

# Dramatic response to lamotrigine in two patients with refractory epilepsy due to calcium channel mutations

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Early-infantile epileptic encephalopathy-69 (EIEE-69) is caused by *CACNA1E* gene variants. It is characterized by early-onset refractory seizures, hypotonia, developmental disorders, macrocephaly and congenital joint contracture [1]. Helbig *et al.* [1] reported that 80% of the patients had poor response to a variety of anti-seizure medication. Epilepsy with myoclonic-atonic seizure (EMAS) can be caused by variants of *SCN1A*, *SLC6A1* and *SYNGAP1* genes [2], and most patients present with developmental regression and various types of seizures. Here, we report two cases with *CACNA1E* and *CACNA1H* gene variants.

Patient 1 was born full-term to unrelated healthy parents. At the age of one month, he underwent correction for foot varus deformity. He suffered from recurrent clusters of spasms (more than 10 times per day) at four months of age. ACTH was discontinued because of severe infection. He was then treated with valproic acid (35 mg/kg) and topiramate (4 mg/kg) with slight remission (the patient experienced hypohidrosis at a topiramate dosage of 4.7 mg/kg). Later, he developed focal motor seizures and tonic seizures, once per few days to several times a day. Levetiracetam (40 mg/kg) was subsequently added but produced no effect. He was referred to our hospital at the age of one year and five months. Physical examination on admission revealed head circumference of 49 cm and bilateral hypotonia of the lower limbs. He was incapable of speaking a word, raising his head,

and sitting alone. Genetic analysis revealed a *de novo* variant (NM\_000721.3, c.2104G>A, p. Ala702Thr) in the *CACNA1E* gene, which was previously reported as pathogenic [1]. Levetiracetam was discontinued and lamotrigine (2 mg/kg) was gradually administered, resulting in dramatic seizure-free status, nearly four months later. In addition, he could also sit by himself and say "mama" and "dada" (for further information, refer to *supplementary figures 1, 2*).

Patient 2 was born healthy. He developed febrile seizures on three occasions with no obvious abnormality on EEG. After the third febrile convulsion, he gradually developed walking instability and language delay. At the age of two years and four months, he was admitted to our clinic with numerous daily episodes of head nodding. Coinciding with the onset of the episodes, which occurred several times a day, he had a loss of consciousness and dropped objects from his hand. Physical examination was unremarkable. Several myoclonic-atonic seizures were detected on EEG (*figure 1*). A variant (NM\_021098, c. 3633G > A, p. Arg1215His) in *CACNA1H* was identified. The mutation was confirmed to be *de novo* and has not been previously described according to aggregation databases of the general population (gnomAD and ExAC). He was diagnosed with epilepsy with myoclonic-atonic seizures. The administration of valproate (40 mg/kg) slightly reduced the frequency of the seizures. After the addition of clonazepam (0.02 mg/kg), he presented with an unsteady gait,

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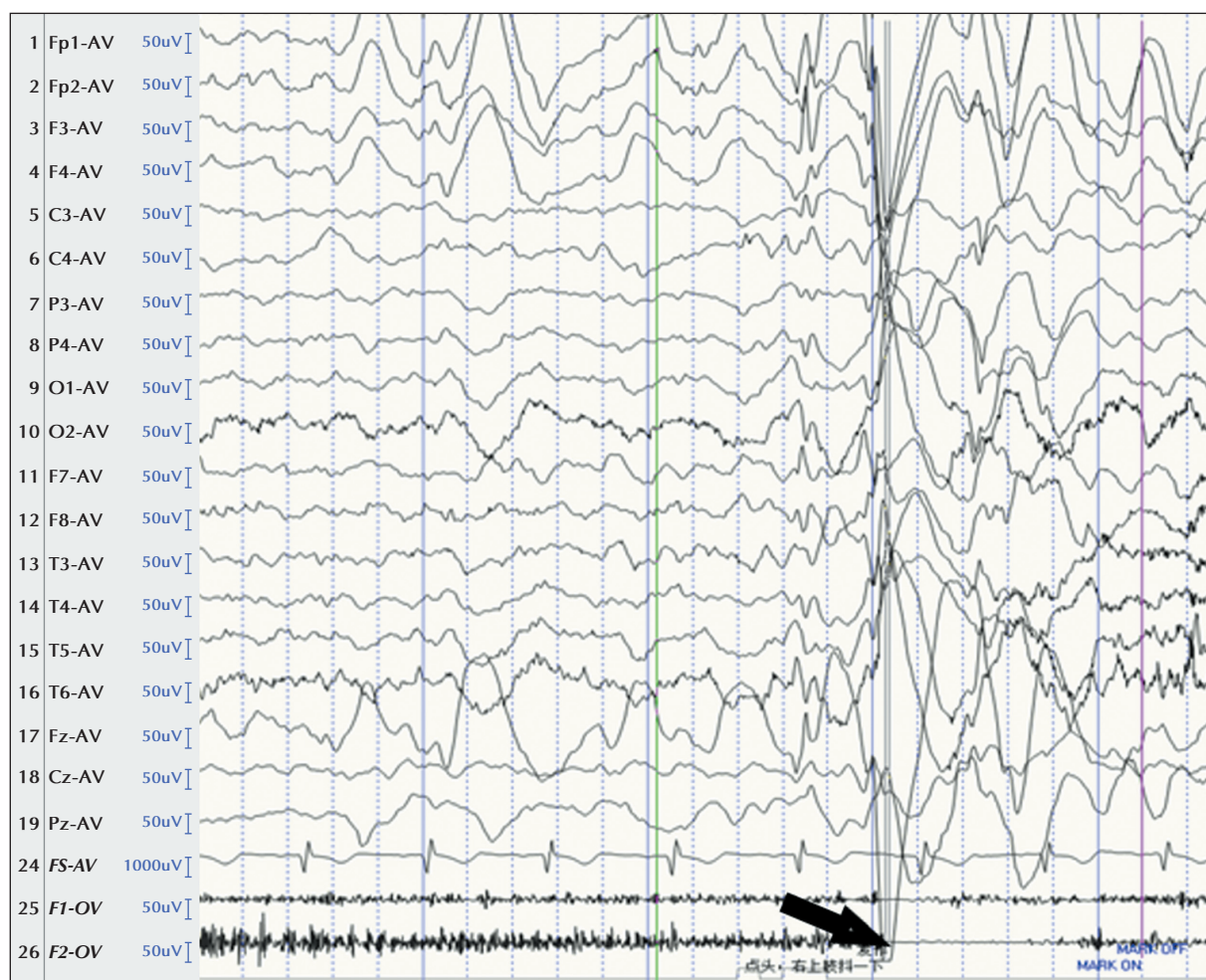
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therefore this was withdrawn. The addition of topiramate (3.1 mg/kg) led to partial seizure freedom, but this was discontinued due to hypohidrosis and hyperthermia. Levetiracetam (50 mg/kg) was added with a poor response. Finally, he was seizure-free with the addition of lamotrigine (3 mg/kg). He also demonstrated global developmental improvement. At present, the patient has been seizure-free for a year and a half (for further information, refer to *supplementary figures 3-5*).

