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FULL-LENGTH ORIGINAL RESEARCH

A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms

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SUMMARY

Purpose: **ACTH is currently the standard first-line therapy for new-onset infantile spasms, but it has significant side effects. We hypothesized the ketogenic diet (KD), previously reported as beneficial for intractable infantile spasms, would have similar efficacy, but better tolerability than ACTH when used first-line.**

Methods: **We conducted a retrospective chart review of all infants started on the KD (n = 13) and high-dose ACTH (n = 20) for new-onset infantile spasms at our institution since 1996.**

Results: **Infants were spasm-free in 8 of 13 (62%) infants treated with the KD within 1 month, compared to 18 of 20 (90%) treated initially with ACTH, p = 0.06. When effective, median time to spasm freedom was similar between ACTH and the KD (4.0 vs. 6.5 days, p = 0.18). Those treated with ACTH were more likely to have a normal EEG at 1 month (53% vs. 9%, p = 0.02), however, use of the KD led to EEG normalization within 2–5 months in all eight who became spasm-free. In the five children in whom the KD was unsuccessful, four became spasm-free subsequently with ACTH or topiramate immediately. Side effects (31% vs. 80%, p = 0.006) and relapse rate after initial success (12.5% vs. 33%, p = 0.23) were lower with the KD.**

Discussion: **In this retrospective study, the KD stopped spasms in nearly two-thirds of cases, and had fewer side effects and relapses than ACTH. ACTH normalized the EEG more rapidly, however. Further prospective study of the KD as, with a 2-week time limit if unsuccesful, first-line therapy for infantile spasms is warranted.**

KEY WORDS: **Infantile spasms, Ketogenic diet, ACTH, Hypsarrhythmia.**

Infantile spasms is an age-specific epilepsy syndrome associated with clustering flexor or extensor tonic spasms, electrographic hypsarrhythmia, and occasional developmental regression (Mackay et al., 2004). Unfortunately, treatments are somewhat limited. A 2004 American Academy of Neurology and Child Neurology Society practice parameter concluded that adrenocorticotropic hormone (ACTH) was "probably" and vigabatrin was "possibly" effective for new-onset infantile spasms, with all other treatments having insufficient evidence for their use (Mackay et al., 2004). In addition, serious concerns exist regarding the side effect profiles of ACTH and vigabatrin, and their use is therefore limited to only several weeks to months (Nabbout, 2001; Mackay et al., 2002). Both agents have difficulties with availability in the United States, since vigabatrin is no longer licensed and ACTH now costs up to $80,000 for a 1-month supply (press release, August 2007 Questcor, Union City, CA, U.S.A.).

As a result of limited options with significant toxicity, researchers have actively investigated second-generation anticonvulsants possessing relatively fewer side effects, including felbamate (Hosain et al., 1997), levetiracetam (Lawlor & Devlin, 2005), topiramate (Hosain et al., 2006; Zou et al., 2006), and zonisamide (Lotze & Wilfong, 2004). However, none of these drugs have demonstrated spasm-free outcomes similar to ACTH, and often have been used primarily for refractory spasms (Mackay et al., 2004).

The ketogenic diet (KD) is a high fat, low carbohydrate diet used for intractable childhood epilepsy (Freeman et al., 2007). Side effects are generally transient, minor, and can be treated without having to discontinue the KD (Freeman et al., 2007). The KD is especially useful in infants due to widely available ketogenic formulas which can be easily prepared and which ensure compliance (Nordli et al., 2001;

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Kossoff et al., 2004). The KD has been shown in three retrospective studies to be very effective for intractable infantile spasms; often after ACTH and vigabatrin have been unsuccessful (Nordli et al., 2001; Kossoff et al., 2002; Eun et al., 2006). Included in two previous studies from our institution, we reported two (Kossoff et al., 2002) and subsequently six (Rubenstein et al., 2005) infants treated with the KD as initial therapy for infantile spasms. In these six children, half were still spasm-free after 6 months (Rubenstein et al., 2005). Since that time, we have started seven additional children using the KD. We report their results in comparison to a control population treated with ACTH over the same time period.

