Case Report

A Novel SCN1A Mutation: A Case Report

Mahmut Aslan, Bilge Ozgor, Serkan Kirik, Serdal Gungor

Department of Pediatrics and Pediatric Neurology, Faculty of Medicine, Inonu University, Malatya, Turkey

Introduction: Dravet syndrome (DS) is characterized by severe infant-onset myoclonic epilepsy with delayed psychomotor development and increased premature mortality. The seizures triggered by fire have been gradually decreased over time, and finally they start to occur without fever at the age of 2–3 years. Along with its initiation of myoclonic seizures in the early period, other types such as atypical absence, versive, and complex partial seizures occur between 1 and 4 years of age. Case Report: A 3-year-old male patient with refractory epilepsy and neuromotor developmental retardation was admitted to our clinic. The patient initially had seizures in the afebrile period, when he was 4 months old, and he had a total of five seizures by the age of 1 year. Neuromotor developmental retardation developed over time in patients with normal neuromotor development in the early stages of his life. His cranial magnetic resonance imaging and metabolic test findings were normal. The SCN1A mutation was investigated, and a new variant mutation of SCN1A, homozygous (p.Y1599Ffs*19-c.4796delA) was detected. The patient’s family was also screened and this new mutation was detected as heterozygous mutation. The patient had hepatomegaly. The etiology of hepatomegaly was investigated but no cause was found. Conclusion: Variant mutations of DS should be kept in mind and diagnostic genetic testing should be done in patients with neuromotor developmental retardation starting with afebrile seizures. In DS, hepatomegaly is not an expected condition. Maybe this new mutation might have caused hepatomegaly.

Keywords: Novel mutation, SCN1A, seizure

INTRODUCTION

Dravet syndrome (DS), which is classified as a type of childhood epileptic syndromes, was first described by Charlotte Dravet in 1978. Its prevalence has been estimated to be 0.5–1 in 20,000 newborns.[1] Although the first seizures are triggered by febrile illnesses, vaccinations, and hot water baths during infancy, they may also begin with afebrile seizures.[1] The seizures triggered by fever have been gradually decreased over time, and finally they start to occur without fever at the ages of 2–3 years. Along with its initiation of myoclonic seizures in the early period, other types such as atypical absence, versive, and complex partial seizures occur between 1 and 4 years of age.[2]

The cognitive functions and behaviors of the patients in whom neurological development is appropriate with the age in the early period begin to be affected by the frequency of seizures.[2] Approximately 60% of the affected children have ataxia, whereas 20% have pyramidal findings. Electroencephalography (EEG) obtained during the interictal period is usually normal within the first year, although rare spontaneous spikes and wave discharges or those triggered by the light stimuli can be seen. Epileptiform EEG findings usually appear at the age of 2–3 years.[3] Cranial magnetic
resonance imaging (MRI) and metabolic tests usually produce normal results.[3,4] The prognosis is usually poor, whereas frequent seizures and status attacks affect cognitive development adversely. During the follow-up, the seizure pattern generally changed as myoclonic and focal onset impaired awareness seizures to the generalized tonic–clonic seizures and focal to bilateral tonic–clonic seizures detected in video-EEG records.[5]

It has been thought that genetic factors play an important role in DS. Epilepsy or the history of seizure is detected in 25%–64.4% of the families. Monozygotic twins have been shown to be affected, and siblings have similar symptoms.[6] Mutations in the SCN1A gene are detected in 30%–80% of cases, and there are approximately 1000 variants of SCN1A. Other than SCN1A, other mutations in the GABRG2, SCN1B, GABRA1, STXBP1, PCDH19, and CHD2 are also common.[8]

Herein, we report a novel mutation in the SCN1A gene associated with the clinical vignette of DS in a pediatric case with seizures that started during infancy.

**Case Report**

A 3-year-old male patient was admitted to our clinic due to epileptic seizures resistant to antiepileptic drug treatment. The initial seizures started as left focal myoclonic type during febrile period, when he was 4 months old. His EEG findings were normal and he had myoclonic seizures accompanied by the loss of consciousness as sudden dullness, lapse in attention, and vacant stare during the first year of life. His afebrile seizures during the follow-up frequently recurred throughout the febrile period. During the follow-up, the developmental stages were normal within the first year, his development slowed down and regressed. The seizures were unable to be controlled and oxcarbazepine, phenytoin, valproic acid, and levetiracetam were added to the current phenobarbital treatment (before DS is diagnosed). Despite all efforts, seizures continued to occur frequently.

