Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 11/26/2020
Approved on: 02/04/2022

CASE REPORT

Scn1a mutations and their different phenotypic expressions - comparison of two cases

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Keywords:
Loss of Function Mutation,
Epilepsy,
NAV1.1 Voltage-Gated Sodium Channel.

Abstract

Introduction: Heterozygous mutations in the SCN1A gene are linked to a wide spectrum of epileptic disorders, ranging from self-limited conditions to epileptic encephalopathies, such as Dravet Syndrome. Seizure control is important to prevent both sudden death and morbidity associated with prolonged seizures. Current evidence suggests that sodium--channel blockers should be avoided. **Objectives:** To report on two cases of patients with a mutation in the SCN1A gene associated with Dravet Syndrome, emphasizing the importance of genetic testing for the diagnosis, prognosis, and correct choice of antiepileptic medications. **Case report:** Case 1: male patient with onset of seizures at four months old following vaccination. After this, he developed prolonged generalized seizures and, over time, other types of seizures. He also developed a severe intellectual deficit and drug-resistant epilepsy exacerbated by infections and use of sodium-channel blockers. Case 2: female patient with first episode of seizure at 26 days. At 13 months, she developed prolonged generalized crises exacerbated by small temperature variations and euphoria or irritability. Aged two, she had an episode of prolonged status epilepticus. As a result, she developed hypoxic-ischemic encephalopathy and drug--resistant epilepsy. **Discussion:** The two patients have a mutation in the SCN1A gene associated with Dravet syndrome and their clinical history reveal similar and discrepant points. The most significant contributions of genetic testing are the identification of precipitating factors, greater attention to the possibility of unfavorable evolution, and guidance for choosing anticonvulsants, including avoidance of sodium-channel blockers.

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Residência Pediátrica; 2023: Ahead of Print.
DOI: 10.25060/residpediatr-2023.v13n2-517

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INTRODUCTION

The SCN1A gene (chromosome 2q24.3) is involved in the production of the alpha subunit (NaV1.1) in type 1 neuronal voltage-gated sodium channels. Heterozygous mutation of this gene can cause channel dysfunction, leading to loss of excitability in GABAergic inhibitory neurons and, consequently, cortical hyperexcitability and epilepsy[1].

The spectrum of mutation-related epileptic disorders is wide[2], ranging from self-limiting conditions responsive to antiepileptic drugs (e.g.: febrile seizures) to epileptic encephalopathies such as Dravet syndrome. Thus, a correlation between the type of mutation in the SCN1A gene and a specific seizure phenotype cannot be clearly established, although nonsense and missense variants in the voltage sensor have been associated with severe involvement[3-6].

Seizure management is very important to prevent sudden unexpected death in epilepsy (SUDEP) and permanent injury from prolonged seizures seen in patients with more severe phenotypes[7,8]. The most commonly prescribed therapies include clobazam, topiramate, valproic acid, levetiracetam, phenobarbital, stiripentol (not sold in Brazil), cannabidiol, and ketogenic diet[9,10]. Sodium channel blockers (e.g.: lamotrigine, carbamazepine, and phenytoin) should be avoided[2].

This article describes two cases of epileptic encephalopathy related to mutations in the SCN1A gene and underlines the importance of such mutations in the diagnosis, prognosis, and correct choice of antiepileptic drugs.

CASE REPORTS

Table 1 shows a summary of the clinical markers of both patients and their respective mutations.

Case 1:

An 11-year-old boy had his first generalized tonic-clonic seizure (GTCS) episode associated with high fever following vaccination with the tetravalent vaccine. Since then, he has had frequent (4 times a week) prolonged (15-20 minutes) episodes of GTCS. Valproic acid and phenobarbital did not yield relevant benefits, and he was prescribed first carbamazepine at the age of two years, achieving a partial improvement in the frequency and duration of seizures. Other ictal phenotypes appeared, with myoclonic and myoclonic-astatic seizures associated with focal seizures with secondary generalization, and lamotrigine was added to the prescription.

The patient was on multiple anticonvulsants (carbamazepine, lamotrigine, phenobarbital, and valproic acid) with epilepsy partially under control at the age of six years, when he developed a behavioral syndrome characterized by motor agitation and aggressiveness. Since he had slow waves on the electroencephalogram (EEG) and no ictal activity, carbamazepine was gradually discontinued.

At 7 years of age, GTCS episodes became more frequent and longer, and began to occur during sleep and more intensely when he had fever. Introduction of levetiracetam brought a partial therapeutic response to seizures and behavioral symptoms.

Table 1. Epileptic encephalopathy clinical markers associated with SCN1A gene mutations.

