

# Seizures Decrease Rapidly After Fasting

## *Preliminary Studies of the Ketogenic Diet*

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**Objectives:** To evaluate the change in atonic or myoclonic seizures associated with the Lennox-Gastaut syndrome during the initiation of the ketogenic diet, and to describe the development of a blinded crossover study of the efficacy of the ketogenic diet.

**Design:** A before-after trial.

**Setting:** The Johns Hopkins Hospital, Baltimore, Md.

**Patients:** Change in clinical seizure frequency was examined in 17 consecutively treated patients with atonic or myoclonic seizures. In a few patients, a 24-hour ambulatory electroencephalogram was obtained before and after diet initiation. We demonstrated the ability to manipulate the ketosis induced by fasting with the addition of glucose (dextrose) in 1 patient.

**Interventions:** Children fasted for 36 hours, and the diet was gradually introduced over 3 days. Parents were instructed to keep a baseline seizure frequency calendar for the month before the initiation of the diet. These cal-

endars continued to be maintained as the diet was initiated.

**Main Outcome Measure:** Seizure decrease from baseline.

**Results:** The atonic or myoclonic seizures decreased in these children by more than 50% immediately. Using a 24-hour ambulatory electroencephalogram, we documented that the seizures reported by a parent represent only a fraction of the electroclinical events; the technique could be used to measure the profound decrease in electrically documented seizures. Ketosis was eliminated with glucose, 60 g/d.

**Conclusions:** It is feasible to evaluate the ketogenic diet's efficacy in atonic or myoclonic seizures in a blinded, crossover study. The diet can be manipulated on a short-term basis in a blinded manner, and ketosis can be achieved or eliminated.

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**Editor's Note:** In this study, Kool-Aid is a cool aid to designing a double-blind, crossover study.

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**T**HE "CLASSIC" high-fat, adequate-protein, low-carbohydrate ketogenic diet was developed in the 1920s based on observations of the benefits of fasting on seizure control.<sup>1-4</sup> The diet was successfully used during the 1920s and 1930s, but use declined after the discovery of phenytoin (Dilantin). Reports<sup>5</sup> of its efficacy and of the efficacy of the medium-chain triglyceride diet continued to occasionally appear during the 1970s and 1980s.<sup>1</sup> Although there has been a recent resurgence of interest in the diet,<sup>6,7</sup> its efficacy has never been evaluated in a placebo-controlled, blinded manner. The rigor of the

diet has made the design of a blinded, crossover study daunting, and the lack of such trials has caused continued skepticism.

The Lennox-Gastaut syndrome (LGS) is characterized by multiple seizure types and a characteristic polyspike and slow-wave electroencephalogram (EEG), and is often associated with mental retardation. It has many causes, and the cause in a specific child is usually undetermined. Children affected with LGS often have many "drop" (atonic or myoclonic) seizures per day, and these drops, whether mild "slumping" or more active "crashes" to the floor, are often associated with substantial impairment of the child's quality of life.<sup>8</sup> Measurement of the change in frequency of the drops would provide an assessment of the efficacy of the diet.

While evaluating the efficacy of the diet in an unblinded manner, we encountered a 4-year-old with LGS who was

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## PATIENTS AND METHODS

In our standard ketogenic diet treatment protocol,<sup>9</sup> children with difficult-to-control seizures, refractory to at least 2 anticonvulsant medications, are admitted to the hospital, made to fast for 36 hours, gradually introduced to their allotted diet, and then discharged from the hospital. During these 4 days of hospitalization, blood sugar levels are monitored, and daily classes are conducted to teach the parents how to calculate and prepare the diet and how to avoid carbohydrate-containing foods and medications. Parents keep calendars of the seizure frequency for a minimum of 1 month before admission, during admission, and after discharge. These data are prospectively collected and recorded in our database. This protocol has been approved by the appropriate institutional review board, and informed consent was obtained from the parent or legal guardian and/or the child, if appropriate.

Seventeen consecutively admitted children with atonic or myoclonic seizures as their primary seizure type were examined for change in seizure frequency according to parental report. The seizure frequency at the initiation of the diet (day

0) was compared with the frequency on subsequent days (1-5).

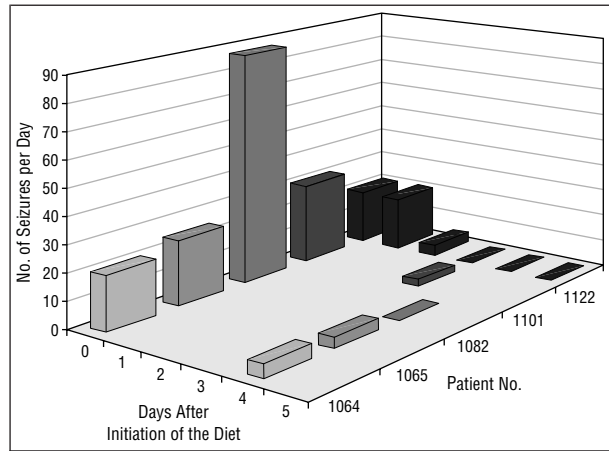
Since it was clear that the diet appeared to have a dramatic and immediate effect on seizure frequency in these children, a method for objective confirmation of the parental seizure reports was sought. During a 24-hour ambulatory EEG, the clinical (push-button) events indicated by the parents were then correlated with the electrical pattern seen at that time. A typical burst that correlated with a clinical event is shown in **Figure 1**. Having learned to recognize the electrical aspects of a clinical seizure from the parents, we could then measure the number of "seizure bursts" during a sustained period, even when the patient was not being observed. These seizure bursts were reviewed and counted by an electroencephalographer (E.P.G.V.). The 24-hour EEG was obtained before diet onset and at the end of the hospital stay (day 5).

