TÜRK PEDİATRİ ARŞİVİ
TURKISH ARCHIVES of PEDİATRİCS

Case Report

A case of Dravet Syndrome with a newly defined mutation in the *SCN1A* gene

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Cite this article as: Öz Tunçer G, Teber S, Albayrak P, Kutluk MG, Deda G. A Case of Dravet Syndrome with a newly defined mutation in the SCN1A gene. Turk Pediatri Ars 2018; 53(4): 259-62.

Abstract

Dravet syndrome is a catastrophic progressive epileptic syndrome. De novo loss of function mutations on the SCN1A gene coding voltage-gated sodium channels are responsible. Disruption of the triggering of hippocampal GABAergic interneurons is assumed as the cause of fall in the seizure threshold. A ten-year-old boy first presented at age 10 months with febrile-clonic seizures, which began when he was aged 8 months. Electroencephalography was found as normal. Phenobarbital was initiated because of long-lasting seizures. However, his seizures continued and the therapy was replaced with valproic acid. On follow-up, different antiepileptics were used, which were stopped due to inefficiency or adverse effects. SCN1A gene analysis was performed and a heterozygous c.4018delC mutation was identified. This new frame-shift mutation resulting from an early stop-codon is thought to be the cause of the disease. Finally, he was prescribed valproic acid and stiripentol. For patients with fever-triggered, treatment-resistant seizures, and delayed psychomotor development, Dravet syndrome should be considered. Genetic diagnosis is important for treatment and follow-up.

Keywords: Dravet Syndrome, epilepsy, *SCN1A* gene

Introduction

Dravet Syndrome is a destructive epileptic syndrome with onset in the first months of life leading to progressive disruption in cognitive, behavioral, and motor functions.

This syndrome, which was considered epileptic encephalopathy, was defined as severe myoclonic epilepsy of infancy (SMEI) in 1978 by Dravet, and similar cases were reported in time in the literature (1). Primarily, focal or generalized seizures are observed at about the age of six months in patients who are normal before seizure. Over time, the duration of seizures prolongs. In addition, afebrile, generalized clonic or hemiclonic seizures occur at the age of one year and seizures including myoclonic seizures and absence seizures occur at the age of 1-4 years. Washing the head with hot water and vaccines may trigger seizures. About half of all patients may present with a picture of status epilepticus. All these seizures are resistant to standard antiepileptic treatment. Although interictal electroencephalograms (EEG) are generally normal in the first six months, EEG disorders including generalized symmetric or asymmetric spike or multiple spike waves and focal abnormalities are observed at the end of three years. These disorders may increase in sleep. The photoparoxismal response is an important finding of the disease. Although neurologic examinations are normal in the beginning, ataxia and pyramidal findings may be observed during the course of the disease. Psychomotor developmental retardation is important for the diagnosis.

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Received: 27.04.2016 **Accepted:** 03.02.2017
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DOI: 10.5152/TurkPediatriArs.2018.4197

In time, atypical/borderline cases (SMEB) were described, in addition to clinically typical cases of SMEI, in which myoclonic seizures and generalized spike wave activity on EEG were not observed and cognitive disruption was more limited (2). The disease was named Dravet syndrome instead of severe myoclonic epilepsy of infancy because of this clinical heterogeneity.

Dravet syndrome is a rare disease with an unclear prevalence ranging between 1/20,000 and 1/40,000 in different publications (3, 4). Most families have a history of febrile seizure or epilepsy. This tendency suggested a genetic cause and the association of the disease with mutations in the *SCN1A* gene encoding the α1 subunit of voltage-gated sodium channels was proven in 2001 (5). A mutation is present in this gene in approximately 75% of patients.

A mutation in the *SCN1A* gene is observed in cases of SMEB, like in cases of SMEI, and the clinical expectation is similar to typical cases. There are publications reporting that an *SCN1A* gene mutation is found with a lower rate in cases of SMEB compared with cases of SMEI (6).

Among the epilepsy genes, the *SCN1A* gene has been associated with clinical presentation most frequently and many mutations have been identified. We would like to present a patient with Dravet syndrome who was followed up in our clinic who had no myoclonic seizures and was found to have a new mutation.

Case

A ten-year-old male patient presented to our clinic at the age of 10 months for the first time. He had recurrent febrile generalized clonic seizures that started at the age of eight months.

The patient was born by normal vaginal delivery without any complications after a trouble-free pregnancy. His mental and motor development was compatible with his peers. His physical examination was found to be normal.

His non-consanguineous parents were healthy. There was no familial history of any neuropsychiatric disease including epilepsy or febrile seizures.

