudinal observational study of 115 infants treated with ketogenic diet (KD) or modified Atkins diet (MAD).

Results: Most patients (70%) received classical KD; 30% received MAD. During follow-up, 90%, 73%, and 61% of the patients remained on the diet at 3, 6, and 12 months, respectively. Seizure-free outcomes were reported in 50%, 44%, and 50% of the patients at 3, 6, and 12 months, respectively. Long-term seizure-free outcomes over 12 months were reported in 43 (74%) of 58 infants who were seizure-free at 3 months. Etiologies were mostly symptomatic (structural brain abnormalities, genetic, or metabolic) in 83 (72%) of 115 patients. According to underlying etiology, long-term seizure-free outcomes were observed in 14 (33%) of 42 patients with structural brain abnormalities, 7 (33%) of 21 with genetic etiologies, 7 (35%) of 20 with metabolic etiologies, and 15 (47%) of 32 with unknown etiologies. There were no etiology-based differences with respect to long-term seizure-free outcomes ($P = 0.63$).

Conclusion: The high rate of long-term seizure-free outcomes can be predicted based on the seizure freedom at 3 months regardless of etiology. Early dietary treatment is beneficial, even in infants < 1 year of age with specific symptomatic etiologies such as genetic, structural brain abnormalities, and metabolic etiology.

1. Introduction

The incidence of epilepsy is highest in the first year of life [1]. In infants, several severe forms of epilepsy present as developmental and epileptic encephalopathy, which encompasses a spectrum of epilepsy disorders; the epileptic activity itself leads to severe cognitive and behavioral impairments, which tend to be intractable to pharmacotherapy [2]. In infants, the higher the seizure burden, the more predictive of further neurological decline [3], and only freedom from seizure protects psychomotor development [4].

Current research shows that the ketogenic diet (KD) is well tolerated and effective in infants with epilepsy. However, a published expert consensus statement [5] recommended the KD only after failure of two antiepileptic drugs (AEDs); moreover, there are inadequate data to support the KD as a first-line therapy [6]. Previous reports have shown good KD outcomes (> 50% seizure reduction) in infants < 2 years of age; however, these studies included small numbers of subjects [7,8]. It is important to determine whether the specific underlying epilepsy etiology affects the ability of the KD to successfully treat epilepsy for infancy and whether the diet can be effectively started as early as possible, depending on the etiology. We aimed to investigate short- and long-term seizure-free outcomes, according to etiology, in a large number of infants < 1 year of age.

Abbreviations: AED, antiepileptic drug; EIEE, early infantile epileptic encephalopathy; EME, early myoclonic encephalopathy; KD, ketogenic diet; MAD, modified Atkin's diet; SMEI, severe myoclonic epilepsy of infancy; MFSI, migrating focal seizures in infancy

* Corresponding author at: 164, World Cup Road, Yeongtonggu, Suwon, Gyeonggido 16499, South Korea.
E-mail address: j978005@naver.com (D.E. Jung).

[1] Igam Riantarini and Heung Dong Kim contributed equally to this manuscript as co-first authors.

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2. Methods

We reviewed data from 119 patients who started dietary treatment before the age of 1 year from January 1, 2006, to June 30, 2016, at Severance Children Hospital, South Korea. A total of 115 cases were subjected to review, with the following inclusion and exclusion criteria. Inclusion criteria included the following: 1) confirmed diagnosis of epilepsy and the initiation of diet treatment at age < 1 year; 2) complete clinical follow-up data and observation from 1 month before starting the dietary treatment. Exclusion criteria were as follow: 1) the absence of seizures in the last month before dietary treatment. We excluded 4 cases because of the absence of seizures before the start of dietary treatment (four cases received dietary treatment due to hypsarrhythmia).