METHODS

A retrospective, case-control chart review was performed of all infants started on either the KD or ACTH at Johns Hopkins Hospital for new-onset infantile spasms from February 1996 to April 2007. All children included were seen and evaluated initially at our institution and counseled regarding treatment options. Infants were identified both from a search of the Johns Hopkins KD database as well as all EEG electronic reports for the terms: "hypsarrhythmia," "infantile spasms," "drops," "disorganized," "ACTH," or "West syndrome." Infantile spasms was defined as flexor or extensor spasms occurring in clusters witnessed by parents and physicians, with EEG evidence of either classic or modified hypsarrhythmia within 1 month of presentation. All EEGs were interpreted by a staff epileptologist. Infants were included for analysis if there was a history of prior seizures, but this was the first presentation of infantile spasms and no anticonvulsant with published evidence for infantile spasms had been ever used (Mackay et al., 2004). No child received both ACTH and the KD concurrently due to theoretical concerns of reduced ketosis with concurrent corticosteroids (Freeman et al., 2006), or in combination with any other treatment. All infants had at least 6 months of follow-up, including a developmental examination performed by a staff neurologist.

The KD was offered typically if a dietitian was available to emergently begin the KD, there were no contraindications (metabolic or mitochondrial disorder, perceived inability to tolerate the KD formula), profound developmental regression coinciding with spasm onset, and the family understood the nontraditional nature of KD therapy for new-onset infantile spasms. For all who subsequently chose to then begin the KD, parents were told that follow-up was crucial and after approximately 1 month a primarily clinical assessment of the effectiveness of the KD would be made by the treating neurologist in conjunction with the parents. This KD duration chosen was based primarily on evidence that >1-month of untreated spasms might lead to worse developmental outcomes (Lombroso, 1983; Kivity et al., 2004). Spasm freedom was defined as complete absence of visible infantile spasms witnessed by the family over a 24-h period. If spasms persisted, the KD would be discontinued immediately and ACTH would be started unless contraindicated. In addition, a 30-min waking and sleep EEG would be repeated at the time of this clinical reassessment. If the EEG was still abnormal, but the child was both spasm-free and not losing developmental milestones, the KD could be continued for an additional month if desired by both the family and neurologist.

The majority of families who chose ACTH instead of the KD did so due to consideration of published evidence for ACTH or concerns regarding discontinuation of breastfeeding. There was no randomization; parents were given both options, time to make their decision, and there was no financial influence involved. No family transferred care to another institution after being started on either KD or ACTH. Cost issues did not influence any family's decision.

The KD was started in all infants as per the Johns Hopkins protocol (Freeman et al., 2007), with gradually increasing calories over 3 days following a 24–48 h fasting period. All infants received multivitamin and calcium supplementation while on the KD as well as periodic serum and urine laboratory monitoring. The KD was provided solely as formula initially, with some children who were spasm-free slowly being started on solid, pureed foods after 3 months. Formulas utilized included either a combination of Ross Carbohydrate-free Ross, Abbott Park, IL, U.S.A., Novartis Microlipid (Novartis, Fremont, MI, U.S.A.), and Ross Polycose (Ross), or Nutricia KetoCal (Nutricia, Gaithersburg, MD, U.S.A.) in all children.

ACTH was started in the hospital using a high-dose, short-term protocol in all children (Mackay et al., 2004). Intramuscular injections were provided of ACTH (ACTHar gel, Questcor) 150 units/m^2/day in two divided doses for the first week, 75 units/m^2/day in one daily dose for the second week, and then 75 units/m^2/day every other day for two final weeks. ACTH was restarted at the 150 units/m^2/day dose for an additional month if spasms recurred. All children received periodic blood pressure and glucose monitoring, and empiric oral ranitidine for gastrointestinal prophylaxis during their 4-week treatment course.

