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De Novo KCNQ2 Mutation in One Case of Epilepsy of Infancy With Migrating Focal Seizures That Evolved to Infantile Spasms

Haolin Duan, MD[1], Jing Peng, PhD[1], Miriam Kessi, MD[1], and Fei Yin, PhD[1]

Abstract

Epilepsy of infancy with migrating focal seizures (EIMFS) is a rare type of early-onset epileptic encephalopathy that is characterized by refractory migratory multifocal seizures that migrate between hemispheres. Its etiology is not well known although it is postulated to occur due to channelopathy. The authors report the first case of EIMFS due to a de novo heterozygous mutation in exon 4(c.881C>T missense mutation, p.Ala294Val, NM_172107.2) in *KCNQ2* gene which later evolved into infantile spasms. However, it is the second case of EIMFS with *KCNQ2* mutation. He presented with multifocal migratory partial seizures which started at the age of 8 days. Electroencephalogram examination revealed multifocal interictal spikes that migrated from one hemisphere to the other within a seizure. It was intractable with antiepileptic drugs and adrenocorticotropic hormone. He later developed spasms from the age of 8 months. Consequently, our case supports the new association between EIMFS and *KCNQ2* mutations. Moreover, it enriches the disease phenotype because of transformation.

Keywords

KCNQ2 gene mutation, epilepsy of infancy with migrating focal seizures, infantile spasms.

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KCNQ2 gene (OMIM 602235) encodes for subunits of potassium channels. It associates with both benign neonatal familial seizures (BNFSs) and early-onset epileptic encephalopathy (EOEE)[1] Spagnoli et al reported the first case of epilepsy of infancy with migrating focal seizures (EIMFS-like) which had *KCNQ2* mutation.[2] Therefore, ours is the second case. Here, the authors report a patient with a de novo *KCNQ2* mutation who presented with EIMFS in early infancy, but later he had a presentation consistent with infantile spasms (ISs). This supports the relationship between *KCNQ2* mutations and EIMFS.

Case Report

The patient was a twin baby boy who was born at term through a cesarean section at gestation age of 37 weeks and weighed 2.74 kg. His family history of epilepsy or hereditary diseases is unremarkable. He has a twin sister who is fine. He had uncontrollable seizures that began at the age of 8 days, but he was seen in our hospital at the age of 32 days. Seizures were tonic in nature, migrated from one side of the body to another side involving both the upper limbs and lower limbs. Additionally, seizures were accompanied by on and off apneic attacks, rolling of the eyes and head to one side. Multiple attacks were encountered per day, and each episode took about 20 seconds to 1 minute. Physical examination revealed him to have a weight of 2.82 kg (< 3rd percentile), and head circumference was 36 cm (50-85th percentile). Neurological evaluation revealed him to have developmental delay and poor eye focus. First video electroencephalogram (EEG) which was done at the age of 32 days (Supplemental Figure S2A, S2B and S2C) showed burst-suppression pattern during sleep, hypsarrythmia, and it captured 2 myoclonic seizures. The second video EEG which was done at the age of 40 days (Figure 1) showed multifocal interictal spikes and partial seizures arising from the right and left parietal lobes independently, at times

[1] Department of Pediatrics, Xiang Ya Hospital, Central South University, Changsha, Hunan Province, China

Corresponding Author:
Fei Yin, PhD, Department of Pediatrics, Xiang Ya Hospital, Central South University, 87 Xiang Ya Road, Changsha, Hunan Province 410008, China.
Email: yf2323@hotmail.com