All patients were admitted for at least 5 days for close observation of adverse effects and family education. The KD (at 3:1 or 4:1 lipid-to-nonlipid ratio) and the modified Atkins diet (MAD) were assigned according to age, body weight, nutritional status, and tolerability. Outpatient visits were regularly performed at 1, 3, 6, and 12 months for the evaluation of efficacy and adverse effects. Screening and follow up examinations were performed according to the protocol reported by Kang et al. [9]. MAD patients followed the Johns Hopkins protocol [10]. Carbohydrates were restricted to 10 g/day for the first month and permitted to increase by only 5 g/day up to 10% carbohydrate by weight with an interval of at least 1 month. Unlike the Johns Hopkins protocol, however, calories were recommended to be restricted to 75% of recommended daily intake. Instead, patients with excessive lethargy were allowed a 100-calorie addition during the first 3 months of therapy. The seizure frequencies before dietary treatment (baseline) and at 3, 6, and 12 months after dietary treatment were obtained. The seizure frequency for the last month before dietary treatment initiation was defined as the "baseline". Long-term seizure-free outcomes to dietary treatment were defined as the maintenance of seizure-free status for more than 12 months. Clinical characteristics were collected from the medical records with the criteria as follows: number of AEDs used before the start of dietary treatment, lead time from seizure onset to dietary treatment initiation, total duration of dietary treatment implementation, epilepsy syndromes before dietary treatment initiation [2], ratio of dietary treatment, electroencephalogram findings, etiology based on positive findings from gene panel test, metabolic workup, and brain magnetic resonance imaging. Adverse effects were based on clinical history during the dietary treatment.

Data were analyzed using SPSS version 22 (SPSS, Chicago, IL, USA) and descriptive statistics when appropriate. Data are presented as the mean (± standard deviation) or percentages. Student's t-tests were applied for parametric data. We used Pearson's chi-square tests for the comparison of categorical variables. The significance level was set at $P \leq 0.05$. This study was approved by the Institutional Review Board of Severance Hospital, and informed consent was waived.

3. Results

3.1. Characteristics of patients

As Table 1 shows, data from 115 children (64 males) were analyzed; 42 infants (37%) had their first onset of seizure between the ages of 4 to 6 months. The patients started dietary treatment at a mean age of 7.5 months (± 2.7 months). The mean lag to treatment was 3.7 ± 2.2 months, and the mean number of AEDs at baseline was 2.8 ± 1.1. The KD was started at a 3:1 ratio in 73 infants (63%), MAD in 34 (30%), and the classic 4:1 ratio in only 8 (7%); the lower KD ratio and MAD were chosen because of the patient's young age and the increased need for protein during growth.

Table 1
Demographic and characteristics of the study population.

Demographics/ characteristics	n = 115
Sex, n (%)	
Males	64 (56.0)
Females	51 (44.0)
Age at the initiation of dietary treatment, mean ± SD (months)	7.5 ± 2.7
Treatment lag to dietary treatment, mean ± SD (months)	3.7 ± 2.2
Number of AEDs used before dietary treatment, mean ± SD	2.8 ± 1.1
Age at seizure onset, n (%)	
≤1 month	29 (25.2)
2–3 months	31 (27.0)
4–6 months	42 (36.5)
7–12 months	13 (11.3)
Duration of dietary treatment, n (%)	
< 3 months	11 (9.6)
≥3– < 6 months	20 (17.4)
≥6– < 12 months	41 (35.6)
≥12 months	43 (37.4)
Ratio of dietary treatment, n (%)	
KD 3:1	73 (63.4)
KD 4:1	8 (7.0)
MAD	34 (29.6)
Etiology, n (%)	
Structural brain lesion	42 (36.5)
Genetic	21 (18.3)
Metabolic	20 (17.4)
Unknown	32 (27.8)
Epilepsy syndrome, n (%)	
Infantile spasms	92 (80.0)
EIEE	13 (11.3)
EME	1 (0.9)
MFSI	2 (1.7)
SMEI	3 (2.6)
Unclassified generalized epilepsy	1 (0.9)
Unclassified focal epilepsy	3 (2.6)

Values expressed as n (%).
AEDs, antiepileptic drugs; EIEE, early infantile epileptic encephalopathy; EME, early myoclonic encephalopathy; KD, ketogenic diet; MAD, modified Atkins diet; SMEI, severe myoclonic epilepsy of infancy; MFSI, migrating focal seizures in infancy; SD, standard deviation.

