Published in final edited form as:

Epilepsy Res. 2011 March ; 94(1-2): 94–101. doi:10.1016/j.eplepsyres.2011.01.012.

Early EEG Improvement after Ketogenic Diet Initiation

Sudha Kilaru Kessler, M.D.^a, Paul R. Gallagher, M.A.^b, Renée A. Shellhaas, M.D., M.S.^c, Robert R. Clancy, M.D.^a, and A.G. Christina Bergqvist, M.D.^a

^a Division of Neurology, The Children's Hospital of Philadelphia, and Departments of Pediatrics and Neurology, University of Pennsylvania School of Medicine, Philadelphia, PA

^b Division of Biostatistics and Epidemiology, The Children's Hospital of Philadelphia, Philadelphia, PA

^c Division of Pediatric Neurology, Department of Pediatrics and Communicable Diseases, Mott Children's Hospital, University of Michigan Medical School, Ann Arbor, MI

Abstract

Purpose—This study examines electroencephalographic (EEG) changes in children with medication resistant epilepsy treated with the ketogenic diet (KD).

Methods—Routine EEGs were obtained prior to KD initiation, then one month and three months later. Changes in EEG background slowing and frequency of interictal epileptiform discharges (IEDs) were evaluated using power spectrum analysis and manual determination of spike index. KD responders were compared to non-responders to determine if baseline or early EEG characteristics predicted treatment response (>50% seizure reduction) at three months.

Results—Thirty-seven patients were evaluated. No differences in baseline EEG features were found between responder groups. Frequency of IEDs declined in 65% of patients as early as one month, by a median of 13.6% (IQR 2-33). Those with a ten percent or greater improvement in IED frequency at one month were greater than six times more likely to be KD responders (OR 6.5 95% CI 0.85 to 75. p=0.03). Qualitative and quantitative measures of EEG background slowing improved in the whole cohort, but did not predict responder status.

Conclusion—Baseline predictors of KD response remain elusive. Most patients experienced a reduction in IEDs and improvement in EEG background slowing after KD initiation. Reduction of IEDs at one month strongly predicted KD responder status at three months.

Keywords

Ketogenic Diet; EEG; spike index; power spectrum analysis

*corresponding author: Sudha Kilaru Kessler, M.D., Robert R. Clancy, M.D., A.G. Christina Bergqvist, M.D., Colket Translational Research Building, Children's Hospital of Philadelphia, 3501 Civic Center Blvd., Philadelphia, PA 19104, Fax: 215-590-1771, kessler@email.chop.edu, bergqvist@email.chop.edu, clancy@email.chop.edu.

Paul R. Gallagher, M.A., Department of Biostatistics, Children's Hospital of Philadelphia, 3535 Market Street, Philadelphia, PA 19104, gallagherp@email.chop.edu

Renee Shellhaas, M.D., M.S., A. Alfred Taubman Health Care Center, 1500 East Medical Center Drive, Floor 1, Room 1924, Reception: D, Ann Arbor, MI 48109-5318, Fax: 734-763-7551, shellhaa@med.umich.edu

Conflicts of Interest

None of the authors has any conflicts of interest to disclose.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

The ketogenic diet (KD) is a high fat, low protein and low carbohydrate diet which is effective in the treatment of medication resistant epilepsy. Half of patients treated with the KD experience a 50% or greater reduction in seizure frequency, and one fifth achieve seizure freedom (Lefevre and Aronson 2000; Neal et al. 2009; Thiele 2003; Vining et al. 1998). Children initiating the KD are asked to complete a minimum three month course of dietary adherence before an assessment of efficacy is made. During this time, they are exposed to all of the risks and burdens of maintaining the KD. A better understanding of the baseline predictors and early indicators of response to the KD is necessary for beginning to characterize which patients are most likely to benefit from KD treatment.