Cranial magnetic resonance imaging performed at the age of nine months in an external center was found to be normal. No pathology was found on an electroencephalogram (EEG), but phenobarbital treatment was initiated because of a febrile generalized clonic seizure that lasted for 45 minutes in the same month. The phenobarbital treatment was switched to valproic acid treatment at the age of 17 months because seizures continued in the follow-up. He was followed up for one and a half years without seizure. When seizures started again at the age of three years and increased, carbamazepine and lamotrigine were tried, but then discontinued because no benefit was obtained. Topiramate treatment was initiated. He spent five years without seizures, but seizures recurred at the age of nine years. His academic success, which was already poor, became worse. An EEG revealed an epileptic anomaly that originated from the left frontotemporal region and showed extension (Picture 1). Drugs including clobazam, levetiracetam, and oxcarbazepine were tried in order, but these drugs were also discontinued because of inefficiency or adverse effects including weight loss and restlessness.

A heterozygous c.4018delC mutation was found in the *SCN1A* gene analysis performed with a prediagnosis of borderline Dravet syndrome in the patient whose seizures were generally triggered by fever, observed rarely in the form of febrile status, became afebrile in time, and had a treatment-resistant course.

Stiripentol, which acts on GABA as an allosteric modulator, was added to the valproic acid treatment and the patient was followed up further. Although the patient had short-term atonic seizures a few times weekly before the stiripentol treatment, his quality of life and academic success improved markedly after treatment. He has been followed up without seizures for 10 months. Written informed consent was obtained from the parents of the patient.

Discussion

Developments in recent years have demonstrated the role of channelopathies in important neurologic diseases. Although de novo loss-of-function mutations in the *SCN1A* gene are responsible for most cases, there are also patients with positive *SCN1B, SCN2A, GABRG2, GABRA1*, *STXBP1*, *PCDH19* mutations or patients clinically diagnosed as having Dravet syndrome who are not found to have any mutations (7, 8). More than 300 *SCN1A* mutations have been identified including de novo mutations found in genetic investigations in patients without a positive familial history. In addition, *SCN1A* anomalies were

found with a frequency of 5-10% in families in whom generalized epilepsy+febrile seizures (GEFS+) were found. However, a mutation generally causes Dravet syndrome (9). Among individuals who carry this mutation, clinical variability may be observed ranging from typical cases to borderline cases. In some of the family members who carry the same mutation, febrile seizure alone or mental retardation and Dravet syndrome may develop. Therefore, the presence of an *SCN1A* mutation should be considered also in mild clinical phenotypes.

It is assumed that the seizure threshold decreases because triggering of the hippocampal GABAergic interneurons is disrupted. It is thought that repair of GABAergic neurotransmission may improve other neurologic functions as well as decreasing seizures.

The earlier the EEG disorders are found, the poorer is the developmental prognosis. Sudden unexpected death in epilepsy occurs more frequently in Dravet syndrome compared with other epileptic syndromes.

In treatment, valproic acid, clobazam, topiramate, levetiracetam, stiripentol, and a ketogenic diet are appropriate options. Carbamazepine and lamotrigine may increase the frequency of seizures, as in our patient. Therefore, it is important to avoid these drugs.

As observed in this case, borderline cases showing a clinical course similar to typical Dravet syndrome in the absence of myoclonic seizures or EEG findings including generalized spike wave activity should also be included in the spectrum. Although knowledge of the absence of myoclonic seizure in a myoclonic epileptic syndrome is already inured, it may be overlooked. Early diagnosis may be difficult because typical clinical findings develop with time. Electroencephalography provides limited help in the diagnosis in the early stage.

Currently, physicians use *SCN1A* gene analysis, especially in the presence of prolonged and lateralized febrile seizures. If a mutation is found, the diagnosis of GEFS+, typical or borderline Dravet syndrome should be reviewed considering the patient's clinical status. Most *SCN1A* mutations occur de novo (82%). In the study conducted by Marini et al. (9), a missense mutation was generally found in patients with SMEB (62.5%), whereas premature termination, splice site

