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FULL-LENGTH ORIGINAL RESEARCH

# Infantile spasms treated with the ketogenic diet: Prospective single-center experience in 104 consecutive infants

***Amanda M. Hong, †Zahava Turner, †Rana F. Hamdy, and †‡Eric H. Kossoff**

***The Johns Hopkins University School of Medicine, Baltimore, Maryland, U.S.A.; †Department of Pediatrics, The Johns Hopkins Hospital, Baltimore, Maryland, U.S.A.; and ‡Departments of Neurology, The John M. Freeman Pediatric Epilepsy Center, Baltimore, Maryland, U.S.A.**

## Summary

**Purpose: In 2002, we reported our preliminary experience using the ketogenic diet (KD) for predominantly intractable infantile spasms (IS) in 23 infants. Since that time, we have increased our use of the KD for this condition including those with new-onset IS.**

**Methods: Infants were referred and prospectively started on the traditional KD from 1996 to 2009 at our institution. Included subjects had documented clinical IS, hypsarrhythmia on electroencephalography (EEG), and parental consent to start the KD. Efficacy was assessed through phone communication, clinic visits, and EEG every 3 months.**

**Results: One hundred four infants, mean age 1.2 years, were started on the KD for IS, of which 74 (71%) had a symptomatic etiology. Previous therapy for this patients included a mean of 3.6 anticonvulsants; 71% including corticosteroids or vigabatrin. Using an intent-to-treat analysis, >50% spasm improvement occurred in 64% at 6 months and 77% after 1–2 years. Thirty-eight (37%) became spasm-free for at least a 6-month period within a median 2.4 months of starting the KD. In addition, 62% reported improvement in development, 35% had EEG improvement, and 29% were able to reduce concurrent anticonvulsants. Adverse effects were noted in 33%, of which 6% had diminished linear growth. Older age at onset of IS and fewer prior anticonvulsants were more likely to be associated with >90% spasm improvement at 6 months.**

**Discussion: The KD is an efficacious therapy for IS in approximately two-thirds of patients treated, and it should be considered strongly after failure of corticosteroids and vigabatrin.**

**KEY WORDS: Ketogenic, Infantile spasms, West syndrome, Epilepsy, Diet, Infants.**

Infantile spasms (IS) is an epilepsy syndrome that typically presents between the ages of 3 and 10 months, and is characterized by flexor or extensor jerks presenting in clusters (Lux & Osborne, 2004). Prognosis is unfavorable, even in cryptogenic cases, and the majority of patients exhibit profound developmental regression (Riikonen, 2001).

Appropriate treatment options for IS have been a topic of much research but are still problematic at this time. The American Academy of Neurology published their recommendations in 2004, stating that adrenocorticotropic hormone (ACTH) was ''probably effective'' and vigabatrin ''possibly effective'' as a short-term treatment (Mackay et al., 2004). Both of these agents, despite being perceived as first-line, have significant side effects that limit their use, in addition to high costs in the United States. Other options, including pyridoxine, sulthiame, valproate, and zonisamide, have only limited reported benefits for IS (Tsao, 2009). Topiramate specifically, which is often anecdotally used as a third-line agent after corticosteroids and vigabatrin are unsuccessful, has published benefits of only 47–53% having a >50% spasm reduction (Hosain et al., 2006; Korinthenberg & Schreiner, 2007).

The ketogenic diet (KD) has emerged as an efficacious nonpharmacologic therapy for intractable IS (Nordli et al., 2001; Kossoff et al., 2002; Eun et al., 2006). The widespread availability of several ketogenic formulas has also led to increased use for infants (Kossoff et al., 2004; Hosain et al., 2005; Eun et al., 2006). In 2002 we reported preliminary results using the KD for 23 patients with refractory IS (Kossoff et al., 2002). Since that time we have seen a significant increase in referrals for the KD for intractable IS. In addition, we have started to use the KD for cases of new-onset IS (Kossoff et al., 2008). The purpose of this study was to use the increased patient cohort to evaluate for predictive factors for success, compare results over time, and evaluate long-term seizure, EEG, and developmental outcomes.

