Severe myoclonic epilepsy of infancy (Dravet syndrome): Clinical and genetic features of nine Turkish patients

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Abstract

Purpose: Mutations of the α-1 subunit sodium channel gene (*SCN1A*) cause severe myoclonic epilepsy of infancy (SMEI). To date, over 300 mutations related to SMEI have been described. In the present study, we report new SCN1A mutations and the clinical features of SMEI cases. **Materials and Methods:** We studied the clinical and genetic features of nine patients diagnosed with SMEI at the Pediatric Neurology Department of Istanbul Medical Faculty. **Results:** Five patients had nonsense mutations, two had missense mutations, one had a splice site mutation and one had a deletion mutation of the *SCN1A* gene. Mutations at c.3705+5G splice site, p.trip153X nonsense mutation and deletion at c.2416_2946 have not been previously described. The seizures started following whole cell pertussis vaccination in all patients. The seizures ceased in one patient and continued in the other eight patients. Developmental regression was severe in three patients, with frequent status epilepticus. The type of mutation was not predictive for the severity of the disease. Two of the three patients with severe regression had nonsense and missense mutations. **Conclusions**: Dravet syndrome can be result of several different types of mutation in *SCN1A* gene. Onset of the seizures after pertussis vaccination is an important clue for the diagnosis and neuro- developmental delay should be expected in all patients.

Key Words

Dravet syndrome, severe myoclonic epilepsy of infancy, α-1 subunit sodium channel gene mutation.

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Introduction

Severe myoclonic epilepsy of infancy (SMEI) was first described in 1978 by Charlotte Dravet.[1] In 2001, it was added to the list of epileptic encephalopathies by the International League Against Epilepsy (ILAE).[2] It constitutes 3-5% of the epilepsies occurring in the first year of life and 6.1-7% of the ones that occur in the first 3 years.[3-7] Clinically, Dravet syndrome (DS) presents with generalized or hemiclonic febrile seizures within the first year of life. Psychomotor and speech development is normal in the early life, but developmental delay may occur during the second year.[8-10] Genetic tests are important in the diagnosis. Gene mutations in alpha subunit sodium channels (*SCN1A*) have been reported in 33.3-100% of SMEI cases. The *SCN1A* gene encodes the neuronal voltage-gated sodium channel α-1 subunit, which is dominantly expressed in the central nervous system. More than 700 new mutations have been identified to date, with missense mutations being the most common in generalized epilepsy with febrile seizures, and more deleterious mutations (nonsense, frameshift) representing the majority of SMEI mutations.[11-14]

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In the present study, we report *SCN1A* mutations and clinical features of patients diagnosed with SMEI in a tertiary hospital.

Materials and Methods

Patients clinically diagnosed with severe myoclonic epilepsy of infancy at the Pediatric Neurology Department of Istanbul Medical Faculty were enrolled in the study. Demographic features, seizure characteristics including age at onset, seizure triggers, frequency and types, physical examination findings and medical treatment of the patients were retrospectively recorded and *SCN1A* gene mutations were studied. Seizure types were determined using the International League Against Epilepsy (ILAE) criteria. Brain morphology was assessed by magnetic resonance imaging (MRI) in all patients, and metabolic examinations were conducted. Sleep and awake electroencephalogram (EEG) recordings of all patients were done with intermittent photic stimulation. Electrodes were placed in accordance to the international 10-20 system.

Psychomotor development in children under 6 years of age was evaluated using the Denver Developmental Screening Test (DDST-II), while the Wechsler Intelligence Scale for Children-Revised (WISC-R) test was used for the three patients over 6 years of age. Personal regression rates were classified as mild, moderate and severe based on the developmental tests and neurological examination. Genomic Deoxyribonucleic acid (DNA) was obtained from peripheral blood lymphocytes of patients. Genetic analysis was performed at the Laboratory of Neurogenetics, Institute Born-Bunge, University of Antwerp.