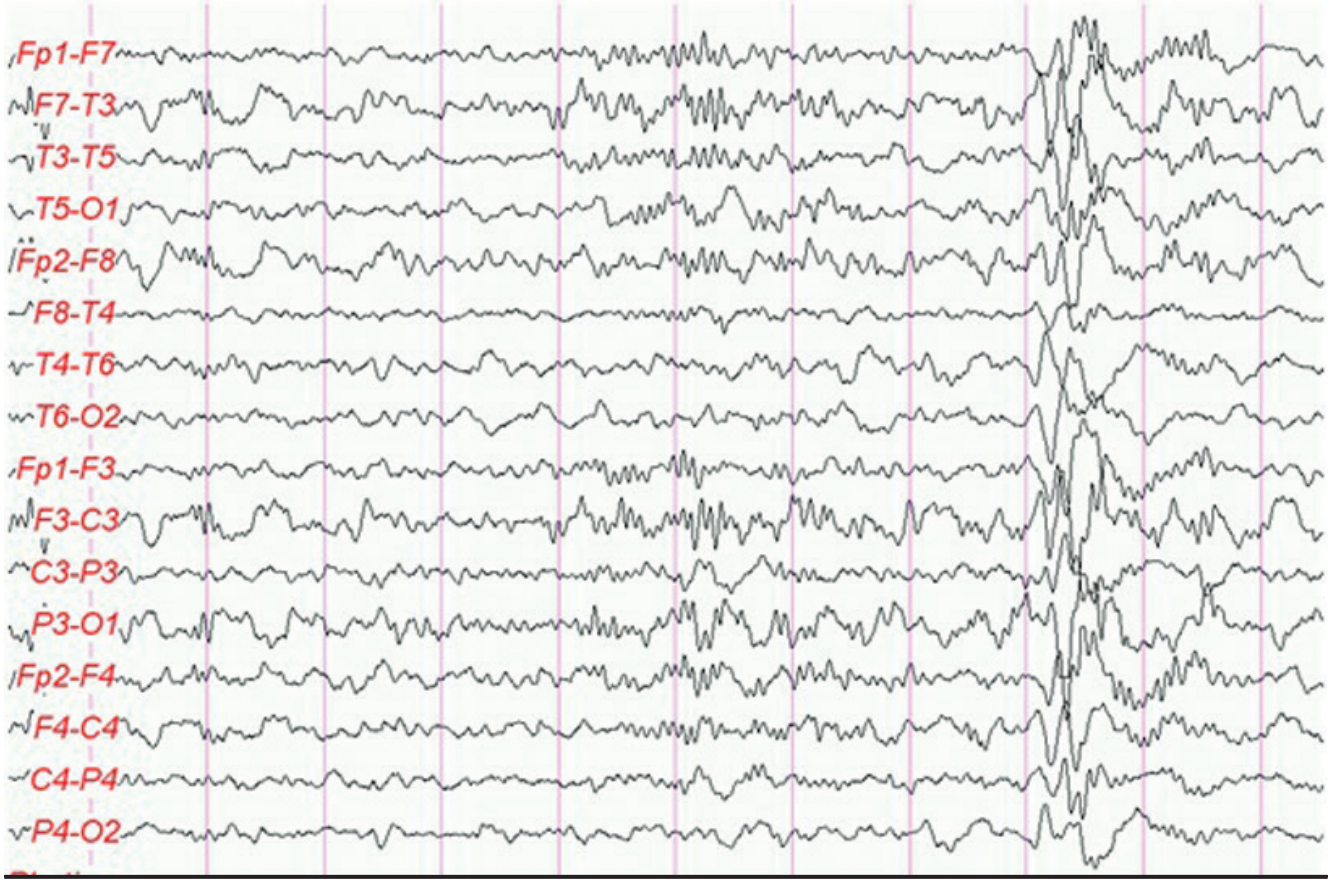

Figure 1. EEG; epileptic anomaly originating from the frontoparietal region in the left hemisphere and showing generalization

or genomic changes were observed in patients with SMEI (64.5%). Similarly, nonsense and frameshift premature termination mutations (63.2%) and missense mutations (36.8%) were found in SMEI, whereas only missense mutations (100%) were observed in SMEB in the study conducted by Fukuma et al. (6). When other publications in the literature are also considered, it is observed that the cause is premature termination of the *SCN1A* molecule because of nonsense, splice site, and frameshift mutations in nearly all cases of SMEI, whereas missense mutations lead to SMEB, which has a milder clinical prognosis (10).

The *SCN1A* mutation found in our patient has not been defined before and was evaluated to be the cause of the disease because it caused frameshift and a premature stop codon. This new mutation, which caused premature termination, led to a picture of SMEB instead of SMEI in contrast to what was expected. When our case and the studies mentioned were reviewed generally, it was observed that all these mutations might cause both pictures with different frequencies. This heterogeneity suggests the presence of other genetic factors accompanying *SCN1A* mutations.

The selection of appropriate antiepileptic drugs in the treatment of this disease, avoiding unnecessary investigations, predicting the prognosis, and genetic diagnosis for awareness of the mortality risk, which reaches 10%, are important because it is known that seizure control contributes to cognitive status even years later. Therefore, borderline cases like ours should be kept in mind and genetic diagnosis should be used.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.T., G.T.; Design - G.T.; Supervision - G.D., S.T.; Data Collection and/or Processing - M.G.K, P.A.; Analysis and/or Interpretation - G.D., S.T.; Literature Review - P.A.; Writing - G.T., M.G.T.; Critical Review - G.D., S.T., G.T., P.A., M.G.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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