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Clinical Observations

Expanding the Phenotypic Spectrum of CACNA1H Mutations

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ABSTRACT

Background: The *CACNA1H* gene mutations encoding the α_{1H} subunit of Cav3.2 T-type calcium channels have been associated with generalized epilepsy. Focal or multifocal epilepsy and systemic (immunologic and gastrointestinal) involvement associated with these mutations have not been described previously. We detail the clinical characteristics of five patients with *CACNA1H* mutations and expand its phenotypic spectrum.

Methods: A case series of five patients with pathogenic *CACNA1H* mutations was evaluated. The pathogenicity of the mutations was predicted by polymorphism phenotyping (Polyphen-2) and sorting-intolerant-from-tolerant analysis.

Results: Mean age of seizure onset was 8.2 ± 3.7 years. Three patients had *de novo* mutations in the *CACNA1H* gene, and two patients inherited the mutation from an asymptomatic parent. The patients experienced different types of seizures including absence, focal seizures without awareness, focal seizures with secondary generalization, and myoclonic, atonic, and generalized tonic-clonic seizures. Electroencephalography showed focal, multifocal, or generalized discharges. One patient had autism and global developmental delay. Two patients had failure to thrive and selective antibody deficiency.

Conclusions: *CACNA1H* mutations can be associated with susceptibility to develop generalized epilepsy and focal or multifocal epilepsy of varying severity. Phenotypic features involving other organ systems (immune, gastrointestinal) can occur in addition to epilepsy, developmental delay, and autism.

Introduction

The *CACNA1H* gene encoding the α_{1H} subunit of the Cav3.2 T-type calcium channel plays an essential role in regulating neuronal excitability and network oscillations in the brain.[1] This mutation has been identified as an important susceptibility gene involved in the pathogenesis of childhood absence epilepsy, and subsequent studies have extended the spectrum of *CACNA1H* variants to be associated with other generalized epilepsies.[1,2] T-type calcium channels are present in a host of non-neuronal tissues, and symptomatic involvement of organs other than central nervous system has not been described previously. We describe the clinical characteristics of five patients with *CACNA1H* mutations and expand the phenotypic spectrum of disease associated with this mutation.

Methodology

Five patients with pathologic *CACNA1H* gene mutations were analyzed. The pathogenicity of the mutations was predicted by polymorphism phenotyping (Polyphen-2) and sorting-intolerant-from-tolerant analysis. Data regarding age, sex, seizure types, brain magnetic resonance imaging, antiepileptic drugs (AEDs), electroencephalographic (EEG) findings, and comorbidities were obtained through electronic medical records. The EEG findings represent ictal and interictal data from the entire EEG obtained from multiple EEG studies done over varying intervals of time in all

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patients. These data were evaluated to elucidate the phenotypic characteristics of patients with pathogenic *CACNA1H* mutation.

Patient descriptions

Patient 1

This child had seizure onset at age three years and experienced multiple seizure types (Table). The focal seizures were described as left arm tonic stiffening followed by secondary generalized tonic-clonic activity. Her EEGs showed the presence of focal, multifocal, and generalized discharges. Despite multiple AEDs, a ketogenic diet, and vagus nerve stimulator (VNS) implantation, she continued to have seizures.

Patient 2

Patient had seizure onset at age two years described as episodes of lip smacking and staring spells with behavioral arrest lasting 15 to 20 seconds. EEG showed focal epileptiform discharges in the left centroparietal region. She was diagnosed with selective antibody deficiency based on history of recurrent infections and poor antibody response to vaccines. Comorbidities included failure to thrive and gastroesophageal reflux.

