Epilepsia, **46**(10):1684–1686, 2005
Blackwell Publishing, Inc.

Brief Communication

Tuberous Sclerosis Complex and the Ketogenic Diet

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Summary: *Purpose:* Tuberous sclerosis complex (TSC) is a condition that is frequently associated with intractable, early-onset epilepsy, and often is first seen as infantile spasms. If medications fail and no clear epileptogenic tuber is identified, nonpharmacologic therapies are often attempted. The use of the ketogenic diet specifically for children with TSC and epilepsy has not been previously described.

Methods: A chart review was performed of patients with TSC treated with the ketogenic diet over a 5-year period at Johns Hopkins Hospital and Massachusetts General Hospital.

Results: Twelve children, ages 8 months to 18 years, were identified. Eleven (92%) children had a >50% reduction in their seizures at 6 months on the diet, and 8 (67%) had a >90% response. Five children had at least a 5-month seizure-free response. Diet duration ranged from 2 months to 5 years (mean, 2 years).

Conclusions: In this limited-duration case series of 12 patients, the ketogenic diet was a generally effective therapeutic modality for the intractable epilepsy occasionally seen in children with TSC. **Key Words:** Tuberous sclerosis complex—Epilepsy—Ketogenic diet.

Tuberous sclerosis complex (TSC) is a condition associated with multiorgan involvement, including skin lesions, kidney tumors, developmental delays, and multifocal dysplastic lesions of the cerebral cortex (tubers). It is caused by a mutation in the *TSC1* (chromosome 9q34) or *TSC2* (16p13) gene, and TSC is inherited in an autosomal dominant manner (1,2). Spontaneous new mutations of *TSC1* and *TSC2* are common, occurring in 50% of cases.

Seizures are common in TSC, seen in as many as 80–90% of patients, typically during childhood (3). In up to one third of children, infantile spasms develop; TSC accounts for 10–20% of the total estimated cases of infantile spasms (3). Treatments for infantile spasms associated with TSC include adrenocorticotropic hormone (ACTH) and vigabatrin (VGB) (4–6). VGB appears to be particularly effective (4–6). Neither of these therapies is without side effects, however. Side effects of ACTH include irritability, edema, hypertension, susceptibility to infection, and gastrointestinal hemorrhage (6). VGB can cause irreversible visual field defects, and it is possible that patients with infantile spasms might be at the highest risk (7).

Seizures other than infantile spasms occur frequently and can become intractable. Nearly all other seizure types can occur, both generalized and partial (3). Because epilepsy due to TSC is typically partial in onset, long-term video-EEG monitoring for seizure-onset identification is indicated when seizures become intractable. If a single epileptogenic lesion is identified, surgical resection can be very successful (8,9). If surgery is not an option, vagus nerve stimulation has been described as successful (10). Another major nonpharmacologic approach, the ketogenic diet, although often attempted for many different seizure types, to our knowledge has not been described in the literature specifically for TSC (11).

METHODS

Records were reviewed of children with clinically identified TSC who had been started on the ketogenic diet at Johns Hopkins Hospital (JHH) and Massachusetts General Hospital (MGH) from 1999 to 2004. One child with multifocal seizures discontinued the diet after the admission period because the parents changed their minds and

Accepted June 3, 2005.
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TABLE 1. *Patients placed on the ketogenic diet for tuberous sclerosis complex, 1999–2004*

Patient	Age at diet onset (yr)	Seizure type	Medications tried	Prior infantile spasms?	Ketogenic diet ratio	6-mo seizure reduction	Medications reduced?	Duration of treatment (yr)
1	0.75	CP	3	Yes	3:1	Seizure free	No	1.4
2	2	M	5	Yes	3:1	Seizure free	Yes	3.5
3	3.5	M	5	Yes	4:1	>90%	Yes	2.5
4	5	M	2	No	4:1	>90%	Yes	2.0
5	5	CP	5	Yes	3:1	Seizure free	Yes	2.0
6	5.5	CP	10	Yes	4:1	50–90%	No	0.5
7	6	M	6	Yes	4:1	50–90%	Yes	1.3
8	6	M	4	No	4:1	>90%	Yes	5.0
9	7	M	9	Yes	4:1	>90%	No	1.3
10	7	CP	4	Yes	4:1	>90%	Yes	2.0
11	8	M	9	No	4:1	<50% (at 2 mo)	No	0.2
12	18	M	9	Yes	3:1	50–90%	Yes	2.5

M, multiple seizure types (atonic, tonic, myoclonic in combination); CP, complex partial.

so was not included in this case series. All children had neuroimaging confirmation of multiple cortical tubers. Seizures in these children were intractable to at least two anticonvulsants (AEDs); one had prior epilepsy surgery, and three had implantation of a vagus nerve stimulator. All patients had follow-up for the time on the ketogenic diet and did not change neurologists during the course of their diet exposure. The ketogenic diet, as a 3:1 or 4:1 ratio (fat-to-carbohydrate and protein), was started after a 48-h fast in patients at JHH; those at MGH were not fasted. Patients had their calories advanced over a 3-day period, calcium and multivitamin supplementation was provided, and laboratory values were obtained (11). Seizures were documented at follow-up clinic visits, and children were examined for potential side effects by measuring height, weight, and serum and urine laboratories (complete blood counts, electrolytes, hepatic-function tests, fasting lipid profiles, urine calcium, and urine creatinine).

