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Clinical Letter

PLCB1 Biallelic Point Mutations Cause West Syndrome

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Introduction

Phospholipase C-beta 1 (*PLCB1*, OMIM 607120), located at 20p12.3, encodes PLCB, an enzyme catalyzing conversion of phosphatidylinositol 4,5-biphosphate to inositol 1,4,5-trisphosphate and diacylglycerol.[1] There have been four reports of patients with early infantile-onset developmental and epileptic encephalopathies (DEEs) secondary to biallelic mutations in *PLCB1*: three patients from consanguineous families with homozygous mutations affecting *PLCB1*[2–4] and a fourth with a maternally inherited deletion and a paternally inherited splice site variant (Table).[5]

We describe a girl with West syndrome and compound heterozygous *PLCB1* mutations. This report further defines the phenotypic spectrum of this genetic disorder and demonstrates that biallelic point mutations are a potential cause.

Patient description

This 12-month-old girl presented at age seven months with focal seizures involving eye deviation, generalized stiffening, impaired awareness, and a frightened appearance typically lasting for 30 seconds. Her development had been normal until six months of age, but over the past month her development had regressed; she had become less interactive and happy. Electroencephalography showed hypsarrhythmia with periods of pseudonormalization. By nine months of age, she had developed more classic clusters of epileptic spasms.

Despite initiation of topiramate, focal seizures continued. Vigabatrin seemed to help focal seizures, but there was no change in hypsarrhythmia. Adrenocorticotropic hormone, pyridoxine, or zonisamide had no clear benefit. She was started on a ketogenic diet at age 11 months, and spasms and hypsarrhythmia resolved two weeks later. She had severe global developmental delay; at 12 months she could not sit or roll, did not clearly fix and follow, had essentially no purposeful movements, and had only rudimentary vocalization (no babbling).

Parents are both of Lebanese descent with no known consanguinity. She has one older brother who is well. There is no known family history of seizures or developmental impairment.

On examination, she had normal growth parameters and was nondysmorphic. Axial hypotonia was observed on her initial presentation, becoming worse as she regressed. Ophthalmologic examination was normal.

Comparative genomic hybridization microarray was normal. On metabolic evaluation, plasma amino acids,

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Table. Previously Published Patients With Epilepsy With *PLCB1* Mutation

Ref	M/F	Age of Onset	Seizures	Epilepsy Syndrome	EEG	Development
Present patient	F	7 months	FIAS, ES	WS	Hypsarrhythmia	Normal to 6 months. Regressed with seizure onset
Schoonjans et al.[4]	M	4 months	Febrile SE, ES, GTC, focal motor	WS	Hypsarrhythmia	Normal to 4 months. Regressed with seizure onset. At 4 years, severe GDD and autistic features
Ngoh et al.[5]	F	10 months	Bilateral upper limb jerking with eye deviation and staring	—	Disorganized background, diffuse slowing, multifocal spikes	From 6 months, hypotonia and GDD. Regression with seizure onset. At 3 years, nonverbal and cannot sit independently
Poduri et al.[3]	M	6 months	FIAS	EIMFS	Multifocal spikes and frequent focal seizures, sometimes migrating from one hemisphere to the other	GDD with regression at seizure onset
Kurian et al.[2]	M	10 weeks	FIAS, ES	EIEE, WS	Normal at 10 weeks. Hypsarrhythmia by 8 months	Normal to 6 months, then regressed. Profoundly impaired GDD. Spastic quadriparesis, hypotonia

Abbreviations:
EEG = Electroencephalography
EIEE = early infantile epileptic encephalopathy
EIMFS = epilepsy of infancy with migrating focal seizures
ES = epileptic spasms
FIAS = focal impaired awareness seizures
GDD = global developmental delay
GTC = generalized tonic-clonic
ID = intellectual disability
SE = status epilepticus
WS = West syndrome

acylcarnitine profile, biotinidase, urine adipic semialdehyde, and urine organic acids were all normal. Urine amino acids showed elevated cystine, of uncertain clinical significance, possibly reflecting immature kidney function. Brain magnetic resonance imaging showed small foci of restricted diffusion in the medial thalami bilaterally, suspected to due to vigabatrin effects (Figure).

A 401-gene epilepsy panel (Fulgent Diagnostics, Temple City, CA) identified two heterozygous variants in *PLCB1*. The first, c.1332T>A, p.Tyr444*, was maternally inherited and is predicted to result in protein truncation. The second, c.2930+1G>A, p.?, was apparently *de novo* (not detected in either parent) but confirmed to lie on the paternally inherited allele; it was predicted to have a deleterious effect on splicing. Neither variant is present in the Genome Aggregation Database.[6] On the basis of the American College of Medical Genetics criteria,[7] both variants are classified as pathogenic.

Discussion

We describe a girl with West syndrome, in whom spasms and hypsarrhythmia were refractory to standard treatments. She has compound heterozygosity for pathogenic variants in *PLCB1*, both of which are a result of single base pair substitutions, making her the first patient to not carry a genetic deletion. She is also the first individual in whom a *de novo PLCB1* mutation has been identified. Her severe phenotype is in keeping with the four previously described children with *PLCB1*-related early infantile DEE, two of whom also had West syndrome.

Taken together with prior published reports, our patient's presentation emphasizes that biallelic *PLCB1* mutations result in a severe DEE. Seizures, with coincident developmental regression, typically begin in the first year of life, and are focal impaired awareness or epileptic spasms. Electroencephalography shows hypsarrhythmia in the majority. Seizures and hypsarrhythmia are usually medically refractory, but our patient had a positive clinical response to vigabatrin and ketogenic diet.

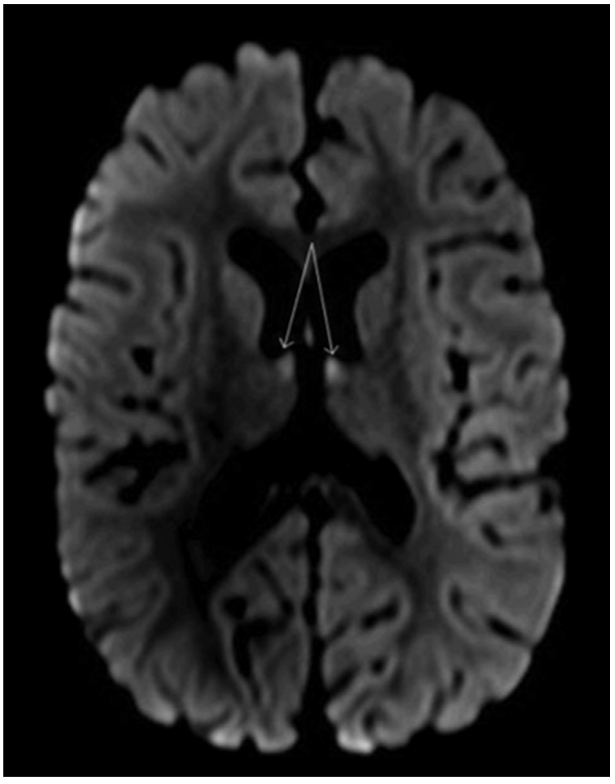

Figure. Brain magnetic resonance imaging at eight months of age. On diffusion-weighted imaging sequence, symmetric small foci of restricted diffusion are seen in the medial thalami (arrows). These changes were suspected to have occurred secondary to vigabatrin use. Otherwise, the brain was structurally normal. The color version of this figure is available in the online edition.

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