Patient 3

Patient had seizure onset at age eight years. Her seizure type was described as brief staring spells with loss of awareness. EEG showed generalized 3-Hz spike and wave provoked by

TABLE.
Phenotypic Description of Patients With *CACNA1H* Mutations

Subject:	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Current age; gender	3 years; female	8 years; female	13 years; female	10 years; female	7 years; male
Onset of seizures	17 m	2 y	8 y	8 y	9 m
Semiology	1. Focal motor tonic onset (left arm) with secondary generalization 2. Myoclonic 3. GTC 4. Head drops 5. Staring spells	1. Staring spells 2. Lip smacking	1. Staring spells	1. Staring spells	1. Myoclonic 2. Staring spells 3. Atonic seizures 4. GTC
MRI brain	Generalized parenchymal volume loss	Normal	Normal	Normal	Normal
Treatment	PB, VPA, ETS, CLB, pyridoxine, ketogenic diet, s/p VNS	LTG, CLB	ETX, ZNS	OXC	LEV, TPM, CLB s/p VNS
Frequency (pretreatment)	Multiple times a day	Multiple times a day	Multiple times a day	Occasional	Multiple times a day
Frequency (post-treatment)	3 per day	1 per week	Seizure free	Rare	1 per month
EEG					
Focal discharges	X	X			
Multifocal discharges	X			X	
Generalized discharges	X		X		X
Cognitive behavior	Normal until seizure onset; then regression	Normal	Normal	Normal	GDD
Comorbidities				Aggression, ADHD	Autism
Recurrent infections/poor vaccine response		X			X
Immunodeficiency		Selective antibody deficiency			Selective antibody deficiency
GI system					
FTT		X			X
GERD		X			X
CACNA1H genotype	p.Ala2108Thr c.6322G>A *De novo*	p.Glu163His c.489G>C Mother heterozygous	p.Leu538Phe c.1612C>T *De novo*	p.Ala2108Thr c.6322G>A *De novo*	p.Pro856Leu c.2567c>t p. Ala1960Val c.5879C>T Father heterozygous

Abbreviations:
ADHD = Attention deficit hyperactivity disorder
CLB = Clobazam
EEG = Electroencephalogram
ETS = Ethosuximide
F = Female
FTT = Failure to thrive
GDD = Global developmental delay
GERD = Gastroesophageal reflux disease
GI = Gastrointestinal
GTC = Generalized tonic-clonic
LTG = Lamotrigine
M = Male
MRI = Magnetic resonance imaging
OXC = Oxcarbazepine
PB = Phenobarbital
s/p = status post
TPM = Topiramate
VNS = Vagus nerve stimulator
VPA = Valproic acid
ZNS = Zonisamide

