Brain Disorders/Neurological

Experience in the Use of the Ketogenic Diet as Early Therapy

James E. Rubenstein, MD; Eric H. Kossoff, MD; Paula L. Pyzik, BS; Eileen P.G. Vining, MD; Jane R. McGrogan, RD; John M. Freeman, MD


Abstract and Introduction

Abstract

The ketogenic diet has traditionally been considered an anticonvulsant therapy of last resort, despite excellent efficacy and limited side effects. We hypothesized that the ketogenic diet would have similar results in patients with new-onset epilepsy. A retrospective study was conducted of patients started on the ketogenic diet since 1994. Thirteen of 460 (2.8%) patients were started on the ketogenic diet as early (zero or one prior anticonvulsant) therapy for seizures. Of those remaining on the diet, 60% (6 of 10) had a >90% seizure reduction at 6 months and 100% (6 of 6) had a >90% reduction at 12 months. Patients with infantile spasms were as likely to achieve >50% seizure reduction at 6 months as patients with other seizure types (75% vs 60%; P = .6). The ketogenic diet can be a valuable therapy before epilepsy becomes intractable. In the 13 patients reported, efficacy without side effects was achieved similarly to that with patients with intractable epilepsy.

Introduction

The ketogenic diet has a long and accepted history for treating seizures in the pediatric population, with biblical references to the efficacy of starvation for controlling epilepsy and myriad publications dating back to the early 1920s documenting its success.[1] It appears to be as efficacious as many of the newer anticonvulsants and vagal nerve stimulation, and few new anticonvulsants have been as thoroughly studied in children.[2,3] The side effects of the ketogenic diet are also relatively limited, with little effect on cognition or concern over drug interactions.[4,5] Thus, the ketogenic diet, theoretically, could be used earlier in the management of epilepsy, before the occurrence of intractability.

The first reason the diet has not been used initially might be difficulty of use in terms of calculating and measuring foods for patients in combination with the diet's perceived palatability. The time and knowledge required can be considerable. Taking an anticonvulsant even several times a day is clearly less complicated. Second, at this time, there are only two neurologic conditions for which the diet is accepted as first-line therapy: glucose transporter protein deficiency and pyruvate dehydrogenase deficiency.[6,7] Last, few health care providers realize the success of the ketogenic diet, and few centers have the nutritional and nursing support to make it successful in their practice.[8]

When epileptologists were surveyed as to their overall treatment strategy for symptomatic generalized epilepsy (eg, Lennox Gastaut) in an adolescent or adult, the ketogenic diet was lower on the list than even a third trial of combination anticonvulsant therapy.[9] For new-onset seizures, it ranked anywhere from 10th to 14th, despite Livingston and Pauli's 1975 report of its efficacy as first-line therapy for 183 of 915 patients treated with the diet for myoclonic seizures.[10]

We have found the ketogenic diet to be a very useful therapy independent of seizure type, age, and frequency. Even families in which the ability to comply was suspect have been successfully educated to maintain the diet at home, and its restrictiveness is rarely the reason for discontinuation.
Knowing that the diet is rarely used early in the course of antiepileptic therapy, we decided to review our experience using the ketogenic diet either as first- or second-line therapy with regard to natural history, reasons for choosing the diet, and its efficacy.

Methods

A retrospective review of the medical records of all patients started on the ketogenic diet between January 1994 and December 2002 was done. Over this time period, 460 patients have been enrolled on the ketogenic diet at our institution.

The diet was initiated using the standard Hopkins protocol.[2] Prediet, parents were asked to describe in writing their reasons for choosing dietary therapy. Children were followed by telephone contact and were seen in the clinic at 3, 6, and 12 months after discharge to monitor seizure control, growth, general health, diet adherence, and ketosis. Patient seizure histories, medications, and symptoms were recorded in our database. Magnetic resonance imaging (MRI) studies were reviewed by both epileptologists and radiologists at our institution. Several families were contacted by telephone to update information. All children who were treated with the ketogenic diet at our institution received comprehensive epilepsy management from our team throughout their therapy.

The Johns Hopkins Institutional Review Board approved this study as part of an ongoing study of the effectiveness of the ketogenic diet for childhood epilepsy. Categorical data were analyzed using Pearson's chi-square for independence of rows and columns. The significance level for all tests was P = .05.

Results

Patient Demographics

We identified 13 patients (2.8%) who were started on the ketogenic diet before any anticonvulsant had been used or for whom only one had been tried. These patients are summarized in Table 1. Ten children were male and three were female. Seven patients were initiated on the ketogenic diet as initial anticonvulsant therapy; six had been exposed to only a single anticonvulsant (valproic acid, three; clonazepam, two; phenobarbital, one). There was no trend over time in enrollment, ranging from zero to three patients annually from 1996 to 2002.

