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CASE REPORT

Deletion at 2q24.3-31.1 resulting in severe Epileptic Encephalopathy and Episodic Autonomic Storming

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ABSTRACT

We describe an 11.5-year-old male who has profound intellectual disability, treatment resistant epilepsy with temperature sensitive seizures, and paroxysms of autonomic storming, atypical brain magnetic resonance imaging, and microcephaly. He has a 5.7 Mb deletion at 2q24.3-31.1, which includes the SCN1A gene. This is the first report of periodic and recurrent autonomic storming associated with Dravet syndrome, which is both prevented and treated with clonidine. Comparison to other reported individuals with the same deletion and genotype-phenotype correlations are discussed.

Keywords: Dravet syndrome; SCN1A; intellectual disability

INTRODUCTION

In 1978, Charlotte Dravet described a rare epileptic encephalopathy: severe myoclonic epilepsy of infancy (SMEI) [1]. Interest in this syndrome has grown, as the genetics of the disorder have become better understood. Approximately 80% of patients with Dravet syndrome have an associated mutation in the *SCN1A* gene [2]. Our patient has an exceptionally severe phenotypic expression of a large deletion containing the *SCN1A* gene and 19 other genes of less certain significance.

CASE REPORT

During gestation, the child's mother experienced unusual intrauterine movements that resembled hiccups. He was born at term vaginally, with no complications. The first concern of seizure occurred at 3.5 weeks. He developed paroxysms of gagging, repetitive swallowing, fist clenching, and back arching. Electroencephalogram (EEG) obtained at that time was normal. At 6 weeks, he had spells characterized by gagging, right head deviation, elevation of both arms, and right eyelid twitching in the presence of fever. At 8.5 weeks, he had similar events without fever. EEG revealed runs of right temporal spikes and slow waves. He developed generalized tonic-clonic seizures at 3 months and myoclonic seizures at 6 months. Seizures were, triggered by warm air or water, fever, and illness and were resistant to trials of pyridoxine, carbamazepine, lamotrigine, phenobarbital, and clobazam. He was started on the Ketogenic diet at 2 years, which reduced seizure burden. He is currently treated with levetiracetam, clonazepam, and the Ketogenic diet. An interictal EEG at 11 years showed generalized spike and slow wave discharges accentuated by sleep superimposed on a generalized slow background in all states of 3-4 hertz.

At 6 years, autonomic storming was identified. Every two to eight weeks, he had periods of tachycardia, tachypnea, hypertension, and sweating without evidence of infection. Following the onset of autonomic symptoms, more frequent seizures were seen. On a few occasions, the spell onset happened just as he was due for his nightly clonidine, which was given to assist with sleep onset. His mother noticed that the spells did not respond to abortive seizure therapies such as rectal diazepam but stopped abruptly when clonidine was administered at onset of the autonomic symptoms. When the spells started during the day and clonidine administration was delayed until evening, the spells went on for days. Video EEG monitoring showed no correlation between the autonomic symptoms and seizure activity. Now he is treated with clonidine at the onset of autonomic storming and symptoms are markedly abbreviated.

Development was delayed from the onset, and there was further regression throughout the first few years of life. Between 2-3 years, he developed choreoathetosis. Now, he utilizes a wheelchair. He smiles, and laughs. He is non-verbal with profound intellectual disability. He has cortical visual impairment. His hearing is normal.

He has acquired microcephaly. His head circumference dropped from the 10th-20th percentile at birth to less than the 2nd percentile after 2 years of age. His initial brain magnetic resonance imaging (MRI) in infancy was unremarkable. MRI performed later in childhood at 11.5 years (Fig 1a-c) demonstrated diffuse cerebral volume loss, ventriculomegaly, and diffuse subcortical white matter hyperintensities in temporal and parietal lobes.

Since age 8, our patient's weight has been in the 50th percentile and his height in the 25-50th percentile. He has mild dysmorphism: micrognathia, slightly high-arched palate, and upslanting palpebral fissures. His toes overlap. Family history is non-contributory.