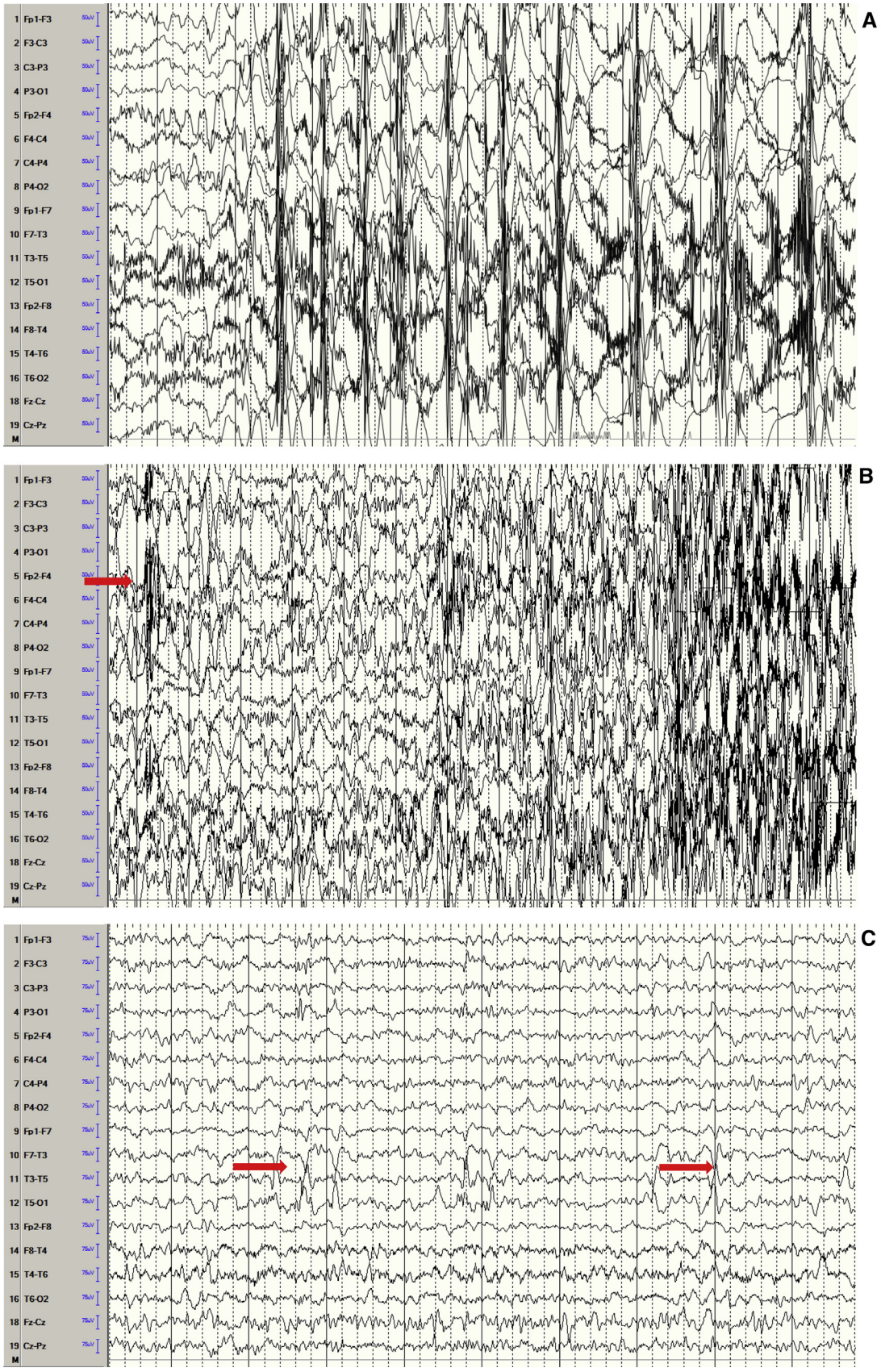

FIGURE 1. (A) Ictal EEG showing generalized tonic-clonic seizure with generalized spike and wave discharges. (B) Ictal EEG showing focal left arm tonic extension with secondary generalization associated with right frontocentral spike/polyspike discharges followed two seconds later by propagation to generalized spike and wave discharges. (C) Interictal EEG showing focal left temporal spike discharges.

hyperventilation. Her seizures are well controlled on ethosuximide and zonisamide.

Patient 4

This child had a history of staring spells with loss of awareness noted in school at age three years and was found to have frequent multifocal discharges on her EEG. Her seizures and behavior have improved with oxcarbazepine.

Patient 5

This patient had seizure onset at age nine months and experienced multiple seizure types (Table). His EEGs showed generalized epileptiform discharges. He was diagnosed with selective antibody deficiency due to history of recurrent infections and poor antibody response to vaccines. Other comorbidities included failure to thrive and gastroesophageal reflux.

Results

Table details the phenotypic description of patients with *CACNA1H* mutations in this case series.

Five patients were included (four female, one male). The mean age at the time of the study was 8 ± 3.7 years. The mean age at seizure onset was four years. Ictal and interictal EEG showed focal discharges in Patient 1 (Fig 1B,C) and Patient 2 (Fig 2) and interictal EEG showed multifocal discharges in Fig 3. Ictal and interictal EEG showed generalized discharges in Patient 1 (Fig 1A), Patient 3 (Fig 4) and Patient 5 (Fig 5). Patient 5 had autism and global developmental delay. Patients 2 and 5 were diagnosed with selective antibody deficiency and responded well to immunoglobulin therapy. Both patients also had similar comorbidities related to failure to thrive and gastroesophageal reflux. Genetic analysis showed *de novo CACNA1H* mutations in three of the patients and heterozygous mutations inherited from a parent in two patients.

