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FULL-LENGTH ORIGINAL RESEARCH

When do seizures usually improve with the ketogenic diet?

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SUMMARY

Purpose: Parents often expect immediate seizure improvement after starting the ketogenic diet (KD) for their children. The purpose of this study was to determine the typical time to seizure reduction as well as the time after which it was unlikely to be helpful in those children started on the KD.

Methods: Records of all children started on the KD at Johns Hopkins Hospital, Baltimore (n = 83) and Children's Memorial Hospital, Chicago (n = 35) from November 2003 to December 2006 were examined to determine the first day in which seizures were reportedly improved.

Results: Of the 118 children started on the KD, 99 (84%) had documented seizure reduction. The overall median time to first improvement was 5 days (range: 1–65 days). Seventy-five percent of children improved within 14 days. In those children who were fasted at KD onset, the time to improvement was quicker (median 5 vs. 14 days, $p < 0.01$) with a higher percentage improving within 5 days (60% vs. 31%, $p = 0.01$). No difference was identified between fasting and nonfasting in regards to long-term outcomes, however.

Discussion: The KD works quickly when effective, typically within the first 1–2 weeks. Starting the KD after a fasting period may lead to a more rapid, but equivalent long-term seizure reduction, confirming prior reports. If the KD has not led to seizure reduction after 2 months, it can probably be discontinued.

KEY WORDS: Ketogenic diet, Epilepsy, Children, Prognosis, Fasting.

The ketogenic diet (KD) is a nonpharmacologic therapy that is primarily used for children with intractable epilepsy (Freeman et al., 2007). Unlike medications, it requires significant parental education, traditionally accomplished during a 4–5 day hospital admission. During this admission period, children are traditionally fasted for 1–2 days in order to rapidly induce a ketotic state that may lead to immediate seizure reduction (Freeman & Vining, 1999). Although most large studies and reviews of the efficacy of the KD report outcomes at 3 and 6 months (Vining et al., 1998; Henderson et al., 2006), it is known that seizure reduction may occur within the first month or even days (Freeman & Vining, 1999; Than et al., 2005).

Many parents expect a rapid seizure improvement with the KD, despite the typically intractable epilepsy their children are faced with, perhaps as a result of occasional media reports of dramatically successful cases. When a child has not had a significant seizure reduction from the KD, parents often question the value for their child of this rigorous therapy and may discontinue prior to the typically recommended 6 month KD trial period (Freeman et al., 2006). The KD may be stopped even sooner for those children in whom surgical intervention is an option, based on the reported relative decreased efficacy of the KD in this situation (Stainman et al., 2007).

At this time, however, there are no published data regarding the observed range of KD duration typically required to detect seizure improvement in those children who do respond. A study of the modified Atkins diet in adults determined that most subjects improved either rapidly or not at all, within 2 months of diet onset (Kossoff et al., 2007a). We hypothesized that the first signs of improvement would be seen also within 2 months using the KD for children.

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METHODS

A retrospective, multicenter chart review was performed of all children started on the KD at Johns Hopkins Hospital, Baltimore, MD (JHH) (n = 83) and Children's Memorial Hospital, Chicago, IL (CMH) (n = 35) over a 3-year period from November 2003 to December 2006. At both centers, children were started gradually on the KD during an inpatient admission by increasing the calories by one-third daily over a 3-day period (Freeman et al., 2007). Children started at JHH from November 2003 to March 2006 were usually fasted for 48 h, and those started from April to December 2006 were fasted 24 h. Subjects from CMH from November 2003 to December 2004 were typically fasted 24 h, and those started after January 2005 were not fasted. Overall, 64 (54%) were fasted 2 days, 18 (15%) 1 day, and 36 (31%) were not fasted. Most children without reported improvement after 2–3 weeks on the KD had dietary manipulations in order to improve efficacy.