Given his overall clinical presentation, molecular genetic testing was pursued in order to determine a unifying diagnosis.

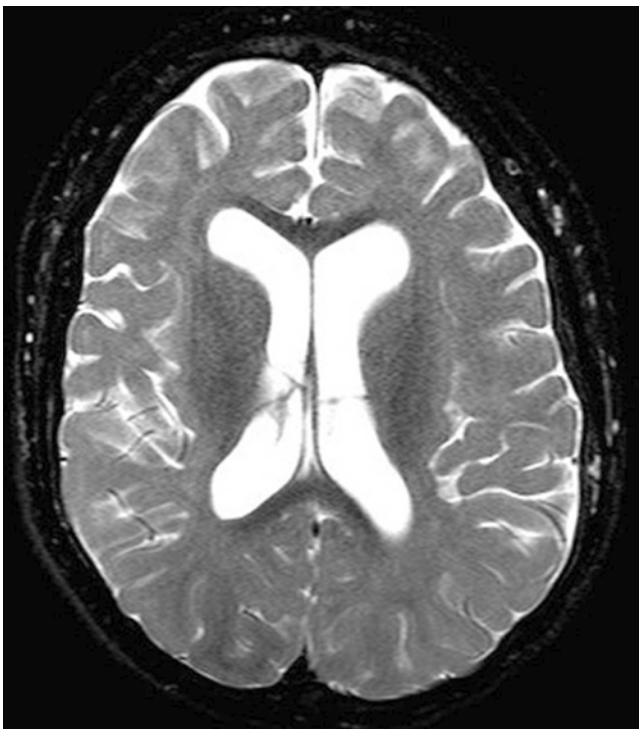

Figure a

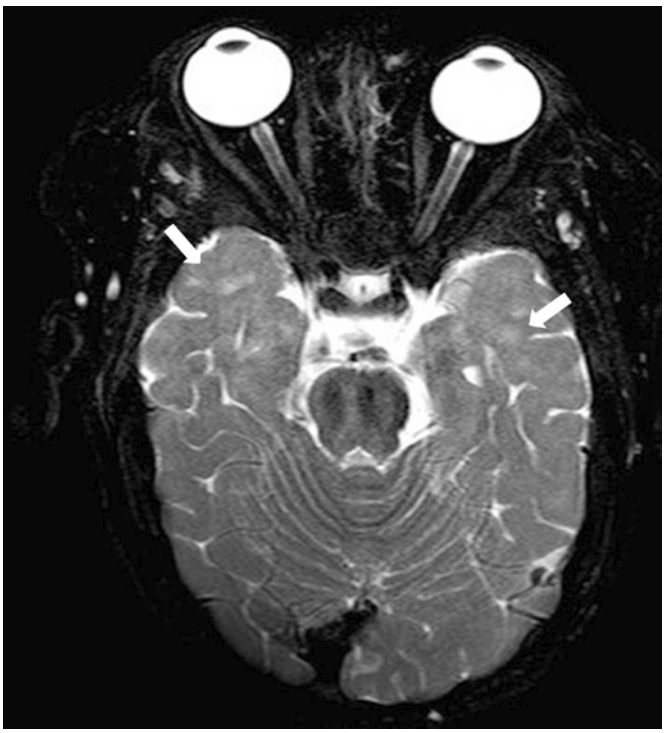

Figure b

Brain MRI findings in a 11.5 year old male with Dravet syndrome: (a and b) Axial T2 GRASE images demonstrate reduced parenchymal volume characterized by sulcal prominence and ventriculomegaly and subcortical white matter hyperintensities (arrows) in the anterior temporal lobes. (a)

Brain MRI findings in a 11.5 year old male with Dravet syndrome: (c) Axial FLAIR image also demonstrates subcortical white matter hyperintensities (arrows) in the bilateral parietal lobes. (b and c)

