DRAVET SYNDROME – EXPERIENCE OF A NEUROPEDIATRIC UNIT
SÍNDROME DE DRAVET – EXPERIÊNCIA DE UMA UNIDADE DE NEUROPEDIATRIA

ABSTRACT

Introduction: Dravet syndrome (DS) is a rare and complex genetic epilepsy syndrome. The first seizures are generally induced by fever in the first year of life of a previously healthy child, and the condition is typically associated with impaired psychomotor development. The authors present a clinical review of DS patients followed at a Neuropediatric Unit of a level III Pediatric Hospital.

Material and methods: Retrospective study of pediatric patients with DS followed at a Neuropediatric Unit between 2001 and 2019.

Results: Twenty-two patients were diagnosed and followed in this institution. The median (interquartile range [IQR]) age at first seizure was 4.5 (4-5.75) months, which was described as generalized tonic-clonic, focal seizure, or focal to bilateral tonic-clonic seizure, and 95% of patients had fever during this first episode. Neuroimaging and first electroencephalogram (EEG) were normal in all patients. SCN1A gene mutations were detected in 21 (95%) patients. All patients underwent multiple antiepileptic drug (AED) regimens. Psychomotor development was delayed in 20 (91%) patients, and 13 (59%) presented ataxia. At the end of follow-up, the median (IQR) age was 19 (8-23) years, with no reported deaths.

Discussion: The characteristics of the first DS seizures are crucial for diagnosis, which can be supported by genetic sequencing, with most patients presenting an SCN1A gene mutation. Neuroimaging and EEG are typically normal at disease onset, but most patients present EEG abnormalities over time. Seizure management can be challenging, requiring a combination of multiple AEDs.

Conclusion: DS is a progressive disease associated with poor cognitive and motor skill outcomes, resulting in great morbidity. Early diagnosis can help avoid unnecessary studies, optimize the therapeutic strategy, allow genetic counseling, and improve long-term outcomes.

Keywords: Dravet syndrome; SCN1A gene; severe myoclonic epilepsy in infancy

RESUMO

Introdução: A síndrome de Dravet (SD) é uma síndrome epileptica genética rara e complexa. As primeiras crises são habitualmente induzidas por febre no primeiro ano de vida de crianças previamente saudáveis e a doença está tipicamente associada a atraso no desenvolvimento psicomotor. Os autores apresentam uma revisão clínica de doentes com SD seguidos numa Unidade de Neuropediatria de um Hospital Pediátrico de nível III.
INTRODUCTION

Dravet syndrome (DS) is a genetic epilepsy syndrome characterized by a variety of drug-resistant seizures. It has an estimated incidence between 1:15700 and 1:40000 live births and affects both genders equally.\(^1\)\(^-\)\(^4\) It was first described in 1978 by Charlotte Dravet under the name of “severe myoclonic epilepsy in infancy”, and several classification reviews have been proposed since.\(^5\) In 1989, it was classified by the International League Against Epilepsy (ILAE) as an antiepileptic drug-resistant seizure entity.\(^6\) The first seizure is typically induced by fever in the first year of life of a previously healthy child and often leads to severe motor and cognitive impairment. It can emerge with temperature-sensitive seizures, including generalized tonic-clonic and unilateral clonic seizures, but other seizure types may follow. Electroencephalogram (EEG) and neuroimaging, including magnetic resonance imaging (MRI), are frequently normal at disease onset, making diagnosis challenging, with some abnormalities only becoming evident during the course of the disease.\(^1\)\(^,\)\(^5\)\(^-\)\(^7\)

Most (70-85%) DS patients present heterozygote loss-of-function mutations in the voltage-gated sodium channel type I alpha subunit gene SCN1A on chromosome q2.\(^1\)\(^,\)\(^2\)\(^,\)\(^3\) More than 700 mutations randomly distributed along the SCN1A gene have been identified, with most being de novo mutations, although familial or germline mutations are found in 5-10% of cases.\(^1\)\(^,\)\(^9\)

DS diagnosis is clinical, and even though genetic testing for SCN1A mutations is recommended, it is not required for diagnosis.\(^2\)\(^,\)\(^10\)

The authors present a clinical review of DS patients diagnosed at a Neuropediatric Unit of a level III Pediatric Hospital.
illness at first seizure. Neuroimaging with CT scan and first EEG were normal in all patients. Twelve patients (52%) started an antiepileptic medication after the first seizure.

During the following years, the course of disease was characterized by myoclonic, atonic, focal, and generalized seizures resistant to antiepileptic therapies. All patients had seizures with fever at some point during follow-up, and 19 (86%) also had seizures without fever.

Follow-up neuroimaging with MRI was performed in all patients. Two (9%) showed abnormalities described as supra and infratentorial cortical/subcortical atrophy and hippocampal abnormalities consistent with left hippocampal sclerosis. Twenty patients (91%) had EEG abnormalities at some point, presenting as diffusely slow background and multifocal or generalized interictal discharge, and two patients with one and three years old had normal EEG.

Genetic analysis was performed in all patients, with 21 (95%) presenting SCN1A gene mutations in gene sequencing. Despite the clinical diagnosis, SCN1A mutations were not detected in one patient.

All patients underwent multiple antiepileptic drug (AED) regimens, with combinations of two or more AEDs. All patients were treated with valproic acid, 21 (95%) with topiramate, 15 (68%) with clobazam, and 10 (45%) with stiripentol. Several AED combinations were used, with cannabidiol being used in one patient. Only two (9%) patients were seizure-free by the end of follow-up.

