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Early-onset epileptic encephalopathy with myoclonic seizures related to 9q33.3-q34.11 deletion involving *STXBP1* and *SPTAN1* genes

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ABSTRACT – We describe a 10-month-old boy with early-onset epileptic encephalopathy who was found to have a hemizygous deletion in 9q33.3-q34.11 involving *STXBP1* and *SPTAN1* genes. He presented at the age of 2.5 months with frequent upper extremity myoclonus, hypotonia, and facial dysmorphisms. Interictal EEG showed multifocal polyspike and wave during wakefulness and sleep. Ictal EEG revealed low-amplitude generalized sharp slow activity, followed by diffuse attenuation. Metabolic testing was unrevealing. Brain MRI showed thinning of the corpus callosum with an absence of rostrum. This patient is the second reported case with 9q33.3-q34.11 deletion involving *STXBP1* and *SPTAN1* genes associated with epileptic encephalopathy and myoclonic seizures. Larger case series are needed to better delineate this association.

Key words: encephalopathy, Early Infantile Epileptic Encephalopathy, Early Myoclonic Encephalopathy, microdeletion, Ohtahara syndrome, *STXBP1*, *SPTAN1*

The early-onset epileptic encephalopathy (EOEE) syndromes include early myoclonic encephalopathy (EME) and early infantile epileptic encephalopathy (EIEE) or Ohtahara syndrome. Common aetiologies include structural malformations and metabolic disorders, respectively (Beal *et al*., 2012; Yamatogi and Ohtahara, 2002). Genetic abnormalities are increasingly recognized in association with these epilepsy syndromes (Beal *et al*., 2012; Campbell *et al*., 2012; Saitsu *et al*., 2012; Nicita *et al*., 2015). Deletions in the 9q33-q34 region are associated with EOEEs (Nicita *et al*., 2015; Stamberger *et al*., 2016). Here, we describe the clinical features of an infant with EOEE and myoclonic seizures who was found to have 9q33.3-q34.11 deletion.

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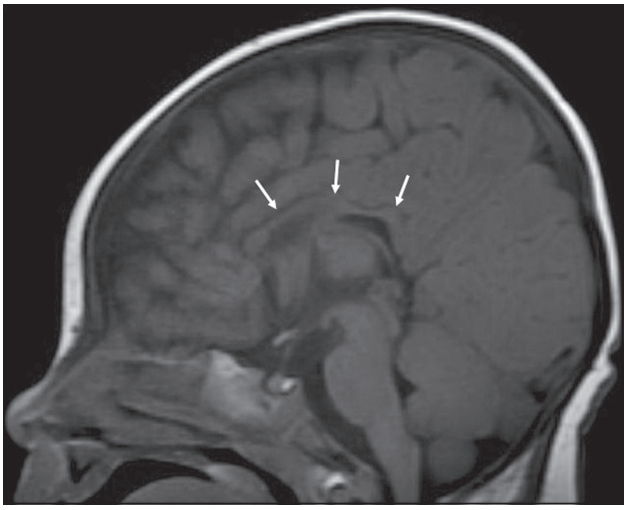

Figure 1. Sagittal T1 brain MRI showing thinning of the corpus callosum and absent rostrum.

Case study

A 10-month-old Hispanic boy presented at 2.5 months of age with a three-day history of multiple seizures. The seizures were characterized as episodes of bilateral jerking of the upper extremities and behavioural arrest. Each episode would last for less than a minute and episodes would occur in clusters throughout the day. He was born at term via repeat C-section after an uncomplicated pregnancy. Birth weight, length, and head circumference were appropriate for gestational age. He was noted to have a sacral dimple and a left pre-auricular tag. Spinal ultrasound was normal. Renal ultrasound showed horse shoe kidney. His mother had three previous pregnancies that resulted in two children who were dead within the first week of life due to extreme prematurity and a complex cardiac defect, respectively. The surviving nine-year-old sister has learning disabilities. Medical and family history was otherwise unremarkable.

