Use of Dietary Therapy for Status Epilepticus

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Abstract

One of the newest and yet fastest growing indications for dietary therapy is the emergency treatment of refractory status epilepticus. Ten retrospective publications since 2008 have reported benefits in 32 children and adults, of which 25 (78%) became seizure-free. Most of the patients who responded did so within 7-10 days of the initiation of nasogastrically-administered ketogenic formulas. Encephalitis and febrile-illness related epilepsy syndrome (FIRES) causing status epilepticus highly refractory to AEDs may be particularly amenable to dietary treatment. Prospective, multicenter studies are underway to help clarify who best will respond, how quickly, and the optimal diet duration after success.
In 2008, the International Ketogenic Diet Consensus Statement was published in *Epilepsia.* Table 1 of the Consensus Statement discussed potential indications for the use of dietary therapy, comprised of 8 “probable” and 5 “possible” epilepsy conditions for which the ketogenic diet was particularly helpful. These conditions included GLUT-1 deficiency and Dravet syndrome, both of which were discussed at the Chicago conference and in this Special Issue in detail. The use of the ketogenic diet for medically-resistant status epilepticus was not listed in Table 1 at the time as no publications regarding its use for this situation were then available.

In the four short years between the Consensus Statement and this conference, there has been a remarkable revolution in the concept of using dietary therapy for emergency situations. Evidence for using the ketogenic diet for new-onset infantile spasms was published several months earlier, but after the Consensus Statement was written. Continued research demonstrating the benefit of the ketogenic diet for myoclonic-astatic epilepsy suggests that an earlier onset of treatment is indicated, potentially warranted a prospective, randomized trial versus anticonvulsants after one has been tried unsuccessfully for this rare form of epilepsy. Widespread recent availability of the genetic test for solute carrier family 2, facilitated glucose transporter member 1 (SLC2A1), the cause of GLUT1 (glucose transporter 1) deficiency, has led to quicker diagnosis of this condition for which the ketogenic diet is the treatment of first choice. In cases for which this condition is diagnosed early, the ketogenic diet should be started perhaps emergently.

Perhaps most exciting has been the rapid emergence of publications related to the use of dietary treatment, both the ketogenic and modified Atkins diets, for the emergency treatment of status epilepticus. To our knowledge, there have been 10 publications describing the dramatic
benefits of dietary therapy for status epilepticus. The first case report was published in 2008 by Bodenant and colleagues about a 54 year old adult with refractory partial status epilepticus who responded within 7 days to the ketogenic diet. In quick succession, 9 additional case series have been published from other centers, in the range of 1-3 per year (Table). To date, 32 patients with status epilepticus treated with dietary therapy have been reported. The patients are quite varied, including children and adults, treated with the ketogenic diet, modified Atkins diet, and low glycemic index treatment, and with differing etiologies for status epilepticus.

There are remarkable similarities amongst these 10 studies that may suggest it is possible to predict who will best respond and how quickly. First, many of these patients had underlying autoimmune or inflammatory conditions leading to their status epilepticus, including encephalitis and Rasmussen syndrome. Thirteen of the 32 patients reported (41%) had febrile illness related epilepsy syndrome (FIRES) as the etiology, a condition that may be due to inflammation. Second, when dietary therapy was successful, it typically worked within 7-10 days (often when anesthesia such as pentobarbital was successfully weaned). It is possible that the effects occurred sooner, however improvement was clearly documented by this time period. Third, the vast majority of patients were treated using the traditional ketogenic diet provided as a ketogenic formula via nasogastric tube. Although intravenous administration of the ketogenic diet has been recently reported, we are unaware of any reports of its use for status epilepticus.