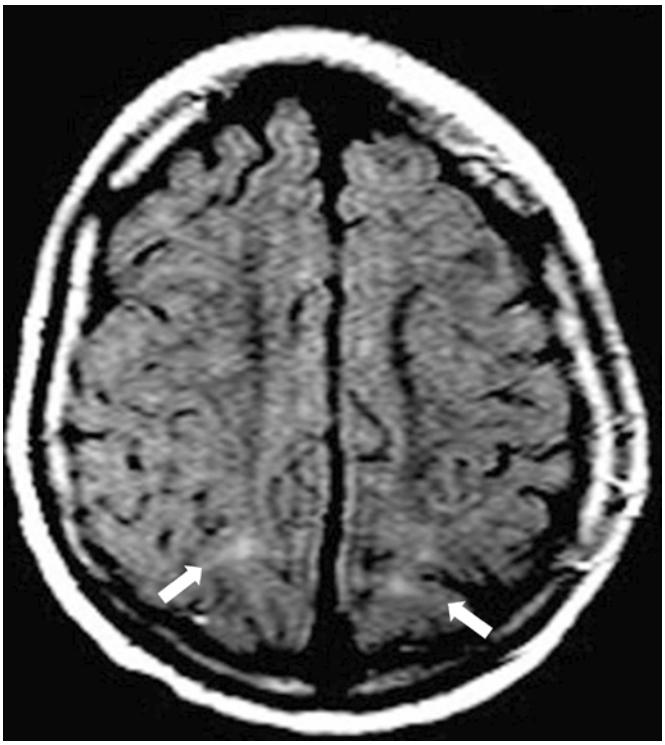

Figure c

RESULTS

ARX, *STK9*, and *MECP2* molecular analyses were all negative. Mitochondrial 37 gene resequencing analysis revealed that our patient is homoplasmic for the G8839A alteration in the ATPase6 gene within Complex V. His healthy mother was also found to be homoplasmic, indicating a likely polymorphism. No other mitochondrial alterations were identified.

500K SNP microarray analysis revealed a 5.7 Mb deletion at 2q24.3-31.1 [chr2: 164,240,531 – 169,939,018]. There are at least 19 genes within the 2q24.3-31.1 region, including the *SCN1A* gene. Mutations and deletions within the *SCN1A* (neuronal sodium channel alpha 1 subunit) gene, as well as whole gene deletions, are predominantly associated with Dravet syndrome [3]. Additionally, genes in the deleted 5.7 Mb region include *GRB14*, *SCN3A*, *SCN2A*, *GALNT3*, *SCN9A*, *STK39*, and *ABCB11* (Table 1), and likely contribute to our patient's complex phenotype.

Table 1 – Additional Genes in the Deleted 5.7 Mb Region

GENE	FUNCTION
GRB14	may play a role in signal pathways for growth and metabolism
SCN2A	sodium channel subunit gene; associated with epilepsy, but not specifically with Dravet syndrome
SCN3A	sodium channel subunit gene; not currently associated with a particular phenotype
GALNT3	hyperphosphatemic familial tumoral calcinosis [15]
SCN9A	may be associated with insensitivity to pain, autonomic dysfunction, and primary erythermalgia
STK39	may influence blood pressure [16] and has also been proposed as a gene associated with autism [17]
ABCB11	associated with progressive familial intrahepatic cholestasis 2 and benign recurrent intrahepatic cholestasis [18]

DISCUSSION

Dravet syndrome (SMEI) is an epileptic encephalopathy that occurs in seemingly otherwise normal infants. Focal myoclonic seizures often occur around 5-8 months and are shortly followed by focal or generalized clonic seizures, which may be precipitated by fever, heat, or vaccinations. Atypical absence seizures can develop as early as 4 months and tonic seizures are rare. Initial EEGs are often normal. Seizures are treatment resistant. Development may be normal initially and then around 2 years, delay is more evident. Pyramidal signs and ataxia may follow [4].