Examination of our patient revealed central and appendicular hypotonia, dysmorphic facial features (left pre-auricular tag, epicanthic folds, and telecanthus), and sacral dimple. He was able to track objects, but not past the midline, and pay attention to faces; the examination was otherwise within normal limits. The following laboratory tests were also within normal limits: complete and differential blood counts; renal, liver, and thyroid function tests; serum ammonia; acyl carnitine profile; CSF cell counts; chemistry; plasma and CSF amino acids; urinalysis; and urine organic acids. Brain MRI revealed thinning of the corpus callosum with an absence of rostrum (*figure 1*). Interictal EEG showed a lack of normal organization, paucity of complexity for expected age, and multifocal polyspike and wave during wakefulness and sleep (*figure 2*). Ictal EEG was characterized by a diffuse recruiting rhythm that evolved into a low-amplitude generalized sharp slow activity, followed by diffuse attenuation for 6-7 seconds and well organized 3-4-Hz spike and wave discharges (*figure 3*). Corresponding clinical seizures were bilateral, erratic, fragmented myoclonias at a frequency of 1-2 Hz that occurred in clusters lasting between 60 and 140 seconds (*figure 4*). There were no myoclonic jerks without ictal correlates. No tonic seizure or spasm was noted during the build-up or attenuation phase between the myoclonic seizures. EEGs did not reveal hypsarrhythmia or a burst suppression pattern during sleep or wakefulness. Comparative genomic hybridization microarray revealed a hemizygous 2.1-MB deletion of 9q33.3-q34.11 (129670852-131750313) and several regions of homozygosity in multiple chromosomes encompassing approximately 1% of the genome.

Seizures were controlled with zonisamide (5 mg/kg/day) and clobazam (1 mg/kg/day). EEG monitoring at the age of four months showed continuous asymmetric slowing over the right hemisphere, predominantly in the fronto-central region, and frequent epileptiform discharges over the right fronto-central region during sleep and wakefulness (*figure 4*). The patient did not have any clinical or subclinical seizures during this monitoring period. At the age of six months, he started experiencing frequent right leg myoclonus for which zonisamide was increased to 6.5 mg/kg/day and clobazam was continued. Currently, at the age of 10 months, he continues to have occasional myoclonus. His developmental milestones are delayed. He is not able to consistently track across the midline, sit with support, pull to stand, or reach for objects. He has poor head control, microcephaly, and truncal hypotonia.

Discussion

EIEE and EME typically present within the first three months of age with tonic spasms and focal, erratic or fragmentary myoclonus, respectively. The characteristic EEG finding of EIEE includes a continuous suppression burst, while that of EME is a discontinuous pattern with suppression burst occurring often during sleep that may not be seen at disease onset. Focal structural abnormalities are typical of EIEE, whereas EME is more commonly associated with metabolic abnormalities, particularly non-ketotic hyperglycinaemia (Beal *et al.*, 2012). Our patient's clinical and electrophysiological features could not be classified as EIEE or EME. Therefore, he was diagnosed with unspecified EOEE with myoclonic seizures. Zonisamide was preferred for our patient due to its broad spectrum antiepileptic activity and reported effectiveness in controlling myoclonic seizures and treating EIEE (Wheless and Sankar, 2003).

