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Case study

# The effects of the ketogenic diet in refractory partial seizures with reference to tuberous sclerosis

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ABSTRACT

*Purpose*: Tuberous sclerosis complex (OMIM 191100) is a multiorgan disease commonly associated with epilepsy refractory to anticonvulsants. Individual reports indicate that seizures in children with tuberous sclerosis might benefit from a ketogenic diet. We studied the effects of the diet introduced at 3.5 years of age in three boys with tuberous sclerosis and refractory partial seizures.

*Methods*: On admission a classical LCT ketogenic diet was initiated and patients were followed for 12 months. Antiepileptic drugs were maintained unless adverse effects required reduction.

*Results*: Two patients became seizure-free within 2 months on the diet. In the third patient drop attacks decreased significantly. On follow-up the diet was well accepted and without adverse effects.

*Conclusion*: The ketogenic diet should be considered as a treatment option for children with tuberous sclerosis and partial seizures refractory to anticonvulsants. Our data support the need for further studies in larger cohorts to confirm the effectiveness of the ketogenic diet in this entity.



## 1. Introduction

The ketogenic diet (KD) is a rigidly calculated, high-fat, adequate protein, low carbohydrate diet, in which results have shown a decrease in both generalized and partial seizures.[1,2] One of the main efforts in recent years is defining a clear-cut relationship between the effectiveness of a KD, patient age, and a single type of epilepsy or epileptic syndrome. The KD has been suggested as a potential alternative treatment for refractory partial seizures due to tuberous sclerosis complex (TSC).[3] TSC is a multiorgan disease commonly associated with epilepsy typically partial in onset and frequently refractory to anticonvulsants. Among the non-pharmacological therapies the KD has been individually tried in 12 children and adolescents with TSC and refractory partial seizures.[4] In this retrospective, chart review study the KD succeeded in decreasing more than 50% of seizures in 92% of patients, with eight children showing >90% improvement.

*Abbreviations:* KD, ketogenic diet; TSC, tuberous sclerosis complex; AEDs, antiepileptic drugs.

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Except for Kossoff et al.[4] there are no detailed descriptions specifying the efficacy of KD in children with TSC.[3] Even in a small series in which the KD was evaluated for infantile spasms, there are no reported cases associated with TSC.[5–7]

In this prospective study we describe the clinical efficacy of KD initiated at 3.5 years of age in three young boys with TSC and refractory partial seizures.

## 2. Methods

All patients underwent an initial alimentary and caloric inquiry. In patients nos. 1 and 3 a classic 4:1 ratio (lipid/carbohydrate and protein) KD was gradually introduced, avoiding the 1st day of fasting.[8] A liquid KD formula was applied or incorporated in a classic 4:1 diet. Meeting parental concerns about high (4:1) KD ratio, a classic 3:1 ratio KD was initiated in patient no. 2. Patients and caregivers were admitted, educated in the use of the KD, and discharged after 5 days. During hospitalization, levels of blood glucose and urine ketone bodies were monitored, together with the consumption of allowed meals and proper parent/caregiver training. Baseline AEDs were not modified during the 1st month on the KD, unless adverse effects such as excessive drowsiness or sedation occurred that required reduction, preferably benzodiazepines or phenobarbitone. Various laboratory tests and procedures were performed before the KD was introduced and on follow-up at 3-months intervals. The laboratory profile included a full blood count, a serum lipid profile, and the analysis of hepatorenal function. Ultrasounds of the heart, kidney, and liver were performed as well as weight and height evaluations, and wake and sleep EEG recordings. Parents/caregivers were requested to maintain a diary and record seizure frequencies and side effects. Patients were followed in the outpatient department every 3 months or when required.

## 3. Patient no. 1

M.R. is a three and half year old male, and the only child of a non-consanguineous couple in which the mother is affected by tuberous sclerosis complex. Despite the mother's condition, there was no complication with either the pregnancy or the delivery. M.R.'s birth weight was 2900 g and his Apgar score was 8 and 10 after 1 and 5 min, respectively. Psychomotor development was normal, though language skills appeared somewhat limited. Presently, the child is being treated with language therapy.

The first tonic seizure manifested at 2 months of age, followed by daily episodes of generalized tremors and a fixed gaze at 7 months. A cerebral CT scan confirmed a diagnosis of TSC by showing the presence of multiple subependymal nodules. First, vigabatrin was used but was ineffective. However, carbamazepine monotherapy fully controlled his seizures for 7 months. Later, partial complex seizures reappeared and were poorly controlled by different combinations of carbamazepine, valproate, topiramate, vigabatrin, levetiracetam, lamotrigine, clonazepam, clobazam, and stiripentol. At 22 months, an MRI was performed and the results showed several frontal and parietal cortical and subcortical tubers over both hemispheres. The results also indicated bilateral occipital hamartomas combined with multiple subependimal nodules. At the age of 3 years the patient had experienced frequent secondary generalized partial complex seizures when falling asleep and daily episodes of staring and loss of consciousness lasting from 20 to 30 s. At this time the child was started on a glucose and calorie restricted diet that lead to a 60% seizure reduction. A month later, the child was started on a classic 4:1 ratio KD combined with an antiepileptic therapy, consisting of carbamazepine, valproic acid, vigabatrin, and clonazepam. A month after KD was instituted, there was a further 30% decrease in seizure activity for a total of 90% compared with baseline seizure frequency. During the 3rd month and to the end of the 6th month, the seizures disappeared. During the 7th month of treatment, sporadic and brief episodes of fixed gaze and loss of consciousness seizures had reoccurred, despite adjustments in the KD. Regardless of the mild constipation present during the 1st weeks of treatment, the parents reported an improvement in the alertness and vigilance in their child. After 14 months on ketogenic diet, the child is presently seizure free.

