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ORIGINAL ARTICLES

DRAVET SYNDROME – EXPERIENCE OF A NEUROPEDIATRIC UNIT

SÍNDROME DE DRAVET – EXPERIÊNCIA DE UMA UNIDADE DE NEUROPEDIATRIA

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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 epilética 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.

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Material e métodos: Estudo retrospetivo de doentes pediátricos com SD seguidos numa Unidade de Neuropediatria entre 2001 e 2019.

Resultados: Vinte e dois doentes foram diagnosticados e seguidos na instituição. A mediana de idades aquando da primeira crise foi de 4.5 meses (intervalo interquartil [IQR] 4-5.75 meses), que foi descrita como tónico-clónica generalizada, focal ou focal com evolução para tónico-clónica bilateral, e 95% dos doentes apresentaram febre associada. O estudo de neuroimagem e o primeiro eletroencefalograma (EEG) foram normais em todos os doentes. Vinte e um doentes (95%) tinham mutação no gene SCN1A. Todos os doentes foram submetidos a múltiplos esquemas de antiepiléticos. Verificou-se atraso do desenvolvimento psicomotor em 20 (91%) doentes e 13 (59%) apresentaram ataxia. No final do período de seguimento, a mediana (IQR) de idades foi de 19 (8-23) anos, não tendo sido reportadas mortes.

Discussão: As características das primeiras crises de SD são essenciais para o diagnóstico, o qual pode ser apoiado por estudo genético, com a maioria dos doentes a apresentar mutações no gene SCN1A. Na apresentação, o estudo de neuroimagem e EEG são tipicamente normais, mas a maioria dos doentes apresenta alterações no EEG ao longo do tempo. As crises podem ser de difícil controlo e requerem o uso de múltiplos antiepiléticos.

Conclusão: A SD tem um carácter progressivo e está associada a mau prognóstico cognitivo e motor, resultando em grande morbilidade. O diagnóstico precoce pode evitar investigação desnecessária, ajudar a otimizar a estratégia terapêutica, permitir o aconselhamento genético e melhorar os resultados a longo prazo.

Palavras-chave: epilepsia mioclónica grave da infância; gene SCN1A; síndrome de Dravet

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.[1,2,8] 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.[1,10]

The authors present a clinical review of DS patients diagnosed at a Neuropediatric Unit of a level III Pediatric Hospital.

MATERIAL AND METHODS

A retrospective descriptive study was conducted by reviewing all medical records of pediatric patients with a clinical diagnosis of DS according to Wirrell *et al* (2017) consensus, supported or not by genetic testing, followed at the Neuropediatric Unit of a level III Pediatric Hospital between 2001 and 2019.[10] Demographic, clinical, and neuroimaging data were analyzed. Descriptive analysis was performed with SPSS (*v23*).

RESULTS

During the 20-year period considered, 22 patients were diagnosed with DS and followed in the study institution, 14 (64%) of whom were female. At the end of follow-up, the median (interquartile range [IQR]) age was 19 (8-23) years, with the oldest patient having 31 years and eleven patients (45%) being under 18 years of age. The median (IQR) follow-up time was 11 (5-18) years, with no reported deaths.

Seven (32%) patients had first or second-degree relatives diagnosed with epilepsy (4; 18%) or febrile seizures (3; 14%). None had developmental delay or other conditions before first seizure onset.

The median (IQR) age at first seizure was 4.5 (4-5.75) months, with all patients presenting the first seizure before the age of nine months. First seizures were described as generalized tonic-clonic, focal, or focal to bilateral tonic-clonic. Thirteen patients (65%, 13/20 - 2 clinical records with missing data) were hospitalized at first seizure, and five (25%, 5/20) evolved to status epilepticus requiring treatment in an Intensive Care Unit. Nineteen patients (95%, 19/20) had febrile

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. Autism spectrum disorder was present in five (23%) patients, and seven (32%) had behavior problems reported by parents. Severe 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.[1] 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.[10] 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, KCNA2, and GABRG2.[1,15] 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.[1,8]

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

combination with VPA. Like VPA, evidence for the use of clobazam is mostly based on expert opinion.[10,18] Frequently, there is the need to combine other AEDs with those drugs, like topiramate or stiripentol.