Predictors of response to the KD are not well understood. Differences in age at KD initiation and sex have not been found between responders and non-responders (Vining et al. 1998), but shorter duration of epilepsy prior to KD initiation may increase likelihood of response (Dressler et al. 2010). In some studies, seizure type and epilepsy syndrome have differed between responders and non-responders, but the evidence is far from robust. Children with complex partial seizures as the major seizure type may have a lower likelihood of experiencing an early, dramatic response to the KD (Than et al. 2005), while the presence of generalized tonic clonic seizures may marginally predict an increased likelihood of response (Dressler et al. 2010). Other studies have shown no association between epilepsy type and KD efficacy (Neal et al. 2008; Vining et al. 1998). As noted in the recently issued recommendations of the International Ketogenic Diet Study Group, children with certain epilepsy syndromes and genetic disorders may derive greater benefit from the KD (Kossoff et al. 2009). Several groups have observed that the KD may be particularly effective in severe myoclonic epilepsy of infancy (SMEI; Dravet Syndrome) and myoclonic astatic epilepsy (MAE; Doose Syndrome), with larger than expected rates of seizure freedom in these patients (Caraballo et al. 2006; Kilaru and Bergqvist 2007; Korff et al. 2007; Oguni et al. 2002).

Few studies have examined differences between KD responders and non-responders in electrophysiologic characteristics. A study of fifty patients who underwent routine EEGs within 6 months before starting the KD showed that subjects with interictal epileptiform discharges (IEDs) in the temporal regions were more likely to be non-responders to the KD treatment, but no other EEG characteristics were found to be predictive (Beniczky et al. 2010). No prospective investigations of the predictive value of baseline EEG, or early changes in EEG, for KD treatment response have been reported. One prior retrospective study of 18 children treated with the KD revealed that early reduction of IEDs correlated with a reduction in seizure frequency at three months (Hallbook et al. 2007). In 24 patients undergoing 24 hour EEG recording, improvements in the amount of interictal epileptiform activity and background slowing was seen in slightly more than half (Remahl et al. 2008). The purpose of the present study was to examine whether KD responders had greater improvement in EEG characteristics compared to KD non-responders, and to evaluate whether EEG features at baseline or at one month predict treatment response at three months.

1. Patients and Methods

2.1 Subjects and Protocol

This investigation was performed using a cohort study design, with prospectively collected data from a previously conducted randomized controlled trial examining two different approaches to KD initiation (Bergqvist et al. 2005). The exposure variables of interest were EEG variables, discussed below. The primary outcome was response to the KD, defined as a

50% or greater reduction in frequency of target seizures after three months of therapy compared to baseline. Forty-eight pre-pubertal children ages one to 14 years with medication resistant epilepsy were enrolled in the initial trial. Medication resistant epilepsy was defined as having one or more seizures per 28 days despite treatment attempts with at least three appropriate antiepileptic medications. Children with inborn errors of metabolism, genetic disorders known to effect growth, or progressive neurodegenerative disorders were excluded. Subjects were randomized to one of two methods for KD initiation, a fasting or a gradual protocol, described previously (Bergqvist et al. 2005). Seizure frequency was determined by caregiver-reported daily seizure logs kept for 28 days prior to KD initiation (baseline seizure frequency), and continued for three months after KD initiation. No changes to antiepileptic medication regimens were made during this three month period. This protocol was approved by the Children's Hospital of Philadelphia Institutional Review Board; informed consent was provided by subjects' parents and assent was given by children who were cognitively able.

2.2 EEG Evaluation

A baseline EEG was performed within one week prior to KD initiation. Follow up EEGs were recorded one and three months after initiation of KD treatment. The time of day of each EEG for a subject did not vary by more than one hour, to minimize the effect of circadian differences and drug level fluctuations. Thirty minute EEGs were performed in the outpatient EEG laboratory of the Children's Hospital of Philadelphia using standard electrode placements according to the 10–20 International System. EEG data were recorded digitally on TECA (Teca Corporation, Pleasantville, NY) from 2000 to 2003, and Biologic Ceegraph EEG (Natus Medical, San Carlos, CA) after 2003 using a sampling rate of 200 Hz with 0.3 to 70 Hz band pass filtering. Recordings were digitally converted for further analysis using Insight II (Persyst, Inc, Prescott, AZ, U.S.A).