## 4. Patient no. 2

L.L. is a 6-year-old male born to healthy parents. The family history is negative for TSC or other neurological disorders. Following an uneventful pregnancy and delivery he developed a first febrile seizure at the age of 4.5 months, followed by atypic absences and non-febrile focal tonic seizures with a maximum of 25 seizures/day. At 6 months of age the diagnosis of cryptogenic focal epilepsy was made. A full diagnostic workup including metabolic studies was uninformative. He was successively treated with oxcarbazepine, clobazam, acetazolamide, and sultiam without effective seizure control. Subsequent treatment with valproate, lamotrigine, and ethosuximide also failed to control his epilepsy. At 18 months of age the diagnosis of TSC was made based on multiple white spots with Wood lamp, intractable epilepsy, and calcifications in the cerebral CT scan. The awake and sleep EEG recordings showed right temporal spikes and a moderate generalized and bilateral temporal slowing. A consecutive brain MRI showed multiple bilateral cortical, subcortical, and subependymal nodules characteristic for TSC. Within the next 2 years levetiracetam was added without success and epilepsy surgery was evaluated but found not practicable due to the multifocal character of seizures. At 39 months of age on valproate treatment he displayed 4–6 focal tonic seizures/day, psychomotor arrest with oral automatisms lasting 5–10 s, sometimes occurring in clusters. He was started on a 3:1 ketogenic diet following an initial fast. With the onset of ketosis seizures were completely controlled and parents observed an increased alertness and interest. Valproate was initially maintained but then slowly discontinued after 12 months on the KD. To date he has remained seizure free on a KD for 31 months without adverse effects. A cautious withdrawal of the diet as suggested for the treatment of intractable childhood epilepsy with the KD is currently considered.

## 5. Patient no. 3

F.C. is a three and half year old male, second of two siblings, and born to healthy parents. Familial history was negative. He was born after 35 weeks of uneventful gestation, by Cesarean section. F.C. weight at birth was 2080 g, and his Apgar scores were 8 and 9 at 1 and 5 min, respectively. Psychomotor development was normal. At 3 months of age, the child demonstrated the first episodes of seizure disorder. These seizure disorders were represented by clonic jerks of the mouth, brief flexion of the right arm followed sometimes by generalized clonic jerks. At 6 months of age, clusters of asymmetrical flexor spasms started, together with a hypsarrhythimc EEG pattern. A CT scan showed several cortical–subcortical frontal and parietal areas of hyperdensity and subependimal nodules in both lateral ventricules. Cutaneous examination by means of Wood's fluorescent light disclosed multiple hypomelanotic patches, thus confirming the diagnosis of tuberous sclerosis. In the beginning, initial improvements were seen in the patient using up to 150 mg/kg/day of vigabatrin. However, asymmetrical spasms and episodes of eye and head deviation recurred almost daily. Carbamazepine, clonazepam, clobazam, topiramate, and valproic acid, combined with vigabatrin were ineffective. Also, sudden drop attacks of the head and trunk manifested themselves many times daily. At this age, video EEG recordings showed frequent seizures represented by unresponsiveness with the eyes having a staring or fixed gaze lasting a few seconds. Besides these symptoms, F.C. demonstrated sudden backward falls or right hemiclonic jerks associated with rhythmic sharp wave discharges over the left central and parietal leads. Psychomotor evaluation at 30 months of age showed a mild delay on the Brunet–Lezine scale. Due to the persistence of more than 10 daily seizures, at 37 months of age, the child was started on a classic 4:1 KD added to carbamazepine combined with valproic acid and clonazepam. During the 1st month of KD, the seizures had decreased by 50%, and in the 2nd and 3rd months, the seizures had been lowered by 75 and 85%, respectively. However, only a 30% improvement from seizure disorders had occurred during the 4th to the 7th month the patient was on KD. Despite this limited efficacy, mainly linked to frequent violations of the diet, the child's parents, while waiting for surgical treatment, did not want to discontinue the KD. They reported that the seizures were less intense and brief than they were before KD was started. Furthermore, their child was described as being more alert and attentive. At the age of four and half year, the child underwent the surgical removal of tubers localized in the left frontal lobe, as serial video EEG recordings showed a persisting onset of focal epileptic discharges from these brain region. Table 1 and Fig. 1 summarize the clinical features of the three patients.

