Novel Mutation in *ATP6V1A* Gene with Infantile Spasms in an Indian Boy

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Abstract

A 7-month-old boy with a novel mutation in *ATP6V1A* gene is described. The *ATP6V1A* gene has been recently identified to be associated with epileptic encephalopathies. Clinical features in this patient are different from cases reported so far, thus broadening the spectrum of *ATP6V1A*-associated epileptic encephalopathy.

Keywords

- *ATP6V1A*
- epileptic encephalopathy
- infantile spasms

Case Report

We describe a 7-month-old boy who presented with flexor spasms for 2-weeks. He is the first-born child to unrelated parents.

The patient was born at term to unrelated parents after an uneventful pregnancy with Apgar's score, weight, length, and head circumference in normal range. The neonatal period was unremarkable followed by normal development milestones until 7 months of age. Parents witnessed flexor spasms for 2 weeks associated with loss of previously acquired milestones. On examination, he had a small head (head circumference at 3rd centile for age) with closed anterior fontanelle. Fundus examination was normal, mild hypotonia, no extrapyramidal movements, no abnormal ocular movements were present. No dysmorphism or other abnormalities detected on other system examination. Electroencephalography (EEG) was suggestive of hypsarrhythmia with multifocal interictal discharges.

Initial etiological investigations were performed with negative results: magnetic resonance imaging (MRI) brain, chemical and physical examination of cerebrospinal fluid, pyruvic acid and lactic acid in plasma, plasmatic and urinary amino acids, urinary organic acids, cerebrospinal fluid (CSF) glycine, CSF amino acids, and biotinidase levels were normal. Exome sequencing of a multigene epilepsy panel for early infantile epileptic encephalopathy (EIEE) detected *ATP6V1A* mutation c.416A > G(p.Lys139Arg). Both parents were tested and found negative for carrier state.

The child was initially treated with adrenocorticotrophic hormone (ACTH) with complete cessation of spasms; however, he had recurrence after 5 months of stopping steroids. Valproic acid, levetiracetam, and zonisamide were added sequentially, he continues to have flexor spasms in clusters though his seizure frequency has reduced by >50% of his baseline seizure frequency. Repeat interictal EEG showed resolution of hypsarrhythmia with slow background and multifocal epileptiform discharges. On follow-up after 1 year, his development quotient is <70.

Discussion

Four cases with *ATP6V1A* mutations have been reported so far, all of them had preexisting developmental delay and fever-associated seizures, followed by epileptic encephalopathy.[1] Index child was developmentally normal, there were no episodes of fever-associated seizures. He presented with infantile spasms (IS) and neuroregression followed by refractory seizures. Comparison of index child with previously reported cases of epileptic encephalopathy associated with *ATP6V1A* mutation has been illustrated in ►**Table 1**.

This is the first case report of *ATP6V1A* mutation presenting as IS and refractory epilepsy in a developmentally normal

received
April 4, 2019
accepted after revision
November 26, 2019

DOI https://doi.org/10.1055/s-0040-1701657.
ISSN 0174-304X.

Table 1 Comparison of index child with previously reported cases of epileptic encephalopathy associated with *ATP6V1A* mutation