Investigators conducting the EEG evaluation were blinded to the time point of the EEG and the subject's clinical information, including responder status. Qualitative assessment of EEGs included subjective assessment of the degree of slowing: absent/mild versus moderate/severe. Quantitative assessment of regional brain frequencies (δ : 1 to 4 Hz; θ : 4 to 7 Hz, α : 8 to 12 Hz, and β : 13 to 30 Hz) by power spectra analysis was performed as follows. Sixty artifact-free and spike-free EEG segments recorded during wakefulness, each lasting two seconds, were chosen by visual inspection, and subjected to Fast Fourier Transform analysis (half second overlap with Hamming windowing). For subjects with IEDs occurring so frequently that spike-free segments could not be selected, representative epochs with no artifacts were chosen for analysis. Absolute power (μV^2) and relative power (%) in each of four frequency bands (δ , θ , α , and β) were calculated using Insight II software. Because of ocular movement artifact, values from FP1 and FP2 were excluded. Values were averaged across all other electrodes, and for three specified areas of interest: posterior (T5-O1, T6-O2, P3-O1, P4-O2), central (C3-P3, C4-P4), and frontal (F3-C3, F4-C4).

Each EEG was then visually inspected again by one investigator (SK) to count the number of seconds during wakefulness containing at least one epileptiform discharge. Baseline EEGs were evaluated twice, with the evaluator blinded to this repetition, to allow assessment of intra-rater reliability. The spike-index (SI) was expressed as the number of one second bins containing one or more IEDs, divided by the total number of seconds of wakeful recording, and multiplied by 100, to yield a percentage of the tracing containing IEDs. Seconds in which cerebral electrographic activity was obscured by artifact were excluded. Sleep recording was excluded from analysis because each recording contained different amounts of wakefulness and sleep, and the frequency of epileptiform discharges may vary by behavioral state.

2.3 Statistical Analysis

Baseline characteristics were compared between the responder and non-responder groups using Mann-Whitney tests or t-tests of independent samples for continuous variables, and chi-square or Fisher's exact tests for dichotomous variables.

Intra-rater reliability for the initial subjective assessment of slowing was evaluated using the kappa statistic. The Kendall tau rank correlation coefficient, a non-parametric statistic used to measure the degree of correspondence between two rankings, was used to assess intra-rater reliability between the two evaluations of the baseline EEGs in which spike discharges were counted.

Median spike-index at each of the three time points were compared using the Kruskal-Wallis test. Pairwise difference scores for spike index were calculated between baseline, one month, and three months, and compared between responders and non-responders using Mann-Whitney tests. Difference scores were further dichotomized into those subjects with any improvement in spike index from baseline to one month, and baseline to three months, versus those which were unchanged or worsened. A chi-square test was used to evaluate the association between improvement in SI at one month and responder status, and between SI improvement and method of KD initiation (gradual versus fasting).

Qualitative categorical assessment of slowing (moderate/severe slowing versus mild/absent slowing) was compared between responders and non-responders across time points using Fisher's exact test. For evaluation of relative power in each of the four frequency bands, at each of three regions, mixed effects models were used to examine the effect of time point. Additional mixed effects models were used to determine the effect of time point and responder status. Type I error rates for statistical comparisons were set at 0.05.

Data were analyzed using STATA/IC 10.1 (StataCorp LP, College Station, TX) and SPSS for Windows, Release 15 (Chicago, IL: SPSS Inc.).

2. Results

3.1 Patient characteristics

Of the 48 subjects enrolled in the original study, seven were excluded from this analysis because they exited the study early or lacked one or more EEGs. In addition, four subjects had baseline hypsarrhythmic EEGs. Because of the fundamentally different nature of this EEG background pattern, these subjects were excluded from subsequent spike index and power spectrum analyses. Among these four subjects, three were KD responders and demonstrated resolution of hypsarrhythmia at three months. One had complete resolution of interictal epileptiform discharges but continued to have slow background rhythms for age by conventional analysis. Among the remaining 37 subjects included in this study, 23 (62%) were boys. The median age at time of KD initiation was 5.6 years (range 1.3 to 12.2). Thirty subjects were white (of whom, two were Hispanic), four were black, and three were Asian. A summary of baseline characteristics by responder status is given in Table 1.

The broad range of epilepsy etiologies and electroclinical epilepsy syndromes characterizing these subjects is summarized in Table 2. Overall, 13 subjects had symptomatic focal epilepsy, 3 had cryptogenic focal epilepsy, 18 had generalized epilepsy, and 3 had features of both focal and generalized epilepsy. Etiology of epilepsy did not correlate well with the degree of slowing or spike index at baseline.

