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Clinical Observations

Dramatic Response After Lamotrigine in a Patient With Epileptic Encephalopathy and a *De Novo CACNA1A* Variant

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ABSTRACT

BACKGROUND: Channelopathies are a group of monogenic disorders that affect a single ion channel and can result in neurological disease. While a rare cause of epilepsy, channelopathies offer unique insight to the molecular basis of epilepsy and treatment opportunities. Calcium homeostasis is tightly regulated by a series of interacting subunits. *CACNA1A* encodes the principal pore-forming subunit of the voltage-gated P/Q-type calcium channel, alpha1. Patients with epileptic encephalopathy due to pathogenic variants in *CACNA1A* have been previously described and are challenging to treat. **PATIENT DESCRIPTION:** We describe a child with epileptic encephalopathy, ataxia, cognitive impairment, and significant social-behavioral abnormalities due to a *de novo* pathogenic variant, p.S1373L in the *CACNA1A* gene. After failing zonisamide and divalproex sodium, she had a dramatic response to lamotrigine with a precipitous decrease in seizure frequency and severity. This improvement has persisted over one year. **CONCLUSION:** While classically thought to act at sodium channels, lamotrigine also modulates the activity of the P/Q-type calcium channel, making it a candidate for precision therapy for patients with epileptic encephalopathy due to *CACNA1A* pathogenic variants. The rarity and clinical heterogeneity of epilepsy due to variants in *CACNA1A* presents challenges to clinical diagnosis. However, genetic analysis for patients with epilepsy continues to expand; additional patients are likely to be identified molecularly. Lamotrigine should be considered as a first-line treatment in patients with epileptic encephalopathy due to pathogenic variants in *CACNA1A*.

Keywords: *CACNA1A*, epilepsy, epileptic encephalopathy, channelopathy, calcium, genetic, lamotrigine

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Background

The adoption of comprehensive genetic testing in children with epilepsy has led to an increased understanding of the underlying genetic causes of epilepsy and the identification of precision therapies. Genetic ion channelopathies are an important field of neurological disease. This group of disorders is due to the alteration of a specific ion channel and can lead to transient abnormalities in neural circuit excitability and episodic neurological dysfunction. While a rare cause of epilepsy, channelopathies offer unique insight to the molecular basis of epilepsy and therapeutic treatment.

CACNA1A, located at chromosome 19p13, encodes the principle pore-forming subunit of the P/Q-type calcium channel, alpha1 (also known as Cav2.1). The P/Q-type calcium channel plays a fundamental role in coupling calcium influx to vesicular exocytosis, mediating depolarization-induced calcium influx into dendrites, cell bodies, and nerve terminals. As such, it plays a role in several neurological processes, including fast neurotransmission, postsynaptic cell signaling,

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and neuronal plasticity.[1,2] Calcium homeostasis is tightly regulated, and calcium channels interact with a host of accessory subunits. As such, even a minor alteration of voltage-gating or receptor expression can lead to clinically significant neurological abnormalities.[2-4]

Pathogenic variants in *CACNA1A* have previously been described in three allelic disorders, each with a different molecular effect. Loss-of-function variants have been described in episodic ataxia type 2 (OMIM: 108500), gain-of-function variants in familial hemiplegic migraine type 1 (OMIM: 141500), and polyglutamine repeat expansion in spinocerebellar ataxia type 6 (OMIM: 183086). There is significant inter- and intrafamily variability and phenotypic overlap between the three conditions.[5-7] A minority of patients with pathogenic variants in *CACNA1A* have epilepsy with multiple seizure types.[1,7-9] Tantsis et al.[10] described various eye movement disorders, including paroxysmal tonic upward gaze, abnormal saccades and nystagmus as some of the earliest signs in individuals with a *CACNA1A* pathogenic variant. Patients with additional features have been described, including a cohort of patients with epileptic encephalopathy, cognitive impairment, and cerebellar dysfunction and a patient with congenital hypotonia and developmental delay, further expanding the phenotypic spectrum.[5,11]

Here we describe a six-year-old girl with a *de novo* mutation in *CACNA1A*. She had epileptic encephalopathy, global developmental delay, abnormal eye movements, lethargy, and poor social behavior. After progressive worsening of her epileptic encephalopathy, she had a dramatic and persistent clinical response when lamotrigine was added as adjunctive therapy to divalproex sodium. Lamotrigine acts on the P/Q-type calcium channel[4] and should be considered in all patients with epileptic encephalopathy due to mutations in *CACNA1A* gene.

Patient Description

This child was the product of a 36-week twin gestation conceived via *in vitro* fertilization using an ova donor, paternal sperm, and two implanted embryos. The postnatal period was complicated by feeding difficulties, a weak cry, and truncal hypotonia. At birth, she had persistent, unexplained elevation of the right diaphragm and left tongue deviation, which resolved at a year of life. Gaze abnormalities were observed from birth. At eight months of age, she was diagnosed with visual inattention, intermittent esotropia, and an upward gaze preference. Nystagmus has never been appreciated by parents or on numerous clinical examinations by multiple pediatric neurologists, ophthalmologists, or other physicians involved in her care.