Results

Nine patients were enrolled in the study. Six patients were male and three were female. Age at first evaluation was 2-10 months (average - 6.5+1.8 months). The follow-up periods varied from 4 years to 15 years and 9 months (average - 7.21 ± 3.8 years). Age at first seizure was 2-6 months (average - 4.75 ± 1.16 months). In all patients the first seizures were triggered by fever and were related to whole cell pertussis vaccination. Four patients (45%) had family history of epilepsy or febrile seizures. The father of patient 9 had history of prolonged febrile seizures [Table 1]. Four patients had generalized seizures and five had focal seizures (two with alternating side). All patients had at least one episode of status epilepticus triggered by fever. The initial EEG recordings of the patients were normal. After 2 years of follow-up, all patients had both generalized and focal myoclonia. EEG revealed multifocal spikes and background slowing in five patients, three of which had frequent status epilepticus. Four patients only had focal sharps in the frontal regions. None of the patients had photosensitivity. Atypical absence seizures were seen in seven patients. These seizures occurred several times a day in two patients, 1-2 times a day in two patients and less frequently in three patients. In five patients, seizures and myoclonia were aggravated by antiepileptic drugs, vigabatrin, carbamazepine, oxcarbazepine, lamotrigine, and phenytoin. Valproate reduced seizure severity in all patients. Benzodiazepines were added to the treatment of seven patients. Topiramate was chosen for add-on treatment of four patients. In two patients, seizures were controlled with a combination of three drugs.

Developmental delay and behavioural disorders (hyperactivity) were evident especially in the periods of frequent seizures (1-4 years). Developmental regression was moderate in six patients and severe in three. Severe developmental regression was seen in patients with frequent status epilepticus. Five patients had nonsense mutations, two had missense mutations, one had a splice site mutation and one had a deletion mutation of the *SCN1A* gene. Mutations at c.3705+5G splice site, p.trip153X nonsense mutation and deletion at c.2416_2946 have not been previously described. Two of the three patients with severe SMEI had nonsense and missense mutations [Table 1].

Discussion

According to the corrected criteria of the ILAE (1989), Dravet syndrome is characterized by febrile, afebrile, generalized or unilateral clonic or tonic-clonic seizures that appear in the first year of life in previously healthy infants. After the first year, the clinical features are accompanied by myoclonia, atypical absence and complex partial seizures. It is not classified as focal or generalized epilepsy by the ILAE, but rather as an epileptic syndrome.[15] All seizure types are resistant to antiepileptic drugs. The patients generally have frequent episodes of status epilepticus.[1] The aforementioned seizure types and status epilepticus were seen in our patients. After the initial epileptic seizures, all patients had status epilepticus that was mainly associated with fever. Status epilepticus episodes were considerably frequent in two patients and decreased in frequency after antiepileptic treatment. In our older patients, generalized or secondary generalized seizures persisted. Myoclonia appeared most frequently between 1-4 years of age. After the second year of life, in which seizures occur more frequently, developmental and cognitive regression with behavioural disorders, hyperactivity and autistic behaviours are reported.[9] Our cases displayed similar features. Sudden occurrence of seizures and developmental regression after the pertussis vaccine in previously healthy children may confound as that it may be related with vaccination.[16,17] There are several reasons for seizures and developmental regression in infancy. Some of them were incorrectly identified as vaccine encephalopathies.[18] However, later studies did not support the link between permanent brain damage and vaccines.[19-21] On the other hand, similarities were observed between clinical progressions of SMEI and vaccine encephalopathy as more data was gained about special epilepsy syndromes like SMEI. Berkovic *et al*. detected *SCN1A* gene mutations in 11 out of 14 patients who were diagnosed with vaccine encephalopathy. It was reported that the cause of vaccine encephalopathy was not vaccination but rather the genetically determined age-specific epileptic encephalopathy.[22] In our patients, convulsions started after whole cell pertussis vaccination. Similarly, recent data from a study by McIntosh *et al*. showed that 37 patients out of 40 in the cohort had their first seizure after at least one DTP vaccination. They concluded that while the pertussis vaccine is a trigger for earlier onset of the disease, it does not affect its outcome.[23]

Myoclonia is the most frequent type of seizures that occur in SMEI patients after the first year of life. However, the diagnosis should not be excluded if the patient exhibits the clinical and laboratory findings of SMEI without myoclonia.[8] Patients whose EEGs with photic stimulation show atypical absence seizures, sporadic multifocal or diffuse spike waves and, less frequently, multiple spike and paroxysmal multiple spike waves but no myoclonia are considered borderline SMEI.[24] Our patients had focal and generalized myoclonia associated with SMEI.