Categorical data were analyzed using Fisher's exact test and medians were compared using a Wilcoxon two-sample test. The significance level for all tests was $p = 0.05$. All parents choosing to start the KD signed informed consent solely to maintain information in a KD database as part of our ongoing study of the effectiveness of the KD prior to participation. Verbal consent regarding the 1-month period of KD duration, importance of close follow-up, and potential switch to ACTH if the KD was ineffective was obtained in all children receiving the KD. The retrospective record review of infants treated with ACTH was also separately approved by the Johns Hopkins Institutional Review Board.

Table 1. Baseline patient demographics for both treatment options. Values provided in median (range) or n (percentile)

	KD (n = 13)	ACTH (n = 20)	p-value
Age at spasms onset (months)	5 (2–10)	6 (1–12)	0.33
Median duration of spasms prior to treatment (days)	10 (3–45)	23.5 (3–100)	0.02
Clusters of spasms per day	5 (3–10)	4 (2–10)	0.08
Male gender	6 (46%)	13 (63%)	0.16
Symptomatic etiology	8 (62%)	14 (70%)	0.45
Classic hypsarrhythmia	7 (54%)	12 (60%)	0.50

RESULTS

Baseline subject demographics

Over this time period, 13 infants were treated with the KD as first-line therapy and 20 were treated initially with ACTH (Table 1). Thirty infants had no prior anticonvulsant exposure, two had received phenobarbital, and one had been treated with carbamazepine. The median age of reported spasm onset was 5 months (range: 1–12 months). Twenty-two (67%) had symptomatic etiologies identified, six (18%) were idiopathic, five (15%) were cryptogenic (etiology suspected, but not identified). There was no difference in regard to age at onset, gender, symptomatic etiology, or presence of classic hypsarrhythmia between ACTH or KD groups (Table 1). A significantly shorter history of infantile spasms, however, was present for those who started KD compared to ACTH (median 10 vs. 24 days, $p = 0.02$), due to physicians' and parents' greater willingness to attempt the KD first-line if spasms had been occurring for only a brief period.

Spasm reduction and relapse rate

Outcomes for children treated initially with the KD (Table 2) and ACTH (Table 3) are presented. After 1 month, the KD resulted in spasm-freedom in 8 of 13 (62%) infants, compared to 18 of 20 (90%) treated with ACTH, $p = 0.06$. The median time to spasm-freedom was slightly more rapid with ACTH (4.0 days) compared to KD (6.5 days), $p = 0.18$. When efficacious, the KD was continued for 6 months in all but two children (Patients 1 and 2), who discontinued the diet after 3 and 42 months, respectively.

Table 2. Demographics and outcomes of children started on the KD (n = 13). Patients are ordered based on the sequence in which they were treated over the 11-year study period

Patient	Age at spasm onset (months)	Duration of spasms (days)	Gender	EEG[a]	Etiology (specified if symptomatic)	Spasm-free at 1 month?	Time to spasm freedom (days)	EEG at 1 month[a]	Spasm-free with ACTH after therapy switched	Developmental outcome at 6 months
1	5	24	Male	Modified	Cryptogenic	Yes	18	Modified	N/A	Mild delay
2	5	14	Female	Modified	Congenital CMV	Yes	7	None (normal at 4 months)	N/A	Moderate delay
3	2	21	Male	Classic	Hypoxic-ischemic encephalopathy	Yes	1	None (normal at 2 months)	N/A	Severe delay
4	5	5	Female	Classic	Idiopathic	Yes	6	Classic (normal at 3 months)	N/A	Normal
5	5	30	Male	Modified	Cryptogenic	No	N/A	Modified	Yes	Severe delay
6	5	3	Female	Classic	Congenital hydrocephalus	No	N/A	Modified	Yes	Moderate delay
7	10	4	Female	Classic	Group B streptococcal meningitis	Yes	9	Modified (normal at 5 months)	N/A	Mild delay
8	5	10	Male	Classic	Idiopathic	No	N/A	Classic	Yes	Normal
9	10	3	Male	Modified	Left hemispheric astrocytoma and infarction	No	N/A	Modified	Yes (topiramate used, not ACTH)	Mild delay
10	5	4	Female	Classic	Partial agenesis of the corpus callosum	Yes	3	Modified (normal at 2 months)	N/A	Mild delay
11	8	45	Male	Modified	Periventricular leukomalacia	Yes	10	Normal	N/A	Mild delay
12	5	7	Female	Classic	Idiopathic	Yes	3	Minor asymmetry (normal at 2 months)	N/A	Normal
13	3	14	Female	Modified	Aicardi syndrome	No	N/A	Modified	No	Moderate delay

