Case Report

The Dysfunctional Gangway: SZT2-associated Epilepsy with Thick Corpus Callosum

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Mutations in seizure threshold 2 (SZT2) gene on chromosome 1p34.2 are an as yet unidentified cause of epilepsy and epileptic encephalopathy. We report a 3-year-old girl who presented with developmental delay, dysmorphic facies, refractory seizures, and subsequent developmental regression. Despite significant multifocal epileptiform abnormalities on her electroencephalogram, she had a paucity of generalized discharges indicating a functional deficiency of corpus callosum in spite of its increased thickness seen on magnetic resonance imaging. Her clinical exome sequencing revealed a homozygous single base pair duplication in the SZT2 gene that resulted in a frameshift mutation and premature truncation of the protein. Our case emphasizes the role of SZT2 gene in the diagnostic algorithm of early childhood refractory epilepsy especially in the context of a thick yet dysfunctional corpus callosum.

Keywords: Developmental delay, epilepsy, exome sequencing, intellectual disability, thick corpus callosum

Introduction

Seizure threshold 2 (SZT2) gene located on chromosome 1p34.2 is a regulator gene with 71 exons. Mutations in SZT2 have been identified as a cause of epileptic encephalopathy characterized by a constellation of seizures, neurodevelopmental delay, dysmorphic corpus callosum (CC), and occasionally macrocephaly.[1] Animal studies have identified SZT2 to reduce the seizure threshold in knockout mouse model.[2] Functional studies have further clarified a constitutive hyperactivation of mechanistic target of rapamycin complex 1 (mTORC1) signaling after loss-of-function mutations in SZT2 resulting in heightened epileptogenesis.[3] The increased availability of clinical exome sequencing has helped broaden the phenotypic and genotypic spectrum of this abnormality.

Case Report

A 3-year-old girl, born of a nonconsanguineous parentage, presented with developmental delay followed by regression and seizures. She was born of a term vaginal delivery with no perinatal complications. Her developmental milestones were significantly delayed and she had not attained pincer grasp. Onset of epilepsy was at 15 months of age as focal seizures with impaired awareness (hypomotor events) followed by generalized tonic seizures at a frequency of one per day. Gradually the seizure frequency increased to six attacks per day which was associated with a regression of milestones. On examination, she had normal head circumference, mild facial dysmorphism in the form of prominent forehead and antimongolid slant of palpebral fissures. Her height and weight were normal for age. Auditory regard was present but visual regard was poor despite a normal fundus. There was truncal hypotonia with normal tone of limbs. Power was essentially normal with sluggish deep tendon reflexes and mild truncal ataxia.

Her electroencephalogram (EEG) showed multifocal epileptiform abnormalities which were maximum...
bifrontally. However, there was a paucity of generalized discharges; generalized paroxysmal fast activity (GPFA) or burst attenuation (BA) pattern were conspicuously absent. Magnetic resonance imaging (MRI) of the brain [Figure 1] showed thickened, dysmorphic CC with a knob-like outpouching from the superior edge of anterior half of body, lacking the normal isthmic narrowing. Tectal plate thinning was seen with inconspicuous superior and inferior colliculi. Height of pons was reduced, and medulla appeared elongated with a straightened out pontomedullary cleavage. Superior cerebellar peduncle was thin with vermian atrophy and T2, FLAIR hyperintensities were noted in bilateral parieto-occipital regions.

Metabolic screening, including tandem mass spectroscopy and urine gas chromatography, was negative. Clinical exome sequencing revealed a homozygous single base pair duplication in exon 52 of the SZT2 gene (chr1: g.43907028dup; depth: 106×) resulting in a frameshift mutation and premature truncation of the protein, 18 amino acids downstream to codon 2440 (p. Asp2440ArgfsTer18; ENST00000562955.1). She was tried on multiple antiepileptic drugs (sodium valproate, phenobarbitone, levetiracetam, and clobazam) in the past without relief and was therefore optimized on a combination of sodium valproate, perampanel, and zonisamide to which she responded.

**DISCUSSION**

Our case emphasizes the role of SZT2 gene in the diagnostic algorithm of early childhood refractory epilepsy especially in the context of a thick yet dysfunctional CC. SZT2 mutation usually presents with epilepsy and neuroregression. Till date, 21 cases with SZT2 mutation have been described in the literature.[1,4-14] The phenotypic spectrum and imaging findings of all the cases including ours are summarized in Table 1. The phenotypic spectrum can be variable. Refractory epilepsy and epileptic encephalopathy were the most common presentations in 19 of 22 patients (including our case); however, three patients presented with mild-to-moderate intellectual disability without seizures.[4] Four patients expired due to complications secondary to refractory epilepsy and status epilepticus. EEG data was available in 21 of 22 patients. A total of 11 patients showed a background slowing; nine patients had multifocal interictal epileptiform discharges (IEDs); however, it was noteworthy that none of the patients had generalized discharges, GPFA or BA pattern. This striking electrical hallmark was seen in our case also, signifying the functional deficiency of CC even in cases where the callosal thickness was increased as seen in MR images (in 7/22 patients). This could be due to the defective axonal pruning in the dysmorphic CC as explained in previous reports.[1] Bilateral parieto-occipital region white matter hyperintensities were noted despite the lack of perinatal insult. This finding has also been noted in previous cases.[8] Twelve of 20 patients had macrocephaly. Global developmental delay was almost universal with speech and motor milestones being most severely affected.