3.2. Etiology and epilepsy syndrome

Of 115 infants, 83 (72%) had symptomatic/proven etiology (Table 1). Structural brain abnormalities were identified in 42 (37%) patients; 18 had developmental malformations, and 24 had acquired brain abnormalities. The acquired brain lesions, which were mostly hypoxic-ischemic encephalopathy, were present in 18 patients. Genetic causes were identified in 21 (18%) patients and metabolic causes in 20 (17%) patients. The genetic mutations, including *STXBP1* (n = 4), *KCNT1* (n = 2), *SCN2A* (n = 2), *KCNQ2* (n = 2), *ARX* (n = 2), *SCN1A* (n = 2), *SCN4A* (n = 1), *SCN8A* (n = 2), *ADGRV1* (n = 1), *CLCN4* (n = 1), *PCDH19* (n = 1), and *PNKP* (n = 1), were confirmed by genetic studies, including a targeted next-generation sequencing epilepsy gene panel. The metabolic positive findings were mitochondrial cytopathy in 18 patients and pyruvate dehydrogenase complex and glucose transporter-1 deficiency in one patient each. The majority (92, 80%) of the patients had infantile spasms. Despite the rarity of the infantile epilepsy syndromes, early infantile epileptic encephalopathy (EIEE) was observed in 13 infants, early myoclonic encephalopathy (EME) in 1, migrating focal seizures in infancy (MFSI) in 2, and severe myoclonic epilepsy in infancy (SMEI) in 3. Genetic mutations of *STXBP1* (2 patients), *SCN1A* (1 patient), *KCNQ2* (2 patients), and *SCN4A* (1 patient) were confirmed in 6 of 13 EIEE patients. *SCN1A* mutation was confirmed in 2 of 3 SMEI patients and *KCNT1* mutation was confirmed in 2 MFSI patients.

Table 2
Treatment response after 3, 6, and 12 months of dietary treatment.

Treatment response	At 3 months	At 6 months	At 12 months
Patients remaining on the diet	104 (90.4%)	84 (73.0%)	70 (60.9%)
Seizure free	58 (50.4%)	50 (43.5%)	57 (49.6%)
≥90% reduction	5 (4.3%)	14 (12.2%)	2 (1.7%)
50–89% reduction	29 (25.2%)	15 (13.0%)	7 (6.1%)
< 50% reduction	12 (10.4%)	5 (4.3%)	4 (3.5%)

3.3. The efficacy at 3, 6, and 12 months after dietary treatment

The efficacy of dietary treatment at multiple time points was as follows (Table 2): at the first 3 months of follow-up, 90% remained on the diet and 50% were seizure free. At the 6 months follow-up, 73% remained on the diet and 43% were seizure free. At the 12 months follow-up, 61% remained on the diet and 50% were seizure free.

3.4. Short- and long-term seizure-free outcomes for etiology and epilepsy syndrome

The etiologies were mostly symptomatic (structural brain abnormalities, genetic, and metabolic) in 83 (72%) of 115 patients. Short-term seizure-free outcomes at 3 months after dietary treatment were shown in 58 (50%) of 115 patients. According to the underlying etiology, short-term seizure-free outcomes were observed in 19 (45%) of the 42 patients with structural brain abnormalities, 11 (52%) of the 21 patients with genetic etiology, 11 (55%) of the 20 patients with metabolic etiology, and 17 (53%) of the 32 patients with unknown etiology. There were no significant differences according to etiology with respect to short-term seizure-free outcomes (P = 0.86).

Long-term seizure-free outcomes, defined as the maintenance of seizure-free status for more than 12 months, were achieved in 43 (74%) of the 58 patients who were seizure-free at 3 months. According to underlying etiology, long-term seizure-free outcomes were observed in 33% (14/42) of patients with structural brain abnormalities, 33% (7/21) of patients with genetic etiology, 35% (7/20) of patients with metabolic etiology, and 47% (15/32) of patients with unknown etiology. There were no significant differences according to etiology with respect to long-term seizure-free outcomes (P = 0.63) (Table 3).

According to the epilepsy syndromes, infantile spasms was the most frequently observed syndrome (80%, 92/115). Short-term seizure-free outcomes occurred in 47 (51%) at 3 months, and long-term seizure-free outcomes occurred in 36 (39%) of the 92 infants with infantile spasms. The numbers of patients with other epilepsy syndromes were too small to allow statistical examination of differences among epilepsy syndromes. Seizure-free rates within syndromes were 46.2% (6/13) for EIEE, 50% (1/2) for MFSI, and 100% (3/3) for SMEI at 3 months. However, the response was low in EME, unclassified generalized epilepsy, and unclassified focal epilepsy (Table 4).