Patients with febrile-illness related epilepsy syndrome specifically seem to be good responders and febrile illness related epilepsy syndrome should be considered strongly as an “indication” for the ketogenic diet in the next Expert Consensus Statement. The largest series was published by Nabbout regarding 9 children from 5 centers in France and Argentina, ages 5-8 years. All patients had refractory status epilepticus and had failed to respond to 3-6
anticonvulsants used as long as 55 days. The traditional ketogenic diet was started via nasogastric tube and patients achieved ketosis within a mean of 2.8 days and seizure control within 4-6 days in 7 of 9 children. Unfortunately, a 6-year-old boy whose seizures were controlled on the ketogenic diet went back into status epilepticus and died after the ketogenic diet was abruptly discontinued by the intensive care unit. The remaining 6 children continued to have sporadic seizures, similar to a 14-year-old girl reported from Johns Hopkins.11

One major drawback of all these studies is the lack of a denominator: how likely is the ketogenic diet to work for status epilepticus of all patients in which it is tried? The only way to scientifically answer this question is with a prospective study with strict inclusion and exclusion criteria. A multicenter study for adults with refractory status epilepticus is underway; Dr. Mackenzie Cervenka from Johns Hopkins is the principle investigator along with several other institutions in the United States collaborating. Inclusion criteria include age > 17 years, failure of status epilepticus to respond to pentobarbital infusion with burst suppression for >24 hours with failure to wean without recurrent seizures. Exclusion criteria include unstable metabolic condition, inability to tolerate enteral feeds, liver failure, hemodynamic instability, coagulopathy, known fatty acid oxidation disorder, concurrently receiving hemodialysis or plasmapheresis, or exposure to propofol within the past 24 hours.16

As a result of these 10 publications and subsequent discussion in the epilepsy community, the ketogenic diet is being considered for status epilepticus cases with increasing frequency throughout the world. However, there are several important practical issues that may preclude its implementation. All centers need to have a ketogenic diet team, including a trained neurologist and dietitian, easily accessible for the myriad issues (e.g. hypoglycemia, ensuring carbohydrates are removed from medications and intravenous fluids, measuring ketosis, etc) that often arise in
the intensive care unit. The team also needs ensure the appropriate long-term follow-up of those cases in which the diet is successful; the ketogenic diet should not be started if it cannot be continued. Not only does the hospital require a ketogenic diet team, but the team must be immediately available in an emergent manner and able to initiate the diet within hours of the request. Finally, the intensive care unit physicians and nurses need to be invested in the process and willing to avoid changing anticonvulsants during the 7-10 days the ketogenic diet is allowed to work. Despite the often weeks of refractory status epilepticus prior to initiation of the ketogenic diet, intensive care physicians may not always believe the diet will be successful and may both add anticonvulsants and occasionally give supplements of glucose unnecessarily for mild hypoglycemia.

At the Chicago meeting there was clear excitement and discussion about the value of the ketogenic diet for status epilepticus. Before more widespread recommendations can be made, however, important unanswered questions remain. As stated earlier, a prospective study is mandatory in order to fully be able to adequately counsel families regarding the true likelihood of improvement with the diet. A larger study would provide information regarding which etiologies best respond, and if it truly includes conditions with inflammation or infection, perhaps that may provide a clue as to the mechanism of action of dietary therapies in general. Some data would suggest an anti-inflammatory action of dietary therapy, which could be demonstrated with these studies.17,18 How best should the diet be provided? The ideal protocol remains to be described including optimal duration of fasting (or whether or not it is required), ketogenic ratio (fat: protein and carbohydrate grams), how long to attempt its use before discontinuation, and then potential duration of use if successful. At what stage in the treatment of refractory status epilepticus should the diet be best implemented? Are there long-term benefits
and improved prognosis for conditions that otherwise would be neurologically devastating (e.g. herpes encephalitis, metastatic brain tumors)? The availability and safety of intravenous ketogenic diet preparations would also be potentially very helpful for patients in status epilepticus with an ileus or unable to tolerate enteral feeds for another reason. For simplicity sake and to encourage widespread use, could a pre-determined ketogenic diet formula feeding rate (based on the average weight of an adult with no metabolic issues) be created to avoid the often lengthy calculations by a dietitian, allowing the ketogenic diet to be implemented quickly.