Recent functional studies have shown that SZT2 is a component of the KICSTOR complex, which regulates the kinase activity of mTORC1 known to regulate mitochondrial respiration.[3] mTORC1 signaling pathway hyperactivation is notably associated in the etiology of epilepsy, developmental delay, and macrocephaly. SZT2 variants have also been shown to reduce the mitochondrial OXPHOS activities in fibroblast cultures.[15]

**CONCLUSION**

We highlight the fact that if a child with refractory epilepsy or epileptic encephalopathy has a thick CC on MRI and an EEG which shows significant multifocal...
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Epileptiform abnormalities with a conspicuous paucity of generalized discharges (e.g. GPFA and BA pattern), it points toward a functional deficiency of the interhemispheric connecting white matter bundle. Parieto-occipital region white matter hyperintensities should not be misinterpreted as perinatal injury-induced periventricular leukomalacia. Such patients should be evaluated for the SZT2 gene mutation by next-generation sequencing. By using this diagnostic tool, we have identified a homozygous single base pair duplication in the SZT2 gene leading to developmental delay, epilepsy, and neuroregression––case of a dysfunctional gangway identified electro-radiologically, confirmed by genetic study.

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Conflicts of interest
There are no conflicts of interest.

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Table 1: Clinical characteristics, investigation findings (EEG and MRI), and type of mutations in patients with SZT2 aberration (includes all previously reported cases and current case) (n = 22)

| Characteristic | Value |
|---------------|-------|
| Mean age of presentation | 7 years (4 months–19 years) |
| Male:female ratio | 13:9 |
| Mean age of onset | 11.5 months (4 days–4 years) |
| Clinical presentation | Epilepsy 86.4% (19), Intellectual disability 13.6% (3) |
| Developmental delay | Motor and speech delay 77.3% (17), Isolated motor delay 13.6% (3), Isolated speech delay 9.1% (2), Regression 22.7% (5), Facial dysmorphism* 61.9% (13), Macrocephaly 54.5% (12), Family history (suspected or proven) 69.1% (13) |
| Consanguinity (third degree) | 31.8% (7) |
| Type of seizure* | Focal seizures 19% (4), Focal and generalized 57.1% (12), Generalized seizures 4.8% (1), Status epilepticus 14.2% (3), No seizures 14.2% (3) |
| EEG* | Focal IEDs 28.6% (6), Multifocal IEDs 42.9% (9), Partially generalized IEDs 4.8% (1), Generalized IEDs 0% (0), BGA slowing 52.4% (11), Normal 19% (4) |
| MRI brain | Normal 22.7% (5), Thick CC 31.8% (7), Short CC 27.3% (6), Volume loss of callosum 9.1% (2), Persistent-cavum septum pellucidum 18.2% (4), Migration disorder* 13.6% (3), Dilated ventricles 13.6% (3), Delayed myelination 9.1% (2), Knob-like outpouching on superior edge of CC 4.5% (1), Widening of sylvian fissure 9.1% (2) |
| Type of mutation | Homozygous 40.9% (9), Compound heterozygous 59.1% (13) |

Values in parenthesis indicate absolute number of cases

Table 1: Continued

| Clinical feature | Description |
|-----------------|-------------|
| BGA = background activity, CC = corpus callosum, EEG = electroencephalogram, IEDs = interictal epileptiform discharges, IVS = interventricular septum, SIADH = symptom of inappropriate secretion of antidiuretic hormone |
| Scoliosis, pectus carinatum, microcephaly and high arched palate |
| Lower limb contractures and hypotonia |
| Agenesis of left kidney, hypoplasia and cryptorchidism |
| Chronic lung disease |
| Chronic pancreatitis |
| SIADH |
| Thrombocytopenia |
| # Periventricular heterotopia, frontal polymicrogyria, and subependymal nodule |
| *Excludes one patient where limited data was available |

epileptiform abnormalities with a conspicuous paucity of generalized discharges (e.g. GPFA and BA pattern), it points toward a functional deficiency of the interhemispheric connecting white matter bundle. Parieto-occipital region white matter hyperintensities should not be misinterpreted as perinatal injury-induced periventricular leukomalacia. Such patients should be evaluated for the SZT2 gene mutation by next-generation sequencing. By using this diagnostic tool, we have identified a homozygous single base pair duplication in the SZT2 gene leading to developmental delay, epilepsy, and neuroregression—case of a dysfunctional gangway identified electro-radiologically, confirmed by genetic study.

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