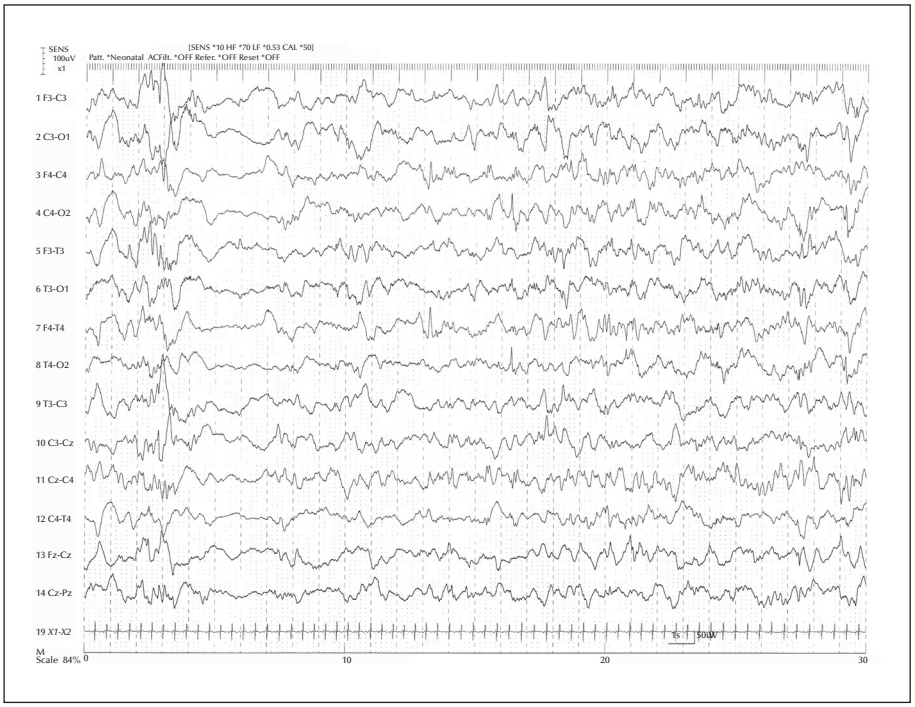

Figure 2. Interictal EEG during sleep at the age of 2.5 months showing paucity of complexity and multifocal spikes.

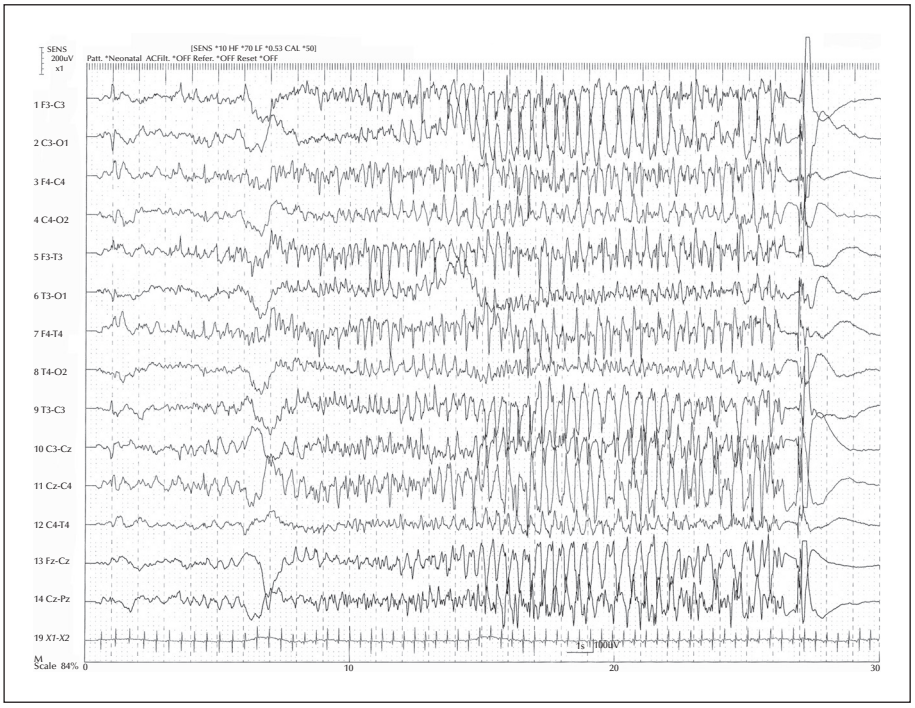

Figure 3. Ictal EEG during wakefulness at the age of 2.5 months showing a diffuse recruiting rhythm that evolves into generalized spike-and-wave discharges, followed by diffuse attenuation.

Deletions in the 9q33-q34 region are described in patients with a wide phenotypic array based on the size of deletion and genes involved within the deleted region (Saitsu *et al*., 2010, 2012; Campbell *et al*., 2012; Nicita *et al*., 2015; Stamberger *et al*., 2016). The majority of patients with the deletion exhibit drug-resistant seizures (Nicita *et al*., 2015). Myoclonic seizures were described in one patient in association with EME;