The most common epilepsy type in these patients was infantile spasms, with eight patients being diagnosed with this disorder by a neurologist within 1 month of diet onset. Five of the seven patients placed on the diet as their initial therapy had infantile spasms. The other diagnoses were Lennox-Gastaut syndrome (three) and myoclonic seizures (one). One patient with myoclonic and atonic seizures was later diagnosed with late infantile neuronal ceroid-lipofuscinosis. Six of 13 patients had documented MRI abnormalities ranging from lissencephaly to cortical atrophy. Two patients had chromosomal abnormalities (inverted duplicate 15 and translocation of chromosome 22).

Fat to protein and carbohydrate ratios were 4:1 in five patients and 3:1 in eight patients. Younger patients were started on 3:1 ratios, and these patients tended to be those with no prior anticonvulsant exposure.

The range in age of first seizure was 0 to 3.5 years (mean 1.0 years). The range in age at diet onset was 0.25 to 4.25 years (average 1.6 years). However, the median age at diet onset was considerably younger (6 months), with 62% (8 of 13) under 1 year old at initiation owing to the high percentage of patients with infantile spasms. The median time between first seizure and diet initiation was 2 months. The mean seizure frequency based on parental report was 2055 per month (range 300–7500/month).
The mean diet duration was 1.25 years (range 0.06–4.5 years). Ten of 13 (77%) patients were still on the diet at 6 months and 6 of 13 (46%) at 12 months. Two patients remain on the diet. Reasons for discontinuation in the other 11 patients were ineffectiveness (4), seizure freedom (3), illness (2), growth failure (1), and restrictiveness (1).

**Reasons for Starting the Diet**

Charts were examined and parents were contacted by telephone for information about their reasons for starting the diet so early. Sixty-nine percent (9 of 13) were either nervous about potential drug side effects (predominantly those of ACTH) or had been sensitized by side effects from their first attempted agent (emesis with valproic acid and sedation with clonazepam). In three patients, the reasons were more physician directed, with patients felt to be good candidates for the diet based on early, frequent seizures without an identifiable surgically resectable lesion. One of these patients was started on the diet emergently during an inpatient stay for frequent myoclonic seizures. Another was started initially owing to the dramatic improvement using the ketogenic diet in her twin brother with previously diagnosed seizures.

**Efficacy**

More than half of patients had a >90% reduction in their seizures over a 12-month follow-up period. At 3 months, 11 of 13 (85%) were >50% improved and 7 of 13 (54%) were >90% improved. By six months, 8 of 10 (80%) patients remaining on the diet were >50% improved and 6 of 10 (60%) were >90% improved. At 12 months follow-up, all six patients remaining on the diet were >90% improved (none were 50 to 90%). At this time, six are seizure free regardless of diet duration. Seizure type was not correlated with having a >50% seizure reduction: 6 of 8 patients (75%) with infantile spasms started on dietary therapy within 1 month of diagnosis responded compared with 3 of 5 patients (60%) for other diagnoses (P = .6).

Side effects were seen in a single patient, who had delayed growth without a clear endocrinologic cause. His seizures remained>90% improved on the diet, and his height accelerated when the diet was eventually discontinued at 1.7 years. Another patient had a hip dislocation while on the ketogenic diet, clearly attributable to his underlying spastic quadriplegic cerebral palsy rather than the ketogenic diet.

**Discussion**

The typical patient placed on the ketogenic diet has intractable epilepsy, having failed multiple anticonvulsants. Because patients with less difficult to control seizures can do just as well on anticonvulsants typically reserved for more intractable patients, we hypothesized that patients started on the ketogenic diet as first-line therapy would have efficacy similar to that of more traditional patients. In comparing the results in these patients with those from our institution overall, we saw similar efficacy, time to response, and absence of side effects.[3]

However, there were certain distinct differences between our patient group and the broader population treated with the diet. Ours were younger children (mean 1.6 years compared with 5 years) with more seizures (2055/month vs 410/month). In addition, a large percentage had infantile spasms and/or MRI abnormalities. Dietary therapy duration in our early treatment group was slightly lower at 12 months (45% vs 55%), likely indicating interest in their families to initiate anticonvulsants if the diet proved unsuccessful.

The majority of patients were aged 1 year or less, when it is relatively easy to initiate the ketogenic diet. The ketogenic diet can be provided as a formula at home by mixing Ross Carbohydrate-free formula with Ross Polycose and Novartis Microlipid. The taste is similar to that of other infant formulas, and compliance is therefore almost never an issue.[11] Recent articles have demonstrated its efficacy and safety in the infant population.[12,13] For those with infantile spasms in our group, efficacy was particularly good. The majority (5 of 7) of the patients placed on the diet with no prior anticonvulsants had infantile spasms. Many of these families were offered ACTH but chose to avoid the potential serious side effects.
effects by trying the ketogenic diet first. As a result of this study, we are currently organizing a trial of the ketogenic diet as first-line therapy for infantile spasms.

Considering the frequent seizures seen in these children at onset, many of whom have abnormal MRI findings, families were counseled regarding suspected intractability and likely therapeutic options, including the ketogenic diet. When presented in a favorable manner and compared with the unknown effects of many anticonvulsants on the developing brain, it is not surprising that parents elected to initiate the ketogenic diet rather than wait until their child experienced multiple anticonvulsant failures.