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Address correspondence to Eric H. Kossoff, M.D., Suite 2158 – 200 North Wolfe Street, David M. Rubenstein Child Health Building, The John M. Freeman Pediatric Epilepsy Center, The Johns Hopkins Hospital, Baltimore, MD 21287, U.S.A. E-mail: ekossoff@jhmi.edu

## Methods

Between February 1996 and May 2009, 104 consecutive infants diagnosed with IS were started prospectively on the KD. The diagnosis of IS was based on the presence of witnessed flexor or extensor jerks in clusters and a classic or modified hypsarrhythmia pattern on electroencephalography (EEG). All patients followed the KD protocol approved by the Johns Hopkins Committee on Clinical Investigation, and informed parental consent was obtained prior to the start of therapy. This cohort includes the 23 initial patients from our institution (Kossoff et al., 2002), 13 with new-onset IS (Kossoff et al., 2008), and 68 additional infants.

All patients except for three fasted prior to diet initiation to allow for faster transition to ketosis and potential benefit. A 3:1 or 3.5:1 ratio (grams of fat to combined carbohydrate and protein) was used in 68 (65%); this lower ratio was typically chosen due to the young age of patients and their increased need for protein for growth. The ratio was adjusted after KD onset as clinically necessary. The median number of starting kilocalories was 700 per day (range 416–1,240 kcal/day). Sixteen patients were started on 4:1 KetoCal formula (Nutricia, Inc., Gaithersburg, MD, U.S.A.), which became commercially available in 2002.

Diet efficacy was assessed through patient clinic visits at 3, 6, 9, 12, and 24 months, as well as telephone and email contact in the interim. An intent-to-treat analysis was employed for this study and the last known seizure improvement data point was carried forward for patients that were lost to follow-up. Parents were asked to keep records of daily seizure frequency on a calendar along with biweekly urine ketones and weekly weight. Improvement in spasm frequency was classified into four categories: spasm-free, >90% improvement, 50–90% improvement, or <50% improvement. Assessment of developmental progress was based on parental reports and clinical examination; no formal developmental assessment tests were utilized. Follow-up EEG was obtained after 6–12 months in those children with intractable IS and 2–4 weeks in those with new-onset IS.

Numerical data were analyzed using a two-tailed *t*-test. Categorical data were analyzed using Pearson's chi-square test for independence of rows and columns. Multivariate analysis of data was accomplished using logistic regression. Significance level for all tests was $p = 0.05$.

## Results

### Demographics

Baseline patient demographics for the 104 infants are presented in Table 1. The mean age at KD onset was 1.2 years [standard error of the mean (SEM) 0.1] and infants were treated a mean duration of 1.3 years (SEM 0.2). The mean number of prior anticonvulsants was 3.6 (SEM 0.2); 71% had tried corticosteroids (ACTH in 66 and high-dose oral prednisolone in two) and/or vigabatrin before starting the KD. Eighteen infants were treated with the KD as first-line therapy.

**Table 1. Patient baseline demographics**

| | |
|---|---|
| Male gender | 59 (57%) |
| Symptomatic etiology | 74 (71%) |
| Age of spasm onset (years) | 0.4 (0.02) |
| Duration of spasms prior to KD (years) | 0.8 (0.1) |
| Age at KD initiation (years) | 1.2 (0.1) |
| Number of spasms/month prior to KD | 1749 (221) |
| Number of anticonvulsants tried prior to KD | 3.6 (0.2) |
| Number of anticonvulsants at KD onset | 1.4 (0.1) |
| Previously tried corticosteroids (ACTH or prednisolone) | 68 (65%) |
| Previously tried vigabatrin | 21 (20%) |
| Previously tried either corticosteroids or vigabatrin | 71 (68%) |

Values expressed as n (%) or mean (SEM).