Charts, electronic records, seizure calendars, and occasionally emails and phone calls were reviewed to determine the first reported day in which seizures were described as reduced compared to baseline. Seizure calendars were examined on a day-by-day basis to determine when this change occurred. This seizure reduction could be of any amount, but had to be for at least two consecutive days (to demonstrate a trend toward improvement). Day 1 of the KD was considered the first day of the fasting period (if the child was fasted) and hospitalization. Most children had seizures at least daily at the time of KD onset; in those with fewer seizures, the best estimate of improvement in seizure frequency was made based on seizure calendars. Seizure calendars and records for all children receiving the KD during this time period were examined for signs of improvement, regardless of eventual diet duration or level of response.

This study was approved by the institutional review boards of both centers, and unique patient identifiers were not maintained. Categorical data were analyzed using Fisher exact test and medians were compared using Wilcoxon two-sample test. Multiple linear regression was then used to examine the relationship between covariates potentially predicting the time to detect seizure reduction. A Kaplan–Meier survival analysis was used to compare time to improvement of those in the fasting versus the nonfasting group. The significance level for all tests was $p = 0.05$.

RESULTS

Baseline subject demographics

One-hundred and eighteen children were evaluated from both institutions. Sixty-five (55%) were female; the median age at KD onset was 3 years (range: 0.3–15 years). Children had been treated with a median of five anticonvulsants total (range, 0–10 medications), were actively receiving two anticonvulsants at KD onset (range: 0–4 medications), and were having 250 seizures per month (range: 1–15,000 per month). There was no statistical difference in these patient demographics between JHH and CMH. More children at CMH were started on a 3:1 ratio (fat: carbohydrate and protein grams) than JHH, 63% versus 39%, respectively ($p = 0.01$). Otherwise, KD composition and supplementation was similar between the two institutions.

The majority of patients had generalized seizures, including infantile spasms (n = 23), Lennox-Gastaut syndrome (n = 22), atonic and myoclonic seizures combined (n = 18), myoclonic-astatic epilepsy (Doose syndrome) (n = 16), myoclonic seizures (n = 8), severe myoclonic epilepsy of infancy (Dravet syndrome) (n = 4), atonic seizures (n = 1), Ohtahara syndrome (n = 1), and eyelid myoclonia (n = 1). Twenty-four had a partial epilepsy, including more children at JHH than CMH, 21/83 (25%) versus 3/35 (9%), ($p = 0.02$).

Time to improvement

Of the 118 children, 99 (84%) had some level of seizure reduction reported by their parents during treatment with the KD. Five children had a seizure reduction of 25–50% compared to baseline when this improvement first occurred, however all were having a minimum of three seizures per day and a slight decrease was therefore noted which continued to improve further in all cases. Nineteen (16%) had no reported seizure reduction and remained on the KD a median of 5 months (range: 1–8 months).

These 99 children were then evaluated to determine at what time this improvement first occurred. The median time to first improvement was 5 days (range: 1–65 days). Seventy-five percent had improvement within the first 14 days of the diet and 90% within 23 days (Fig. 1). Only four children (5%) had no reported improvement until 60–65 days after diet onset, at which time three began to have 50–90% seizure reduction and one suddenly became seizure-free.

Time to improvement was subanalyzed further, focusing only on those with >90% seizure reduction at 3 months (n = 55), for whom the median time to improvement was also 5 days (range: 1–60 days). Similarly, when those children with at least daily seizures were analyzed in order to improve accuracy in detecting any seizure reduction (n = 88), the median time to reduction was 5 days (range: 1–65 days).