Over the past decade at our institution, there has not been an increased trend toward enrolling patients with new-onset epilepsy on the diet. In an era of new anticonvulsants extolling fewer cognitive side effects and interactions, the pediatric neurologist has more choices than ever before. The ketogenic diet certainly remains harder to initiate and maintain than anticonvulsants and requires a team approach for success. However, in a motivated family, one might consider the diet before epilepsy actually becomes intractable. Considering its safety and efficacy, the early use of the ketogenic diet appears to be a reasonable choice.


Table 1. Patients on Either Zero or One Anticonvulsant Prior to Diet Initiation

<table>
<thead>
<tr>
<th>Patient</th>
<th>Prior Medication</th>
<th>Age at Diet Onset (yr)</th>
<th>Seizure Duration Prior to Diet (yr)</th>
<th>Seizure Type</th>
<th>6-Month Efficacy (% reduction)</th>
<th>Diet Duration (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>0.33</td>
<td>0.33</td>
<td>Myoclonic</td>
<td>&lt; 50</td>
<td>0.50</td>
</tr>
<tr>
<td>2</td>
<td>None</td>
<td>0.42</td>
<td>0.00</td>
<td>Infantile spasms</td>
<td>Seizure free</td>
<td>0.50</td>
</tr>
<tr>
<td>3</td>
<td>None</td>
<td>0.50</td>
<td>0.06</td>
<td>Infantile spasms</td>
<td>&lt; 50</td>
<td>0.06</td>
</tr>
<tr>
<td>4</td>
<td>None</td>
<td>0.51</td>
<td>0.09</td>
<td>Infantile spasms</td>
<td>90</td>
<td>3.22</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>0.66</td>
<td>0.08</td>
<td>Infantile spasms</td>
<td>&lt; 50</td>
<td>0.36</td>
</tr>
<tr>
<td>6</td>
<td>None</td>
<td>1.08</td>
<td>0.16</td>
<td>Lennox-Gastaut syndrome</td>
<td>50–90</td>
<td>1.73</td>
</tr>
<tr>
<td>7</td>
<td>None</td>
<td>3.00</td>
<td>0.00</td>
<td>Infantile spasms</td>
<td>Seizure free</td>
<td>0.42</td>
</tr>
<tr>
<td>8</td>
<td>Valproic acid</td>
<td>3.25</td>
<td>0.25</td>
<td>Lennox-Gastaut syndrome</td>
<td>90</td>
<td>1.00*</td>
</tr>
<tr>
<td>9</td>
<td>Valproic acid</td>
<td>4.25</td>
<td>0.75</td>
<td>Neuronal ceroid-lipofuscinosis</td>
<td>&lt; 50</td>
<td>0.75</td>
</tr>
<tr>
<td>10</td>
<td>Valproic acid</td>
<td>6.00</td>
<td>5.67</td>
<td>Lennox-Gastaut syndrome</td>
<td>90</td>
<td>1.50</td>
</tr>
<tr>
<td>11</td>
<td>Clonazepam</td>
<td>0.40</td>
<td>0.07</td>
<td>Infantile spasms</td>
<td>90</td>
<td>0.86</td>
</tr>
<tr>
<td>12</td>
<td>Clonazepam</td>
<td>0.42</td>
<td>0.17</td>
<td>Complex partial (prior infantile spasms)</td>
<td>50–90</td>
<td>4.50*</td>
</tr>
<tr>
<td>13</td>
<td>Phenobarbital</td>
<td>0.50</td>
<td>0.50</td>
<td>Infantile spasms</td>
<td>Seizure free</td>
<td>1.87</td>
</tr>
</tbody>
</table>

*Currently on the ketogenic diet.

References

   1991;325:703-709; .
8. Hemingway C, Pyzik PL, Freeman JM. Changing physician attitudes toward the ketogenic diet: A "parent-centered" approach to physician education about a medication alternative Epilepsy Behav 2001;02:574-578.

Address correspondence to Dr James E. Rubenstein, Meyer 2-147, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287-1000. Tel: 410-955-9100; fax: 410-614-0373; e-mail: jrubens2@jhmi.edu .

James E. Rubenstein , MD *, Eric H. Kossoff , MD *, Paula L. Pyzik , BS , Eileen P.G. Vining , MD , Jane R. McGrogan , RD , John M. Freeman , MD

From the Departments of Neurology and Pediatrics ( Drs Rubenstein , Pyzik , Vining , McGrogan , and Freeman ), The Pediatric Epilepsy Center, The Johns Hopkins Medical Institutions, Baltimore, MD.
*Authors who contributed equally to this work as first authors.

Reprinted with Permission

Legal Disclaimer

The content and information provided within this site is for informational and educational purposes only. Consult a doctor before pursuing any form of therapy, including Hyperbaric Oxygen Therapy. The Information provided within this site is not to be considered Medical Advice. In Full Support of the F.D.A., Hyperbaric Oxygen Therapy is considered Investigational, Experimental, or Off Label.

Please consult with your Treating Medical Physician