## 6. Discussion

The ketogenic diet (KD) has been used for decades to treat intractable childhood epilepsy. Despite its effectiveness confirmed in several recent studies[9] there is no sufficient data on the specific effectiveness of the KD in epileptic syndromes nor on the influence of patients' age and gender. The advantages of the present study are the individual assessment of the effects of a KD in (i) three boys with refractory complex partial seizures, (ii) with a definite diagnosis of tuberous sclerosis complex (TSC), (iii) initiated at the same age. One of the key criticisms of the ketogenic diet is the missing data on the effectiveness of the diet in specific diseases or epileptic syndromes. Our data indicate that TSC could represent an entity especially responsive to the ketogenic diet. The KD effectively controlled seizures in two patients (patients nos. 1 and 2) and significantly decreased drop attacks in the third (patient no. 3). In line with observations summarized by Than et al.[10] patient no. 1 responded early to the KD by a significant reduction in seizure frequency within the first 2 weeks of the diet. Also, complete seizure control persisted up to 8 months. Sporadic and brief episodes of fixed gaze and staring reoccurred after 7 months on the KD but were significantly controlled by readjusting dietary parameters.

Patient no. 2 became seizure-free with the onset of ketosis and anticonvulsants could be completely discontinued. In patient no. 3 seizure-control was not complete yet clinically significant, despite a declining compliance to the diet. The KD remained the only therapeutic option for seizure control while the child was waiting for a multistage surgical intervention. Of note is that the ketogenic diet allowed for development and alertness, before surgery was performed. Two months after surgical removal, the child is seizure free and his EEG is free of epileptic discharges. In two children the compliance with the KD was very good.

Recently, Kossoff et al.[4] retrospectively reported a significant improvement on KD in about 90% of 12 children and adolescents with refractory partial seizures and TSC. Five

**Table 1 – Characteristics of the three patients**

| Patient no. | Age at diet onset (years) | Diet duration (months) | Prior medications | Efficacy (% of seizure decrease) | Adverse events |
|---|---|---|---|---|---|
| 1 | 3.7 | 14 | VPA, CBZ, VGB, CZP, TPM | ≥98% | Mild constipation |
| 2 | 6 | 31 | OXC, CLOB, AZM, Sulth., LTG, ETS, LEV | Seizure free | – |
| 3 | 3.6 | 15 | CBZ, CZP, CLOB, TPM, VPA, VGB | ≥50% | – |

VPA, valproic acid; CBZ, carbamazepine; VGB, vigabatrin; CZP, clonazepam; TPM, topiramate; LEV, levetiracetam; Sulth., sulthiame, AZM, acetazolamide; ETS, ethosuccimide; OXC, oxcarbazepine; LTG, lamotrigine.

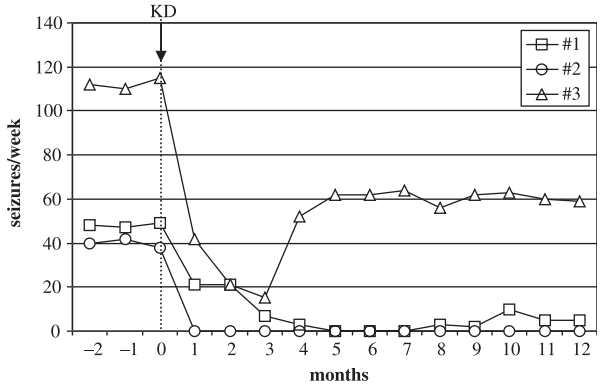


**Fig. 1 – Seizure frequency before and on ketogenic diet in patients nos. 1–3. The start of the ketogenic diet (KD ↓) is indicated.**

children had at least a 5-month seizure-free response. The diet was maintained for 2 months to 5 years (mean 2 years). The overall tolerability of the diet was good and no child developed renal stones, symptomatic acidosis, or significant hyperlipidemia. Of note, in this series only three children were 3 years of age or younger. Other individual cases treated with the KD have been included in previous trials with the KD.[10] In addition, Thiele[3] postulated that the KD could be an effective treatment for intractable epilepsy in TSC, with efficacies similar to those in seizures from other etiologies.

Young children with TSC often initially present focal seizures or epileptic spasms and later develop intractable seizures with multifocal EEG abnormalities.[11] These patients share clear-cut unfavorable prognostic factors which include seizure onset earlier than 1 year of age, the presence of multiple seizure types (spasms, focal motor or complex partial seizures, drop attacks), and multifocal discharges in the awake state that tend to bilateralise in sleep.[12] Vagal nerve stimulation has been described as an alternative treatment for TSC.[13] This option was not considered in the patients described here because of the very good response to the KD in two patients and the potential surgical option in the third patient. The present study suggests that the KD should be considered as an early treatment option[14] in a therapeutic program for difficult-to-treat children with TSC and refractory partial seizures waiting for surgical intervention, or if surgery fails or is not indicated. In addition, the KD could be successfully performed between serial surgical removal of multiple tubers in a multistage treatment strategy.[15] Further studies, however, need to be performed to confirm the preliminary data.

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