[a]classic, classic hypsarrhythmia; modified, modified hypsarrhythmia.

Table 3. Demographics and outcomes of children started on ACTH (n = 20). Patient numbers are ordered based on the sequence in which they presented over the 11-year study period

Patient #	Age at onset (months)	Duration of spasms (days)	Gender	EEG[a]	Etiology (specified if symptomatic)	Spasm-free at 1 month?	Time to spasm freedom (days)	EEG at 1 month[a]	Developmental outcome at most recent follow-up
1	4	16	Male	Classic	Dysgenesis of the corpus callosum	Yes	1	Modified	Normal
2	7	22	Female	Modified	Idiopathic	Yes	3	Normal	Normal
3	5	3	Male	Classic	Trisomy 21	Yes	1	None (normal at 6 months)	Moderate delay
4	5	25	Female	Classic	Trisomy 21	Yes	3	Normal	Mild delay
5	9	14	Male	Modified	Idiopathic	Yes	4	Normal	Mild delay
6	6	42	Male	Classic	Hemispheric atrophy	Yes	5	Normal	Normal
7	6	12	Male	Classic	Pachygyria	Yes	14	None	Moderate delay
8	5	30	Female	Modified	Periventricular leukomalacia	Yes	21	None (modified at 3 months)	Mild delay
9	6	25	Male	Classic	Cryptogenic	Yes	5	Focal spikes	Mild delay
10	7	90	Female	Classic	Trisomy 21	Yes	1	Normal	Moderate delay
11	1	50	Male	Modified	Periventricular leukomalacia	Yes	5	Focal spikes	Severe delay
12	6	4	Female	Classic	Periventricular leukomalacia, hydrocephalus	Yes	6	Focal spikes	Severe delay
13	5	21	Male	Classic	Cryptogenic	Yes	2	Normal	Normal
14	8	35	Female	Modified	Idiopathic	Yes	6	Normal	Normal
15	8	18	Male	Modified	Schizencephaly	Yes	2	Modified	Mild delay
16	5	25	Female	Classic	Chromosome 5,9 translocation	Yes	1	Modified	Mild delay
17	12	90	Male	Classic	Trisomy 21	Yes	5	Normal	Mild delay
18	6	21	Male	Classic	Linear nevus sebaceous syndrome	Yes	4	Normal	Normal
19	1	100	Male	Classic	Cryptogenic	No	N/A	Modified	Moderate delay
20	6	21	Male	Modified	Hearing loss, optic nerve atrophy	No	N/A	Modified	Moderate delay

[a]classic, classic hypsarrhythmia; modified, modified hypsarrhythmia.

Five infants did not respond to the KD within 1 month, of which four were then switched to ACTH. Three became spasm-free, but one (Patient 13) did not respond to subsequent trials of topiramate or vigabatrin. One infant (Patient 9) was treated with topiramate (due to concerns regarding ACTH side effects) and became spasm-free after 7 days. ACTH was unsuccessful initially in two infants (Patients 19 and 20), both of whom were subsequently treated with topiramate with only partial success and were later treated with the KD after 4 and 6 months, respectively. Both remain on the KD at this time and currently have Lennox-Gastaut syndrome.

