Low-glycemic-index treatment: A liberalized ketogenic diet for treatment of intractable epilepsy

Abstract—The ketogenic diet is often effective for intractable epilepsy, but many patients have trouble complying with the strict regimen. The authors tested an alternative diet regimen, a low-glycemic-index treatment, with more liberal total carbohydrate intake but restricted to foods that produce relatively little increase in blood glucose (glycemic index < 50). Ten of 20 patients treated with this regimen experienced a greater than 90% reduction in seizure frequency.

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The ketogenic diet (KD) has been considered an effective treatment for epilepsy since the early 1920s and remains valuable for treatment of pharmacoresistant epilepsy. Historically, one-third of patients initiated on the KD have had greater than 90% reduction in seizure frequency.[1] However, it is difficult for patients and families to adhere to the rigid constraints of the KD. The KD includes approximately 80% to 90% fat, much higher than the typical American diet, which makes it unpalatable for some patients. These dietary restrictions are accompanied by psychosocial issues: patients feel isolated from peers because they eat completely distinct foods. Although attempts have been made to make the diet more palatable, the classic KD remains the best dietary therapy available for epilepsy.

Because acute carbohydrate intake can rapidly terminate the protective effect of the KD,[2] we have tried a liberalized dietary regimen guided by the principle of minimizing the increase of blood glucose. The glycemic index (GI) describes the tendency of foods to increase blood glucose, compared with an equivalent amount of reference carbohydrate, usually glucose.[3] It is calculated from the incremental area under the (blood glucose) curve after feeding, indexed to glucose = 100. Our low-glycemic-index treatment (LGIT) uses a liberalized but still low carbohydrate intake, with carbohydrates supplied only in the form of low-GI foods (GI < 50 relative to glucose). Some examples of low-GI foods are lentils, grapefruit, and whole grain high-fiber bread. Our review of this treatment in 20 patients suggests that this diet is efficacious and more palatable than the classic KD.

Methods. We reviewed the charts of patients who were initiated on the LGIT for intractable epilepsy from 2002 to 2004 (see table E-1 on the *Neurology* Web site at www.neurology.org). Seizure frequency was assessed on a monthly basis by contemporaneous parental report. Some patients were placed on a LGIT while waiting to initiate the traditional ketogenic diet (LGIT-alone group), either because of scheduling constraints for admitting children to start the diet or because families were not sure their child could comply with the complexity of the full ketogenic diet. Others had demonstrated improved seizure control on the KD but were unable to tolerate the constraints of the KD and were therefore transitioned to the LGIT (after-KD group). Reduction in seizure frequency was calculated relative to the prediet baseline. In the case of those that initiated LGIT after the KD, the baseline before initiation of the KD was used. The LGIT is detailed in table E-2.

Results. The LGIT reduced seizure numbers for the majority of patients (figure and table E-3). All patients had previously not responded to at least 3 anticonvulsant medications (an average of 6.7; see table E-1). Eight of the 11 patients in the LGIT-alone group demonstrated a greater than 50% reduction in seizure frequency, and 4 of these became completely seizure free. One of the 10 had an increase in seizure frequency, and 1 patient had a less than 50% reduction. We were unable to determine the effect of the diet in 1 patient because the patient's seizure frequency occurred every 6 weeks, and the KD was initiated in the fifth week of treatment. During LGIT, 2 of the 10 LGIT-alone patients were able to reduce anticonvulsant medications. Three of the 10 patients required an increase in their anticonvulsant medication dosages to optimize seizure control (2 of these achieved > 90% reduction, and 1 had < 50% reduction in seizure control).

A majority in the after-KD group maintained the seizure control previously achieved on the KD. Four patients maintained the greater than 90% reduction in seizure frequency obtained with the KD. One of these became seizure free. Of the remaining five patients, one maintained a greater than 50% reduction, three had less than 50% reduction (a decrease from > 50% for one), and one returned to baseline seizure frequency. This last patient, who had greater than 90% reduction while compliant on the KD, had compliance difficulties with the LGIT.

Anticonvulsant medication adjustments were made in a minority of both groups (see table E-1), but most of the patients improved with no increases (and some decreases) in anticonvulsant drugs.