Table 3
Short- and long-term seizure-free outcomes according to etiology.

Etiologies	Baseline	Short-term seizure-free outcomes		Long-term seizure-free outcomes	
		Yes	No	Yes	No
Structural	42	19 (45.2%)	23 (54.8%)	14 (33.3%)	28 (66.7%)
Genetic	21	11 (52.4%)	10 (47.6%)	7 (33.3%)	14 (66.7%)
Metabolic	20	11 (55.0%)	9 (45.0%)	7 (35.0%)	13 (65.0%)
Unknown	32	17 (53.1%)	15 (46.9%)	15 (46.9%)	17 (53.1%)
Total	115	58 (50.4%)	57 (49.6%)	43 (37.4%)	72 (62.6%)

3.5. Adverse effects of dietary treatment

Adverse effects of any kind during the dietary treatment were reported in 62 (54%) infants (Table 5). Twenty-two patients (19%) discontinued the dietary treatment because of adverse effects. The adverse effects that caused discontinuation were severe infections (n = 8), Gastrointestinal disturbances (n = 3), poor oral intake (n = 3), and acidosis (n = 2). Although there were many adverse effects, most patients recovered and tolerated the adverse effects well.

4. Discussion

This study revealed that dietary treatment, including KD and MAD, is effective for the management of epilepsy in infants < 1 year old regardless of underlying etiology. Our study showed seizure freedom by dietary treatment was achieved within 3 months in about 50% of infants, and long-term seizure-free status for more than 12 months was maintained in 37% infants (< 1 year) regardless of underlying etiology. Long-term seizure-free outcomes were achieved in 43 (74%) of the 58 patients who were seizure-free at 3 months. The efficacy of dietary treatment can be predicted on the basis of seizure freedom at 3 months, which is significantly related to seizure freedom at 12 months [11]. Furthermore, in the first 3 months, it can be decided whether dietary treatment is suitable for a patient, which can potentially increase the patient's compliance [12]. Our results were better than those observed in other studies in infants aged < 2 years or in older children [7,8]. Long-term seizure freedom is the primary goal of dietary treatment to preserve cognitive function regardless of etiology or primary disease, especially in infancy [4]. Therefore, we focused in particular on long-term seizure-free outcomes (for more than 12 months) in infants. In this study, a high rate of seizure-free outcome occurred due to a larger sample with infants < 1 year of age than previous studies.

In the past, KD was not recommended for infants becuase infancy was a critical period for neurodevelopment and the perceived high risk of inadequate nutrition. Current studies have shown that KD is highly effective and well tolerated in infants with epilepsy [7,8]. Recently, the ketogenic diet guideline for infants with refractory epilepsy is published [13]. The creation of these recommendations for infants encourages safe and effective implementation of KD in these vulnerable group of patients. At younger ages, it is easier to control the diet due to the simple menu plan; this is related to compliance of dietary treatment. With the availability of several ketogenic formulas, KD has also become more widely used in infants [14–16]. Compared with adults, neonates and infants have the advantage of having a metabolism associated with the use of ketone bodies [17–19]. The efficacy of dietary treatment in infants is due to the higher amounts of enzymes that metabolize ketones and the production of monocarboxylic acid transporters, leading to more ketone bodies that can cross the blood-brain barrier [17,20]. It has also been shown that ketones play an important role in the formation of myelin because they are transformed into brain sterols and fatty acids when myelination occurs most actively [21].

Due to advances in magnetic resonance imaging and genetic testing technologies, including next-generation sequencing, symptomatic etiologies were identified in 72% of patients in this study. We analyzed our cohort in terms of the seizure-free outcomes for underlying etiology such as structural abnormalities, genetic, metabolic, and unknown etiologies. The seizure-free outcome was maintained for longer especially in patients with glucose transporter-1 deficiency and pyruvate dehydrogenase complex deficiency. Dietary treatment is well-accepted as a first-line therapy for these conditions [22]. Our data showed fairly good responses in infants with a focal cortical malformation, which is a surgically remediable etiology, similar to our previous study [23]. The KD could be considered before surgery or while waiting for surgery, especially in infants < 1 year of age because the risks of brain surgery are highest in this age group. In our study, there were no significant differences regarding short- and long-term seizure-free outcomes

Table 4
Short- and long-term seizure-free outcomes according to epilepsy syndrome.

