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Original Article

Ketogenic Diet Efficacy in the Treatment of Intractable Epileptic Spasms

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ABSTRACT

OBJECTIVE: To determine the efficacy of the ketogenic diet in controlling epileptic spasms after failing traditional antiepileptic medication therapy. **METHODS:** This is a prospective, case-based study of all infants with epileptic spasms who were referred for treatment with the ketogenic diet at our hospital between 2009 and 2012. All subjects continued to have epileptic spasms with evidence of hypsarrhythmia or severe epileptic encephalopathy on electroencephalography despite appropriate medication treatments. The diet efficacy was assessed through clinic visits, phone communications, and electroencephalography. Quality of life improvement was charted based on the caregiver's perspective. **RESULTS:** Twenty infants (15 males) were included in the study. The mean age at seizure onset was 4.5 months. Age at ketogenic diet initiation was 0.3 to 2.9 years (mean 1.20, standard deviation 0.78). Fifteen patients had epileptic spasms of unknown etiology; three had perinatal hypoxic ischemic encephalopathy, one had lissencephaly, and one had STXBP1 mutation. Fifteen infants failed to respond to adrenocorticotropin hormone and/or vigabatrin before going on the ketogenic diet. Three months after starting the diet, >50% seizure reduction was achieved in 70% of patients (95% CI 48-86). These results were maintained at 6- and 12-month intervals. All eight of the patients followed for 24 months had >50% seizure reduction (95% CI 63-100). At least 90% seizure reduction was reported in 20% of patients at 3 months (95% CI 7-42), 22% (95% CI 8-46) at 6 months, and 35% (95% CI 17-59) at 12 months. The majority of patients (63%) achieved improvement of their spasms within 1 month after starting the diet. Sixty percent of patients had electroencephalographic improvement. All caregivers reported improvement of the quality of life at the 3-month visit (95% confidence interval 81-100). This ratio was 94% at 6 months (95% CI 72-99) and 82% at 12 months (95% CI 58-95). **CONCLUSION:** The ketogenic diet is a safe and potentially effective method of treatment for patients with epileptic spasms, especially those who do not respond to customary medication therapies.

Keywords: epileptic spasms, ketogenic diet, intractable seizures, hypsarrhythmia

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Introduction

Epileptic spasms (ES) constitute a unique seizure type that often starts in infancy accompanied by neurodevelopmental regression and an electroencephalogram (EEG) pattern of hypsarrhythmia. The incidence is 2 to 3 per 10,000 live births,[1,2] and the lifetime prevalence rate is 1.5 to 2 per 10,000 children.[3] Prognosis is often unfavorable and the majority of patients exhibit poor developmental outcome.[4]

Appropriate treatment options for ES have been a topic of much discussion; however, the agents used, dosage

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regimen, and treatment duration vary significantly among studies. As a result, considerable variation remains in the management. In 2012, The American Academy of Neurology published an update to their 2004 recommendations on the treatment of ES. They stated that low-dose adrenocorticotropin hormone (ACTH) or vigabatrin (VGB) should be considered for the treatment of ES, with ACTH considered preferentially over VGB in cases of unknown etiology.[5] Both of these agents, despite being widely used as first-line therapy, have significant side effects that limit their use, in addition to the high cost of ACTH in the United States. Other agents, including pyridoxine, valproate, and zonisamide, have only limited reported benefits.[6] Topiramate, which is often anecdotally used as a third-line agent after ACTH and VGB, has reported efficacy of >50% spasm reduction in 47% to 53% of patients.[7,8]

The ketogenic diet has been reported as a potentially efficacious nonpharmacologic treatment option for ES, especially when conventional medication therapy fails to control seizures.[9-11] The largest cohort was reported by Hong et al. and consisted of 104 infants with intractable ES. In this study, the authors reported >50% spasm reduction in 64% of the study subjects at 6 months and 77% after 1 to 2 years. A total of 37% became spasm-free for at least a 6-month period within a median of 2.4 months of starting the diet.[11] The same group reported the use of the diet for cases of new-onset ES.[12]

In this study, we report our experience regarding the efficacy, safety, and tolerability of the ketogenic diet in treating intractable ES and we compare our results with previous reports to further validate the efficacy of this therapy.