During the chart review of the patients treated with the LGIT, we also looked at levels of glucose, β-hydroxybutyrate, and carbon dioxide. While on the LGIT, the pa-

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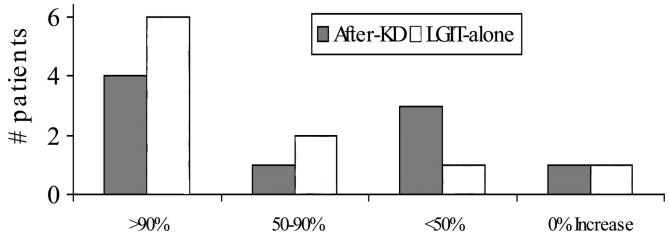

Figure. Reduction in seizure frequency with low-glycemic-index treatment. KD = ketogenic diet; LGIT = low-glycemic-index treatment.

tients' randomly sampled blood glucose levels ranged between 63 and 90 mg/dL (average 76.8 mg/dL); those patients with a greater than 90% seizure reduction averaged 72.6 mg/dL. β-Hydroxybutyrate levels were available for only 8 of the 19 patients. Among this group, there was a wide range from 0.1 to 3.4 mM, with an average of 0.8 mM; those patients with greater than 90% seizure reduction had an average β-hydroxybutyrate level of 1.07 mM. The levels of this ketone body were notably lower than on the classic KD (figure E-1) but still higher than the laboratory reference levels of normal. Plasma carbon dioxide levels ranged from 14.6 to 30.2 mM (average 24 mM).

Discussion. Although the therapeutic mechanisms of the KD remain unknown, some of the metabolic changes that accompany the diet have been investigated. One of those metabolic changes is the stability of blood glucose levels, even during prolonged periods of time when additional energy substrates are not provided.[4] During the fasting state or during consumption of a ketogenic diet, the rate of glucose production and utilization are both significantly decreased, with a net small decrease in blood glucose.[5] With fasting and probably also with the KD, brain energy production is supported substantially by ketone bodies,[6] which are produced in the liver and possibly also in brain astrocytes[7] by oxidation of fatty acids. This alternative energy supply reduces brain glycolysis and glucose utilization by the brain.[6]

It is not known whether the therapeutic effect of the KD for epilepsy derives from the change in brain fuel utilization, from changes in neuroendocrine signaling in response to metabolic status, or from other unknown factors.[8] In animals, a comparable anticonvulsant effect (against spontaneous seizures in epileptic EL mice) can be produced with a calorie-restricted diet, which, like our LGIT, produces reduced blood glucose.[9] In the case of human patients, particularly growing children, caloric restriction is not appropriate. An alternative method for reducing blood glucose is to alter not only the quantity but also the types of carbohydrates consumed, specifically by using foods with a lower GI.[3]

The LGIT is considered to be easier than the KD for many reasons. It is more palatable than the KD because of the liberalization of carbohydrates and decrease in fat content. The patients and their families no longer have to weigh out food portions; because of the decreased fat content, the palatability is increased; it allows families to eat outside the home without having to pre-prepare meals; and because the food is viewed as "normal," the psychosocial aspect is improved.

As with any other medical treatment, the LGIT is not without side effects. Our patients reported some minimal side effects: one patient reported increased lethargy and vomiting, which was thought to be due to acidosis (laboratory values were not available), and one patient reported increased diarrhea and seizures. This latter patient's laboratory values indicated slightly increased acidosis with concurrent increase in blood glucose. The use of low-carbohydrate diets should be used with caution because they do alter the body's normal metabolism. A review of popular low-carbohydrate diets used for weight loss found no increased incidence of adverse changes in serum lipid levels, fasting serum glucose, fasting insulin levels, or blood pressures of the dieters.[10] Common side effects that have been reported with the classic ketogenic diet are renal calculi, increased bruising, cardiomyopathy, metabolic acidosis, acute pancreatitis, constipation, hypocarnitinemia, hyperlipidemia, transient hyperuricemia, and hypertriglyceridemia.[1] As a prudent measure, we therefore recommend initial and follow-up monitoring of blood chemistry for patients initiating the LGIT, including lipid profile, β-hydroxybutyrate, and bicarbonate levels.