Epilepsy syndrome	Baseline	Short-term seizure-free outcomes		Long-term seizure-free outcomes	
		Yes	No	Yes	No
Infantile spasms	92	47 (51.1%)	45 (48.9%)	36 (39.1%)	56 (60.9%)
EIEE	13	6 (46.2%)	7 (53.8%)	3 (23.1%)	10 (76.9%)
MFSI	2	1 (50%)	1 (50%)	1 (50%)	1 (50%)
EME	1	0 (0%)	1 (100%)	0 (0%)	1 (100%)
SMEI	3	3 (100%)	0 (0%)	3 (100%)	0 (0%)
Unclassified generalized epilepsy	1	0 (0%)	1 (100%)	0 (0%)	1 (100%)
Unclassified focal epilepsy	3	1 (33.3%)	2 (66.7%)	0 (0%)	3 (100%)
Total	115	58 (50.4%)	57 (49.6%)	43 (37.4%)	72 (62.6%)

EIEE, early infantile epileptic encephalopathy; EME, early myoclonic encephalopathy; SMEI, severe myoclonic epilepsy of infancy; MFSI, migrating focal seizures in infancy.

Table 5
Reported adverse effects during dietary treatment.

Adverse effects (n)	Recover (n)	Discontinuation because of adverse effects (n)
GI disturbance (diarrhea/constipation/ vomiting) (19)	16	3
Infection (sepsis, pneumonia, myocarditis) (15)	7	8
Hypercalciuria/hypercalcinosis (10)	9	1
Hypoglycemia (9)	9	0
Acidosis (5)	3	2
Poor oral intake (5)	2	3
Hypertriglyceridemia/ hypercholesterolemia (4)	4	0
Dehydration (2)	1	1
Renal stone (2)	2	0
Lipoid pneumonia (1)	1	0
Hepatitis (1)	1	0
Pancreatitis (1)	1	0
GI bleeding (1)	0	1
Body weight loss (1)	1	0
Chorea/dystonia (1)	0	1
Allergic reaction/rash (1)	0	1
Metabolic encephalopathy (1)	0	1
Total (79)	57	22

according to underlying etiology. Therefore, dietary treatment can be administered early in infants despite having symptomatic etiologies such as surgery-eligible structural brain abnormalities or genetic or metabolic etiologies.

Efforts to identify epilepsy syndrome can help to predict which patients will show a better response to KD. In our study, infantile spasms was the most frequently observed syndrome (80%). Short-term seizure-free outcomes were 51% at 3 months, and the long-term seizure-free outcomes were 39% for infantile spasms. It is well known that the KD is effective for children with epilepsy syndromes such as infantile spasms, Dravet syndrome, Lennox-Gastaut syndrome, and epilepsy with myoclonic atonic seizures [8,24–29]. However, little is known about the effects of KD on epilepsy syndromes such as EIEE, EME, SMEI, and MFSI confined to infants under the age of 1 year. Although the numbers in each epilepsy syndrome were too small to allow for meaningful examination of differences among them, 6 (46%) of 13 patients with EIEE became seizure free at 3 months, and half of them maintained long-term seizure-free status. One of two patients with MFSI became seizure free at 3 months, whereas the other patients started to show seizure reduction after 3 months but eventually discontinued the diet due to an adverse event (gastric disturbance). These results are similar to those of Caraballo et al. [30]. However, the KD response was low in EME, unclassified generalized epilepsy, and unclassified focal epilepsy.

The limitations of this study are its retrospective nature and the single-institution bias, which is difficult to compare with other reports. The randomized controlled prospective trials constructed according to the underlying etiology may show greater predictive value and allow for precise treatment in the future.

5. Conclusion

This study evaluated short- and long-term seizure-free outcomes of dietary treatment, according to etiology, in a larger sample of infants under 1 year of age than were evaluated in previous studies. Our results suggest that dietary treatment is beneficial for infants < 1 year of age with epilepsy and that it results in a high rate of seizure freedom, regardless of underlying etiology. The high rate of long-term seizure-free outcomes can be predicted based on the seizure freedom at 3 months. Early dietary treatment could be administered, even in infants with specific symptomatic etiologies such as genetic, structural brain abnormalities, and metabolic etiology.

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Conflict of interest statement

The authors have no conflicts of interest relevant to this article to disclose.

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