The mean serum betahydroxybutyrate (BHB) level was 3.7mmol/L (SD 1.3) at the one month visit and 4.4mmol/L (SD 1.7) at the three month visit. Twenty-six subjects (70%) were treatment responders and ten subjects (27%) were seizure free.

3.2 EEG Slowing and Frequency Analysis

When qualitative assessment of EEG slowing – categorized as absent/mild versus moderate/severe --was compared between two separate evaluations of the baseline EEG, agreement was good (kappa 0.704). The number of subjects deemed to have moderate/severe slowing declined from 22 at baseline, to 19 at one month, and 15 at three months, but this finding was not statistically significant ($p = 0.29$). Presence of moderate/severe slowing at baseline or one month did not predict responder status ($p = 0.29$, $p = 0.64$ respectively).

Changes in mean relative power in the four frequency bands were seen over the three time points across the whole cohort, see Figure 1. Over the frontal regions, a small increase in mean beta relative power occurred ($6.0\% \pm 4.5$ at baseline, $7.8\% \pm 6.9$ at one month, $7.2\% \pm 5.8$, at three months, $p=0.03$). Over the central region, modest increases were seen in mean alpha relative power ($10.1\% \pm 6.1$, $11.5\% \pm 7.9$, $11.9\% \pm 7.5$, $p = 0.02$) and mean beta relative power ($4.4\% \pm 2.8$, $5.4\% \pm 3.9$, $5.7\% \pm 4.6$, $p = 0.04$). Over the posterior region, a modest but statistically significant increase in mean alpha relative power was seen ($9.0\% \pm 6.0$, $11.4\% \pm 8.3$, $11.2\% \pm 7.8$, $p<0.001$). Also in the posterior region, a shift away from delta relative power (mean $60\% \pm 15.2$, $56.2\% \pm 14.3$, $57.4\% \pm 12.3$, $p=0.06$) to theta relative power (mean $33.5\% \pm 13.0$, $37.3\% \pm 13.1$, 36.1 ± 12.0 , $p=0.09$) was seen, but the trend did not reach statistical significance. Overall, a reduction in delta relative power over the posterior region from baseline to one month occurred in 26 subjects, by a median of 8% (range 0.5 to 28), and no change or an increase in delta relative power was seen in 11 subjects, by a median of 6% (range 0 to 24.5%). An increase in theta relative power over the posterior region from baseline to one month was seen in 23 subjects, with a median increase of 5% (range 0 to 37), and a decline was seen in 14 subjects, by a median of 5.1% (range .15 to 25).

There were no significant differences between responders and non-responders at baseline in relative power in the delta, theta, alpha, or beta ranges over any of the regions. No significant differences in degree of change between baseline and subsequent time points were seen between responders and non-responders in any of the frequency bands. In addition, there were no differences between the gradual initiation group and the fasting group in the degree of change between baseline and one month or three months in any of the frequency bands.

3.3 Interictal Epileptiform Discharges

Evaluation of spike index by manual counting was performed two times independently in each baseline EEG, and assessment of intra-rater reliability yielded a Kendall's tau β of 0.83 ($p < 0.0005$), indicating a high degree of agreement.

Median spike index across all subjects was 7.7 (interquartile range 1–49.2) at baseline, and dropped to 1.4 (IQR 0–10.7) at one month and 1.5 (IQR 0–16) at 3 months, but these differences were not statistically significant ($p=0.9$) and a large degree of variability existed across subjects. As illustrated in figure 2, in responders, median spike index declined from 9.35 (IQR 1–43.3) at baseline to 1.2 (IQR 0–10) at one month and 1 (IQR 0–8.3) at three months ($p=0.05$), but showed no decline in non-responders. At one month, 13 subjects had no change or increased SI (median 0.25, IQR 0–22), and 24 experienced a decline in SI (median 13.65, IQR 2–33.4). Of those with a drop in SI, 14 had a decline of 10 percent or more (median 27.9, IQR 17–50). Twelve of these 14 were KD responders. Response to the

KD was over six times more likely in those with improvement in SI of 10% or more at one month, compared to those with no improvement or worsening of SI (unadjusted OR 6.5, 95% CI 0.85 to 75.4, $p=0.03$).