Symptomatic etiologies were identified in 74 (71%), and included cortical dysgenesis (22), chromosomal abnormalities (6), tuberous sclerosis complex (6), Aicardi syndrome (6), infection (5), stroke (5), hypoxic-ischemic encephalopathy (3), mitochondrial disorders (2), hydrocephalus (2), and malignancy (1). Sixteen children had profound developmental delay of unclear etiology prior to IS and were also classified as symptomatic. Structural abnormalities on neuroimaging were identified in 39 (38%). Fifty-five (53%) had a secondary seizure type (e.g., complex partial, myoclonic) at the time of KD initiation along with the predominant spasms.

### Overall outcomes

Improvement in spasm frequency was analyzed using an intent-to-treat analysis, and is shown in Table 2. Overall, >50% spasm improvement was seen in 66 (63%) at 3 months, 67 (64%) at 6 months, 76 (73%) at 9 months, 80 (77%) at 12 months, and 80 (77%) at 24 months. More specifically, >90% improvement was seen in 33 (31%) at 3 months, 41 (39%) at 6 months, 48 (46%) at 9 months, 45 (43%) at 12 months, and 46 (44%) at 24 months. Thirty-eight (37%) achieved at least 6 months of spasm-freedom during treatment with the KD, with median time to spasm-freedom of 2.4 months (range 0.1–20.4 months). Of the 38 infants who achieved spasm-freedom, 30 (79%) did not relapse. Of the eight who relapsed, seven were temporally associated with changes in KD composition (3), illnesses (3), or decreases in medications (1). Another patient relapsed 1 year after starting the KD (after 10 months of spasm freedom) for unclear reasons and this child remained on the KD for an additional 0.9 years. Four children started vigabatrin after the KD was unsuccessful; one became spasm-free.

The number of patients actively being treated with the KD at each time point is presented in Table 2. Ten (10%) currently remain on the KD at this time, five are lost to follow-up, and three have died. Of the 86 patients who have

**Table 2. Spasm reduction outcomes for all 104 infants started on the KD at each follow-up time period**

| | 3 months | 6 months | 9 months | 12 months | 24 months |
|---|---|---|---|---|---|
| Spasm reduction | | | | | |
| Spasm-free[a] | 19 (18%) | 29 (28%) | 33 (32%) | 31 (30%) | 34 (33%) |
| >90%[a] | 14 (13%) | 12 (11%) | 15 (14%) | 14 (13%) | 12 (11%) |
| 50–90%[a] | 33 (32%) | 26 (25%) | 28 (27%) | 35 (34%) | 34 (33%) |
| <50%[a] | 38 (37%) | 37 (36%) | 28 (27%) | 24 (23%) | 24 (23%) |
| Number actively receiving the KD | 86 (83%) | 76 (73%) | 53 (51%) | 47 (45%) | 28 (27%) |
| >90% spasm reduction[b] | 33 (38%) | 33 (43%) | 27 (51%) | 24 (51%) | 17 (61%) |

[a]Intent-to-treat analysis.
[b]Of those receiving the KD at each time point.

discontinued the KD to date, the most common reason was reported inefficacy [48 (56%)]. Reasons for discontinuation were related to the timing of this occurrence; 20 of 28 (71%) who stopped the KD prior to 6 months were more likely to do so because of reported inefficacy compared to after 6 months, 28 of 58 (48%), p = 0.02. The median follow-up to date since starting the KD is 1.8 years (range 0.5–13 years).

### First-line use

Ten of the 18 (56%) treated for new-onset IS became spasm-free within 2 weeks of treatment. Thirteen of these patients have been previously reported (Kossoff et al., 2008). In all situations, the KD was offered as a 2-week trial alternative to corticosteroids or vigabatrin when infants were brought to medical attention rapidly. Those who became spasm-free were maintained on the KD for 6 months and then the KD was discontinued without recurrence. In these children, all had normal EEGs within 2 months of treatment. For the eight who did not respond to the KD as first-line therapy, ACTH was immediately started in five, oral prednisolone in two, and topiramate in one. These therapies led to spasm freedom in six of the eight KD nonresponders, with one infant who did not respond to prednisolone and then was successfully being treated with vigabatrin. Predisposing etiologies were similar to those with intractable IS.