Discussion

We describe the phenotypic characteristics of five patients with pathogenic *CACNA1H* mutations found to have focal and multifocal epilepsy in addition to generalized epilepsy. This finding is consistent with similar studies that showed that *CACNA1H* gene mutations are associated with a range of generalized epilepsy phenotypes.[2-4] T-type calcium channels underlie the generation of neuronal burst-firing and generation of network synchrony within the thalamocortical relay.[5] Mutations in the *CACNA1H* gene alters the firing and gene expression in these thalamocortical networks to increase seizure susceptibility in these patients.[4]

An association of *CACNA1H* gene mutation with focal or multifocal epilepsy has not been previously reported. It has been demonstrated that the burst-firing generated by the T-type calcium channels varies in the voltage dependences and duration, as well as in the rates of depolarization and repolarization.[6] If these multiple neuronal burst-firings occur out of phase with each other, this differential burst-firing in distinct local areas can generate higher frequency output for a specific regional population of neurons.[7] Based on these observations, we hypothesize that although ubiquitous in brain tissue, differential expression of the mutated T-type calcium channels encoded by the *CACNA1H* gene can lead to localized and/or asynchronous burst-firing, leading to focal or multifocal epileptiform discharges.

The burden of epileptic seizures in our series ranged from mild in three patients to severe intractable epilepsy in two patients. Three patients had satisfactory response to AEDs. Patient 1 required both VNS and a ketogenic diet, whereas Patient 5 required VNS