No significant association was found between subjects with reduction in SI at one month and those with an improvement in background slowing, defined as any decrease in delta relative power over the posterior or central regions ($p=0.13$, $p=1$ respectively). There were no differences in change in SI at one month between subjects who underwent gradual initiation of the KD compared to those who fasted.

Two subjects who showed no improvement in SI at one month showed reduction in SI at 3 months (one by 46.7% and the other by 8.5%). All but two subjects who showed improvement at one month continued to have a lower SI at three months than at baseline.

As summarized in Table 3, changes in EEG characteristics (SI improvement, and proportion of subjects with moderate/severe slowing) did not vary substantially by epilepsy syndrome type.

3. Discussion

While the KD has been established as an effective therapy for reducing seizures in patients with medication-resistant epilepsy, its broader effects on cerebral neurophysiology are less well understood. Our study, utilizing a large prospectively collected cohort and quantitative evaluation of EEGs, adds to the limited but growing body of literature suggesting that KD therapy is associated with improvement in electroencephalographic parameters in epilepsy patients (Freeman et al. 2009; Hallbook et al. 2007; Remahl et al. 2008; Ross et al. 1985). Prior studies evaluating KD induced EEG changes have focused on reduction in IEDs. The median spike frequency in 18 children undergoing 24 hour EEG monitoring was reduced after KD therapy, particularly during sleep, but the magnitude of changes at the individual level was not reported (Hallbook et al. 2007). In 13 of 23 children whose IED frequency was assessed by categorical measures, improvement was seen 3 months after KD initiation, but with considerable variability in the degree of change among subjects (Remahl et al. 2008). Our study assessed EEG changes during wakefulness, and found a reduction in epileptiform discharges in a majority of patients, though here too, the magnitude of the decline was highly variable among individuals. In our cohort, a reduction in epileptiform discharges was seen as early as one month after KD initiation, a change which was sustained at 3 months. Longer term favorable changes in EEG have been reported as well, with improvement in the rate of epileptiform discharges and background activity six months after KD initiation (Dressler et al. 2010).

No predictors of response were found among the baseline clinical or electrographic characteristics we investigated, a finding consistent with prior studies. However, unlike prior studies where reduction in IED frequency failed to distinguish responders and non-responders (Remahl et al. 2008), we observed that patients with substantial improvement in spike index at one month were six times more likely than those without improvement to be KD responders at three months. The practical utility of this finding may be limited in those who show clinical improvement as well at the one month mark, but EEG improvement may be an encouraging sign for patients whose seizure reduction is not immediate.

Our findings suggest that the KD may exert salutary electrophysiologic effects akin to some antiepileptic drugs, such as valproate and lamotrigine, which are known to reduce the frequency of IEDs (Bruni et al. 1980; Loscher 2002);(Eriksson et al. 2001). Changes in EEG may be driven by different mechanisms than reduction in seizure frequency, accounting for subjects who continued to have seizures but showed improvement on EEG. In some clinical

circumstances, EEG improvement may be a desirable outcome, independent of seizure control. For example, children with epileptic encephalopathy syndromes characterized by continuous spike and slow wave discharges in sleep (CSWS) may respond to KD diet treatment (Bergqvist et al. 1999), though the overall effectiveness of the KD for this syndrome is still unclear (Nikanorova et al. 2009).

In our cohort, reduction in background slowing was also seen as early as the one month time point, but did not distinguish between responders and non-responders. This finding suggests that the effect of the KD is not limited to its anticonvulsant effects. The most robust changes in power were seen over the central regions. Increases in beta frequency activity, akin to the drug effects of benzodiazepines or barbiturates, have been seen as a short term effect of the KD in normal human subjects (Cantello et al. 2007), lending strength to the hypothesis that the KD affects GABAergic pathways. The magnitude of our findings regarding increases in beta power over the central regions mirrors what was reported in the Cantello study.

There were no differences in EEG outcome between the group of patients who were initiated on the KD using a gradual protocol compared to those initiated using a fasting protocol. This result is consistent with previous findings that initiation protocol does not influence treatment response at three months (Bergqvist et al. 2005), suggesting that the fasting method, which may be less well tolerated method, is not necessary to achieve a benefit.