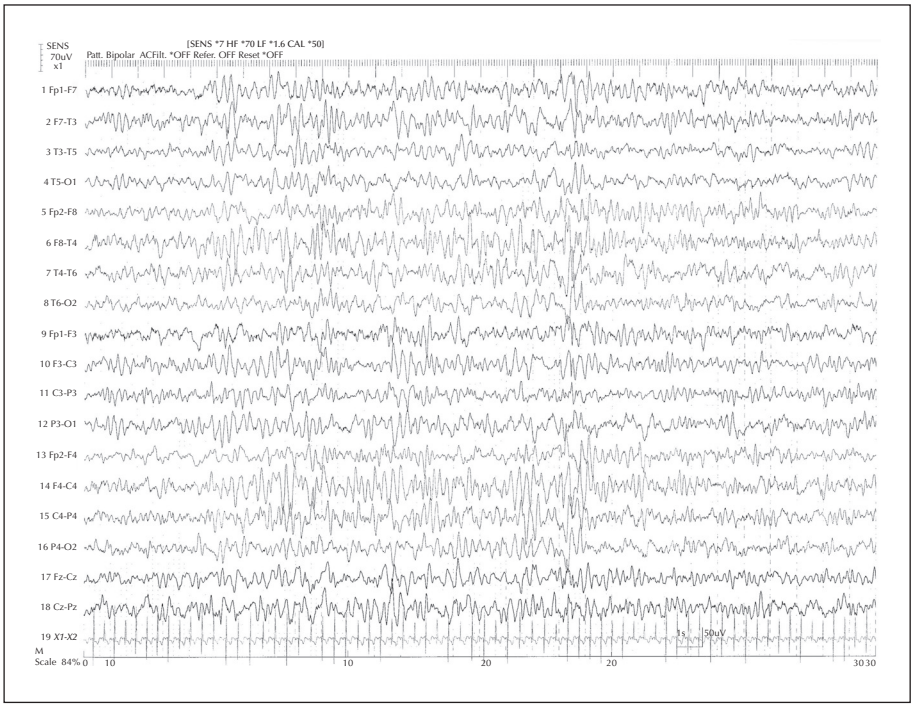

Figure 4. EEG during sleep at the age of four months showing right fronto-central slowing and epileptiform discharges.

a 15-month-old girl who presented at the age of 5 weeks with erratic left palpebral and buccal myoclonic activities, correlating with rhythmic spike-and-slow-wave activity in the right hemisphere (Nicita *et al*., 2015). The patient exhibited tonic spasms and focal motor seizures at two and 10 months of age, respectively, and a 9q33.3-9q34.12 deletion spanning about 4 MB (129, 509, 718 to 133, 647, 818) was identified. In comparison, an overlapping 2.1-MB deletion from 129, 670, 852 to 131, 750, 313 was identified in our patient. The common clinical features for these two patients include myoclonic seizures, developmental delay, hypotonia, microcephaly, facial dysmorphisms, and thinning of the corpus callosum. Our patient did not have a burst suppression pattern on EEG, sensorineural hearing loss, cleft lip/palate, or umbilical hernia, as described in the girl by Nicita *et al*.

The hemizygous deletion found in our patient contains two key genes: syntaxin-binding protein 1 (STXBP1) and alpha II spectrin (SPTAN1). *STXBP1* gene encodes a neuron-specific protein that is essential for synaptic vesicle release. Decreased expression of *STXBP1* causes GABA and glutamate synaptic depression, leading to hyper-excitability and epileptic activity. The occurrence of epileptic encephalopathy associated with deletions involving this gene might be largely attributable to *STXBP1* haploinsufficiency (Stamberger *et al*., 2016). The phenotypic spectrum associated with disruption of this gene comprises severe to profound intellectual disability, non-syndromic early-onset epilepsy and encephalopathy, Ohtahara syndrome, West syndrome, autistic features, movement disorders, and very rarely, EME (Campbell *et al*., 2012; Barcia *et al*., 2014; Nicita *et al*., 2015; Stamberger *et al*., 2016). The *SPTAN1* gene encodes alpha-II-spectrin, a protein involved in myelination in zebrafish (Voas *et al*., 2007). The role of *SPTAN1* in epilepsy and epileptic encephalopathies was recently further characterized; the majority of patients were described to have infantile epileptic encephalopathy including the distinct phenotype of EIEE5 with in-frame deletions, duplications, or missense variants in the gene (Syrbe *et al*., 2017). A wide phenotypic spectrum, including generalized epilepsy, intellectual disability with or without epilepsy, and behavioural disorders, has also been described in association with disruption of *SPTAN1* (Nicita *et al*., 2015; Syrbe *et al*., 2017). Thus, we suspect that EOEE with myoclonic seizures seen in our patient is related to *STXBP1* and *SPTAN1* deletion.