These and additional questions will need to be answered, but regardless, this unique indication for dietary therapy will hopefully continue to be used regularly. For new ketogenic diet centers, the dramatic and rapid resolution of status epilepticus can lead to instant recognition of the value of dietary therapy. No one today would argue that the ketogenic diet can improve the quality of life for children and adults dealing with intractable epilepsy on a daily basis. In the case of status epilepticus, the ketogenic diet can possibly save lives, which is the ultimate reward for any physician or dietitian.

Author Contributions

EHK and RN were the authors equally for this manuscript.

Declaration of Conflicting Interests

The authors declared a potential conflict of interest (e.g. a financial relationship with the commercial organizations or products discussed in this article) as follows: Dr. Kossoff has received consultant fees from Nutricia, Inc., and Atkins Nutritionals, Inc., unrelated to this review. Dr. Nabbout has received consultant fees from Novartis, Viropharma, and Eisai but none were related to this review.

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Table 1. Studies examining the ketogenic diet for status epilepticus.

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Age range (years)</th>
<th>Number of subjects</th>
<th>Diet tried</th>
<th>Seizure-free rate (%)</th>
<th>Time to response</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodenant (2008)⁵</td>
<td>54</td>
<td>1</td>
<td>Ketogenic</td>
<td>1 (100%)</td>
<td>7 days</td>
<td>Partial</td>
</tr>
<tr>
<td>Villeneuve (2009)⁶</td>
<td>1-10</td>
<td>5</td>
<td>Ketogenic</td>
<td>4 (80%)</td>
<td>1-10 days</td>
<td>Cryptogenic (2), Sturge-Weber, encephalitis, hypomelanosis of Ito</td>
</tr>
<tr>
<td>Kumada (2009)⁷</td>
<td>5</td>
<td>2</td>
<td>Modified Atkins</td>
<td>2 (100%)</td>
<td>5-10 days</td>
<td>Frontal lobe epilepsy, heterotopias</td>
</tr>
<tr>
<td>Wusthoff (2010)⁸</td>
<td>29-34</td>
<td>2</td>
<td>Ketogenic</td>
<td>2 (100%)</td>
<td>4-8 days</td>
<td>Rasmussen syndrome, head trauma</td>
</tr>
<tr>
<td>Nabbout (2010)⁹</td>
<td>5-8</td>
<td>9</td>
<td>Ketogenic</td>
<td>7 (78%)</td>
<td>4-6 days</td>
<td>Febrile-illness related epilepsy syndrome</td>
</tr>
<tr>
<td>Ismail (2011)¹⁰</td>
<td>14</td>
<td>1</td>
<td>Ketogenic</td>
<td>1 (100%)</td>
<td>10 days</td>
<td>Febrile-illness related epilepsy syndrome</td>
</tr>
<tr>
<td>Cervenka (2011)¹¹</td>
<td>49</td>
<td>1</td>
<td>Ketogenic then modified Atkins</td>
<td>1 (100%)</td>
<td>7 days</td>
<td>Idiopathic, possibly autoimmune</td>
</tr>
<tr>
<td>Nam (2011)¹²</td>
<td>4-40</td>
<td>5</td>
<td>Ketogenic</td>
<td>2 (40%)</td>
<td>7-19 days</td>
<td>Viral encephalitis</td>
</tr>
<tr>
<td>Vaccarezza (2012)¹³</td>
<td>1-14</td>
<td>5</td>
<td>Ketogenic</td>
<td>4 (80%)</td>
<td>2-3 days</td>
<td>Febrile-illness related epilepsy syndrome</td>
</tr>
<tr>
<td>Martikainen (2012)¹⁴</td>
<td>26</td>
<td>1</td>
<td>Low-glycemic index treatment</td>
<td>1 (100%)</td>
<td>4 days</td>
<td>Mitochondrial polymerase gamma (POLG)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1-54</strong></td>
<td><strong>32</strong></td>
<td><strong>Various</strong></td>
<td><strong>25 (78%)</strong></td>
<td><strong>1-19 days</strong></td>
<td><strong>Various</strong></td>
</tr>
</tbody>
</table>
References