A key limitation to our study was the use of single 30 minute EEG recordings at each time point. Because spontaneous variability in IED frequency between recordings may be substantial, longer recordings may improve the ability to distinguish true improvement from expected variation (Camfield et al. 1995; Martins da Silva et al. 1984). Long term EEG monitoring for this cohort was not feasible at the time the data was collected, and in practice, evaluation of patients initiating the KD would be limited to routine outpatient EEG recordings. By keeping the time of day of recordings consistent, we attempted to limit the effects of medication level and circadian variability. By restricting observations to wakeful EEG, we limited variability due to behavioral state. Recordings of this length also allowed for manual evaluation of spike index, which we felt was a rigorous way to measure this parameter.

In addition, though ours is the largest cohort reported among studies of KD induced electrographic changes, our modest sample size limited the power to detect small differences between responders and non-responders. Finally, our sample size also limited evaluation of subgroups, such as those defined by location of IEDs.

In conclusion, the ketogenic diet had substantial effects on EEG, particularly on suppressing IEDs, as early as one month after initiation. Patients with reduced IED frequency at one month were more likely to have improved seizure control by three months. Improvement in background slowing was seen, but these changes were modest. Increases in beta frequency activity after short term exposure to the KD suggest a pharmacologic effect akin to that seen with drugs mediated by GABAergic mechanisms. The clinical utility of the findings in this exploratory study remain unclear. While EEG improvement may offer supportive evidence of KD response, we do not believe that the parameters we studied here are accurate enough predictors to act as surrogate markers of later KD success. Further studies are needed to understand the range of KD effects on the cerebral electrophysiology and resultant clinical response of children with medication resistant epilepsy.

Acknowledgments

This study was supported by NIH NCRR K23RR016074, CTCR UL1-RR-024134, and the Catherine Brown Foundation. Dr. Kessler receives support from NIH NINDS K12 NS049453. Dr. Shellhaas receives support from

NIH NINDS K12 HD02882018. We would like to thank the children, parents, and care providers who participated in this research study. We would also like to thank Damon Lees for his help in converting EEG data, as well as the Children's Hospital of Philadelphia ketogenic diet team.

We confirm that we have read the Journal's position on issues involved with ethical publication and affirm that this report is consistent with those guidelines.