Interestingly, the LGIT produced a smaller increase in ketone body levels than is typically seen in the KD, but it seems to be no less effective for seizure control in this limited sample of patients. This observation is at odds with previous suggestions that the level of ketosis is well correlated with efficacy[2] and seems to argue against direct pharmacologic effects of the increased ketone body levels. However, despite the less pronounced ketosis, the LGIT (and the calorie restriction diets in animals) might still alter fuel utilization by the brain.

We propose that the LGIT be considered as a possible alternative to the classic KD. The LGIT can be provided to patients when a KD center is not available, if the KD is not tolerated, or if there is an extended wait time for KD initiation. We recommend that patients be followed by a dietitian who is well versed in LGIT to aid with compliance.

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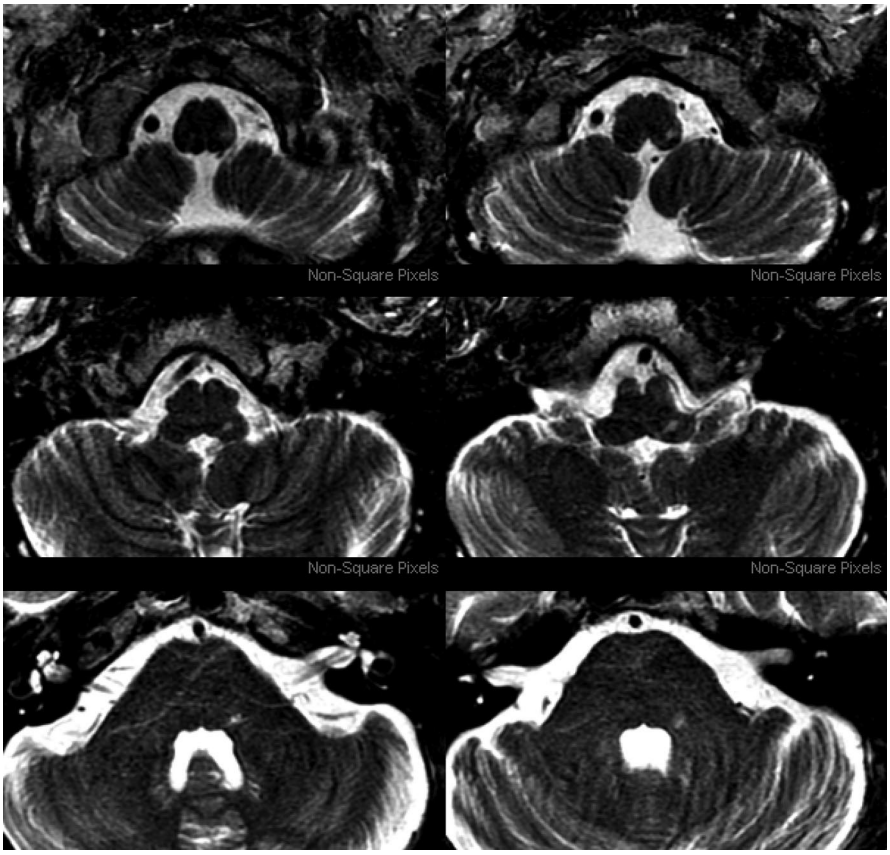

Figure. Axial T2-weighted MRI reveals abnormal increased signal in the left lower pons and medulla posteriorly and laterally near the fourth ventricle, extending into the upper cervical cord, corresponding to the location of the spinal trigeminal nucleus and tract. Lesion was iso-intense on T1-weighted image and did not enhance (not shown).

MRI of trigeminal zoster

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A 65-year-old man on low dose hydrocortisone for stem cell transplantation for primary amyloidosis developed zoster rash of the left face and ear with persistent ipsilateral jaw pain and earache causing difficulty in sleeping and eating. MRI obtained 6 weeks after the onset of the rash revealed increased T2 signal in the lower pons and medulla, extending into the upper cervical cord, corresponding to the anatomic location of the spinal trigeminal nucleus and tract (figure). A greater incidence of post-herpetic neuralgia has been reported in patients with an MRI abnormality corresponding to the dermatomal pain.[1] However, our patient was without pain 14 months after the zoster eruption.

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