SHORT COMMUNICATION

The relationship of ketosis and growth to the efficacy of the ketogenic diet in infantile spasms

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Summary

The ketogenic diet (KD) is a treatment of infantile spasms (IS). Here, we examine the efficacy of KD in medically refractory IS, examine its impact on growth in infants, and explore its mechanism of action. At 1–3 months after the initiation of the KD, 46% of twenty-six patients had a greater than 90% reduction in IS. No significant relationships between reduction in IS and serum β-hydroxybutyrate, or glucose levels were identified. Also, the KD had not significantly altered patient’s growth parameters. Thus, in corroborating with prior studies, we demonstrate the KD is a well-tolerated and efficacious treatment of IS.

Introduction

Infantile spasms (IS) are one of the catastrophic epilepsy syndromes. The ketogenic diet (KD) is a long-recognized treatment of epilepsy, including IS. Several hypothesis exist regarding the anti-epileptic effects of the KD; recent evidence suggests the direct inhibitory effects of ketone bodies, either beta-hydroxybutyrate or acetoacetate, on neurons via a subset of potassium channels may play a role (Ma et al., 2007). Though, to date, ketonuria or ketonemia have not been shown to reliable predictors of epilepsy outcome (Kang et al., 2007; Nordli et al., 2001; Peterson et al., 2005).

The efficacy of the KD in the treatment of epilepsy, irrespective of underlying etiology, has been now substantiated by randomized controlled trials (Neal et al., 2008a). Though the KD does have side effects, and can potentially impair weight and growth, the latter findings have not been well investigated in early childhood (Neal et al., 2008b; Peterson et al., 2005; Vining et al., 2002). In the present investigation, we examine the effect of the KD in treating medically refractory IS, as well as the predictive value of laboratory and anthropometric data in this population.

Methods

This study was approved by the Institutional Review Board of the Massachusetts General Hospital (MGH). A retrospective chart review was performed on patients at MGH with IS that had not resolved with prior treatment of at least one anti-epileptic drug, and who initiated the KD at our institution. Patients with evidence of infantile spasms clinically at the time of KD initiation and who had a prior EEG...
demonstrating classic or modified hypsarrhythmia were included in this study.

The KD had been initiated at a 3:1 and 4:1 ratio (fat to carbohydrate/protein) without initial fast. At diet initiation, a detailed record of seizure type(s) and frequency were made, as well as current and prior AEDs. Follow-up visits were scheduled at 2 weeks, again between 1 and 3 month post-KD initiation, and approximately every 3 months thereafter. All patients were on the KD for at least one month. Treatment efficacy was evaluated by calculating percent reduction in seizure frequency from baseline (<50% reduction, 50–90% reduction, or >90% reduction) based on family report prior to KD initiation at each follow-up visit. Symptoms suggestive of possible side effects were investigated. If patients continued to have seizures at follow-up, the KD was adjusted; AED were also adjusted as necessary for optimal seizure control. Weights and height data were converted to z-scores for age using the Epi Info™-Version 3.5.1 software package containing the Centers for Disease Control and Prevention growth curves (Atlanta, 2000).

Statistical analysis

Fisher’s exact tests and Student’s t-tests were used to analyze categorical and continuous variables. ANOVA with repeated measures and two-way ANOVA were used to assess relationships between response of IS on KD and predictor variables at several time points. Statistical tests were performed with SPSS version 15.0 (Chicago, IL). Values are presented as mean ± standard error unless otherwise stated. All tests considered significant at p < 0.05.

Results

Patient demographics

Twenty-six patients met inclusion criteria. Symptomatic etiologies were identified in 17 (65%) of patients and included phakomatoses (6), pre/perinatal injury (5), cortical dysgenesis (3), chromosomal abnormalities (2), and hydrocephalus (1). IS were diagnosed in patients at 6.5 ± 0.8 months of age. At KD initiation patients were 19.5 ± 2.2 months of age. All patients had been treated with an anti-epileptic drug (AED) without cessation of IS, with a mean of 4.6 ± 0.5 AEDs. Seventeen (65%) patients had received ACTH and 20 (77%) had received vigabatrin. Additional seizure types were evident in 16 of 26 (62%) patients. Duration of KD treatment in this cohort ranged from 1.2 months to 7.7 years with an average of 3.6 years.

KD and seizure reduction

At 1–3 months after initiation of the KD, 12 of 26 (46%) of patients had a >90% reduction in IS, including nine with cessation of spasms (Table 1). In responders, there had been no increases or additions of AED and six of 26 (23%) patients had their AED dosages decreased. Moreover, the observed decreases in IS frequency persisted in nearly all responders at 5–7 months and at 10–13 months after KD initiation. Similar efficacy was found with regard to patients’ other seizure types (Table 1). There was an association between reductions in IS and reductions in other seizure types at 1–3 months (p = 0.02).

In this cohort, patients had initial EEG evidence of hypsarrhythmia or modified hypsarrhythmia prior to KD initiation. After starting dietary therapy, ten of 26 patients (38%) had improvement in their EEG, one (4%) had normalization of EEG, 11 (42%) had no change or evolution to Lennox-Gastaut, and four (15%) had no EEG data available for interpretation. At the 10–13 month time point, five of 26 (19%) patients had terminated the KD due to perceived lack of efficacy or difficulty maintaining the KD (four of these patients had done so prior to the 5–7 month time point); one of 26 patients was lost to follow-up; one of 26 patients had not yet reached that age point. Using an intent-to-treat analysis, 11 of 26 (42%) patients had >90% reductions in infantile spasm frequency at 5–7 months after KD initiation, and 12 of 26 (46%) had >90% reductions at 10–13 months; both values are similar to reductions found at 1–3 months after initiation of KD.