References

- Beniczky S, Jose Miranda M, Alving J, Heber Povlsen J, Wolf P. Effectiveness of the ketogenic diet in a broad range of seizure types and EEG features for severe childhood epilepsies. *Acta Neurol Scand.* 2010; 121(1):58–62. [PubMed: 19951269]
- Bergqvist AG, Chee CM, Lutchka LM, Brooks-Kayal AR. Treatment of acquired epileptic aphasia with the ketogenic diet. *J Child Neurol.* 1999; 14(11):696–701. [PubMed: 10593544]
- Bergqvist AG, Schall JJ, Gallagher PR, Cnaan A, Stallings VA. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. *Epilepsia.* 2005; 46(11):1810–1819. [PubMed: 16302862]
- Bruni J, Wilder BJ, Bauman AW, Willmore LJ. Clinical efficacy and long-term effects of valproic acid therapy on spike-and-wave discharges. *Neurology.* 1980; 30(1):42–46. [PubMed: 6765986]
- Camfield P, Gordon K, Camfield C, Tibbles J, Dooley J, Smith B. EEG results are rarely the same if repeated within six months in childhood epilepsy. *Can J Neurol Sci.* 1995; 22(4):297–300. [PubMed: 8599774]
- Cantello R, Varrasi C, Tarletti R, Cecchin M, D'Andrea F, Veggiotti P, Bellomo G, Monaco F. Ketogenic diet: electrophysiological effects on the normal human cortex. *Epilepsia.* 2007; 48(9):1756–1763. [PubMed: 17561954]
- Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. Ketogenic diet in patients with myoclonic-astatic epilepsy. *Epileptic Disord.* 2006; 8(2):151–155. [PubMed: 16793577]
- Dressler A, Stocklin B, Reithofer E, Benninger F, Freilinger M, Hauser E, Reiter-Fink E, Seidl R, Trimmel-Schwahof P, Feucht M. Long-term outcome and tolerability of the ketogenic diet in drug-resistant childhood epilepsy--the Austrian experience. *Seizure.* 2010; 19(7):404–408. [PubMed: 20598586]
- Eriksson AS, Knutsson E, Nergardh A. The effect of lamotrigine on epileptiform discharges in young patients with drug-resistant epilepsy. *Epilepsia.* 2001; 42(2):230–236. [PubMed: 11240595]
- Freeman JM, Vining EP, Kossoff EH, Pyzik PL, Ye X, Goodman SN. A blinded, crossover study of the efficacy of the ketogenic diet. *Epilepsia.* 2009; 50(2):322–325. [PubMed: 18717710]
- Hallbook T, Kohler S, Rosen I, Lundgren J. Effects of ketogenic diet on epileptiform activity in children with therapy resistant epilepsy. *Epilepsy Res.* 2007; 77(2–3):134–140. [PubMed: 17996423]
- Kilaru S, Bergqvist AG. Current treatment of myoclonic astatic epilepsy: clinical experience at the Children's Hospital of Philadelphia. *Epilepsia.* 2007; 48(9):1703–1707. [PubMed: 17651420]
- Korff C, Laux L, Kelley K, Goldstein J, Koh S, Nordli D Jr. Dravet syndrome (severe myoclonic epilepsy in infancy): a retrospective study of 16 patients. *J Child Neurol.* 2007; 22(2):185–194. [PubMed: 17621480]
- Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, Buchhalter JR, Caraballo RH, Helen Cross J, Dahlin MG, Donner EJ, Klepper J, Jehle RS, Kim HD, Christiana Liu YM, Nation J, Nordli DR Jr, Pfeifer HH, Rho JM, Stafstrom CE, Thiele EA, Turner Z, Wirrell EC, Wheless JW, Veggiotti P, Vining EP. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia.* 2009; 50(2):304–317. [PubMed: 18823325]
- Lefevre F, Aronson N. Ketogenic diet for the treatment of refractory epilepsy in children: A systematic review of efficacy. *Pediatrics.* 2000; 105(4):E46. [PubMed: 10742367]
- Loscher W. Basic pharmacology of valproate: a review after 35 years of clinical use for the treatment of epilepsy. *CNS Drugs.* 2002; 16(10):669–694. [PubMed: 12269861]

- Martins da Silva A, Aarts JH, Binnie CD, Laxminarayan R, Lopes da Silva FH, Meijer JW, Nagelkerke N. The circadian distribution of interictal epileptiform EEG activity. *Electroencephalogr Clin Neurophysiol*. 1984; 58(1):1–13. [PubMed: 6203698]
- Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol*. 2008; 7(6):500–506. [PubMed: 18456557]
- Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, Whitney A, Cross JH. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia*. 2009; 50(5):1109–1117. [PubMed: 19054400]
- Nikanorova M, Miranda MJ, Atkins M, Sahlholdt L. Ketogenic diet in the treatment of refractory continuous spikes and waves during slow sleep. *Epilepsia*. 2009; 50(5):1127–1131. [PubMed: 19220407]
- Oguni H, Tanaka T, Hayashi K, Funatsuka M, Sakauchi M, Shirakawa S, Osawa M. Treatment and long-term prognosis of myoclonic-astatic epilepsy of early childhood. *Neuropediatrics*. 2002; 33(3):122–132. [PubMed: 12200741]
- Remahl S, Dahlin MG, Amark PE. Influence of the ketogenic diet on 24-hour electroencephalogram in children with epilepsy. *Pediatr Neurol*. 2008; 38(1):38–43. [PubMed: 18054691]
- Ross DL, Swaiman KF, Torres F, Hansen J. Early biochemical and EEG correlates of the ketogenic diet in children with atypical absence epilepsy. *Pediatr Neurol*. 1985; 1(2):104–108. [PubMed: 3939741]
- Than KD, Kossoff EH, Rubenstein JE, Pyzik PL, McGrogan JR, Vining EP. Can you predict an immediate, complete, and sustained response to the ketogenic diet? *Epilepsia*. 2005; 46(4):580–582. [PubMed: 15816955]
- Thiele EA. Assessing the efficacy of antiepileptic treatments: the ketogenic diet. *Epilepsia*. 2003; 44(Suppl 7):26–29. [PubMed: 12919336]
- Vining EP, Freeman JM, Ballaban-Gil K, Camfield CS, Camfield PR, Holmes GL, Shinnar S, Shuman R, Trevathan E, Wheless JW. A multicenter study of the efficacy of the ketogenic diet. *Arch Neurol*. 1998; 55(11):1433–1437. [PubMed: 9823827]

Figure 1. Mean relative power of four frequency ranges in the frontal, central, and posterior regions over three time points. The error bars represent standard deviations.