The predominant clinical feature seen in patients with 9q33-9q34 deletion includes EOEE (Nicita *et al*., 2015). Myoclonic seizures were reported in only one patient in association with EME (Nicita *et al*., 2015); our case is the second with myoclonic seizures in the setting of an unclassified EOEE. The majority of patients with deletion involving both *STXBP1* and *SPTAN1* genes have hypotonia and developmental delay, similar to our patient. Thinning of the corpus callosum and microcephaly, observed in our patient, were found in 66% and 67% of patients with deletions involving both genes, respectively (Nicita *et al*., 2015). Facial

dysmorphisms present in our patient, including telecanthus and epicanthic folds, as well as other features, such as up-slanting palpebral fissures, hypertelorism, low-set ears, clinodactyly, and smooth philtrum, were described in patients with 9q33-9q34 deletion (Ehret *et al*., 2015; Nicita *et al*., 2015). However, a uniformly identifiable pattern was not observed. A left pre-auricular tag seen in our patient has not been described with 9q33-9q34 deletion. It is uncertain whether these facial dysmorphic features are related to the deletion of *STXBP1*, *SPTAN1,* or other genes contained within the deleted region. Other Mendelian genes identified in the deleted region in our patient included *ENG* and *LRRC8A* that are associated with autosomal dominantly inherited hereditary haemorrhagic telangiectasia type 1 and agammaglobulinemia 5, respectively. However, our patient did not have signs or symptoms of these disorders.

In conclusion, the patient described in this report adds to the repertoire of 9q33-q34 microdeletion involving *STXBP1* and *SPTAN1* genes associated with myoclonic seizures. Further cases are needed to support this association. □

Disclosures.

None of the authors have any conflict of interest to declare.

References

Barcia G, Chemaly N, Gobin S, *et al*. Early epileptic encephalopathies associated with STXBP1 mutations: could we better delineate the phenotype? *Eur J Med Genet* 2014; 57: 15-20.

Beal JC, Cherian K, Moshe SL. Early-onset epileptic encephalopathies: Ohtahara syndrome and early myoclonic encephalopathy. *Pediatr Neurol* 2012; 47: 317-23.

Campbell IM, Yatsenko SA, Hixson P, *et al*. Novel 9q34.11 gene deletions encompassing combinations of four Mendelian disease genes: *STXBP1*, *SPTAN1*, ENG, and TOR1A. *Genet Med* 2012; 14: 868-76.

Ehret JK, Engels H, Cremer K, *et al*. Microdeletions in 9q33. 3-q34. 11 in five patients with intellectual disability, microcephaly, and seizures of incomplete penetrance: is STXBP1 not the only causative gene? *Mol Cytogenet* 2015; 8: 72.

Nicita F, Ulgiati F, Bernardini L, *et al*. Early myoclonic encephalopathy in 9q33-q34 deletion encompassing *STXBP1* and *SPTAN1*. *Ann Hum Genet* 2015; 79: 209-17.

Saitsu H, Tohyama J, Kumada T, *et al*. Dominant-negative mutations in alpha-II spectrin cause West syndrome with severe cerebral hypomyelination, spastic quadriplegia, and developmental delay. *Am J Hum Genet* 2010; 86: 881-91.

Saitsu H, Kato M, Shimono M, *et al*. Association of genomic deletions in the *STXBP1* gene with Ohtahara syndrome. *Clin Genet* 2012; 81: 399-402.

Stamberger H, Nikanorova M, Willemsen MH, *et al*. *STXBP1* encephalopathy: a neurodevelopmental disorder including epilepsy. *Neurology* 2016; 86: 954-62.

Syrbe S, Harms FL, Parrini E, *et al*. Delineating *SPTAN1* associated phenotypes: from isolated epilepsy to encephalopathy with progressive brain atrophy. *Brain* 2017; 140: 2322-36.

Voas MG, Lyons DA, Naylor SG, Arana N, Rasband MN, Talbot WS. AlphaII-spectrin is essential for assembly of the nodes of Ranvier in myelinated axons. *Curr Biol* 2007; 17: 562-8.

Wheless JW, Sankar R. Treatment strategies for myoclonic seizures and epilepsy syndromes with myoclonic seizures. *Epilepsia* 2003; 44: 27-37.

Yamatogi Y, Ohtahara S. Early-infantile epileptic encephalopathy with suppression-bursts. Ohtahara syndrome; its overview referring to our 16 cases. *Brain Dev* 2002; 24: 13-23.

TEST YOURSELF

(1) What is (are) the common cause(s) of Ohtahara syndrome?

(2) What is the most common cause of Early Myoclonic Encephalopathy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".