Pediatric Neurology 70 (2017) 67–69

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Myoclonic Absence Seizures in Dravet Syndrome

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ABSTRACT

BACKGROUND: Dravet syndrome is a developmental and epileptic encephalopathy that occurs as a result of *SCN1A* mutations in more than 80% of affected individuals. The core clinical features of Dravet syndrome include febrile and afebrile seizures beginning before 12 months; multiple seizure types, usually medically refractory, including hemiclonic, generalized tonic-clonic, focal impaired awareness, myoclonic, and absence seizures; status epilepticus; and normal early development with plateau or regression by age two years. Myoclonic absence seizures have not previously been described. **PATIENT DESCRIPTION:** This 20-year-old man had infantile-onset epilepsy with the classical clinical features of Dravet syndrome and a *de novo* A1326P *SCN1A* mutation. By five years of age, photosensitive myoclonic absence seizures had become his dominant seizure type, occurring up to 20 times per day. **RESULTS:** The seizures were refractory to multiple antiepileptic medications and a vagus nerve stimulator. **CONCLUSIONS:** Although photosensitivity is well recognized in Dravet syndrome, myoclonic absence seizures have not been previously reported. This rare seizure type may be underreported in Dravet syndrome, as the myoclonic features may be subtle and can be missed if thorough history taking and video recordings are not available.

Keywords: Dravet syndrome, SCN1A, myoclonic absence seizures, epileptic encephalopathy, absence seizures

Pediatr Neurol 2017; 70: 67-69

Introduction

Dravet syndrome is a developmental and epileptic encephalopathy in which individuals typically present prior to 12 months of age with febrile seizures, which are often prolonged.[1] Development is initially normal, but plateau or regression eventually occurs at around age two years. Individuals have multiple seizure types, usually refractory to therapy, including hemiclonic, generalized tonic-clonic, focal impaired awareness, myoclonic, and atypical absence seizures. Tonic seizures are rarely reported, usually in adolescence or adult life.[1,2] Mutations in *SCN1A* (OMIM #182389), the gene encoding neuronal voltage-gated sodium channel subunit $Na_v1.1$, are identified in more than 80% of patients with Dravet syndrome, occurring *de novo* in 90% of these.[3]

Here, we present the first description of a patient with myoclonic absence seizures, as well as the core clinical features of Dravet syndrome and an *SCN1A* mutation.

Patient Description

This 20-year-old man presented with a two-minute febrile generalized tonic-clonic seizure (temperature 38.1°C) at six months, following an uncomplicated pregnancy and delivery at term. At seven months, he had his first afebrile hemiclonic seizure. During the first five years of life, he had more than 100 generalized tonic-clonic or hemiclonic seizures. Convulsive status epilepticus occurred with clusters of seizures over one to four hours without return to baseline in between, as well as prolonged generalized tonic-clonic seizures lasting up to 25 minutes. Subsequently, he developed focal impaired awareness and myoclonic seizures around three and five years, respectively.

When first seen at age 5.5 years, his dominant seizure type was myoclonic absences lasting ten to 60 seconds (Figure) and occurring more than 20 times per day at their most frequent. These comprised bilateral 3-Hz myoclonic jerks superimposed on tonic upper limb abduction with loss of awareness. If standing, he had loss of posture but

Article History:
Received December 24, 2016; Accepted in final form January 4, 2017

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http://dx.doi.org/10.1016/j.pediatrneurol.2017.01.004

FIGURE.
Myoclonic absence seizure: A seven-year-old boy with Dravet syndrome. Before seizure onset, he is looking out a flywire screen door on a sunny day, where both photosensitivity and pattern sensitivity could be provoking factors. Both arms demonstrate tonic elevation and abduction, and rhythmic whole body jerks are observed at approximately 3 Hz. Loss of postural tone is seen with the torso flexing forward severely; however, the patient does not fall. The event lasted 12 seconds, and he immediately returned to baseline awareness postictally. The video related to this figure can be found at http://dx.doi.org/10.1016/j.pediatrneurol.2017.01.004. (The color version of this figure is available in the online edition.)

did not fall to the ground. These events were occasionally followed by generalized tonic-clonic seizures lasting up to 15 minutes. Seizures were frequently provoked by sunlight and by sitting close to the television and also occurred with photic stimulation during electroencephalography (EEG). His seizures were refractory to multiple medications, including valproate, clobazam, acetazolamide, carbamazepine, lamotrigine, topiramate, levetiracetam, stiripentol, ethosuximide, and clonazepam. A vagus nerve stimulator did not significantly improve seizure frequency; however, the frequency of myoclonic absences improved considerably following an increase in topiramate dose to 12 mg/kg/day at age 11 years.