CASE 1: 11-year-old boy						
Age at the onset of seizures	**Semiology of seizures**	**Prescribed antiepileptic drugs**	**Exacerbation factors**	**Global development**	**Abnormal neurological examination findings**	**Genetic test results**
4 months	Myoclonic Myoclonic-astatic Focal seizures with or without secondary generalization	Valproic acid Carbamazepine Clobazam Phenobarbital Lamotrigine Levetiracetam	Vaccine Temperature fluctuations Infections Use of sodium channel blockers	Delays in cognitive, language, and personal-social behavior development seen at 13 months of age	Ataxic syndrome and severe intellectual disability	Heterozygous nonsense mutation in the SCN1A gene (incidence: 1 in 125,000 individuals)
CASE 2: 4-year-old girl						
Age at the onset of seizures	**Semiology of seizures**	**Prescribed antiepileptic drugs**	**Exacerbation factors**	**Global development**	**Abnormal neurological examination findings**	**Genetic test results**
26 days	Focal seizures with or without secondary generalization Myoclonic Seizures	Valproic Acid Carbamazepine Clobazam Phenobarbital Levetiracetam Oxcarbazepine Topiramate	Temperature fluctuations Infections Euphoria Irritability Use of sodium channel blockers	Mild delays in personal-social behavior, language, and cognitive skills until 2 years and 6 months of age. After a cardiac arrest, the patient regressed in all areas.	Pyramidal syndrome with axial hypotonia, appendicular hypertonia, and global hyperreflexia; extrapyramidal syndrome with dystonia and choreoathetosis	Heterozygous missense mutation in the SCN1A gene (incidence 2 in 125,000 individuals)

Source: The authors (2020).

When he was aged 8-9 years, myoclonic seizures began to occur daily and triggered GTCS episodes seizures, requiring higher doses of lamotrigine and valproic acid.

Lamotrigine was discontinued after genetic tests identified a heterozygous Chr2:166.848.051G>A mutation in the SCN1A gene (defining a stop codon in protein translation).

At the age of 11 years, the patient was on phenobarbital, valproic acid, levetiracetam, and clobazam, with complete remission of myoclonic seizures and only a few focal seizures and GTCS episodes.

In regard to global development, delays in cognitive, language, and personal-social behavior were observed when the patient was 13 months old. Currently, he has severe intellectual disability.

Family history included two paternal uncles and two paternal cousins with epilepsy.

Physical examinations performed since he was aged four years have shown signs of ataxic syndrome, with etiology probably related to epileptic encephalopathy and hypoplasia of the cerebellar vermis seen in head nuclear magnetic resonance (NMR) scans.

The electroencephalograms performed over the years showed diffuse slow waves and predominance of bilateral sharp waves in the frontal region.

Case 2:

A four-year-old girl without gestational or perinatal complications had seizures 26 days after birth characterized by central cyanosis, hypotonia and a blank stare (< 1 min), followed by an episode of GTCS 15 minutes later. Screening tests for central nervous system infections, electroencephalograms, and transfontanellar ultrasound scans performed at the time were normal.

During an episode of fever when she was aged one year, the patient had a generalized tonic-clonic seizure lasting for more than 40 minutes, which ceased only with the administration of intravenous medication. Since then, seizures began to occur every two weeks and during sleep, with eye deviation, snoring, and hypertonia. A similar episode with prolonged duration occurred when she was aged 18 months, and since then she began to have GTCS episodes during the day, triggered by irritability/euphoria and low-grade fever (37º and 37.5ºC).

At the age of two years and four months, upon a change from carbamazepine to valproic acid, she experienced an exacerbation of seizures with changes in semiology (vertical eye deviation, repetitive lateral head movements, and irresponsiveness) and longer duration (one hour), which subsided only with intravenous medication.

When she was aged two years and six months, the patient had a urinary tract infection accompanied by an episode of GTCS lasting for five hours, during which she went into cardiac arrest four times. She stayed in an intensive care unit for four months to control the status epilepticus and have a gastrostomy performed due to hypoxic-ischemic encephalopathy sequelae. Therapy with levetiracetam, phenobarbital, oxcarbazepine, and clobazam resulted in the complete control of seizures.

At the age of four years, she developed focal motor clonic seizures with jerking lateral movements of the head and right arm, which occurred 8-10 times a day associated with multiple myoclonic seizures.

Therapy was changed after a genetic test identified a heterozygous Chr2:166.895.946C>T mutation in the SCN1A gene. She is currently on levetiracetam, topiramate, clobazam, and baclofen and still has focal seizures 3-5 times a day.

Until the age of two years and six months, the patient showed mild global development delays in personal-social behavior, language, and cognitive skills. She developed hypoxic-ischemic encephalopathy with dystonia, choreoathetosis, pyramidal and extrapyramidal syndromes with complete cognitive regression after the cardiac arrests.

Family history included a paternal half-brother with epilepsy.

