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Dramatic Response Following 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 neurologic 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.

METHODS—Case report of 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.

RESULTS—After failing zonisamide and divalproex sodium, the child 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

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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

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 neurologic 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 neurologic 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, alpha-1 (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 neurologic processes, including fast neurotransmission, post-synaptic cell signaling 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 neurologic 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 (EA2, OMIM: 108500), gain-of-function variants in familial hemiplegic migraine type 1 (FHM1, OMIM: 141500), and polyglutamine repeat expansion in spinocerebellar ataxia type 6 (SCA6, OMIM: 183086). There is significant inter- and intra-family 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 and colleagues described various eye movement disorders, including paroxysmal tonic upgaze, abnormal saccades and nystagmus as some of the earliest signs in individuals with a *CACNA1A* pathogenic variant.[10] 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]

Herein, we describe a six-year-old patient 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.

CASE REPORT

The patient 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, weak cry and truncal hypotonia. At birth, she was noted to have persistent, unexplained elevation of the right diaphragm and left tongue deviation, which resolved at a year of life. Gaze abnormalities were noted from birth. At eight months of life, the patient was diagnosed with visual inattention, intermittent esotropia and an upward gaze preference. Nystagmus has never been appreciated by parents or on numerous clinical exams 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 early on, the patient's movements were described as slow and deliberate. She had gross motor delay and walked at three years of age. 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 four years of age. A Wechsler Preschool and Primary Scale of Intelligence performed at age five years of age 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 a first seizure at three years, 11 months of age. This event was characterized by a two to three minute upward deviation of the eyes and unresponsiveness with no involuntary movements or loss of tone, followed by a four-hour post-ictal period. Electroencephalogram (EEG) showed diffuse 3-4 Hertz (Hz) delta slowing and frequent, multifocal 2 - 3.5 Hz epileptiform transients, most prominent in the bi-occipital regions lasting up to 70 seconds with no associated clinical signs, supporting a diagnosis of epileptic encephalopathy. She had occasional whole 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 five-years of age, the patient 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 noted to have lost some of her communication skills. EEG at that time demonstrated 2 - 3 Hz spike and wave activity with diffuse 4-5 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 patient 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 1). Lamotrigine was initiated in order to treat the epileptic encephalopathy and increased to 10 mg twice a day (0.9 mg/kg/day). Divalproex sodium, 250 mg twice a day (24 mg/kg/day) was continued.

Shortly thereafter, the patient experienced dramatic improvement in her overall status that has now persisted for over 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. While 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. Twenty-four hour EEG performed 10 months after initiation of lamotrigine therapy showed a diffusely slow background with no posterior dominant rhythm, frequent bi-occipital generalized 2.5-3.5 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. Three Tesla brain magnetic resonance imaging studies were normal. Singleton whole exome sequencing was performed on an Illumina HiSeq platform. Mean coverage was greater than 100X and over 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 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 Aggregate Consortium (ExAC) 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, Demaj and colleagues published a case series of patients with pathogenic variants in *CACNA1A* that included subjects with epileptic encephalopathy, cognitive impairment and cerebellar signs.[5] Referencing this citation, our patient's exome report was amended and the *CACNA1A* c. 4118 C>T (p.S1373L) variant re-classified as likely pathogenic. Our group submitted this variant to ClinVar.

DISCUSSION

Patients with *CACNA1A* mutations and epileptic encephalopathy offer a unique opportunity for understanding the molecular basis of epilepsy and designing precision therapies. Given the rarity of *CACNA1A* mutations causing epileptic encephalopathy and the impracticality of assembling a large enough cohort for a therapeutic trial, the response and experience of

the patient described herein has relevance for other patients with similar molecular pathology. Additional research is warranted.

The alpha-1 subunit is comprised of four highly homologous domains, each containing six linked transmembrane repeats referred to as S1–S6. A positively charged amino acid on S4 acts as the voltage sensor. S5-S6 lines the interior pore; a group of conserved glutamate residues in S5-S6 confers ion selectivity. The molecular change described in our patient results in the missense substitution of a small, polar amino acid by a neutral, hydrophobic amino acid with an aliphatic-branched side chain. It is located in the highly conserved, critical cytoplasmic linkage region between the voltage-gated sensing (S4) and pore-forming domains (S5).[1] Pathogenicity of the *CACNA1A* variant in our patient is supported by the absence in healthy family members, *in silico* analysis, high conservation and a mean allele frequency of zero. Based on literature review, the patient's phenotype is most consistent with a loss-of-function effect; we did not perform functional studies.[5,8] Several naturally occurring mouse models with homologous variants in *CACNA1A* are characterized by ataxia, absence seizures and paroxysmal dyskinesia, though a mouse model with a pathogenic variant in the cytoplasmic linkage domain from S4 to S5 does not exist.[9,12]

