■ Case vignette

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Epileptic Disorders

Ketogenic diet for focal epilepsy with *SPTAN1* encephalopathy

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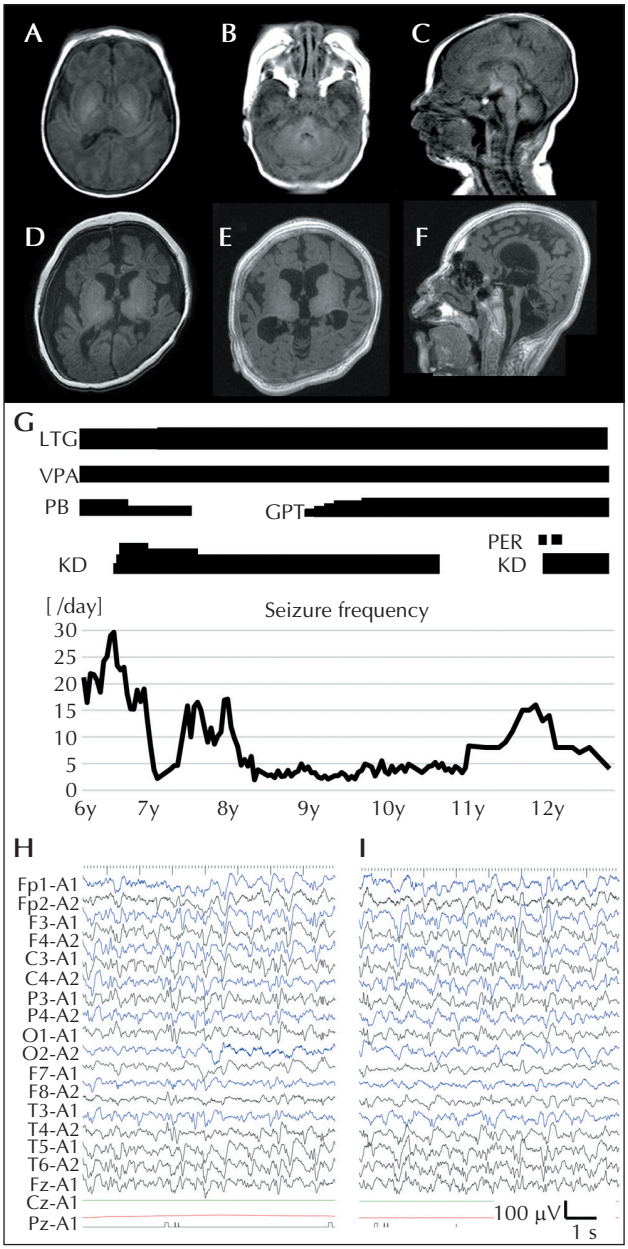
SPTAN1 (non-erythrocytic alpha-spectrin-1) encephalopathy is a wide spectrum of neurodevelopmental disorders that includes epilepsy which is highly resistant to antiepileptic drugs [1]. There is no effective treatment for focal seizures following resolution of epileptic spasms by adrenocorticotropic hormone (ACTH) or vigabatrin. In our regular epilepsy practice, the ketogenic diet (KD) is rarely adopted as an early treatment for epilepsy relative to drug therapy. Although the KD has successfully reduced the frequency of seizures in one case of *SPTAN1* encephalopathy, its efficacy remains unclear [2]. Here, we describe a case in which the KD was applied as a treatment for *SPTAN1* encephalopathy with residual focal seizures after ACTH and discuss the benefits of the KD considering previous reports.

A male patient was born to non-consanguineous parents at 39 weeks of gestation after an uneventful pregnancy. His birth weight, length and head circumference were 2,888 g (standard deviation [SD]: -0.27), 51.5 cm (SD: +1.2), and 32.4 cm (SD: -0.70), respectively. He had an older healthy brother. The day after birth, he exhibited apnea and clonic seizures, which were relieved by phenobarbital; EEG findings were normal. At four months of age, he exhibited infantile spasms and focal seizures, and the EEG showed hypsarrhythmia leading to the diagnosis of West syndrome. ACTH eliminated epileptic spasms, however, daily focal seizures persisted despite treatment. Serial brain MRI showed a lack of myelination and progressive atrophy of the cerebral white matter, corpus callosum, cerebellum, and brain stem (*figure 1A-F*).