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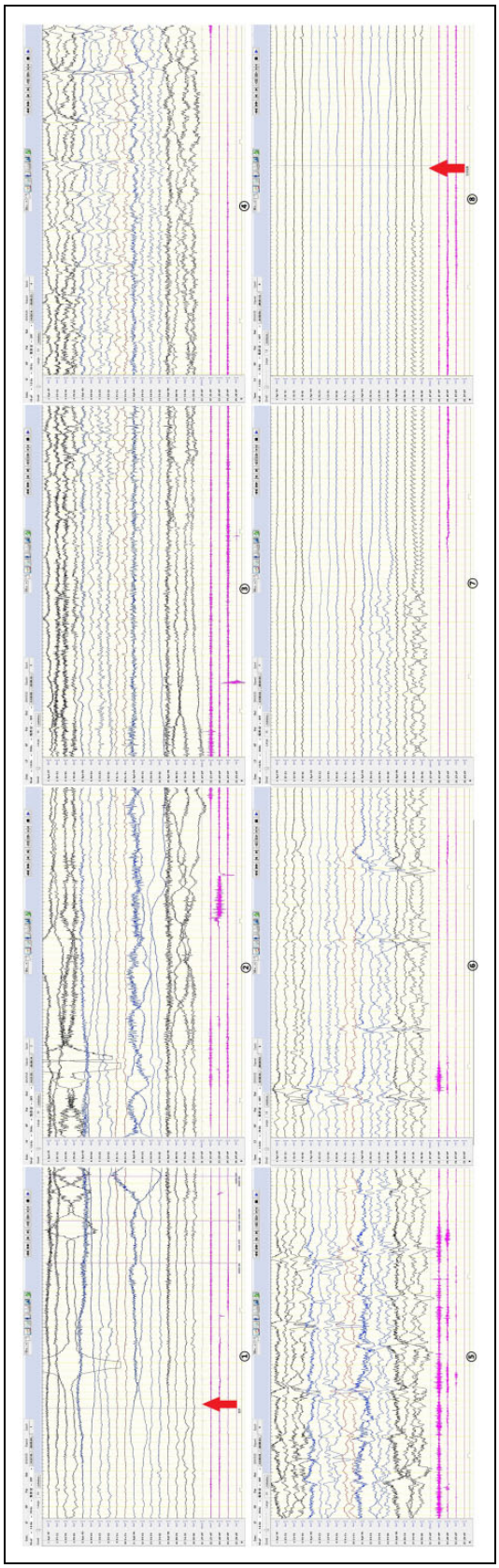

Figure 1. Electroencephalogram which was done at the age of 40 days showing seizures originating from the left parietal region (left arrow in Figure 1). After 30 seconds, ictal discharges shift to the right rear-temporal region, and then after 60 seconds, the seizures terminated (right arrow in Figure 1). It signifies migratory epileptic activity which is typical for epilepsy of infancy with migrating focal seizures (EIMFS).

with migration from one hemisphere to the other within a seizure.

Magnetic resonance imaging of the brain was normal. Laboratory investigations for inborn errors of metabolism were performed which yielded no significant results.

Treatment was attempted with multiple antiepileptic drugs without any significant improvement. Administered drugs included midazolam, phenobarbital, levetiracetam, sodium valproate, topiramate, and adrenocorticotropic hormone.

Comprehensive epilepsy DNA sequencing panel was performed which identified a de novo heterozygous mutation in exon 4 (c.881C>T missense mutation, p.Ala294Val, NM_172107.2) in *KCNQ2* gene. The mutation which was confirmed by direct Sanger sequencing was not found in either parent (Supplemental Figure S4).

He developed clusters of flexion spasms involving the trunk and the extremities from the age of 8 months. They were noticed more prior sleeping and waking up. The last evaluation was done at the age of 15 months, and he was found to have uncontrollable seizures and severe developmental delay, as he could hardly control his head and he had no speech. He had microcephaly head circumference below the third percentile (44.5 cm) and normal body weight. EEG revealed a series of seizures and multifocal epileptiform activities (Supplemental Figure S3A and S3B).

Discussion

Epilepsy of infancy with migrating focal seizures is a rare type of EOEE that occurs in infants aged below 6 months. Its etiology is poorly understood but postulated to occur due to genetic causes. Recently, de novo *KCNT1* gene mutations were described as pathogenic variation in about 50% of all cases with EIMFS.[1] Moreover, few gene mutations have been reported to associate with this condition including *TBC1D24* mutation[3] and *SCN1A* missense mutation.[1] The fact that some patients with EIMFS failed to reveal genetic abnormalities in those genes point out the probability of having other undiscovered pathogenic genes.

The clinical presentation of our patient together with EEG findings met the criteria for the diagnosis of EIMFS according to Coppola et al.[4] Our patient presented with early-onset seizures at the age of 8 days which was recurrent migrating multifocal seizures involving eyes and limbs, and it was associated with psychomotor developmental delay and poor response to multiple drugs that concurs with other reported cases. Ictal phase in EEG was characterized by migratory sharp and spike waves that were shifting from left hemisphere to the right hemisphere, which concurs with diagnostic criteria for EIMFS. One case of *KCNQ2* mutation with EEG findings similar to EIMFS was reported by Spagnoli et al.[2] At the age of 1 month, EEG was characterized by hypsarrythmia and burst suppression pattern without spasms. He developed spasms later from the age of 8 months, and diagnosis of infantile spasms (ISs) was made.

