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Annals of Pediatrics & Child Health

Case Report

Duplication of 2q23.3-2q31.2: A Sodium Channel Epilepsy Syndrome Responsive to Phenytoin

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Submitted: 30 August 2015

Accepted: 13 October 2015

Published: 16 October 2015

Keywords

- Epilepsy
- Neonatal seizures
- Voltage-gated sodium channel
- 2q24
- Duplication
- Partial trisomy 2q

Abstract

Duplication of the 2q24.3 region containing the SCN sodium channel genes has recently been described as a cause of neonatal epilepsy. Here we describe a patient with duplication of 2q23.3-2q31.2 who presented with neonatal epilepsy, developmental delay and associated congenital anomalies (dysmorphic features, horseshoe kidney, small VSD and right ventricle hypertrophy, and mild brain anomalies). After multiple daily seizures despite treatment with phenobarbital, levetiracetam, and topiramate, initiation of phenytoin led to cessation of seizures. This case highlights the efficacy of anti-epileptic medications that act on sodium channels in patients with neonatal epilepsy due to 2q24.3 duplication, as well as the importance of screening for associated congenital anomalies in such patients.

INTRODUCTION

Neonatal seizures have diverse etiologies that include hypoxic ischemic injury, intracranial hemorrhage, ischemic insult, infection, electrolyte disturbances, metabolic disorders, and neonatal epilepsy syndromes [1]. Various epilepsy syndromes have been described in newborn infants; a growing number of these syndromes have been shown to be associated with specific genetic mutations. For example, KCNQ2/3 mutations affect potassium channels in benign neonatal familial epilepsy, and SCN2A mutations affect sodium channels in benign familial neonatal infantile epilepsy [2]. Recently, duplication of region 2q24.3 which contains five sodium channel genes (SCN1A, 2A, 3A, 7A, and 9A) has emerged as a cause of intractable familial neonatal seizures and developmental delay. Here we describe a case of neonatal epilepsy due to a duplication of 2q23.3-2q31.2, the largest 2q24.3 duplication confirmed on microarray to date.

CASE PRESENTATION

This female was delivered at 38 weeks gestation by caesarian section due to breech position with no complications during the immediate perinatal period. Pregnancy was complicated by late gestational hypertension. Parents were unrelated, and family history was significant for a maternal great uncle with childhood onset epilepsy. At 20 hours of life, she developed up to fifteen daily seizures, characterized by head bobbing, head twitching, rhythmic blinking, gasping, and behavioral arrest that ranged in duration from fifteen seconds to two minutes, confirmed by video EEG (Figure 1B-1C). She was placed on phenobarbital 5mg/kg/day (serum levels 30-40 mcg/mL), levetiracetam100mg/kg/day and topiramate14mg/kg/day with a decrease in seizure frequency but continued daily events. Trial of pyridoxine 100 mg daily brought no discernable improvement. Seizures abruptly resolved after loading with fosphenytoin 10mg PE/kg. She was started on maintenance dose of 6 mg/kg/day (serum levels 3-5mcg/mL) at one month of life, and ultimately increased to 17 mg/kg/day (serum levels 9-11 mcg/mL). Levetiracetam and pyridoxine were successfully weaned, and she was discharged from the hospital at two months of age on phenytoin, phenobarbital, and topiramate. She remained seizure free until five months of age when phenytoin wean caused several breakthrough seizures, but has subsequently been seizure free after restarting phenytoin. Phenobarbital was weaned, and topiramate decreased to 6 mg/kg/day with no breakthrough seizures.

At eight months of age, she is feeding orally. General examination is remarkable for dysmorphic features including upslanting palpebral fissures, bilateral epicanthal folds, a broad nasal bridge, anteverted nasal tip, long smooth philtrum, and a thin upper lip. On neurological exam, she has good visual tracking, smiles socially and makes a variety of sounds. She has esotropia of her right eye. Motor exam is notable for decreased axial tone. She has good head control and is able to roll; she sits and stands with support but not independently. She brings objects to mouth