Seizures in SMEI cases can be treated with classical antiepileptics. The best combination appears to be valproate and benzodiazepines (clobazam, clonazepam, lorazepam). Such drugs as ethosuximide and piracetam could decrease myoclonia. Topiramate is also an effective drug.[25] In our patients, good results were obtained with sodium valproate and benzodiazepines in combination with topiramate. Before the diagnosis of DS was made, response to drugs like carbamazepine, phenytoine, vigabatrine and lamotrigine was not satisfying, and instead myoclonia was observed to increase. Stiripentol, zonisamide, bromides and ketogenic diet have also been reported to be effective.[26-28]

Table 1: Clinical and laboratory features of 9 patients of severe myoclonic epilepsy of infancy during the study

Sex	Age (y = year and mo = month)	First seizure			Seizure type				MR	SCN1A mutation	Status epilepticus	MRI	Family history of febrile seizure / epilepsy
		Age (months)	Precipitating factors	Seizure type	GTCS	AS	MS	PS	HS				
M	15y 9mo	5	Vaccination	PS	+	+	+	+	+	Severe	Asp1497Gly missense	+ (5)	n	-
M	5y 5mo	5	Vaccination	PS	+	-	+	+(a)	+	Moderate	p.asp1484X nonsense	+ (1)	n	+
M	6y	4	Vaccination	GTC	+	+	+	+	+	Moderate	p.arg1912X nonsense	+ (1)	n	-
F	6y 8mo	2	Vaccination	PS	+	+	+	+	+	Moderate	p.Ala1370Val missense	+ (2)	n	+
F	5y 3mo	5	Vaccination	PS	+	+	+	+ (a)	+	Moderate	p.Leu1127X nonsense	+ (2)	n	-
M	6y 5mo	6	Vaccination	GTC	+	+	+	+	+	Moderate	p.trip153X nonsense	+ (1)	n	-
M	6y	6	Vaccination	GTC	+	+	+	+	-	Moderate	c.3705+5G splice site	+ (1)	n	+
M	6y 10mo	4	Vaccination	PS	+	-	+	+	-	Severe	p.Asp936X nonsense	+ (5)	n	-
F	14y 7 mo	4	Vaccination	GTC	+	+	+	+	-	Severe	c.2416_2946 del	+ (3)	n	

+ = Present;- = Absent, (a) = Alternate; MRI = Magnetic resonance imaging; FS = Febrile seizures; GTCS = Generalized tonic–clonic seizures; AS = Absence seizures; MS = Myoclonic seizures; PS = Partial seizures; HS = Hemiclonic seizures; MR = Mental retardation

The *SCN1A* gene mutation is responsible for most (40-100%) cases of SMEI and 5-10% of generalized epilepsy with febrile seizures plus (GEFS+) families.[11,29,30] Over 300 mutations (missense, nonsense, deletion and splice site) related to SMEI have been detected in the neuronal sodium channel α1 subunit gene (*SCN1A*).[11-14] Existence of febrile seizures in some families with *SCN1A* mutations and of SMEI in others is dependent on polygenic inheritance. Kanai *et al*. have stated that mutations in SMEI cases occur more frequently in the "pore" regions of *SCN1A* compared to GEFS+ cases.[31] *SCN1A* gene mutation analysis showed mutations in all (100%) of our SMEI patients. The fact that *SCN1A* mutations are reported in wide ranges has been linked to the number of patients, patient selection criteria and ethnical differences.[13,32,33] San and Ohmari have reported *SCN1A* gene mutation rates to be as high as 83.3% and 82.7% in Chinese and Japanese patients, respectively. They considered the high rates of *SCN1A* mutations to be connected to the low patient number, typical SMEI features, and ethnic and geographic similarities.

In conclusion, Dravet syndrome can be result of several different types of mutation in *SCN1A* gene. Pertussis vaccination acts as a trigger for the onset of the disease. Neuro-developmental delay and behavioral problems that appear after two years of age should be expected in all patients as long-term complications of the disease.

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