Case Report
Yonsei Med J 2021 Apr;62(4):370-373
https://doi.org/10.3349/ymj.2021.62.4.370
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Ketogenic Diet in Infants with Early-Onset Epileptic Encephalopathy and *SCN2A* Mutation

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Research has shown mutations in the voltage-gated sodium channel gene *SCN2A* to be associated with developmental delays and infantile seizures in patients with early-onset epileptic encephalopathies (EOEEs). Here, we report the case of an infant with a de novo *SCN2A* mutation with EOEE who had medically refractory seizures that improved with a ketogenic diet (KD) implemented at an age less than 2 months. On the day of his birth, the infant presented with a pattern of convulsions with dozens of episodes per day. An initial video electroencephalogram revealed poor reactivity of background activity, with multiple partial episodes starting from the right temporal region, and abnormal electrical activity in the right hemisphere. The seizures previously were not controlled with successive therapy with phenobarbital, topiramate, and levetiracetam. Genetic testing revealed the presence of a mutation in the *SCN2A* gene (c.4425C>G, p.Asn1475Lys). The infant's seizures decreased significantly with a combination of KD and medication. The present case exemplifies the potential for personalized genomics in identifying the etiology of an illness. Furthermore, the KD appears to feasible in infants younger than 2 months and might elicit good responses to EOEE associated with *SCN2A* mutation.

Key Words: Early-onset epileptic encephalopathy, *SCN2A* mutation, ketogenic diet, infant, de novo mutation

INTRODUCTION

Early-onset epileptic encephalopathies (EOEEs) present with developmental impairment and disastrous seizures starting in early infancy, for which a range of genetic mutations have been implicated. Mutations in the *SCN2A* gene, which encodes the α2 subunit of the neuronal sodium channel, have been identified in association with a number of encephalopathy phenotypes, ranging from benign familial neonatal-infantile seizure to more severe forms of epileptic encephalopathy.[1] In the present study, we describe the case of an infant with a de novo *SCN2A* mutation with EOEE.

Received: August 12, 2020 **Revised:** December 18, 2020
Accepted: December 28, 2020
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•The authors have no potential conflicts of interest to disclose.

CASE REPORT

A 27-day-old male infant with unrelated healthy parents was referred to our clinic with generalized tonic convulsions that started on his first day of life. He had been hospitalized at the neonatal intensive care unit of a local hospital due to meconium inhalation and suffocation. The neonate was the parents' first child, and there were no known prenatal or perinatal complications. There was no family history of epilepsy, mental retardation, and dyskinesia, and his mother had no history of exposure to poison or trauma during pregnancy. On the day of birth, the neonate's convulsions were characterized as orthocolosis and strabismus in both eyes lasting for one to several minutes at a time and occurring with a frequency of more than 10 times per day. Magnetic resonance imaging and magnetic resonance angiography revealed no significant structural abnormalities. Routine blood work and blood biochemistry, as well as genetic metabolic disease testing, yielded normal results. An initial video electroencephalogram revealed poor background reactivity during episodes; a large number of irregular spikes during the episode, which were clustered and recorded in the right temporal region; and abnormal activity of the right hemisphere (Fig. 1). The seizures still occurred frequently