On physical examination, meaningless word repetitions and hand stereotypic movements were observed, whereas there was no verbal cooperation appropriate with his age. The patient had hepatomegaly. The etiology of hepatomegaly was investigated—except liver biopsy—but no cause was found. On neurological examination, there was no finding, except for ataxic walking without support, whereas other system examinations were normal. Urine blood amino acids, tandem mass spectrometry (MS) results, urine organic acids, and cranial MRI findings were normal. Repeated EEG showed frequent repetitive generalized spike-slow waves and multiple spike-slow wave activities. His antiepileptic treatment was modified as valproic acid, topiramate, and clobazam, and the seizures reduced by more than 50%. A previously unidentified (p. Y1599FFs*19-c.4796delA) [Figure 1] homozygous mutation was detected in the SCN1A, as there was resistant epilepsy, neuromotor developmental retardation, and regression during this period. The patient’s family (siblings and parents) was also screened, and this new mutation was detected as heterozygous mutation with both parents. This mutation has been evaluated as a cause of the disease because of mutation tester evaluation and frame shift by genetic doctors.

**Subjects and Methods**

Screening for genetic analysis was performed using a next-generation sequencing kit (Nextera V2). Before the application, polymerase chain reaction amplification and deoxyribonucleic acid fragmentation were conducted, and the genetic material was analyzed by the following workflow:

**Discussion**

In DS, seizures often start under 1 year of age, whereas the clinical findings usually start under 5 years of age.[1] The initial febrile seizures are accompanied by afebrile-resistant seizures and they are characterized by neurological regression.[2] In our case, he had afebrile clinical seizures, and febrile seizures (with high body temperature [>37.5°C] related with infection) were occasionally accompanied by fever and antiepileptic treatment–resistant seizures, starting when he was 4 months old, and he was diagnosed with DS.

The similarity of the clinical course with that of DS and the onset of afebrile seizures in the early infancy may be a finding associated with the novel mutation. As new cases of this novel mutation are defined over time, the onset of afebrile seizures may be significant. In DS cases, EEG obtained during the interictal period is usually normal within the first year, whereas the occasional spike wave discharges, which appear spontaneously or those triggered by a light stimulus, can be seen, although rare.[3] Similarly, the epileptic abnormalities were detected in the follow-up EEGs, although the initial EEG findings were normal in our case.

Cranial MRI and metabolic test results of DS cases are usually normal.[5] The mental development pauses and regresses within the years, and the mental retardation, then, develops overtime.[2] Although the cranial MRI and metabolic evaluation and the development stages of the life within the 1 year of age were normal in our...
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case, frequently recurrent seizures and neurological regression developed overtime.

Several studies have shown that DS is accompanied by resistant seizures, and multiple antiepileptic administration is required. Valproic acid and clobazam are the most effective medications to control seizures in DS, whereas the addition of stiripentol, a new antiepileptic drug, to the therapy has been reported to reduce the frequency and severity of the seizures in the early phase. In addition, medications, such as carbamazepine and phenytoin, have been shown to exacerbate the seizures. Therefore, the clinical distinction for choosing the most appropriate treatment is of utmost importance in terms of increasing the treatment success. Despite the multiple antiepileptic drug therapy, our case had resistant seizures. We reduced the frequency of the seizures by modifying the treatment, including valproic acid, clobazam, and topiramate.

The most common mutation in DS is SCN1A, and this mutation is known to have about 1000 variants. In our case, we detected a novel mutation of SCN1A (p.Y1599Ffs*19-c.4796delA), which would contribute to the literature. However, a higher number of cases are needed to identify the phenotypic features of this mutation. The patient had hepatomegaly. The etiology of hepatomegaly was investigated but no cause was found. In DS, hepatomegaly is not an expected condition. Maybe this new mutation might have caused hepatomegaly.

In conclusion, DS is an epileptic syndrome with poor prognosis, which begins with recurrent febrile seizures and continues with persistent seizures and severe neuromotor developmental retardation. In addition to this novel mutation-associated DS, hepatomegaly was thought to develop. However, the cases except for typical clinical course should be also kept in mind. It is extremely important that these cases should be identified to tailor an effective antiepileptic treatment.

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Conflicts of interest
There are no conflicts of interest.

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Figure 1: SCN1A mutation's figure
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