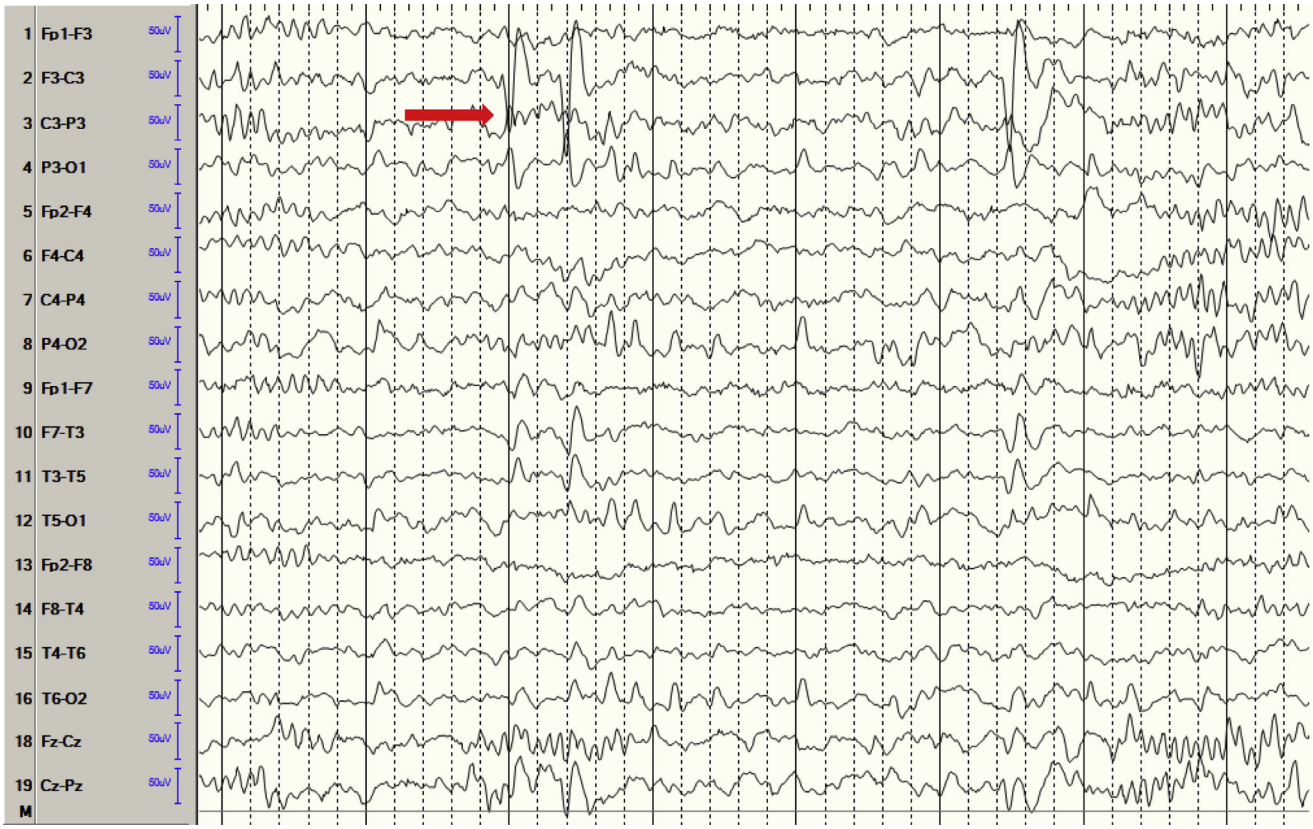

FIGURE 2. Interictal EEG showing focal left centoparietal spike discharges.

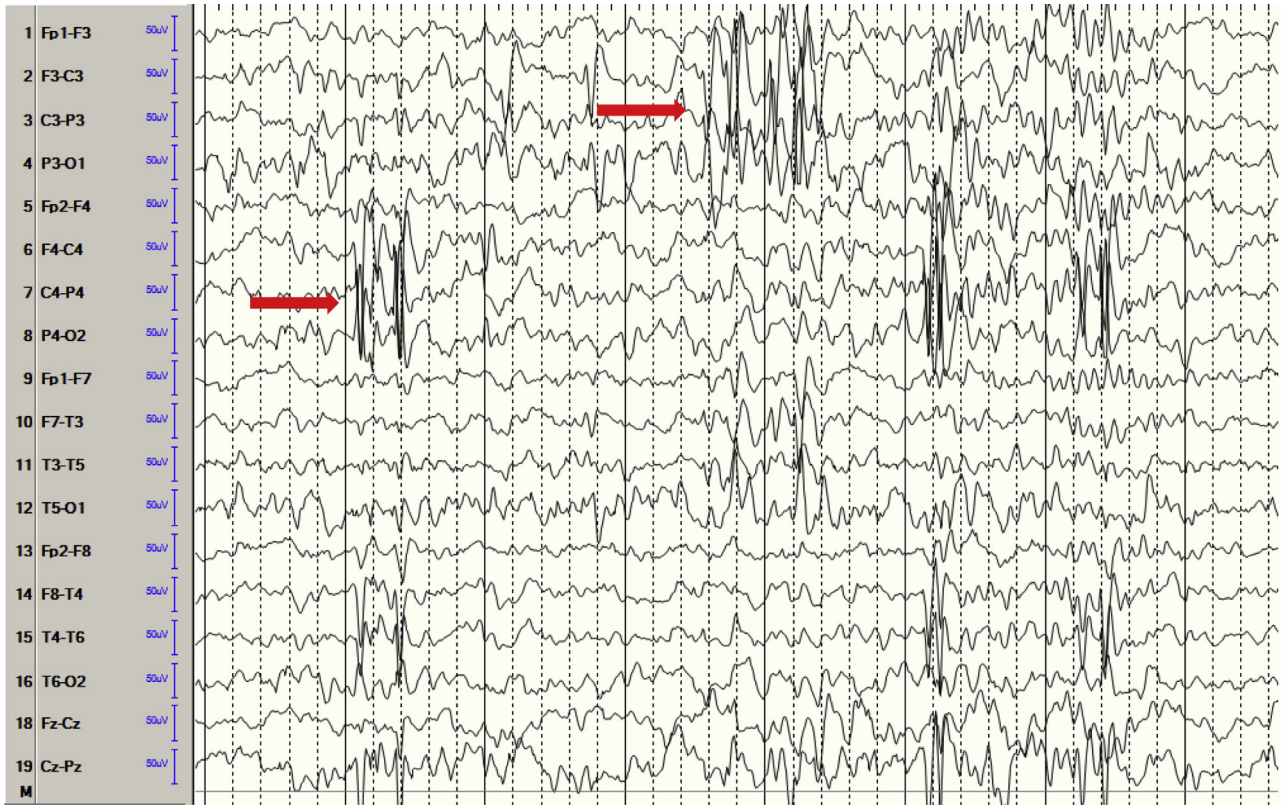

FIGURE 3. Interictal EEG showing bilateral central, parietal, and temporal spike discharges.