Figure 2. Box plot showing median (white line), interquartile range (box), adjacent values (whiskers) and outliers (points). A decline in median spike index from baseline to 1 month and 3 months was seen among responders, but not among non-responders.

TABLE 1**Baseline characteristics by responder status**

	Responder	Non-responder	P value
N	26	11	
Male/Female	15/11	8/3	0.47
Age at KD initiation (mean, SD)	5.01 (2.2)	6.3 (1.9)	0.25
Age at seizure onset (mean, SD)	1.7 (1.5)	2.5 (2.6)	0.18
Number AED at initiation (mean, SD)	2.2 (0.8)	2.5 (0.7)	0.24
Gradual/Fasting Initiation	13/13	5/6	1.00
MRI Abnormal (%)	55	63	0.73
Electroclinical Epilepsy Type			
Generalized	15	3	0.18
Focal	9	7	0.18
Mixed	2	1	0.18
EEG characteristics at baseline			
Moderate/Severe Slowing (%)	54	73	0.46
Posterior Delta RP (mean, SD)	59.4, 16	59.5, 13.4	0.90
Posterior Theta RP (mean, SD)	34.2, 13.5	33.2, 12.1	0.78
Posterior Alpha RP (mean, SD)	9.2, 6.6	8.8, 4.3	0.81
Subjects with no spikes at baseline (%)	19	36	0.40
Spike Index (median, range)	9.35 (0–100)	1 (0–60)	0.40

Responders were defined as subjects with (50% or greater reduction in target seizure type in 28 days before the 3 month time point compared to baseline). P values were obtained using Fisher's exact tests for categorical variables, t-tests for normally distributed continuous variables, and Wilcoxon rank sum for non-normally distributed variables. RP, relative power.

TABLE 2**Epilepsy Etiology and Syndrome Type**

Etiology	Electroclinical Epilepsy Syndrome			
	Total	Focal	Generalized	Mixed
Malformations of Cortical Development				
Cortical Dysplasia	5	4	1	
Cortical Dysplasia + Mesial Temporal Sclerosis	2	2		
Band Heterotopia	1			1
Lissencephaly	1		1	
Hemimegalencephaly	1	1		
Acquired Injuries				
Congenital CMV	1	1		
Herpes Encephalitis	1	1		
Presumed Perinatal Stroke	2	2		
Periventricular Leukomalacia	2		2	
Diffuse Hypoxic Ischemic Injury	1			1
Tumor Resection (Astrocytoma)	1			1
Genetic Syndromes				
Fragile X	1	1		
SCN1A mutation	1		1	
ARX mutation	1		1	
Chromosomal anomaly	1	1		
Etiology Unknown				
Myoclonic Astatic Epilepsy (Doose Syndrome)	4		4	
Lennox-Gastaut Syndrome	2		2	
Childhood Absence Epilepsy	1		1	
Electrical Status Epilepticus of Sleep	1		1	
Other unknown	7	3	4	

TABLE 3

Change in EEG characteristics by Epilepsy Syndrome Type

	Generalized	Focal	Mixed	P value
Drop in SI at 1 month (median, range) ^a	.95 (−22 to 17)	1.4 (−11 to 54)	6.7 (1 to 38)	0.64
Drop in SI at 3 months (median, range) ^a	1.4 (−32 to 63)	0 (−40 to 36.5)	6.7 (1 to 35.8)	0.40
Moderate/Severe Slowing at baseline, n(%) ^b	11 (61)	10(62.5)	1(33.3)	0.78
Moderate/Severe Slowing at 1 month, n(%) ^b	9(50)	9 (56.3)	1 (33.3)	0.80
Moderate/Severe Slowing at 3 months, n(%) ^b	5 (27.8)	9 (56.3)	1 (33.3)	0.24

SI = spike index

^aComparison by Kruskal-Wallis test^bComparison by Fisher's exact test