Another requirement for designing a short-term, blinded, placebo-controlled crossover study would be the ability to rapidly negate the ketosis (and presumably the efficacy of the diet). Studies by Gamble<sup>10</sup> and Huttenlocher<sup>11</sup> suggested that the effects of the ketogenic diet could be eliminated by administering 40 to 60 g of glucose (dextrose). This was done in 1 child.



**Figure 1.** A burst of spike and spike-wave activity that was recorded on a 24-hour ambulatory electroencephalogram and that correlated with a detected push-button clinical seizure by the parent. This prototype was used to establish the criterion for determining additional electroclinical events in reading the rest of the study.

having more than 60 drop seizures per day. The child's parents had kept meticulous computerized records of the number of drop seizures, and as the diet was initiated the records documented a dramatic decline in seizures. These observations piqued our interest in the possibility of using this type of seizure disorder in studying the efficacy of the diet in a short-term crossover study.

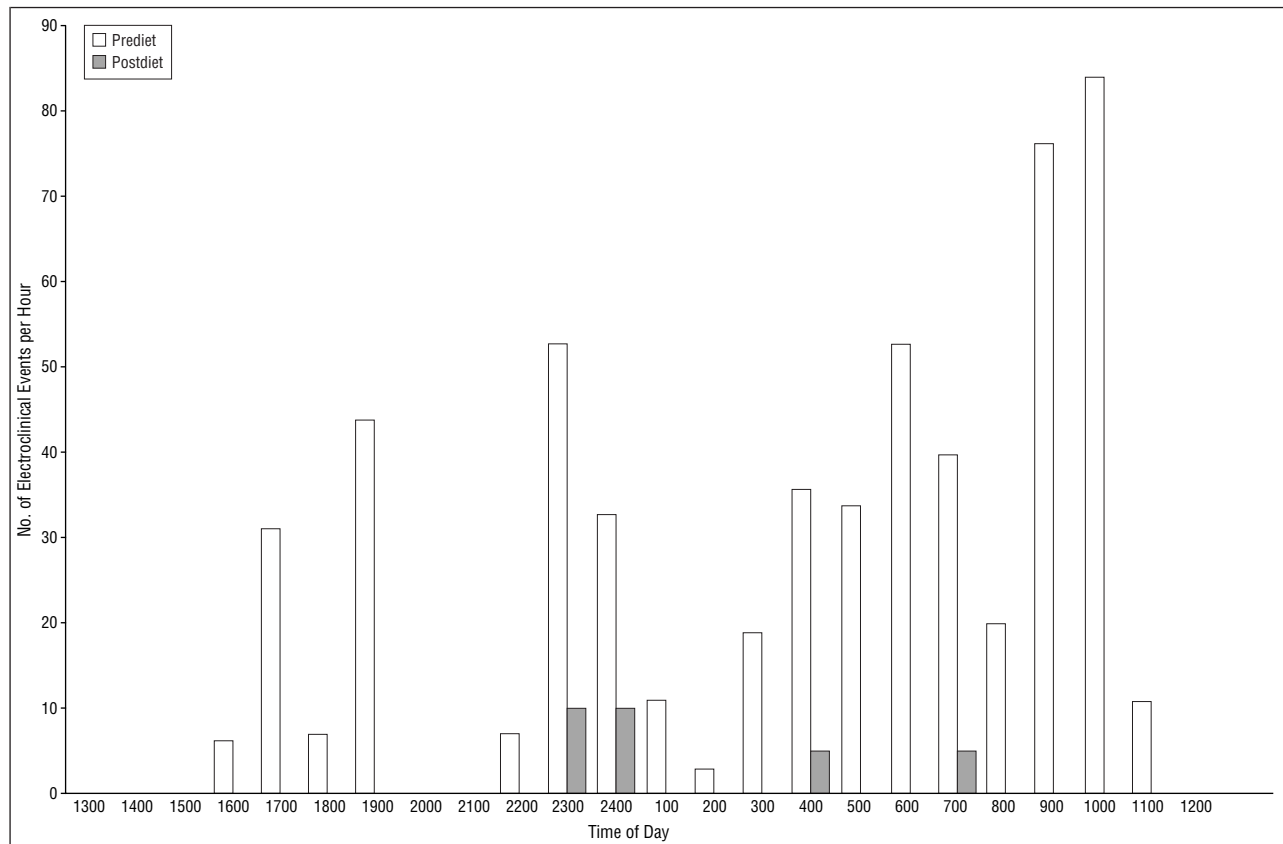


**Figure 2.** The change in seizure frequency during the 5 days after initiation of the ketogenic diet in 5 children whose predominant seizure type was atonic or myoclonic. In all children, there was a greater than 50% decrease in seizures. Each bar represents an individual patient. Seizure frequency was recorded by the parents before fasting and on days after fasting and diet initiation.