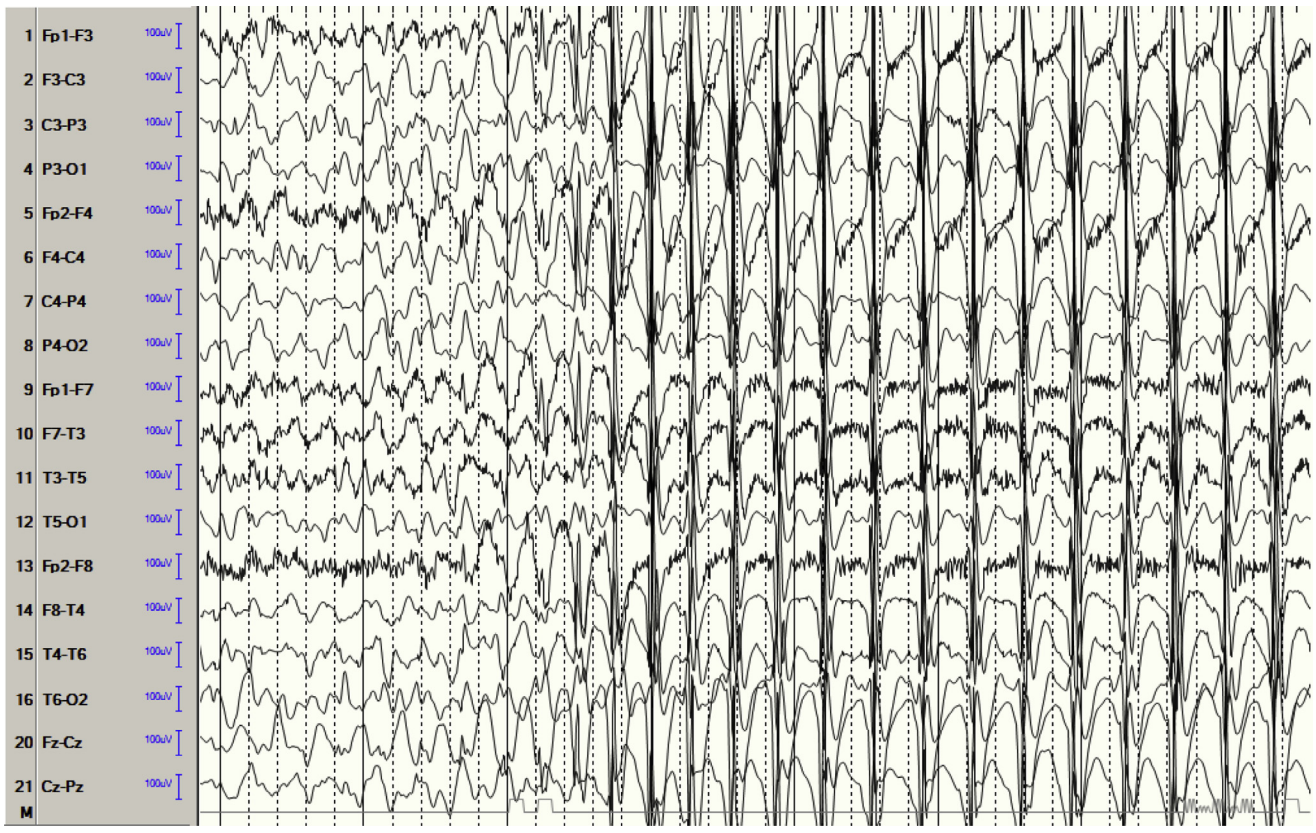

FIGURE 4. Ictal EEG showing absence seizure with generalized 3-Hz spike and wave discharges.