### Other outcomes

Anticonvulsants were reduced while on the KD in 29 patients (28%), of which 14 became completely anticonvulsant-free. This reduction typically occurred after the first month of KD treatment if the child was showing early signs of spasm reduction. One child had a relapse of spasms coinciding with discontinuation of valproic acid. Conversely, only seven patients were started on a new anticonvulsant during KD treatment, and these included topiramate (2), vigabatrin (2), clonazepam (1), oxcarbazepine (1), and zonisamide (1).

At the time of KD initiation, 80 (77%) had developmental delay, of which 20 were profoundly delayed. After at least 6 months of follow-up, 8 (8%) patients had observed or reported normal development and 56 (54%) showed some degree of developmental improvement compared to baseline but still were delayed. Twenty-four (23%) did not show any improvement, and the remaining 16 were lost to follow-up or did not have any developmental evaluation on record after starting the KD. Five of 30 (17%) of those with a cryptogenic etiology had normal developmental outcomes compared to 3 of 74 (4%) with symptomatic causes (p = 0.04). All eight infants with subsequent normal development were treated with the KD before 6 months of ongoing IS.

Nineteen (18%) eventually had a normal EEG during KD treatment and 18 (17%) showed resolution of hypsarrhythmia but periodic spikes or focal slowing, in both situations, typically by KD duration of 6 months. In general, these 37 children had clinical improvements that corresponded directly with the EEG changes, with 25 (68%) being seizure-free and 10 (27%) having >90% spasm reduction. In a similar fashion, 25 (24%) showed no change in hypsarrhythmia and 25 (24%) showed evolution into Lennox-Gastaut syndrome corresponding with a lack of clinical benefit. The remaining 17 (16%) did not have any follow-up EEG information on record while being treated with the KD.

### Predictors of response

Several baseline demographic factors were analyzed as possible predictors of positive outcomes. At 6 months after KD initiation, none were found to be predictive of >50% improvement in spasm frequency. Table 3 shows the results that were predictive of >90% improvement in spasm frequency at 6 months. After multiple logistic regression to adjust for all potentially predictive factors, only an older age at spasm onset (0.5 vs. 0.4 years) remained statistically significant (p = 0.03). Better outcomes for those infants who had tried fewer anticonvulsants (2.6 vs. 4.3 anticonvulsants) prior to KD initiation trended toward significance after logistic regression (p = 0.16).

### Adverse effects

Adverse effects were reported in 34 (33%) infants. These included constipation (7), gastroesophageal reflux (6), behavioral problems (3), hematuria (3), diarrhea (3), kidney

**Table 3. Prognostic factors for likelihood of a >90% spasm reduction using an intent-to-treat analysis at 6 months**

| | <90% (n = 63) | >90% (n = 41) | p-Value |
|---|---|---|---|
| Male gender | 37 (59%) | 22 (54%) | 0.61 |
| Symptomatic etiology | 46 (73%) | 29 (71%) | 0.81 |
| Classic hypsarrhythmia at KD onset | 52 (83%) | 29 (71%) | 0.16 |
| Age at spasm onset (years) | 0.4 (0.04) | 0.5 (0.03) | 0.03 |
| Spasm frequency (per month) | 1786 (392) | 1693 (264) | 0.84 |
| Age at KD onset (years) | 1.4 (0.1) | 1.1 (0.1) | 0.05 |
| No. AEDs tried prior to diet | 4.3 (0.3) | 2.6 (0.3) | <0.01 |
| Prior steroid use (%) | 48 (76%) | 20 (49%) | <0.01 |
| No. AEDs at KD onset | 1.6 (0.2) | 1.1 (0.1) | 0.01 |
| 4:1 Ketogenic ratio | 20 (32%) | 17 (41%) | 0.31 |
| Daily kilocalories | 745 (23) | 726 (22) | 0.56 |
| Started on KD after 9/12/2000 (n = 81)[a] | 45 (71%) | 32 (78%) | 0.45 |

[a]Since the previous preliminary study results (Kossoff et al., 2002).
AED, antiepileptic drug.

stones (3), acidosis (3), hair thinning (2), hypercalcemia (2), dry skin (1), and pica (1). Dyslipidemia was identified in 17 (16%), with only one child requiring dietary intervention to reduce lipid values (addition of medium chain triglyceride oil) due to total cholesterol of 641 mg/dl, which then normalized 3 months later.