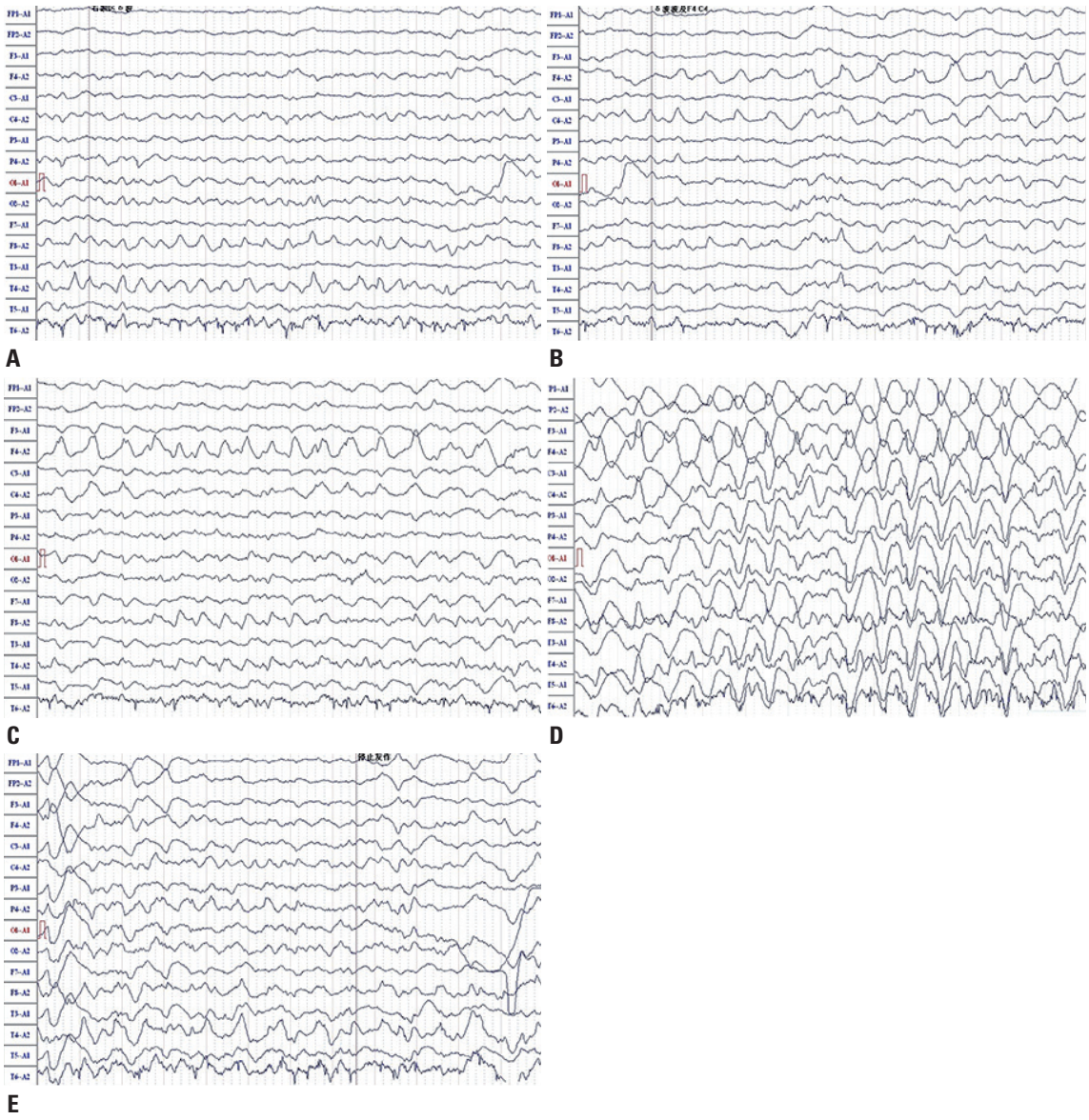

Fig. 1. EEG at disease onset. (A) Initial EEG revealed poorly reactive of background activity during episodes, a number of irregular spikes in the episode period were recorded in the part of the right temporal region. (B and C) Irregular spikes were recorded in the part of the right temporal, central, and frontal regions. (D) Irregular spikes were clustered and recorded in the whole right hemisphere. (E) Irregular spikes were disappeared along with seizure arrest. EEG, electroencephalogram.

despite administration of 5 mg/(kg/day)$^{-1}$ of phenobarbital sodium, 40 mg/(kg/day)$^{-1}$ of levetiracetam, 5 mg/(kg/day)$^{-1}$ of topiramate, and 2 g/kg of γ-globulin.

Gene testing revealed the presence of a c.4425C>G (p.Asn-1475Lys) mutation in the *SCN2A* gene with a mutation ratio of 13/58 (Fig. 2). The parents did not carry this mutation, suggesting that it was a newly developed mutation and possibly a chimera. This clinical feature associated with genetic results suggested that it was EOEE.