Our patient had an exceptionally early onset of seizures. The hiccups his mother felt during gestation may have been intrauterine seizures. Postnatal spells were first noted at 3.5 weeks. The initial EEG was normal (as are most EEGs early in the course of the epilepsy). The first definite clinical seizures with an EEG correlate occurred at 8 weeks.

Although Dravet syndrome is known to be associated with autonomic dysfunction, to our knowledge, this is the first report of periodic, recurrent episodes of autonomic storming in Dravet syndrome, which is both prevented and treated with clonidine. Autonomic symptoms may be an ictal or post-ictal manifestation of seizure, but in our patient, there was no correlation between seizures and the autonomic symptoms on video EEG. *SCN1A* is primarily a neuronal gene, but several studies have shown the product of the *SCN1A* gene is present in various regions of the heart in rat and mouse, in rabbit neonates, and in dogs [5]. Normal functioning of these channels is required for normal activity of the sinoatrial node and thus for normal heart rate variability in rodents [6]. Delogu et al. [7] showed abnormal regulation of heart rate in the sinoatrial node in patients with Dravet syndrome. The periodic paroxysms of autonomic dysfunction, responsive to Clonidine in our patient, are likely explained by the predominance of sympathetic versus parasympathetic activity noted to be present in children with Dravet syndrome [7].

MRI findings in Dravet syndrome are typically non-specific in the chronic stage. Some of the findings that have been described include cerebral and cerebellar volume loss, ventriculomegaly, and white matter hyperintensities [8]. Our patient demonstrated cerebral volume loss and diffuse subcortical white matter hyperintensities. Due to the history of choreoathetosis, we specifically looked for abnormalities in the basal ganglia, which on detailed evaluation appeared unremarkable. There have been studies in patients with Dravet demonstrating an association of hippocampal sclerosis following febrile seizures [9,10], although later studies did not support this association [8]. The majority of patients with Dravet do not demonstrate abnormal MRI findings [8,10]. However, when abnormal MRI findings are present, they are typically in individuals without a demonstrated *SCN1A* gene mutation [8,10].

Suls et al. [11] described one patient whose 2q deletion matched our patient's, yet he had no additional features outside of the core SMEI phenotype. Davidson et al. [12] described an individual with the same deletion as our patient (in addition to reviewing 42 other individuals (21 of whom had seizures) who have varying degrees of overlap with our patient's 2q deletion). Their patient exhibited refractory seizures beginning at 8 weeks, had micrognathia (like our patient) and had a cleft palate, high anal atresia, and atrial septal defect (unlike our patient). Marini et al. [13] described several patients with *SCN1A* deletions. None had the exact size deletion as our patient, except one, had a larger deletion (~9.3Mb) that encompassed the entire deletion of our patient. The individual had early severe intellectual disability, autistic features, mild dysmorphic facial features, and extreme photosensitivity (not described in our patient).

In conclusion, this case report adds to the literature of genotype-phenotype correlations associated with 2q microdeletions that include the *SCN1A* gene. Also, this is the first report of episodic autonomic storming, which can be both prevented and treated with clonidine, in Dravet syndrome. The clinical importance and expression patterns of over half of the genes deleted in the 2q region are currently unknown. Genes in the deleted 5.7 Mb region for which some expression pattern and/or function is known include *GRB14*, *SCN3A*, *SCN2A*, *GALNT3*, *SCN9A*, *STK39*, and *ABCB11* (Table 1). The large size of the 5.7 Mb deletion, including the *SCN1A* gene, likely explains our patient's complex medical picture and seizure disorder. We hypothesize that this deletion also is responsible for episodic autonomic storming described in our patient. Our findings further support the role of using microarray analysis for patients who have Dravet syndrome or atypical Dravet syndrome [14] without a *SCN1A* mutation demonstrated by sequence analysis.

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Competing interests
The authors have declared that no competing interest exists.

Author contributions

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