Table 1. Main Clinical Features of the Patients with *KCNQ2*-Related Encephalopathy Due to c.881C>T p.A294 V *KCNQ2* Gene Mutation.[a]

Patient no	Character of the Seizure	Inheritance	EEG Appearance	Diagnosis	Seizure Progress	Outcome	Reference
1	T	De novo	Multifocal discharges, discontinuous, asynchronous	KCNQ2-Encephalopathy	Seizure free at 5 months	DD	8
2	C	De novo	Suppression burst	OS	Seizures free at 3 months	DD	5
3	T	De novo	Suppression burst	OS	2-9 years: seizure-free. > 9 years: monthly GTC seizures.	DD	5
4	M	De novo	Suppression-burst	OS	Seizure free at 3 months	DD	5
5	T	De novo	Suppression burst, hypsarrhythmia at 3 months	OS	Seizure free at 6 months	DD	7
6	T	De novo	Suppression-burst	OS	Intractable seizure	DD	7
7	T	Inherited	Suppression-burst	OS	Seizure free at 2 months	DD	6
8	T	De novo	Suppression-burst	OS	Unknown, death at 6 weeks	DD	6
9	T	Inherited	Slow background activity, and bilateral discharges	EOEE	Seizure free at 3 months	DD	6
10	T	De novo	Suppression-burst	OS	Seizure free at 3 months	DD	6
11	T (F or G)	De novo	Suppression-burst, hypsarrythmia and migration	EIMFS	Intractable seizure	DD	This case

Abbreviations: C, clonic; DD, developmental delay; EOEE, early-onset epileptic encephalopathy; EIMFS, epilepsy of infancy with migrating focal seizures; F, focal seizure; G, generalized seizure; GTC, generalized tonic clonic; M, myoclonic; OS, ohtahara syndrome.
[a]Table summarizing the main clinical features of the previous patients reported to have KCNQ2-related encephalopathy due to c.881C>T p.A294 V *KCNQ2* gene mutation in comparison with our patient.

Lee et al[5] described 1 case of EIMFS which evolved to IS similar to our case, and he considered that EIMFS can be a continuum of infantile epileptic encephalopathy.

The patient was found to have a de novo heterozygous mutation (c.881C>T, p.Ala294 Val) in *KCNQ2* gene by next-generation sequencing epilepsy panels. *KCNQ2* gene is responsible for encoding a voltage-gated potassium channel. And the *KCNQ2*-related epilepsy spectrum range from *KCNQ2*-related benign neonatal familial seizures (*KCNQ2*-BFNS) with mild outcome to *KCNQ2*-related EOEE (*KCNQ2*-EOEE) with severe outcome.[6]

KCNQ2 gene mutation is acknowledged to cause different kinds of seizures including BNFS which occurs commonly due to p.Ala294Gly mutation and EOEE which occurs commonly due to p.Ala294Val mutation.[7] The authors found 10 cases of EOEE who were reported to carry the same mutation c.881C>T (p.Ala294Val) as shown in Table 1.[6-9] Interestingly, our patient's initial epileptic features were similar to *KCNQ2*-EOEE patients. He shared some common features with this syndrome, such as onset in infancy (below 1 month), tonic seizures, severe developmental delay, and burst suppression pattern in EEG. Nevertheless, he developed features of IS later. However, it is not the first case that had transition due to *KCNQ2* gene mutation. Samanta et al[10] reported a case of myoclonic epilepsy that evolved into IS, and Milh et al[6] and Kato et al[8] reported cases of OS which evolved to IS.

In conclusion, our case report supports the relationship between *KCNQ2* mutation and EIMFS. Moreover, it enriches the disease phenotype because of transformation.

Author's Note

The authors confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Author Contribution

Duan contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval. J. Peng contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; and gave final approval. M. Kessi contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript, and gave final approval. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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Ethical Approval

This case report was reviewed and approved by the Ethic Committee of the Xiangya Hospital of Central South University.

Supplemental Material

Supplementary material for this article is available online.

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