After undergoing routine laboratory evaluations, the infant was started on a ketogenic diet (KD) at a ratio of 0.5:1. KD formulas (Qitong) were provided by Shenzhen Zeneca Biotechnology Co., Ltd (Shenzhen, Guangdong, China). His seizures decreased slightly on his first 3 days on the KD. Except for day 5 of the diet, when he experienced 50 seizures, the patient had fewer than 10 seizures daily, and this was a lower frequency than that before initiation of the diet (Fig. 3). The KD ratio was gradually increased until a ratio of 2:1 was reached, and the patient continued to receive a KD at this stable ratio with good efficacy. He was discharged from the hospital after 2 weeks due to gradual decreases in seizures. The dietitian followed up the patient every week by telephone. After being on the KD for 1 month, he was re-examined and found to have mild seizures fewer than 5 times/day. The infant was then completely seizure-free 3 months later, and the anti-epileptic drugs were gradually reduced from the fifth month of age. At the time of

writing this paper, the infant is still on a KD. Ethical approval for publication was obtained from the Second Hospital of Hebei Medical University and the parents of the patients.

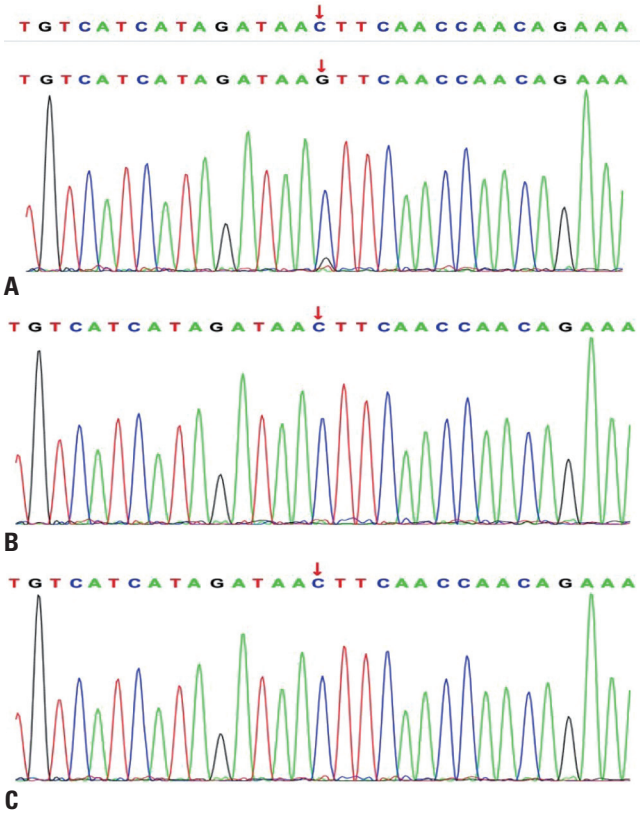

Fig. 2. Sanger sequencing confirming the *SCN2A* gene with de novo mutation. (A) Infant. (B) Father. (C) Mother.

DISCUSSION

Voltage-gated sodium channels, which consist of one major α-subunit and one or more β-subunits, have been shown to be associated with the conduction of action potentials in the brain.[2] In our case, the infant had a mutation in the *SCN2A* gene at c.4425C>G, p.Asn1475Lys. By searching the website http://smart.embl-heidelberg.de/, we determined that the mutation in the protein encoded by this gene is near a predicted domain called the transmembrane region, which played an important role in the function of the protein. De novo mutations are common in patients with focal seizures of epileptic encephalopathy, which, similar to our case, could not be controlled using anti-epileptic drugs. While sodium channel blockers were reported to alleviate or reduce seizures caused by mutations in the *SCN2A* gene, this treatment has been found to be ineffective in some patients and to even aggravate seizures in others. It seems that valproic acid, levetiracetam, and topiramate were partially effective. In our case report, the infant was initially treated with phenobarbital sodium. A few days later, levetiracetam was added, but the seizures still could not be controlled. In contrast, in the first few days after addition of topiramate, the seizures improved, although it could not maintain the efficacy. The sodium channel blocker oxcarbazepine was not considered due to its side effects and because of the young age.