Psychomotor development was delayed in 20 (91%) patients. The two patients without psychomotor delay were one and three years old at the end of follow-up. In six (27%) patients, psychomotor development was severely impaired. Motor deficits were evident throughout the course of disease in most patients, with 13 (59%) presenting ataxia at the end of follow-up.

**DISCUSSION**

Infants with DS are usually previously healthy, without significant pathological history, and with normal psychomotor development during their first year of life, as observed in all patients in the present cohort. Most series report a balanced gender proportion or 1:2 female: male ratio, in contrast to the 1.75:1 female: male ratio observed in this series.10,11 DS usually starts with fever-induced seizures, mostly related to infectious disease or vaccination in the first year of life, as observed in almost all patients in this study.10,12 The exception was one patient who did not initially present fever-induced seizures but whose following episodes were triggered by fever, in agreement with other DS series.1 During follow-up, most (87%) DS patients in this cohort also had seizures without documented fever.

The median age at presentation was around five months, consistent with the typical age of onset described by Charlotte Dravet and other authors.1,10 Features of the first seizures are relevant for diagnosis. These may be generalized tonic-clonic, hemiclonic, or other focal seizures, and can evolve to status epilepticus, what explains that 65% of patients were hospitalized and 26% required intensive care at onset. DS can later present as pleomorphic epilepsy, exhibiting other seizure types, including myoclonic and atypical absence seizures.1,2,10,13

Several studies report a family history of febrile seizures or epilepsy in more than 25% of DS patients, which was also verified in seven (32%) patients in this study.2,9,10,12 Wirrell et al. (2017) consensus suggests that genetic testing should be performed in children aged less than 12 months with normal development, normal MRI, and no known seizure etiology who present with more than two prolonged (> 15 minutes) generalized febrile seizures.20 In the present cohort, genetic sequencing revealed SCN1A mutations in 95% of patients. Loss-of-function mutations in the SCN1A gene are reported in most DS patients and, although some (few) patients do not present with SCN1A abnormalities, they may have exon deletions or chromosomal rearrangements involving the same gene.1,2,8,14 Other genes (not always studied in this cohort) have been identified in patients with DS phenotype, including PCDH19, SCN1B, GABRA1, STXBP1, CHD2, SCN2A, HCN1, KCN2, and GABRG2.11,15 SCN1A mutations are also associated with Genetic Epilepsy with Febrile Seizures Plus (GEFS+), and seem to present phenotypic variability.1 Furthermore, some authors suggest that the nature of a mutation may affect disease phenotype, age at seizure onset, seizure type, severity, and cognitive outcomes.14

Neuroimaging was performed in all patients, initially by CT scan and later by MRI, and was normal in all patients at presentation. However, during follow-up two patients presented abnormalities consistent with those described in some DS cases, including mild generalized atrophy and hippocampal sclerosis.10,16 Prolonged seizures appear to cause acute hippocampal injury and may cause the development of sclerosis several months or years later, as reported by Siegler et al. (2005).17 Striano P. et al. (2007), on the other hand, reviewed data of 58 DS patients that did not support the association between prolonged febrile seizures and hippocampal sclerosis.16 Therefore, this subject remains controversial.

Interictal EEG, including wakefulness and sleep, is usually normal or nonspecific at disease onset and during the first year of life, as observed in the present patient population. Over time, 91% of patients presented abnormalities, like diffusely slow background and multifocal or generalized interictal discharges. Typically, and particularly during the second year of life, interictal diffuse background slowing, generalized spikes and waves, and focal or multifocal abnormalities start to emerge and can be more frequent as the disease evolves.7,12,18,19 DS patients typically do not respond to classical AEDs. Valproate (VPA) is usually the first AED administered to infants with seizures and was administered to all patients in this cohort at some point. Nevertheless, there is the need to combine other AEDs when further seizures occur.1,10,18,20 Benzodiazepines like clobazam are often used in
Gene therapies, such as ataluren and anti-natural antisense transcripts (AntagoNAT), represent promising new treatments for Dravet syndrome. These therapies aim to improve long-term outcomes, reduce seizures, and optimize therapeutic strategies, while allowing genetic counseling and preventing premature deaths. Despite the potential benefits of these therapies, further research is needed to determine their effectiveness and safety in different patient populations. The combination of gene therapies with other AEDs, such as stiripentol or clobazam, may be necessary to achieve optimal seizure control in some cases.

Motor skills often become compromised as the child grows. Hypotonia is the earliest sign, detectable around one year of age, and can be responsible for further orthopedic problems. Ataxia appears when patients start to walk, presenting as walking delay and evolving to unsteady, wide-based stance and poorly coordinated movements. Similar to other series, ataxia was reported at the end of follow-up in 57% of patients in this study. A combination of pyramidal signs, tremors, impaired fine motor skills, and ataxia often become more perceptible through time.

CONCLUSION

This study described the demographic characteristics, clinical presentation, and evolution of a cohort of DS patients. A different gender proportion was found compared to other DS series, but the sample included was relatively small. Patients had their first seizure during the first year of life and the disease progressed over time, requiring several AED combinations and experiencing significant morbidity. Early diagnosis may help avoid unnecessary investigations, optimize therapeutic strategies, allow genetic counseling, and improve long-term outcomes.

New therapeutics have shown encouraging results and should be offered to DS patients with difficult seizure control. There is the need for prospective studies with large patient series, investigating disease onset and clinical evolution to clarify DS outcomes.

REFERENCES


CORRESPONDENCE TO
Rafael Figueiredo
Department of Pediatrics
Largo da Maternidade de Júlio Dinis
Centro Materno-Infantil do Norte
Centro Hospitalar Universitário do Porto
4050-651, Porto, Portugal
Email: rafaelcostafigueiredo@gmail.com

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