Side-effects were encountered in six of 26 (23%) of patients on the KD and included irritability, lethargy, decreased appetite, nephrolithiasis, vitamin D deficiency, and persistent hypoglycemia. One patient with IS and without additional seizure types at KD initiation developed tonic seizures at six months of treatment. This occurred in the setting of hydrocephalus secondary to aqueductal stenosis; the additional seizure type remitted after ventroperitoneal shunt placement.
Figure 1  Blood glucose (A), serum \( \beta \)-hydroxybutyrate (B) levels, and weight-to-height z-score (WHZ) of patients while on the ketogenic diet. (A) Glucose levels for non-responders and responders, respectively, at baseline (79 ± 2 vs. 79 ± 3, n = 12, 10) and at 1–3 months (59 ± 3 vs. 57 ± 3, n = 10, 10), at 5–7 months (63 ± 4 vs. 63 ± 3, n = 8, 9), and at 10–13 months (68 ± 4 vs. 59 ± 5, n = 9, 7) after ketogenic diet initiation. (B) \( \beta \)-Hydroxybutyrate levels for non-responders and responders, respectively, at baseline (0.47 ± 0.2 vs. 0.33 ± 0.2, n = 6, 5), and at 1–3 months (5.9 ± 0.5 vs. 5.6 ± 0.4, n = 7, 7), at 5–7 months (4.9 ± 0.6 vs. 5.5 ± 0.3, n = 7, 7), and at 10–13 months (4.3 ± 1.0 vs. 5.7 ± 0.7, n = 5, 8) after ketogenic diet initiation. (C) WHZ for non-responders and responders, respectively, at baseline (0.71 ± 0.4 vs. 0.16 ± 0.3, n = 14, 11) and at 1–3 months (0.87 ± 0.4 vs. −0.14 ± 0.4, n = 12, 9), at 5–7 months (0.98 ± 0.6 vs. 0.24 ± 0.5, n = 8, 7), and at 10–13 months (0.48 ± 0.5 vs. 0.37 ± 0.5, n = 8, 5) after ketogenic diet initiation.

Predictors of response to KD

Demographics
In this cohort, there were no significant relationships between a greater than 50%, nor a greater than 90% reduction in IS and age at onset of spasms, time to initial treatment of spasms with medication, or time to treatment of spasms with the KD. Of note, 11 of 18 males (61%) were responders compared to one of eight (13%) females \( (p = 0.04) \). With respect to etiology of IS, four of five patients with pre/perinatal injury responded to KD (including one female patient). In contrast, three of nine patients with cryptogenic IS responded to KD, and one of three with cortical dysgenesis.

Laboratory data
Glucose levels at baseline were within normal limits and were decreased at all subsequent follow-up visits after KD-initiation \( (p < 0.001; \text{ Fig. 1A}) \). In opposition, \( \beta \)-hydroxybutyrate levels were within normal limits at baseline
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and increased at all follow-up visits \((p < 0.001, \text{ Fig. 1B})\). However, there was no significant difference between mean glucose levels or \(\beta\)-hydroxybutyrate levels among responders and non-responders to the KD when analyzed as a simple effect, nor across all time points (Fig. 1A and B).

**Anthropometric data**

In our cohort, weight-for-height z-score (WHZ) prior to initiation of the KD was \(0.47 \pm 0.3\), which equals the 68th percentile (Fig. 1C). Patient’s WHZ did not differ significantly from baseline after KD initiation. Though patients with a greater than 90% reduction in IS while on the KD had lower mean WHZ at all time points compared to those with a lesser response, this was not significant as a simple effect, \(r\) across all time points.

**Discussion**

In our cohort of patients with medically refractory IS, we corroborate with previous reports that KD is an efficacious treatment of IS. We demonstrate long-term efficacy and its ability to reduce the frequency of concomitant seizure types, irrespective of prior AED usage. Here, the efficacy of the KD, where 46% of patients had a greater 90% reduction in IS after 1–3 months of treatment, is higher than some data; but, in line with investigations utilizing hypsarrhythmic EEG patterns as inclusion criteria (Eun et al., 2006; Hong et al., 2010). However, it is possible our use of parental reports at each visit, as opposed to weekly diaries may have skewed our results. Interestingly, we report males with IS were more likely to respond to KD than females. This may be an artifact of our sample size, as larger cohorts have not demonstrated similar gender-specific findings (Hong et al., 2010). Alternatively, given that etiology of IS may impact treatment efficacy, our result may reflect a sampling bias in the etiology of IS in this cohort of IS (Osborne et al., 2010).

Our analysis showed the KD was well-tolerated in this cohort. Though side-effects were encountered in 23% of our group, none were considered serious to warrant tapering of treatment. Several of our patients began the KD overweight, or greater than the 85th percentile for weight-to-height. In keeping with prior reports, no association was seen in clinical populations will be well-suited to address these questions.

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**References**