For those eight infants who became spasm-free with the KD, the recurrence rate was low over the following 6 months, with only one infant (12.5%) having a relapse at 3 months (Patient 1). The KD was continued and topiramate added with resultant spasm freedom. Conversely, 6 of the 18 (33%) ACTH responders had a relapse within the subsequent 6 months, $p = 0.23$. Four were treated with a second course of ACTH, with resultant spasm freedom in two. Two infants were treated with valproate and topiramate for their recurrences without success.

EEG improvement

EEGs were obtained after 3–4 weeks of therapy in 11 (85%) receiving the KD and 17 (85%) receiving ACTH. After 1 month of using the KD, the EEG showed modified hypsarrhythmia in seven, classic hypsarrhythmia in two, minor asymmetry in one, and was normal in one infant (Table 2). Of the eight infants who were spasm-free with the KD, six had an EEG after 1 month of treatment, and only one (17%) was normal. However, after 2–5 months of KD therapy, all eight children had normal EEGs.

After 1 month of ACTH, the EEG was normal in nine, modified hypsarrhythmia in four, focal spikes in three, and classic hypsarrhythmia in one infant (Table 3). ACTH was more likely to result in a normal EEG at 1 month in those in whom an EEG was obtained after 1 month than the KD, 9 of 17 (53%) versus 1 of 11 (9%), $p = 0.02$.

Developmental outcomes

At the time of presentation with infantile spasms, seven (54%) of those started initially on KD and seven (35%) started on ACTH had moderate or severe development delay. Follow-up developmental examinations were available for a median period of 12 months (range: 9 to 96 months) in all subjects. At the most recent follow-up, there was no difference in outcomes between groups. Poor developmental outcomes (moderate to severe delays) were noted in five (38%) of the initial KD group compared to seven (35%) of the ACTH group, $p = 0.28$.

Predictive factors for improvement

The eight infants who became spasm-free with the KD were compared to those five who had persistent spasms (Table 4). There was no patient demographic or KD treatment option (ratio or fasting period) that predicted a higher likelihood of response to the KD. Only two children did not respond initially to ACTH, therefore, no statistical comparison was attempted.

Adverse effects

Charts were reviewed for potential attributable side effects in all infants during the first 6 months of treatment. Irritability was reported in 12 of 20 (60%) receiving ACTH initially, as well as excessive weight gain in 6 (30%), insomnia in 2 (10%), and hypertension in 1 infant (5%). Side effects reported in those treated with the KD included gastroesophageal reflux, constipation, poor formula tolerability, and weight loss each occurring in one infant. These four infants had either diet modifications or medications added (lansoprazole and polyethylene glycol for the former two) and adverse events improved. No infant receiving the KD had dyslipidemia, kidney stones, or acidosis during the treatment period. There was a significantly lower likelihood of any reported adverse events over the 6-month period with the KD than with ACTH [4 of 13 (31%) vs. 16 of 20 (80%)], $p = 0.006$.

Table 4. Predictive factors in regard to likelihood of spasm-free response to the KD at 1 month. Values provided in median (range) or n (percentile)

	Spasm-free (n = 8)	Not spasm-free (n = 5)	p-value
Age at onset (months)	5 (2–10)	5 (3–10)	1.00
Median duration of spasms prior to treatment (days)	10.5 (4–45)	10 (3–30)	0.55
Male gender	3 (38%)	3 (60%)	0.33
Symptomatic etiology	5 (63%)	3 (60%)	0.43
Classic hypsarrhythmia	5 (63%)	2 (40%)	0.41
Ratio (fat: carbohydrate and protein) of 4:1	4 (50%)	2 (40%)	0.59
Fasting period (24 h)	6 (75%)	4 (80%)	0.69