KDs have been used since the 1920s when it was observed that starvation can decrease the incidence of seizures. These days, it is mainly used to treat infants with intractable seizures.[3] A 2016 study reported that a KD can be used to treat infants with refractory epilepsy.[4] Since then, KD has been used to treat epilepsy caused by genetic defects in the *SCN1A*, *SCN2A*, *SC-*

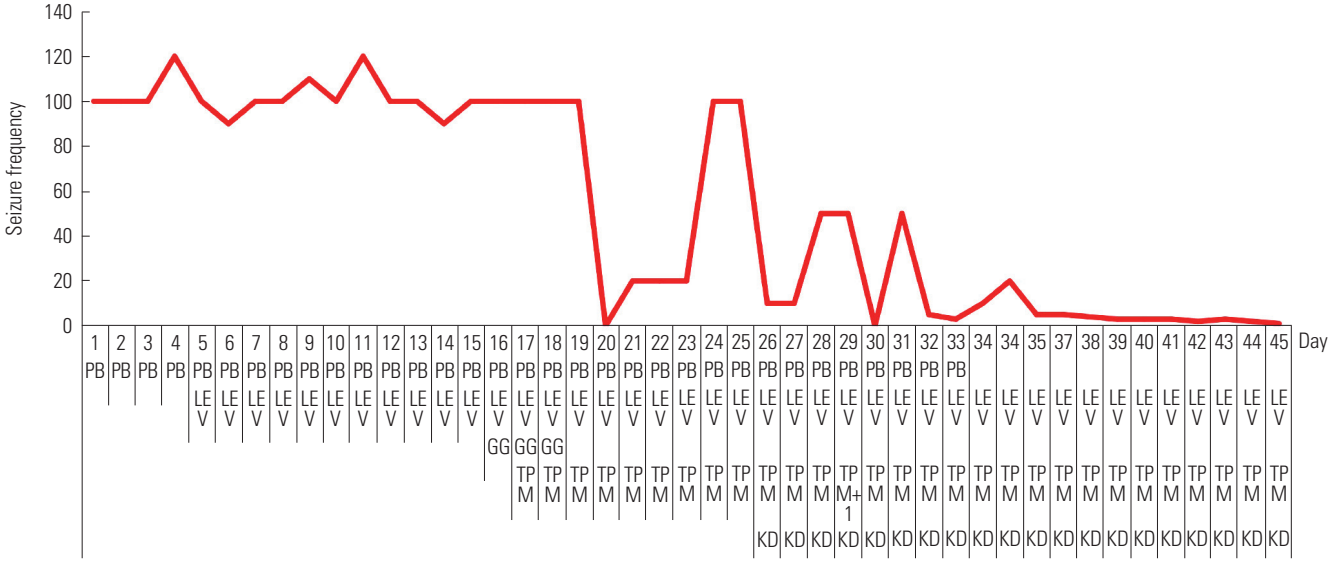

Fig. 3. Daily seizure frequency in the infant and treatments used. The treatment date was calculated from the first day of hospital admission. Initially, the patient was treated with PB; LEV was added on day 5; and TPM was added on day 17. The anti-epileptic drugs were continued in combination with KD from day 26. On days 16–18, GG was added to control infection. On day 29, the TPM dose was increased due to frequent seizures. PB, phenobarbital sodium; LEV, levetiracetam; TPM, topiramate; KD, ketogenic diet.; GG, γ-globulin.

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N9A, and *GABRG2* genes,[1,4,5] being less effective in patients with *CDKL5* mutations.[6] As suggested by Dressler, et al.,[7] children below 2 years of age may be ideal targets for the initiation of a KD. In our case report, the infant was below 2 months of age when a KD was initiated with a lower ratio, and the diet was shown to be safe and effective, consistent with previous reports.[7,8] Few previous studies have reported the case of such a young patient receiving KD therapy, which we suspect could be an adjunctive treatment for infants with *SCN2A* mutations.

In conclusion, the present study identified a *SCN2A* mutation in an infant with EOEE. The results demonstrated the beneficial effects of a KD on seizures in patients with *SCN2A* mutations. Importantly, a KD was effective at a young age of less than 2 months. Further larger scale studies thereof are worth exploring.

AUTHOR CONTRIBUTIONS

Conceptualization: Xiuxia Wang. Data curation: Jinhong Zhang. Formal analysis: Xiaoyu Tian. Investigation: Xiaoyu Tian. Methodology: Yange Zhang. Project administration: Xiuxia Wang. Resources: Xiaoyu Tian and Yange Zhang. Software: Xinyi Men. Supervision: Yan Lu. Validation: Xiuxia Wang. Visualization: Jinhong Zhang. Writing—original draft: Xiaoyu Tian and Yange Zhang. Writing—review & editing: Yan Lu and Xinyi Men. Approval of final manuscript: all authors.

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