Of the 45 patients with documented weight information to compare between baseline and 6 months after KD initiation, 36 (80%) exhibited positive weight change. The mean weight change over this 6-month period was 1.4 kg, compared to a normal mean 1.5 kg increase for a typical infant growing between 6 and 12 months of age (National Center for Health Statistics, 2000). Of the 39 patients with recorded height change at 6 months, 34 (87%) exhibited positive height change. The mean height change was 5.1 cm, compared to a normal average increase for this age of 6.1 cm. Growth issues were believed to be potentially problematic according to patient records in 6 (6%), and the KD ratio was then adjusted downward and calories increased accordingly.

### Comparison of preliminary and current results

To ascertain if patient demographics and outcomes have changed since the initial infants at our institution (Kossoff et al., 2002), we compared infants before (23) and after (81) September 2000. There have been significantly more female patients in the recent cohort (49% vs. 26%, p = 0.03). In addition, more infants have started the KD with initial classical hypsarrhythmia than prior to September 2000 (83% vs. 63%, p = 0.03) (Kossoff et al., 2002). A slightly higher but not significant increase in percentage with spasm reduction was seen in the more recent cohort at each time point. For example, at 6 months in our most recent 81 infants, 68% had >50% improvement compared to 56% in the 2002 study (p = 0.44), and 43% showed >90% improvement now compared to 30% previously (p = 0.39).

## Discussion

With now more than 100 patients, our results continue to demonstrate that the KD is a highly effective therapy for IS. Our study showed spasm-free rates of 18–33% over a 3–24 month period despite the typically intractable nature of these cases. Approximately two-thirds of patients had >50% spasm improvement after 6 months, which is similar to reports from other institutions of a 71–81% response rate (Nordli et al., 2001; Eun et al., 2006). It is possible that some of the spasm-free results with the KD over time could be due to spontaneous remission, although our results are higher than the 9–14% described from 6–9 months (Hrachovy et al., 1991).

Perhaps equally important were the other positive effects of the KD, with significant improvements in development and EEG, as well as reduction in the number of concurrent anticonvulsants. Although there are concerns of the effect of this high-fat diet on adequate growth in infants (Vining et al., 2002), we found that both height and weight growth were generally appropriate for age. Dyslipidemia was also four times less likely in this series than in children receiving a solid-food ketogenic diet; this was likely as a result of the formula-based KD composition (Nizamuddin et al., 2008).

Our analysis showed that patients who are older at time of IS onset tend to have better outcomes. This was different from our previous findings that a better prognosis may be correlated with KD initiation <1 year of age (Kossoff et al., 2002). It is unclear how to interpret these contradictory findings; however, the current difference was only approximately 1 month (0.5 vs. 0.4 years) and, therefore, may not be clinically relevant. Infants who had tried fewer anticonvulsants prior to initiation of the KD also had a slightly better outcome, which was similar to previous results and continues to suggest that earlier, perhaps even first-line, treatment may be valuable (Kossoff et al., 2008). Although a previous study noted that patients with a cryptogenic etiology had better outcomes with the KD (Eun et al., 2006), we did not confirm these findings.

These results would be best confirmed by additional prospective, multicenter studies to account for regional variations on practice. Creating a standardized KD formula ''prescription'' for immediate use in a typical 6-month-old infant might also reduce dietitian time and effort when starting the KD, thus expanding its use for IS. Additional studies in even larger patient cohorts may also be useful in identifying those infants who may be more likely to respond to the KD versus anticonvulsants or corticosteroids. Lastly, further studies could also look for synergistic KD–drug combinations, including possibly vigabatrin, which has now been recently reapproved in the United States.

In summary, the favorable outcome seen in a significant proportion of patients treated with the KD, even after months of continued spasms, suggests that this therapy is a valuable option for IS. Considering also the low adverse effects, benefits for development, and reduction in anticonvulsants, the KD should be considered as a valuable second- or third-line therapy for IS.

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## Disclosure

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