The patient's twin brother is developmentally normal, and thus global developmental delays were rapidly apparent postnatally. From an early age, the patient's movements were described as slow and deliberate. She had gross motor delay and walked at age three years. Loss of deep tendon reflexes at 16 months prompted a neuromuscular evaluation including electromyography, nerve conduction velocity studies, and muscle biopsy, which was unrevealing. The patient also had speech delay and speech apraxia, and she spoke her first words at age four years. A Wechsler Preschool and Primary Scale of Intelligence performed at age five years showed a general intelligence quotient of 42. The patient was able to point and interacted well with her parents; behavior anomalies included inattention, hyperactivity, and aggression.

The patient experienced her first seizure at age three years and 11 months. This event was characterized by a two- to three-minute upward deviation of her eyes and unresponsiveness with no involuntary movements or loss of tone, followed by a four-hour postictal period. Electroencephalograph (EEG) showed diffuse 3 to 4 Hertz (Hz) delta slowing and frequent, multifocal 2- to 3.5-Hz epileptiform transients, most prominent in the bioccipital regions lasting up to 70 seconds with no associated clinical signs, supporting a diagnosis of epileptic encephalopathy. She had occasional entire body myoclonic jerks, approximately once per month and athetoid movement of her fingers. Zonisamide was initiated, and the patient experienced no further clinically overt seizures for over a year.

At age five years, the girl developed clinically apparent motor seizures, characterized by episodes of falling due to loss of tone consistent with atonic seizures. She became increasingly lethargic and was observed to have lost some of her communication skills. EEG at that time demonstrated 2 Hz to 3 Hz spike-and-wave activity with diffuse 4 Hz to 5 Hz background slowing. Divalproex sodium was added, and zonisamide was discontinued, resulting in an improvement in both seizure frequency and lethargy.

After eight months, her seizures worsened; she experienced up to 200 absence and atonic seizures per day with accompanying somnolence. At this point, the she was six years old. She had fewer than 20 words, a wide-based gait with frequent falls, reduced exercise tolerance, social behavior abnormalities, and was not yet toilet trained. Given her clinical worsening, a repeat EEG was performed which demonstrated continuous spike-and-wave activity consistent with spike-and-wave stupor (Figure). Lamotrigine was initiated to treat the epileptic encephalopathy and increased to 10 mg twice daily (0.9 mg/kg/day). Divalproex sodium, 250 mg twice daily (24 mg/kg/day), was continued.

Shortly thereafter, the patient experienced dramatic improvement in her overall status that has now persisted for more than 15 months. The frequency and severity of her seizure activity dropped precipitously. Over the following year, the patient had no motor breakthrough seizures and only rare absence seizures. There has been a remarkable improvement in her activity level, interaction, and alertness. Although she continues to have severe expressive speech delay, the family does not appreciate any deficits in her language comprehension. She continues to have an ataxic gait, moderately poor balance, and occasional falls. A 24-hour EEG performed ten months after the initiation of lamotrigine therapy indicated a diffusely slow background with no posterior dominant rhythm, frequent bioccipital generalized 2.5 Hz to 3.5 Hz spike-and-wave activity, frequent independent multifocal epileptiform transients, and occasional brief bursts of generalized paroxysmal fast activity during sleep. EEG captured two clinically appreciated atypical absence seizures. While still abnormal, this EEG showed a remarkable improvement from all prior studies due to a decreased burden of epileptic activity.

Extensive genetic and biochemical investigation was negative. The results of 3 Tesla brain magnetic resonance imaging studies were normal. Singleton whole-exome sequencing was performed on an Illumina HiSeq platform. Mean coverage was greater than 100×, and more than 70% of reads aligned to the target. Results were negative for pathogenic variants, including in all sodium-channel genes, genes known to cause epilepsy, and medically actionable genes. However, we suspected that a variant of uncertain significance, *CACNA1A* (NM_001127222) c.4118 C>T (p.S1373L), may be causative. This variant was predicted to be deleterious by in silico analysis and had a mean allele frequency of zero in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), Exome Variant Server (http://evs.gs.washington.edu/EVS/), and Exome Aggregation Consortium databases (http://exac.broadinstitute.org). Familial testing on the patient's twin brother, father, and ova donor confirmed this variant was *de novo* in our patient. Shortly after familial testing resulted, Damaj et al.[5] published a series of patients with pathogenic variants in *CACNA1A* that included subjects with epileptic encephalopathy, cognitive impairment, and cerebellar signs. Referencing this citation, our patient's exome report was amended and the *CACNA1A* c.4118 C>T (p.S1373L) variant reclassified as likely pathogenic. Our group submitted this variant to ClinVar.

Discussion

Patients with *CACNA1A* mutations and epileptic encephalopathy offer a unique opportunity for understanding