RESULTS

Twelve children with TSC (seven at JHH and five at MGH), ages 8 months to 18 years, were started on the ketogenic diet (Table 1). In these patients, seizures were occurring at least daily at diet onset. Seven (58%) subjects were boys. Nine (75%) children had a history of infantile spasms, but none had them at the time of diet initiation. Eight (67%) had tried VGB before the ketogenic diet, and spasms resolved in three of them. Only one patient was taking VGB at the time of diet initiation.

At 6 months on the ketogenic diet, 11 (92%) children had a >50% reduction in their seizures overall; and eight (67%) had a >90% response. Five children had at least a 5-month seizure-free period. The only child with a <50% reduction in seizures had the shortest duration on the diet (2 months). Eight (67%) were able to reduce medications while on the diet. No child had renal stones, symptomatic acidosis after diet initiation, or significant hyperlipidemia. One child had symptoms of depression in combination with a newborn sibling at home, so the diet was discontinued after 6 months. Another family discontinued the diet at 1 year because of perceived insufficient weight gain, even though the child was seizure free at the time. The seizures returned but did not improve when the diet was restarted 6 months later. Diet duration ranged from 2 months to 5 years (mean, 2 years). Four patients who had particularly good results are described in greater detail.

Patient 1

An 8-month-old boy with developmental delay and daily complex partial seizures described as a change in consciousness, and staring to the right, lasting several seconds, was started on the diet after treatment with three AEDs failed. At age 4 months, he was treated successfully for infantile spasms with ACTH. EEG showed left temporal epileptiform discharges; magnetic resonance imaging (MRI) revealed bilateral subependymal nodules. He was placed on a 3:1 ratio ketogenic diet with 600 calories per day solely as a ketogenic formula, and within 1 month, he had a 90% improvement in his seizures. By 6 months on the diet, he was seizure free. He remained on the diet for 1.4 years before it was discontinued, and he remains seizure free now at age 5 years.

Patient 2

A 2-year-old boy with a history of infantile spasms in whom mixed seizures subsequently developed, characterized by staring spells and head drops, was started on the diet. He had been treated with five AEDs without success. His seizures were occurring typically 4 to 5 times per day and were occasionally associated with injuries. EEG showed generalized, but left-frontal maximal polyspikes, and MRI revealed bifrontal tubers. After 2 weeks on a 3:1 ratio diet with 1,200 calories per day, he became seizure free. He also became more interactive and verbal, and at 6 months, all medications were slowly discontinued. Other than an elevation in his urine calcium-to-creatinine ratio, for which he was placed on oral urine alkalinization, he has had no side effects. After 3.5 years on the diet, it was

discontinued, and he has remained seizure free, now at age 8 years.

Patient 10

A 7-year-old girl had complex partial seizures several times per day despite prior treatment with four AEDs. Infantile spasms had occurred at age 10 months but resolved with VGB. EEG showed left frontal spikes, and MRI showed multiple cortical tubers. She was placed on the ketogenic diet elsewhere, with a 4:1 ratio and 900 calories per day. Daytime seizures were immediately eliminated, but nocturnal seizures persisted. She continues on the diet to date with >95% seizure reduction and no medications, now at age 9 years.

Patient 12

An 18-year-old man with intractable mixed seizure disorder, global developmental delays, and behavioral difficulties was started on the diet after failing to respond to nine AEDs. At age 11 years, he had a left frontal tuber resection and anterior corpus callosotomy, but seizures persisted. At the time of diet initiation, he was having two or more atonic seizures per day, as well as daily episodes characterized by facial flushing, hyperventilation, and change in responsiveness. EEG showed frequent multifocal spikes and sharp waves with left frontotemporal predominance. He began the diet with a 3:1 ratio, 2,000 calories per day, and subsequently had a >50% reduction in seizure frequency; the atonic seizures were reduced to once every 4 to 5 days. This reduction also was accompanied by neurocognitive improvements: better word retrieval, improved processing time, and increased verbal interaction. While on the diet, he was able to discontinue two of his four AEDs. Unfortunately, after 2.5 years on the diet, his seizures became more frequent, and, because of his increasing difficulty tolerating the restrictiveness of the diet, it was discontinued.

DISCUSSION

The ketogenic diet is an option for patients with TSC and refractory epilepsy. The majority of these patients benefited from improved seizure control with limited side effects from the diet after medications had failed. All but one child had a >50% reduction in seizure frequency; several even had periods without seizures. In this limited case series of only 12 patients, no more definitive recommendations can be made; however, the use of the ketogenic diet for children with intractable epilepsy associated with TSC deserves further study.

Although evidence suggests that children with solely partial epilepsy are perhaps overall less likely to improve on the diet, many such children did have a reduction in their seizures (12,13). The multifocal, mixed seizure type associated with TSC may be more similar to that of the child traditionally started on the ketogenic diet than a patient with standard complex partial epilepsy. In addition, we suspect that although none of these children had infantile spasms at the actual time of treatment, 75% had this diagnosis previously, and the ketogenic diet may have a role for intractable infantile spasms, based on previous work (14). As several of the best outcomes were observed in the youngest patients, earlier treatment with the ketogenic diet during infancy may be of value.

In summary, for this small group of children with TSC and epilepsy, the ketogenic diet appeared to be an effective therapeutic modality. Knowing that medications can be often ineffective, and surgery may not be an option if lateralization or localization of the epileptogenic region is not possible, the ketogenic diet may be a useful option.

Acknowledgment: This study was supported in part at Johns Hopkins by the Vaswani Family and the Pediatric Clinical Research Unit, supported by NIH/National Center for Research Resources grant M01-RR00052.

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