The mechanism of action of most anti-epileptic drugs (AEDs) is incompletely understood. It is thought that lamotrigine exerts many of its anti-epileptic effects via inhibiting voltage gated sodium channels.[13] Lamotrigine (and levetiracetam, to a lesser extent) modulate calcium conductance in cortical neurons via inhibition of N- and P/Q-type calcium channels.[4] This may explain why lamotrigine is considered a first or second line agent in generalized epilepsies while many agents that act at sodium channels are otherwise avoided [14] Positive responses to lamotrigine and valproic acid as well as levetiracetam and valproic acid have been reported in other patients with pathogenic variants in *CACNA1A,* though not as robust as the case described in this report.[5] This could be due to several factors including clinical synergistic effect of lamotrigine and divalproex sodium, a genotype-phenotype response, or lamotrigine dose.[15] Our patient was not trialed on lamotrigine monotherapy, though we would consider this a reasonable strategy if she had not already been on divalproex sodium.

Our patient had improved seizure control with zonisamide and valproic acid which have activity at T-type and L-type calcium channels.[16] Indeed, positive responses to valproic acid have been reported in other patients and may suggest calcium conductance modulation is a treatment strategy in patients with *CACNA1A* variants.[16] However, her encephalopathy was only successfully treated with the addition of lamotrigine, resulting in a dramatic clinical response and suggesting an early trial of lamotrigine in children with *CACNA1A* variants may be warranted.

The phenotypic heterogeneity and rarity of patients with epileptic encephalopathy due to variants in *CACNA1A* make it difficult to identify and treat these patients.[6] While our patient's *CACNA1A* variant was *de novo*, individuals with epilepsy and inherited pathogenic variants in *CACNA1A* have been described within families with phenotypic features more consistent with episodic ataxia.[5,17] This family history should be sought. Interestingly, family members with *CACNA1A* pathogenic variants and phenotypic features more

consistent with episodic ataxia have responded to treatment specific for this, such as acetazolamide, highlighting the importance of carefully considering the phenotype and genotype when devising the best treatment strategy. [5]

We recognize that there are weaknesses to drawing clinical conclusions from a single patient. However, it is unlikely that a large enough cohort of patients with pathogenic variants in *CACNA1A* could ever be assembled for a therapeutic clinical trial, making this report relevant. As clinical use of genetic analysis continues to expand, more patients are likely to be diagnosed molecularly. Children with epileptic encephalopathy and a pathogenic variant in *CACNA1A* should be trialed on lamotrigine with divalproex sodium added if clinical response is incomplete. A medical or biochemical genetics consult should be considered for all patients with an epileptic encephalopathy without a known etiology.

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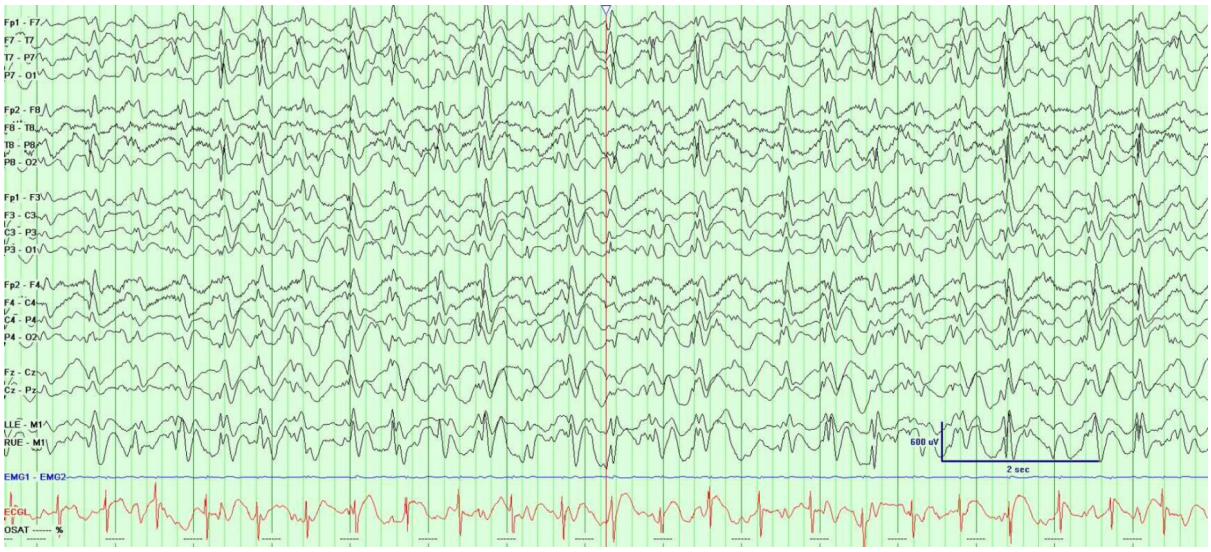

Figure 1.

Electroencephalogram recorded when the patient was six years of age. An anterior-posterior bipolar montage demonstrates continuous 2-2.5 Hertz spike-and-wave activity. Sensitivity of 30 μV/mm, low frequency filter of 1, high frequency filter of 70, time base of 15 mm/sec.