Paroxysmal Choreoathetosis in a Child with SCN2A Mutation and Neonatal Seizures

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Abstract

SCN2A mutations are associated with phenotypes ranging from benign neonatal and infantile seizures to severe epileptic encephalopathy. Movement disorders have been identified with SCN2A phenotypes but mostly in association with epileptic encephalopathies. Recent case series and case reports have described ataxia and dystonia in children with benign neonatal seizures. We describe choreoathetosis in a child with normal development, de novo SCN2A mutation, and a history of neonatal and infantile seizures. Her choreoathetosis responded dramatically to low dose oxcarbazepine.

Keywords: Epilepsy; SCN2A; Genetics; Movement disorders; Neonatal seizures

Introduction

SCN2A mutations are associated with a broad spectrum of neurological phenotypes ranging from neonatal or infantile seizures with normal development to epileptic encephalopathies with severe developmental delay. Recently, movement disorders in children with SCN2A mutations and epileptic encephalopathies including infantile spasms has been described [1,2]. We present a case of a typically developing girl with a history of neonatal seizures due to a novel de novo SCN2A mutation who developed paroxysmal, movement-induced choreoathetosis.

Case Report

A 3.5-year-old girl with history of neonatal seizures and novel SCN2A mutation developed episodes of uncontrollable movements. The episodes consisted of spontaneous falls while walking, associated with repetitive mouth movements and chaotic head, trunk, and limb movements. She appeared irritable and frustrated during the episodes but remained conscious and responsive. Triggers were consistently associated with walking such that the child would preferentially skip for ambulation. These spells were different from her prior seizures, which began at five days of life. Her seizures were characterized by focal eye deviation to either side, color change, and variable progression to bilateral convulsive movements. She had seizure clusters and one episode of status epilepticus. Prior seizures were frequently triggered by viral infections with her last seizure occurring at 18 months of age.

The onset of the spells of abnormal movements was correlated with a slow phenobarbital wean. The spells were first noted when phenobarbital dose was 2.2mg/kg/day (maximum phenobarbital dose was 4.2 mg/kg/day). She was also diagnosed with a sinus infection at the onset of these episodes and treated with antibiotics. She was on topiramate (4.5mg/kg/day) which was increased empirically to 5.5mg/kg/day without significant effect. The episodes persisted for several weeks, occurring up to seven times in a day, lasting 10-30 seconds. A video electroencephalogram (EEG) showed a normal background with no epileptiform discharges. Target episodes were captured and did not have an ictal EEG correlate. The episodes were most consistent with kinesigenic choreoathetosis. The events stopped two days after initiation of low dose oxcarbazepine (20mg/kg/day), after which she was able to walk normally.

She was born at full term with an uncomplicated delivery. Her initial EEG at one week of age captured non-localized electroclinical seizures, but a subsequent EEG at seven months of age was normal. Prior brain magnetic resonance imaging
(MRI) studies at one week and seven months old were both normal. MRI brain was repeated at 3.5 years after the onset of the abnormal movements and it remained normal. She had a genetic epilepsy panel at 18 months of age which showed a heterozygous variant of unknown significance in \textit{SCN2A} (c.4446+9 A>G in intron 24) (GeneDx, Gaithersburg, MD) (Figure 1). This non-coding variant is not reported in multiple population databases (ESP-Exome Sequencing Project; ExAC-Exome Aggregation Consortium; gnomAD-Genome Aggregation Database). In ExAC, the non-coding region has greater than 20x depth of sequencing coverage in >50,000 individuals. The parents were both tested for the presence of this variant and are negative. Therefore, this variant is likely de novo. Splice site algorithms indicate that the +9 variant results in potential novel splice donor sites at c.4464+4 and c.4468+8 (Human Splicing Finder; http://www.umd.be/HSF3/) and a potential novel acceptor sites at c.4446+6 (GeneSplicer; http://www.ncbi.nlm.nih.gov/software/ GeneSplicer/gene_sp.shtml). Based on American College of Medical Genetics (ACMG) variant classification criteria, this variant fulfills multiple criteria for a likely pathogenic variant absent from controls in population databases, assumed de novo based on parental testing, multiple lines of supporting computational evidence, and a patient phenotype which is specific for disease with a single genetic etiology [3].

**Discussion**

There are five major phenotypes of \textit{SCN2A} - benign neonatal infantile, intermediate neonatal infantile, severe neonatal infantile, childhood epilepsy, and isolated autism and intellectual disability phenotypes [1]. Our patient best fits the benign neonatal infantile phenotype. The typical semiology of neonatal onset seizures are head and eye deviation variable secondary generalization, at times occurring in clusters [4]. Children with this syndrome typically have normal development and well controlled epilepsy. Movement disorders have been reported in several epileptic encephalopathies including encephalopathies attributed to \textit{SCN2A} mutations [2]. There are also case reports of ataxia in children with \textit{SCN2A} mutations and benign neonatal seizures [5,6]. However, the episodes reported consisted of ataxia occurring a few times per month, lasting minutes to hours. Our patient, in contrast, had brief events lasting less than 30 seconds multiple times per day and her semiology was characteristic of a paroxysmal kinesigenic choreoathetosis. Prior publications have described choreiform movements in children with \textit{SCN2A} mutations in association with a severe epileptic encephalopathy or infantile spasms [2,7,8]. However, paroxysmal choreoathetosis has not yet been characterized in typically developing children with \textit{SCN2A} mutations. Howell and colleagues published a case series of 12 patients with \textit{SCN2A} related epilepsies with varied phenotypes ranging from epilepsy of infancy with migrating focal features to Ohtahara syndrome. Movement disorders were seen in 10 of 12 patients including dystonia, chorea, stereotypes, opisthotonus, and oculogyric crises. Only 1 of the 12 patients had normal development at onset and this typically developing child had dystonia [1].

This case highlights the expanding understanding of monogenetic diseases and their neurologic phenotypes. We present a 3.5-year-old child with a novel \textit{SCN2A} mutation presenting with neonatal seizures, typical development, and paroxysmal kinesigenic choreoathetosis. Her movement disorder was exquisitely sensitive to low-dose oxcarbazepine providing single case evidence that oxcarbazepine is a potential treatment option for kinesigenic movement disorders related to \textit{SCN2A} mutations. This case also highlights the need to consider \textit{SCN2A} mutations in children with a history of infantile and neonatal seizures presenting with movement disorders in early childhood.

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