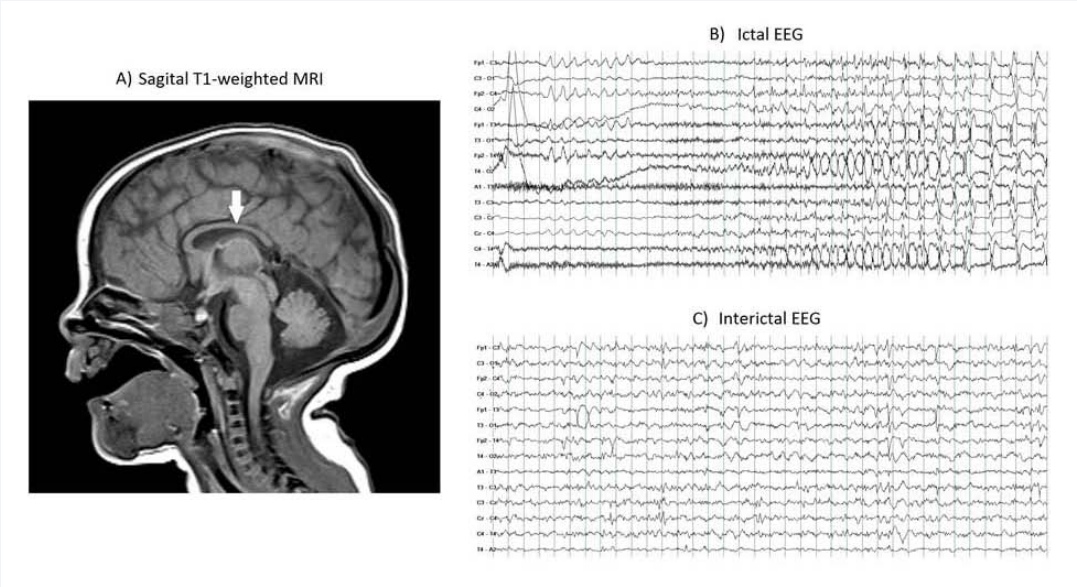

Figure 1 A) Sagital T1 weighted MRI showing mildly foreshortened corpus callosum with small splenium, B) Ictal EEG at 17 days life demonstrating voltage suppression followed by the brief appearance of high amplitude rhythmic frontal delta activity, and later varying multifocal rhythmic patterns, in this case rhythmic theta followed by periodic spike-wave discharges, C) Interictal EEG demonstrating continuous, well-regulated, moderate voltage 1-2 Hz background with frequent sharp transients.

but does not reach out to grab objects. Evaluation of sensory and primitive and deep tendon reflexes is normal.

Brain MRI done in the neonatal period showed anomalies including mildly foreshortened corpus callosum with small splenium and a mildly simplified versus delayed sulcation pattern for age (Figure 1A). Metabolic workup including serum ammonia, lactate, pyruvate, amino acids, acylcarnitine profile, carnitine, B12, total homocysteine, very long chain fatty acids; urine organic acids; and cerebrospinal fluid amino acids, pyruvate, lactate, and neurotransmitters was unremarkable. Microarray analysis identified a duplication of 26.9 Mb from 2q23.3-2q31.2 between markers kgp24541042->exm244966 (linear position of chromosome 2 is approximately 152,409,978 - 179,325,736) inserted into 6p. Paternal karyotype showed a balanced rearrangement with karyotype 46, XY, ins(6;2)(p23;q31.2q23.3). Echocardiography showed small ventriculoseptal defect, mild tricuspid regurgitation, small patent foramen ovale, mildly dilated right ventricle with moderate hypertrophy, and renal ultrasound showed horse-shoe kidney.

DISCUSSION

Duplications within chromosome 2 (also called partial trisomy 2q) were initially detected in the 1970s by karyotyping, and were found to be associated with a variety of dysmorphic features, congenital malformations, and intellectual disability [3]. With the advent of microarray CGH analysis, smaller duplications have been detected, allowing more specific correlation of phenotypes with specific genes. Simonetti et al recently reviewed a series of nine patients with duplications involving the 2q24.3 region with infantile epilepsy and intellectual disability, presumably due to the cluster of sodium channel genes on 2q24.3 [4]. Our patient's seizure semiology and response to treatment was similar to this group, implicating the 2q.24.3 locus as the likely cause for her epilepsy. Additionally, both our patient and one described by Simonetti were found to have hypoplasia of the corpus callosum, suggesting an association with 2q24.3 duplication.

One patient reviewed by Simonetti was noted to have congenital unilateral renal agenesis; no systemic malformations were reported in the other eight patients. In contrast, systemic malformations were noted in a case series of patients with 2q32-33 duplications by Ursi et al, several of which included 2q24.3 [5]. One patient with 2q21-2q33 duplication confirmed with karyotyping and FISH died shortly after birth and was found to have hypoplastic left heart, transposition of the greater arteries, and GU malformation [6]. More recently, a patient with 2q24.3-2q32.1 duplication was reported to have more severe seizure semiology (Otahara syndrome) and hypoplastic left heart syndrome [7]. Although our patient's systemic malformations are milder than those reported by Lin and Matos, her case highlights the importance of screening for congenital anomalies in cases of 2q24.3 duplications.

Neonatal seizures due to 2q24.3 duplication are often refractory to treatment with anti-epileptic medications (AEDs) typically used in neonates, including phenobarbital, levetiracetam, topirimate, and pyridoxine. Our patient had cessation of seizures after initiation of fosphenytoin as well as recurrence of seizures in the setting of decrease in phenytoin dosage. Three other cases had abrupt cessation of seizures after starting carbamazepine or oxcarbazepine [4], [8], and valproate led to seizure freedom in one case [9]. The clinical courses of these patients suggest that sodium channel blockers are a particularly effective treatment for patients with 2q24.3 duplication, and should be strongly considered as a first-line AED if this mutation is identified.

It is interesting that sodium channel blockers are effective in cases of 2q24.3 duplication, given that they are avoided in disorders such as Dravet's syndrome in which SCN genes are affected by a point mutation or deletion. As others have speculated, it may be that multiple copies of the normal sodium channel genes lead to an over-expression of normally functioning sodium channels well suited to treatment with a sodium channel blocker. It is also worth noting there are several patients with 2q24.3 duplications who do not have epilepsy [3,10,11]. It may be that expression of the duplicated gene depends on regulatory genes surrounding the duplication at the point of insertion, modulating the individual's likelihood of developing seizures.

Our case illustrates that duplications involving the sodium channel loci have similar epilepsy features (when present) but variable systemic involvement. Importantly, sodium channel blockers which are ineffective in seizures due to mutations in SCN1a can be effective in cases of 2q24.3 duplications. In addition to MR brain imaging, further screening, such as echocardiogram or kidney ultrasound is useful in identifying other congenital anomalies that are often present in this patient population.

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Cite this article

Knox A, Schapiro M, Venkatesan C (2015) Duplication of 2q23.3-2q31.2: A Sodium Channel Epilepsy Syndrome Responsive to Phenytoin. Ann Pediatr Child Health 3(8): 1084.