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.

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. 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
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.Asn1475Lys) 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

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.
Ketogenic Diet for Infants with SCN2A Mutation

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 \( \alpha \)-subunit and one or more \( \beta \)-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.

KD's 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, SCN...
N9A, and GABRG2 genes,\textsuperscript{1,4,5} being less effective in patients with CDKL5 mutations.\textsuperscript{6} As suggested by Dressler, et al.,\textsuperscript{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.\textsuperscript{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.

**ORCID iDs**

Xiaoyu Tian https://orcid.org/0000-0003-1266-0121

Yange Zhang https://orcid.org/0000-0001-5779-6263

Jinhong Zhang https://orcid.org/0000-0002-1677-1024

Yan Lu https://orcid.org/0000-0003-3952-2343

Xinyi Men https://orcid.org/0000-0002-4404-6313

Xiuxia Wang https://orcid.org/0000-0003-2756-9144

**REFERENCES**

1. Su DJ, Lu JF, Lin LJ, Liang JS, Hung KL. SCN2A mutation in an infant presenting with migrating focal seizures and infantile spasm responsive to a ketogenic diet. Brain Dev 2018;40:724-7.
2. Yu FH, Catterall WA. Overview of the voltage-gated sodium channel family. Genome Biol 2003;4:207.
3. Turkdogan D, Thomas G, Demirel B. Ketogenic diet as a successful early treatment modality for SCN2A mutation. Brain Dev 2019;41:389-91.
4. van der Louw E, van den Hurk D, Neal E, Leendecker B, Fitzsimmon G, Dority L, et al. Ketogenic diet guidelines for infants with refractory epilepsy. Eur J Paediatr Neurol 2016;20:798-809.
5. Sanders SJ, Murtha MT, Gupta AR, Murdoch JD, Raubeson MJ, Willsey AJ, et al. De novo mutations revealed by whole-exome sequencing are strongly associated with autism. Nature 2012;485:237-41.
6. Ko A, Jung DE, Kim SH, Kang HC, Lee JS, Lee ST, et al. The efficacy of ketogenic diet for specific genetic mutation in developmental and epileptic encephalopathy. Front Neurol 2018;9:530.
7. Dressler A, Trimmel-Schwahofer P, Reithofer E, Gröppel G, Mühlebner A, Samuel S, et al. The ketogenic diet in infants--advantages of early use. Epilepsy Res 2015;116:53-8.
8. Wong VC, Fung CW, Kwong AK. SCN2A mutation in a Chinese boy with infantile spasm - response to Modified Atkins Diet. Brain Dev 2015;37:729-32.