Age at follow-up	14 years	8 years	8 years	11 years	Index child at 19 months
ATP6V1A mutation	c.298G > T (p.Asp100Tyr) de novo	c.1045G > A (p. Asp349Asn) de novo	c.1112A > G (p.Asp371Gly) de novo	c.80C > G (p. Pro27Arg) de novo	c.416A > G (p.Lys139Arg) de novo
Clinical diagnosis	Infantile onset epileptic encephalopathy	ID/epilepsy	ID/epilepsy	Infantile onset epileptic encephalopathy	Infantile onset epileptic encephalopathy (nonstructural West's syndrome)
Head circumference	44.5 cm (−7 SD): microcephaly	At birth: 33 cm (−1.2 SD)	Unknown	49 cm (−3.2 SD): microcephaly	At 7 months, 40 cm (−3 SD): microcephaly
Age/symptoms at first clinical presentation	11 mo/ hypotonia, developmental delay, seizures	1 mo/ developmental delay, jerky movement	2 y 6 mo, developmental delay, seizures	7 mo, hypotonia, developmental delay	7 mo, infantile spasms, neuroregression, hypotonia
Epilepsy	Yes	–	–	–	Yes
Age at seizure onset	11 mo	2 y 10 mo	2 y 6 mo	11 mo	7 mo
Seizures types	Convulsive seizures during fever at onset, then infantile spasms, tonic, focal clonic, and focal occipital	Convulsive seizures during fever at onset, then focal occipital	Convulsive seizures during fever at onset, then generalized tonic–clonic	Convulsive seizures during fever at onset, then spasms, tonic, clonic and myoclonic	Infantile spasms
Brain MRI	Hypomyelination, mild brain and cerebellar atrophy	Normal at 7 years	Normal at 7 years	Mild atrophy at 1 year 5 months and 3 years 7 months	Normal at 7 months of age
Clinical phenotype at last follow-up	Profound delay, nonverbal, no visual fixation, hypotonic dyskinetic quadriparesis, nonambulatory, early puberty (9 y)	Moderate ID (DQ: 53), poor language, headache, amelogenesis imperfecta diagnosed at 3 years, optic atrophy	Moderate ID, poor language, mild dysmorphic features (wide forehead, deep set eyes, beaked nose), autistic traits, wide based gait, hypotonia	Profound delay, nonverbal, no visual fixation, coloboma of the iris, hypotonic dyskinetic quadriparesis, nonambulatory	Profound delay, (DQ < 70) hypotonia

Abbreviations: DQ, development quotient; MRI, magnetic resonance imaging; SD, standard deviation.

child. Heterozygous mutations in the *ATP6V1A* gene have been recently identified in patients with epileptic encephalopathy. *ATP6V1A* has been implicated with type-3 EIEE (OMIN 618012), denovo *ATP6V1A* mutation has been associated with developmental delay and seizures.[1] Types of seizures associated with this mutation are febrile seizures, IS, tonic seizures, clonic seizures, myoclonic jerks, generalized tonic clonic seizures, and focal occipital seizures in children with preexisting developmental delay.[1] The clinical phenotype of *ATP6V1A* mutation varies from moderate intellectual disability to severe language and motor delay.[1,2] *ATP6V1A* mutation has also been associated with autism.[3]

The function of *ATP6V1A* is to maintain intracellular pH and this gene encodes a component of vacuolar ATPase (V-ATPase), a multisubunit enzyme that mediates acidification of eukaryotic intracellular organelles. V-ATPase dependent organelle acidification is necessary for such intracellular processes as protein sorting, zymogen activation, receptor-mediated endocytosis, and synaptic vesicle proton gradient generation.[1] The identified mutations in *ATP6V1A* associated with epileptic encephalopathy are c.2985 > T (p.Asp100Tyr), c1045G > A (p.Asp349Asn), c.1112A > G (p.Asp371Gly), and c.80C > G (p.Pro27Arg). Index child had mutation in exon 4 c.416A > G (p.Lys139Arg).

Next-generation sequencing (NGS) with extensive gene panels or whole exome sequencing is routinely used in the etiological workup of children with early infantile epileptic encephalopathies, detection of pathogenic mutations in *ATP6V1A* are expected when larger cohorts of infants with early onset multifocal epilepsy undergo genetic testing.

The present case adds to the few cases of epileptic encephalopathy, so far reported that were caused by *ATP6V1A* gene mutations and expands the clinical spectrum of *ATP6V1A* mutation associated epilepsy. IS is an early-onset catastrophic epileptic encephalopathy of unknown etiology in approximately 40% of patients.[4] *ATP6V1A* mutation should also be considered amongst the genetic etiologies of IS, this gene has not been identified as a genetic etiology of IS.[4,5]

Funding
None.

Conflict of interest
None.

Acknowledgments
The author is grateful to the parents of the patient for their kind cooperation.

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