Long-term outcomes

Using an intent-to-treat analysis (n = 118), 89 (75%) children had >50% seizure reduction and 57 (48%) had >90% seizure reduction at 3 months. At 6 months, 84 (71%) were >50% improved and 51 (43%) were >90% improved. There was no statistically significant difference in any of these outcomes either between institutions or in those who were or were not fasted at either 3 or

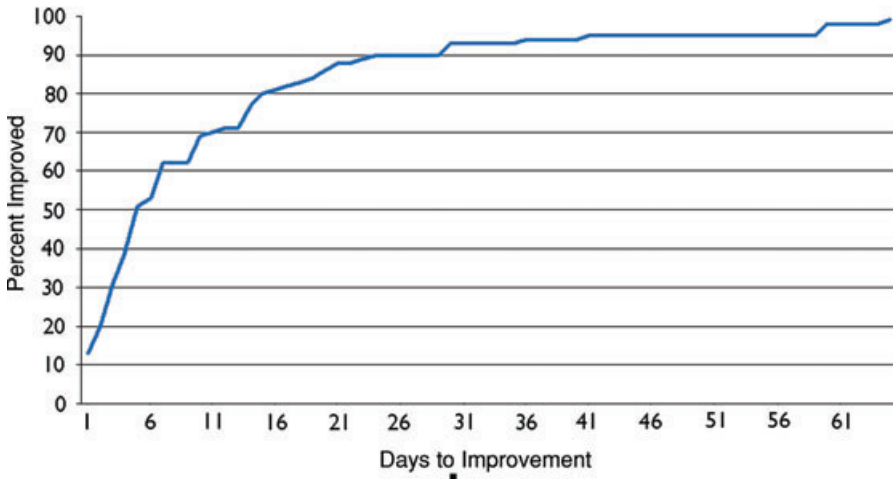

Figure 1.
Day at which seizure reduction was first noted, as expressed as a cumulative percentage of all of those children demonstrating improvement on the ketogenic diet (n = 99).
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6 months. The median diet duration at the time this report was prepared was 12 months (range: 1–64 months). Twenty children (17%) discontinued the diet prior to 6 months; 11 discontinued it because of a lack of perceived seizure reduction. Diet duration did not correlate with time to improvement (p = 0.94).

Over the 6-month study period, for those 99 children with reported seizure reduction, the majority either maintained (n = 54) or continued to improve upon (n = 21) the level of seizure reduction initially reported. Twenty-four children had a subsequent worsening of their seizure frequency after an initial improvement was noted, including seven who had become seizure-free for a period of time.

Factors predicting time to improvement

Patient demographics and diet parameters were examined to determine if there was a correlation with time to improvement (Table 1). The only significant variable was the presence of initial fasting, with a median time to improvement of 5 days (range: 1–65 days) in those fasted compared to 14 days (range: 1–60 days) in those who were not, (p < 0.01). Using multivariate analysis to control for initial ratio and age of diet onset, both variables that trended towards significance, fasting remained statistically significant (p = 0.01). In those who improved, the likelihood of seizure reduction within the first 5 days was twice as likely with fasting, 42/70 (60%) versus 9/29 (31%) (Fig. 2) (p = 0.01). There was no difference between either 1 or 2 days of fasting, median 7 versus 5 days respectively, (p = 0.99).

Table 1. Possible predictive factors in determining time to improvement in subjects who improved on the ketogenic diet (n = 99); values of days to improvement are expressed as median (range)

Factor	Presence	Absence	P value
Ratio (4:1)	5 (1–65)	7 (1–60)	0.15
Fasting at diet onset	5 (1–65)	14 (1–60)	<0.01
Age (> 3 years)	5 (1–60)	6.5 (1–65)	0.13
Seizure frequency (>250 per month)	5 (1–65)	6 (1–60)	0.91
Medications tried (> 5)	5 (1–41)	7 (1–65)	0.33
Medications at diet onset (>2)	7 (1–60)	5 (1–65)	0.57
Partial seizures	6.5 (1–90)	5 (1–60)	0.84

Discussion

In patients successfully treated with the KD, seizures appear to improve rapidly. This is consistent with the anecdotal experience with the KD in children (Freeman et al., 2006) and similar to results from the modified Atkins diet