Discussion

In this retrospective study, the KD was safe, well tolerated, and effective as first-line therapy for infantile spasms. This builds upon our previous results that the KD can be helpful for this population as a new-onset treatment (Kossoff et al., 2002; Rubenstein et al., 2005). Approximately two-thirds of the infants became spasm-free, all within 18 days of beginning the fasting period. ACTH had a higher likelihood of a spasm-free response after 1 month of therapy, although our 90% spasm-free outcome was somewhat higher than the 42%–87% previously reported in Class I–III studies to date (Hrachovy et al., 1980, 1983; Lombroso, 1983; Hrachovy et al., 1994; Baram et al., 1996; Yanagaki et al., 1999; Lux et al., 2004). Outcomes following the KD were similar therefore to ACTH and were higher than the 35%–48% spasm-freedom after 1 month of vigabatrin (Vigevano & Cilio, 1997; Appleton et al., 1999; Elterman et al., 2001; Lux et al., 2005).

The KD required longer treatment duration to normalize the EEG, even in those infants who were clinically spasm-free. Half of infants successfully treated had persistence of some features of hypsarrhythmia after 1 month, suggesting the EEG effect of the KD may be delayed compared to its clinical effect (Panico et al., 2000). This was also found to some extent with ACTH, with 90% of infants spasm-free at 1 month, but only 53% having a normal EEG.

The KD appeared to be well tolerated by infants and easy to administer by parents. Most families in our experience were amenable to a therapy that involved changing their infant's formula rather than intramuscular injections. Side effects were lower with the KD than ACTH, as would be predicted from the literature (Nabbout, 2001; Freeman et al., 2007). Of the five subjects who did not respond to the KD, four (80%) subsequently responded within days to ACTH or topiramate and their long-term seizure and developmental outcomes were similar to children responding to either therapy immediately. We therefore believe it was safe to defer treatment with ACTH for up to 4 weeks with a therapeutic trial of the KD. However, as all but one child responded within 10 days, the results from this study now indicate that a 2-week trial is adequate and longer KD durations unnecessary if ineffective. Published evidence regarding the maximum time allowed for treatment has been controversial, with evidence for benefits of early treatment (Lombroso, 1983; Kivity et al., 2004) in contrast to a lack of influence of spasm duration on long-term development (Glaze et al., 1988; Lux et al., 2005). However, no study advocating early treatment has used a period less than 1-month spasm duration as a theoretical limit (Lombroso, 1983; Kivity et al., 2004). In addition, we now recommend only trying this alternative first-line therapy if spasms have been occurring for shorter than 2 weeks (in order to allow for a maximum potential total spasm time period of 4 weeks prior to hormonal therapy).

There are several limitations of this study. For one, the retrospective nature and small patient numbers did not allow us to definitively demonstrate any KD parameters (e.g., ratio, period of fasting) as more advantageous nor any particular patient demographic more likely to respond to the KD overall. Only routine EEGs were obtained and it is possible prolonged video EEG may have captured electrographic spasms. Future study designs should include video EEG to ensure spasm-freedom as has been suggested (Mackay et al., 2004). There was certainly a potential for physician and parent bias in how the KD was offered as a treatment option, which would be eliminated in a prospective, randomized study.

We believe future studies of a dietary approach for new-onset infantile spasms, assuming a 2-week time limit if unsuccessful, are safe and warranted. As the length of fasting did not correlate with an increased likelihood of spasm-freedom, an immediate calorie-for-calorie switch from standard to KD formula might be effective and shorten the risks, costs, and inconvenience of hospitalization (Vaisleib et al., 2004; Bergqvist et al., 2005). In addition, the typical 6-month KD duration used in this series when successful could possibly be shortened by several months based on EEG normalization, in a similar manner to ACTH administration. Lastly, combination therapy with KD and anticonvulsants (e.g., vigabatrin or topiramate) may further increase the efficacy of the KD.

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Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors have any conflicts of interest to declare.

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