The *CACNA1E* gene encodes for a subunit of the R-type calcium channel. Helbig *et al.* [1] reported 30 individuals with *CACNA1E* gene variants, of whom six shared the same variant as that reported here (p. Ala702Thr). The variant was confirmed as gain of function through functional analysis. Topiramate, which can reduce R-type calcium currents, was used in five of the 30 patients, and seizure freedom was

obtained in some of the patients. However, in contrast, in our patient, convulsions were still frequent with the use of topiramate; seizure freedom was achieved after the addition of lamotrigine, which can also block R-type calcium channel currents.

The *CACNA1H* gene encodes for a subunit of the T-type calcium channel. Although variants have not been reported in EMAS patients, epileptic phenotypes associated with *CACNA1H* gene variants include myoclonic, atonic and absence seizures. Several functional analyses of *CACNA1H* gene variants have confirmed that they can cause gain of function [3, 4]. A previous study has shown that lamotrigine is effective as treatment for absence epilepsy in children with *CACNA1H* gene variants [5]. Lamotrigine can block the T-type calcium channel, and its effect is stronger than that of valproic acid [6].



**Figure 1.** EEG showing extensive high-amplitude spike-and-slow-wave bursts when the child nods (indicated by the arrow), while at the same time, the EMG shows that the deltoids are resting.

Lamotrigine can also block P/Q-type calcium channels, which are composed of subunits encoded by *CACNA1A* [6]. Byers *et al.* [7] reported a case of epileptic encephalopathy caused by a *CACNA1A* variant, in which lamotrigine resulted in a dramatic reduction in seizure frequency.

In conclusion, epilepsy caused by mutations in the genes encoding subunits of calcium channels is often intractable. Lamotrigine can block a variety of calcium channel variants with gain of function. Therefore, lamotrigine may be considered as first-line therapy for children with refractory epilepsy associated with calcium channel mutations. ■

#### Supplementary material.

Supplementary data and summary slides accompanying the manuscript are available at [www.epilepticdisorders.com](http://www.epilepticdisorders.com).

#### Acknowledgements and disclosures.

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None of the authors have any conflicts of interest to declare.

#### Ethics approval and consent to participate.

The use of sample from the patients was approved by the Institutional Ethics Committee of Wuxi Children's Hospital (No. WXCH2019-07-001). Informed consent was obtained from patients prior to analysis.

#### Consent for publication.

Consent to publish was obtained from the guardians of the patients.

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### TEST YOURSELF

(1) Which type of voltage-gated calcium channels can lamotrigine block?

(2) Which types of voltage-gated calcium channels are encoded by the gene *CACNA1A*, *CACNA1E* and *CACNA1H*, respectively?

- A. T-type, R-type, P/Q-type
- B. N-type, L-type, R-type
- C. R-type, T-type, L-type
- D. P/Q-type, R-type, T-type

*Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, [www.epilepticdisorders.com](http://www.epilepticdisorders.com).*