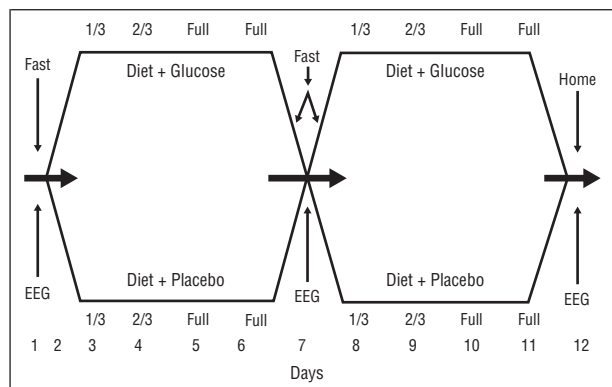
The atonic or myoclonic seizure frequency of 17 patients was known at baseline and was assessed by parents during the initial 5 days of the diet. In all of these children, a greater than 50% decrease in seizures was reported by the fifth day. The rapidity of this decrease is shown in **Figure 2** for the 5 children with the greatest frequency of seizures at onset.

With this clinical confirmation, we then obtained a 24-hour ambulatory EEG in several patients. A discrete change in the EEG was associated with the clinical seizures noted by parents, and this was used to measure electroclinical seizures. The impact of initiation of the diet on this phenomenon is shown in **Figure 3**. In the prediet study, the number of bursts (seizures) per hour was quite variable, but clearly increased markedly during sleep. The family reported no clinical seizures in the 24 hours several days after diet initiation, the EEG documented several electrical events, again usually while the children were asleep.

Finally, negation of the urinary ketosis was confirmed in a pilot patient. This child fasted and received the ketogenic diet and was assigned, in a blinded manner, to a daily "Kool-Aid-like" drink containing glucose, 60 g/d, with saccharin (negating ketosis) or an identical Kool-Aid-like drink that only contained saccharin (preserving ketosis). When this child initially fasted, she



**Figure 3.** An ambulatory electroencephalogram (EEG) of the electroclinical events, bursts of spike or polyspike, and slow waves was performed immediately before fasting and after 5 days of receiving the ketogenic diet. The bars show the number of electroclinical events per hour. During the 24 hours before the diet, the patient had 566 electroclinical events and the parents reported 65 clinical seizures. After 5 days of receiving the diet, the parents reported no seizures and the ambulatory EEG recorded 30 electroclinical events, most of shorter duration than on the preceding recording. Many bursts of activity occurred when the patient was asleep and no clinical seizure was witnessed.



**Figure 4.** The protocol developed for a blinded crossover study of the efficacy of the ketogenic diet in children with atonic or myoclonic seizures. A 24-hour ambulatory electroencephalogram (EEG) will be performed before the onset of fasting and at the end of each arm of the study. The ketogenic diet is instituted on day 3 and again reinstated after fasting on day 8. During one arm, the child will receive a "Kool-Aid-like" fluid containing 20 g of glucose and saccharin to mask the taste 3 times each day. During the other arm, the fluid contains saccharin but lacks glucose. The end point of the study is the number of seizures on the ambulatory EEG at the conclusion of each study arm.

became ketotic, but when the glucose-containing fluid was introduced, the ketosis rapidly disappeared. The child was fasted again and received the same ketogenic diet with fluid containing saccharin (placebo). After this change, she developed ketosis again, which was then maintained.

Based on the data of the 17 patients who dramatically responded to ketosis, our demonstrated ability to measure seizures in a blinded manner (24-hour ambulatory EEG), and our ability to manipulate ketosis rapidly and in a blinded manner, a protocol that would permit a blinded, placebo-controlled, crossover evaluation of the diet's efficacy, was designed. The schematic protocol for such a study is shown in **Figure 4**. The primary end point of the trial would be the number of EEG-documented electroclinical events on the last day of each treatment period.

#### COMMENT

Since efficacy and tolerability are closely linked, in anticonvulsant trials<sup>12</sup> and with the diet,<sup>7</sup> the rigidity and difficulty of the ketogenic diet has made long-term, pla-

cebo-controlled study difficult for the child and family to tolerate. The preliminary evidence of the rapid effect of the diet on the drop seizures of LGS, and the rapid ability to negate the ketosis with the administration of glucose, make it feasible to assess, in a randomized, blinded, crossover, placebo-controlled manner, the short-term efficacy of the ketogenic diet in reducing the number of atonic or myoclonic seizures in children with LGS. The protocol developed has been funded by the National Institutes of Health, Bethesda, Md, and the study has been initiated. If the efficacy of the diet is documented in such a study, it is likely to lead to more acceptable, widespread use of the diet in appropriate populations.

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