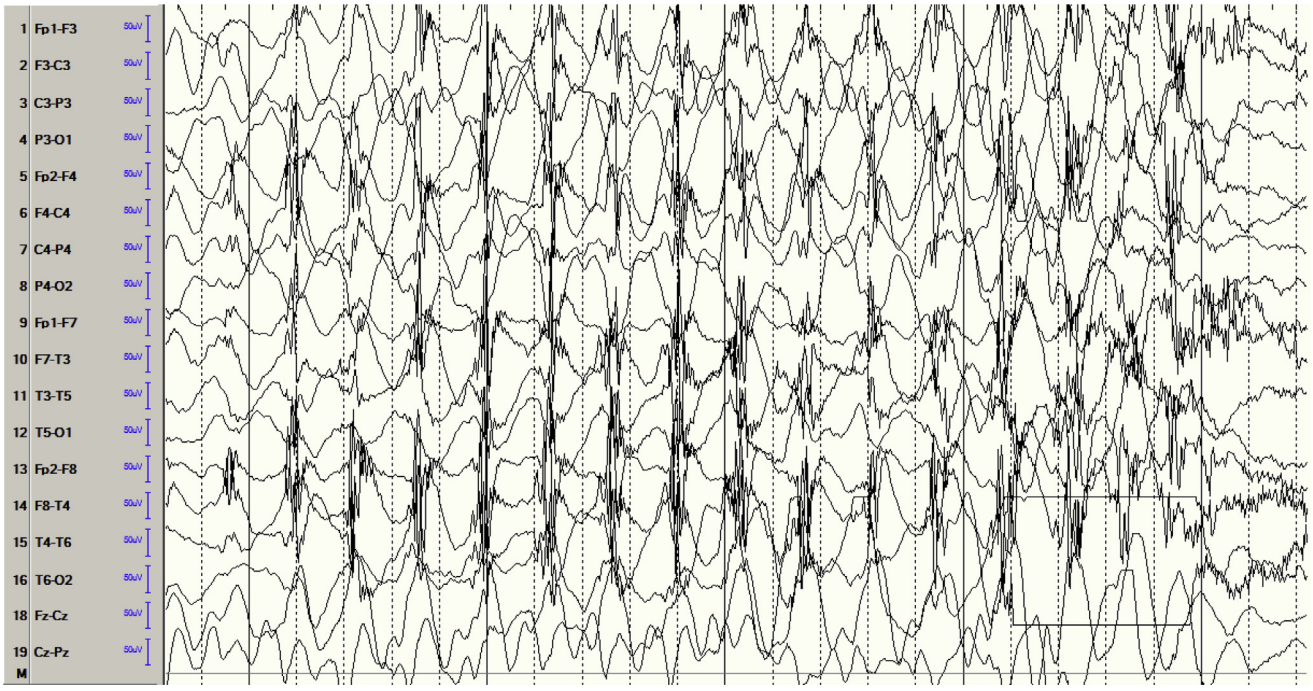

FIGURE 5. Ictal EEG showing rhythmic myoclonic seizure associated with burst of bifrontal predominant generalized rhythmic spike and wave activity.

alone. AED resistance in patients with *CACNA1H* mutation has been predicted to be multifactorial in origin.[8] Variants of *CACNA1H* have also been associated with autism spectrum disorder and other behavioral disorders like intellectual disability, learning difficulties, and attention deficit disorder.[9] This is concordant with our findings wherein one patient had global developmental delay, one had developmental regression, and one had attention deficit disorder. Accumulating evidence suggests that T-type channels are found throughout the body in a host of non-neural, non-cardiovascular tissues, e.g., endocrine tissues, fibroblasts, bone, lung, spleen, liver, gastrointestinal tract, pancreas, kidney, ovary, and testis.[10] Patients 2 and 5 in our series had gastroesophageal reflux and failure to thrive, which may represent altered function of the T-type channels in the gastrointestinal system. Patients 2 and 5 also had frequent infections and were found to have selective antibody deficiency secondary to involvement of the immune system in the setting of the T-type calcium channel mutations. The variability in the degree of involvement of central nervous system and the mechanisms underlying the heterogeneity of phenotypic expression involving other organ systems in patients with T-type calcium channel mutations remain to be further elucidated.

Conclusions

Five children with *CACNA1H* gene mutations exhibited phenotypes consisting of generalized, focal, and multifocal epilepsy ranging in severity from mild to severe intractable epilepsy. The spectrum of *CACNA1H* mutations can involve other organ systems (immunologic and gastrointestinal) in addition to epilepsy, developmental delay, and autism.

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