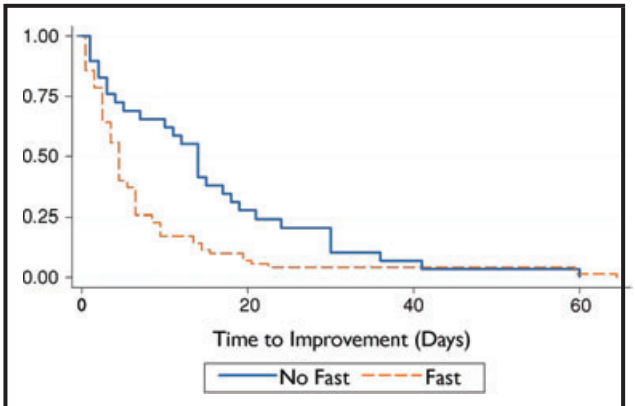

Figure 2.
Time to improvement between fasting and nonfasting approaches to starting the ketogenic diet, expressed as a Kaplan–Meier analysis.
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for adults (Kossoff et al., 2007a). The results of this study provide practical information regarding the expected time to determine improvement for physicians starting children on the KD. Approximately half of children improved before even being discharged from the average 4–5 day hospitalization to begin the KD. Two-thirds of children either continued this level of seizure control or improved over time.

In this group of children, if the KD did not improve seizure frequency within the first 65 days, it did not happen. Although this would be understandably discouraging to a family who has both emotionally and financially invested time and energy into the education and admission process of the KD, it also is useful information in order to avoid perhaps unnecessary potential side effects with its continued use (Kang et al., 2004). Considering also the restrictiveness of the KD, if it is not helpful after 2 months, this study suggests a regular diet could be reintroduced and other treatment options discussed.

Our findings also suggest that the first month(s) of the KD may be the most important for treatment. This correlates with recent results that both a strict initial carbohydrate limit using the modified Atkins diet (Kossoff et al., 2007b) and a higher initial ratio (Seo et al., 2007) led to improved 3-month outcomes. Starting children after a fasting period with a strict, highly KD and then scheduling both close follow-up with frequent dietary manipulations if necessary may be advantageous.

This study also confirms previously published data demonstrating that fasting is not necessary for long-term (3-month) seizure reduction (Wirrell et al., 2002; Kim et al., 2004; Vaisleib et al., 2004; Bergqvist et al., 2005), although it may lead to a more rapid improvement (Freeman & Vining, 1999). This was noted with even a shortened, 24-h fasting period. The fasting period may act in a manner analogous to an intravenous load of an anticonvulsant. In situations of devastating or injurious seizures, in which a family or neurologist desires the quickest improvement possible, the benefits of fasting may therefore be worth the increased hypoglycemia and acidosis reported (Bergqvist et al., 2005).

This study has several limitations. The retrospective nature of this study, including the use of parent-maintained seizure calendars rather than physician or EEG observation, could have led to inaccuracies or bias. However, as a large percentage of children improved even during their initial hospital admission, many of those who improved were first noted by physicians. In addition, parents were generally very reliable in maintaining seizure calendars; children with multiple daily seizures often had a clear date of improvement documented when it occurred. It is unknown if the findings from this study are different than anticonvulsant medications, as this particular outcome measure is not often measured in clinical trials, as opposed to seizure reduction over several weeks (French et al., 2004). In addition, it is possible that the 11 children who discontinued the diet earlier than 6 months due to lack of improvement may have had seizure reduction if the diet was continued longer. Lastly, as daily changes in seizure frequency naturally occur in children with intractable epilepsy, examining for trends over weeks or months may be more accurate.

In summary, the KD appears to lead to seizure reduction quickly when effective, often within the first 1–2 weeks but universally within the first 2 months. Starting the KD after a fasting period may lead to a more rapid, but equivalent long-term seizure reduction and diet duration. In children in whom seizures are not improved after 2 months, the KD probably can be discontinued.

Acknowledgments

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