Electroencephalograms revealed high voltage sharp waves in generalized seizures when she was aged two years and paroxysmal activity during sleep at the age of three years.

Skull MRI scans from when she was aged three years showed cerebral atrophy, hydrocephalus ex vacuo, signal alteration in the globus pallidus and left thalamus, and reduced N-acetylaspartate indicating neuronal loss.

DISCUSSION

SCN1A gene mutations have an autosomal dominant inheritance pattern, most often resulting from a “de novo” mutation. More rarely, it may be inherited from one of the parents with a mosaic mutation (somatic or gonadal).

There are several phenotypes related to this mutation, the main being Dravet syndrome, a condition with prevalence ranging from 1:15,000-1:40,900[3,4]. Mutations in the SCN1A gene may be present in 70-85% of the individuals with Dravet syndrome. This drug-resistant epileptic encephalopathy causes prolonged seizures, related or not to fever or vaccination. Seizures start around the ages of 5-8 months. Children with the condition develop normally until the onset of seizures. As the disease progresses, a change occurs in the semiology of seizures occurs, with the introduction of atypical, focal, myoclonic absences and obtundation (altered consciousness with reduced postural tone and myoclonus), followed by developmental regression (mainly language and cognitive skills) associated with behavioral disorders and ataxia[9,10]. Hyperthermia (fever, physical exertion, heat, hot baths), vaccination, photosensitivity, and use of sodium channel blockers precipitate seizures. Electroencephalogram with photic stimulation usually triggers epileptiform activity[9,10].

The two patients described in this report have mutations in the SCN1A gene associated with Dravet syndrome. They present the main signs and symptoms described for the condition and a few discrepant ones as well.

In line with the signs and symptoms associated with Dravet syndrome are worsening of seizures with hyperthermia, vaccination, drug resistance, multiple ictal phenotypes, prolonged seizure duration, family history of epilepsy, and global developmental regression, especially in personal-social behavior and language skills. Carbamazepine and lamotrigine did not control the seizures of the patient described in Case 1; better control was achieved with polytherapy with valproic acid and clobazam, both regarded as first-line treatment for Dravet syndrome[9,10].

However, in both cases we observed an earlier-than-usual onset of seizures – at four months and 26 days of age, respectively. Interestingly, mood changes (irritability/euphoria) precipitated seizures in the patient described in Case 2. In both patients, myoclonic seizures became more frequent in later stages of the disease, as they got closer to school age.

Although they had similar genotype alterations, some distinctions can be pointed out between the two patients: a) hyperthermia and photosensitivity were more relevant seizures triggers in Case 2; b) no triggering factor for the first seizure was identified in Case 2 when the patient was aged 26 days; c) long period free of new seizures in Case 2 (between 26 days and 13 months of age); d) greater severity of epilepsy in Case 2, with more prolonged seizures, progression to status epilepticus, and cardiac arrest.

It is clear that pathogenic mutations in the SCN1A gene do not cause a specific phenotype. Even patients with the same epileptic syndrome may still see variations in the severity of symptoms. The most significant contributions of genetic testing, especially when performed early on, are the identification of precipitating factors, awareness over potentially unfavorable outcomes, and providing directions over the choice of anticonvulsants to avoid sodium channel blockers.

REFERENCES

1. Escayg A, Goldin AL. Sodium channel SCN1A and epilepsy: mutations and mechanisms. Epilepsia. 2010;51:1650-8.
2. Miller IO, Sotero de Menezes MA. SCN1A Seizure Disorders. GeneReviews® [Internet]. 2007 Nov 29. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. (WA): University of Washington, Seattle; 1993-2023; [acesso em ANO Mês Dia]. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK1318/
3. Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, et al. Incidence of Dravet syndrome in a US population. Pediatr. 2015;136:1310-5.
4. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain. 2012;135:2329-36.
5. Zuberi SM, Brunklaus A, Birch R, Reavey E, Duncan J, Forbes GH. Genotype-phenotype associations in SCN1A-related epilepsies. Neurol. 2011;76:594-600.
6. Meng H, Xu HQ, Yu L, Lin GW, He N, Su T, et al. The SCN1A mutation database: updating information and analysis of the relationships among genotype, functional alteration, and phenotype. Hum Mutat. 2015;36:573-80.
7. Chipaux M, Villeneuve N, Sabouraud P, Desguerre I, Boddaert N, Depienne C, et al. Unusual consequences of status epilepticus in Dravet syndrome. Seizure. 2010;19:190-4.
8. Takayanagi M, Haginoya K, Umehara N, Kitamura T, Numata Y, Wakusawa K, et al. Acute encephalopathy with a truncation mutation in the SCN1A gene: a case report. Epilepsia. 2010;51:1886-8.
9. Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a north american consensus Panel. Pediatr Neurol. 2017;68:18-34.
10. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011 Abr;52(Supl 2):3-9.