Methods

This is a prospective, observational, case-based study of 20 consecutive infants with ES who were referred for the ketogenic diet between April 2009 and July 2012. The diagnosis of ES was based on the presence of witnessed flexor or extensor jerks in clusters. EEGs showed classic or modified hypsarrhythmia pattern or severe diffuse epileptic encephalopathy. Patients were started on the diet after they failed conventional pharmacologic therapy. Informed parental consent was obtained before the start of the diet. Institutional review board approval for the study protocol was obtained. All patients were admitted to our hospital for gradual diet initiation without fasting according to the protocol approved at The Comprehensive Epilepsy Center at Children's Mercy Hospital. A 3:1 or 3.5:1 ratio (grams of fat to combined carbohydrate and protein) was used for initiation of the diet. The ratio was adjusted up or down afterwards as clinically necessary under the supervision of a certified nutritionist. Diet efficacy was assessed through patient clinic visits at 3, 6, 12, and 24 months. Only eight patients were followed for 24 months; the remaining patients have been on the diet for shorter periods. Caregivers were asked to keep a daily seizure log on a calendar. Improvement in spasm frequency was classified into four categories: spasm-free, >90% improvement, 50% to 90% improvement, or <50% improvement. Assessment of developmental progress and overall quality of life improvement was based on caregiver's reports and clinical examination. Follow-up EEG was obtained after 3 to 6 months and as needed afterwards. Data were analyzed using descriptive statistics including means, standard deviations, and proportions with 95% confidence intervals.

TABLE 1.
Patient demographics

Gender	15 (75%) Males
Age of spasm onset (mo)	0-9 (mean 4.5, SD 0.22)
Duration of spasms before diet (yr)	0.05-2.4 (mean 0.83, SD 0.687)
Age at diet initiation (yr)	0.3-2.9 (mean 1.2, SD 0.78)
Etiology	Cryptogenic 15 (75%) Secondary 5 (25%)
Number of anticonvulsants tried before diet	2-5 (mean 3.2)
Number of anticonvulsants at diet onset	1-4 (mean 2.1)
Previously tried ACTH or VGB	15 (75%)

Abbreviations:
ACTH = Adrenocorticotropin hormone
SD = Standard deviation
VGB = Vigabatrin

TABLE 2.
Seizure outcomes after initiating the ketogenic diet

Time	>50% Seizure Reduction (%)	95% CI	>90% Seizure Reduction (%)	95% CI
3 (n = 20)	70	48%-86%	20	7%-42%
6 (n = 18)	72	49%-88%	22	8%-46%
12 (n = 17)	76	52%-91%	35	17%-59%
24 (n = 8)	100	63%-100%	75	40%-94%

Abbreviation:
CI = Confidence interval

Results

Demographics

Main demographics for the 20 infants are presented in Table 1. The mean age at seizure onset was 4.5 months (standard deviation [SD] 0.22). Age at diet initiation was 0.3 to 2.9 years (mean 1.20, SD 0.78). The mean duration of epilepsy before the diet started was 0.83 years (SD 0.687). The cause of spasms was unknown in 15 infants (75%); three infants had perinatal hypoxic ischemic injury, one has lissencephaly, and one has an STXBP1 mutation. Fifteen patients failed to respond to ACTH and/or VGB before going on the diet. In the remaining five patients, ACTH and VGB were refused by caregivers because of concerns about potential adverse effects. However, at least three other antiepileptic medications were tried before the diet was started.

Seizure outcomes

Improvement of epileptic spasm frequency after starting the diet is summarized in Table 2 and Figs 1 and 2. A greater

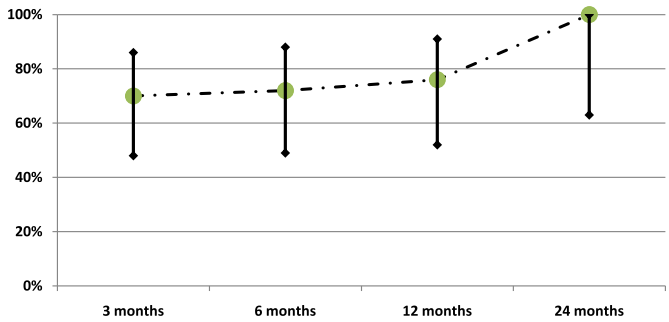

FIGURE 1.
Patients achieved >50% seizure reduction; mean percentage and 95% confidence intervals. (The color version of this figure is available in the online edition.)