The clinical course of West syndrome accompanied by intractable focal epilepsy and the neuroimaging findings led to a suspicion of *SPTAN1* encephalopathy. Genetic analysis was approved by the institutional review boards of Yokohama City University School of Medicine and Yamagata University Faculty of Medicine. Whole-exome sequencing was performed, as previously described [2, 3], and a *de novo* in-frame duplication (c.6908_6916 dup; p.Asp2303_Leu2305 dup) was found within the last spectrin repeat in *SPTAN1*. We considered KD therapy for our patient at six years and eight months of age. At that time, the patient's seizures involved a tonic posture with left elbow extension and right elbow flexion. Seizure frequency was 30–35 times per day, despite treatment with phenobarbital, valproate, and lamotrigine. A diet with a 3:1 ketogenic ratio was initiated and Ketone Formula (Meiji 817-B) was administered through a gastrostomy tube. After KD initiation, the patient did not experience major adverse effects, and the seizure frequency decreased to five times per day. Phenobarbital was successfully reduced and eventually stopped, and his wakefulness improved. At 10 years and six months of age, KD therapy was terminated upon the mother's request, since she no longer felt the therapy was beneficial. Thereafter, tonic seizures gradually increased in frequency to



■ **Figure 1.** (A-F) Brain MRI data over time. T1-weighted imaging at two days of age shows the absence of myelination in the internal capsule and middle cerebellar peduncle, hypoplasia of the corpus callosum (A, B), and lack of atrophy in the cerebellum (C). (D) At six months of age, atrophy was revealed in the cerebral white matter and cerebellum as well as an absence of myelination. (E, F) At five years of age, further atrophy of the corpus callosum, cerebellum, and brainstem was demonstrated. (G) The patient's clinical course after introduction of the KD. Seizure frequency gradually decreased and phenobarbital could be stopped. From approximately nine years of age, his muscle tone began to increase, and gabapentin was started. At 10 years and six months of age, his family opted to terminate the KD after four years, however, his seizures gradually increased and perampanel was not effective. At 11 years and nine months of age, we restarted the KD, after which the seizures improved. (H, I) Interictal EEG results before (H) and two weeks after (I) KD initiation. y: years of age; GPT: gabapentin; KD: ketogenic diet; LTG: lamotrigine; PB: phenobarbital; PER: perampanel; VPA: valproic acid.

approximately 15 times per day. Two years later, at 11 years and nine months of age, we reintroduced the patient to the KD, and his seizures decreased to seven to eight times per day (*figure 1G*). One year after the reintroduction of the KD, his seizure frequency continued to improve, and he did not experience adverse effects during the second period of KD. Interictal EEG results did not change in the two weeks following KD initiation, although epileptic seizures were reduced (*figure 1H-I*).

Despite the antiepileptic mechanisms of the KD being poorly characterized, the KD is sometimes effective for various types of epilepsy, even for drug-resistant epilepsy [4]. In our patient, the KD reduced seizure frequency by >50% in two instances, allowing for antiepileptic drug reduction. To date, six cases of *SPTAN1* encephalopathy, treated with the KD have been reported, including our case [1, 2]. All patients exhibited West syndrome and vigabatrin or ACTH were partially effective for their infantile spasms, however, tonic or polymorphic seizures remained refractory. The KD was partially effective in only one previous case [2] as well as our case. This case supports the possibility that KD therapy may be an effective treatment for *SPTAN1* encephalopathy. Furthermore, our case shows the long-term efficacy of KD, even after interruption. The KD is generally discontinued after a certain period of time, however, the clinical course of this case implies that the KD can be restarted if seizures recur. Considering these findings, KD therapy may be worth trying in early phases when two or three antiepileptic medications fail to control the focal seizures in *SPTAN1* encephalopathy. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
The authors have no conflicts of interest to declare.

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TEST YOURSELF

(1) What are the neuroimaging features associated with a severe phenotype of *SPTAN1* encephalopathy?
A. Progressive cerebellar atrophy and loss of cerebral white matter volume
B. Multiple destructive lesions including porencephaly and schizencephaly
C. Focal cortical dysplasia

(2) What kind of epilepsy is associated with SPTAN1 encephalopathy?
A. Neonatal-onset epilepsy with focal seizures
B. Infantile-onset epilepsy with various types of seizures
C. Childhood-onset epilepsy with generalized seizures

(3) What is the expected benefit of a ketogenic diet?
A. Only a limited group of diseases, such as glucose transporter 1 deficiency syndrome, tuberous sclerosis complex, and Dravet syndrome respond to the ketogenic diet
B. All forms of epilepsy improve to some extent with the ketogenic diet
C. It is not known which type of epilepsy will improve with the ketogenic diet

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.