From a developmental perspective, he was normal in the first months of life but had regression at age eight months, coincident with a cluster of seizures. He sat independently at 18 months, walked at 19 months, and his first word with meaning was spoken at age two years. He had prominent speech dyspraxia but by age 15 years spoke in five- to six-word sentences. Neuropsychological assessment at age seven years classified his intellectual disability as moderate-severe. He had severe behavioral issues with aggression and violence, refractory to risperidone, methylphenidate, atomoxetine, and olanzapine. Family history was significant for his father having a febrile generalized tonic-clonic seizure at age two years. There was no other family history of epilepsy or febrile seizures.

His EEG at age four years showed generalized spike-wave discharges during photic stimulation and normal background activity. By age six years, background slowing and multifocal epileptiform discharges were also noted, and myoclonic and myoclonic absence seizures were captured on a routine study. At 15 years of age, generalized spike-wave and polyspike-wave discharges were present, but photic stimulation did not elicit additional abnormalities. Brain magnetic resonance imaging was normal at age 18 months. Genetic testing identified an A1326P mutation in *SCN1A*, which was not found in either parent.[4]

Discussion

Our patient experienced myoclonic absence seizures, a seizure type not previously reported in Dravet syndrome, which became his dominant seizure type in mid-childhood. His presentation was otherwise classical for Dravet syndrome, with infantile onset of hemiclonic and generalized tonic-clonic seizures and status epilepticus, followed later by focal impaired awareness and myoclonic seizures. His seizures were refractory to multiple antiepileptic medications and a vagus nerve stimulator. His developmental profile was also consistent with Dravet syndrome, with normal early development and regression occurring coincident with a seizure exacerbation in infancy. The electroclinical syndromic diagnosis was further supported by the identification of a *de novo* mutation in *SCN1A*, a gene not previously associated with myoclonic absence seizures.

Myoclonic absence seizures are an uncommon type of seizure, usually involving ten to 60-second episodes of complete or partial loss of awareness, tonic upper limb abduction, and rhythmic jerking at approximately 3 Hz, concordant with the generalized spike-wave discharges on EEG.[5-7] Autonomic manifestations are also common, including apnea and urinary incontinence.[6] This type of seizure has been primarily described in the syndrome of epilepsy with myoclonic absences, a childhood-onset epilepsy syndrome in which affected individuals have frequent daily myoclonic absence seizures.[5,6] When other seizure types occur with epilepsy with myoclonic absences, they are usually typical absences, generalized tonic-clonic seizures, or atonic drop attacks.[6]

The underlying cause of myoclonic absence seizures is presumed to be genetic; however, a monogenic cause is identified in only a small minority of these individuals. There are mostly single reports of patients with myoclonic absence seizures and genetic mutations, including gain-of-function mutation in glutamate dehydrogenase,[8] *SLC2A1* mutation (GLUT1 deficiency syndrome),[9] trisomy 12p,[10-12] maternal 15q11-13 loss,[12] and chromosome 15 inversion duplication.[12]

Although not previously reported with myoclonic absence seizures, mutations in *SCN1A* can result in a number of epilepsy syndromes other than Dravet syndrome, including genetic epilepsy with febrile seizures plus,[13,14] epilepsy of infancy with migrating focal seizures,[15] and epileptic spasms.[4] Our patient clearly had Dravet syndrome for which this rare form of generalized seizure has not been described.[5,6]

In summary, this child demonstrates that myoclonic absence seizures can occur in Dravet syndrome with *SCN1A* mutation and may even become the dominant seizure type during a phase of the child's illness. Myoclonic absence seizures should now be included among the seizure types that may occur in individuals with Dravet syndrome, although these seizures may be rare. However, myoclonic absence seizures may be missed because their diagnosis necessitates a thorough clinical history and, since the rhythmic myoclonic jerks may be subtle, may require video recordings to capture clinical events.

We thank the patient and his family for participating in this research, including supplying the video of the seizure and providing consent for publication. Funding: This work was supported by the National Health and Medical Research Council (project grant number 628952 and practitioner fellowship number 1006110 [for Prof. Scheffer]).