Topiramate can lead to good generalized and focal seizure control, with some studies reporting >50% seizure reduction in 35–78% of DS patients.[18,21,22] It has been commonly used since FDA approval in 1996 as an adult AED, namely in children over two years, and was one of the most used AEDs in this study, despite being currently recommended as second-line therapy after stiripentol, a more recent drug.[18,20,23]

Stiripentol, approved in Europe as adjunctive therapy in DS in 2007, acts as an allosteric modulator of the γ-aminobutyric acid (GABA) A receptor and increases clobazam metabolite concentration. It is associated with a significant reduction in the frequency of seizures (50% reduction in around 71% of patients), status epilepticus (50% reduction in 41% of patients), hospitalizations, and use of rescue medication, when used as adjunctive therapy. It is currently one of the first options, as adjunctive therapy to VPA and/or clobazam.[10,18,20] Because stiripentol is a relatively new drug and this is a retrospective study of patients over the last 20 years, this agent has not been widely used in patients included in this cohort.

Cannabidiol was only authorized in Portugal for DS patients at the beginning of 2019 and it was administered in one patient. In a trial of cannabidiol for DS patients, Devinsky O. *et al.* (2017) showed a ≥50% reduction of convulsive seizure frequency in 43% of patients receiving the drug compared to 27% receiving placebo.[24] In an extension of the previous trial (GWPCARE1 Part B), the authors evaluated long-term cannabidiol outcomes and showed a median reduction of 38% to 44% of convulsive seizures and 39% to 51% of total seizures compared to baseline. New therapies, like fenfluramine, also show promising results. In the study by Lagae L. *et al.* (2019), this drug significantly reduced mean monthly convulsive seizure frequency in 32.4−62.3% compared to placebo. Nabbout R. *et al.* (2020) reported a 54.0% reduction in the mean monthly convulsive seizure frequency in DS patients taking stiripentol-containing AED regimens, with patients presenting only mild adverse effects and no cardiovascular events.[23,25,26]

Although not evaluated in this case series, other therapeutic options, like ketogenic diet, have also shown effectiveness in seizure control in 35–70% of patients and could be considered a second-line option, with positive impact on cognition and behavior.[10,18] Surgical therapies, like vagus nerve stimulation, can be offered to patients after failure of first- and second-line therapies, despite low-to-moderate impact on seizure reduction.[10,18,20] Gene therapies, such as ataluren and anti-natural antisense transcripts (AntagoNAT), represent promising new treatment options for DS patients.[18,27]

Cognitive outcomes are typically poor in DS patients, with mild to severe intellectual disability and language impairment. After emerging in apparently normal infants, cognitive impairment gradually becomes more evident after the second year of life and seems to be related to epilepsy severity during the first two years of life.[1,12,28] In this cohort, most patients (91%) presented neurodevelopmental abnormalities, and a significant number (27%) was severely impaired, with significant comorbidities. Behavioral disorders, including autism, were reported in a significant number of patients, similarly to other DS series.[1,2,28,29]

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.[1]

DS children have an increased risk of premature death, with a calculated 15% risk of death within ten years after diagnosis and a median age at death of seven years. The most common death causes are Sudden Unexpected Death in Epilepsy (SUDEP) and status epilepticus.[2,18,29–31] In this study, no patient died until the end of follow-up. Nonetheless, close follow-up and family education are key to preventing premature deaths.

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

1. Dravet C, Guerrini R. Topics in epilepsy: Dravet syndrome, 3rd ed, John Libbey Eurotext, 2011. p119.
2. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain. 2012;135(8):2329–36.
3. Hurst DL. Epidemiology of Severe Myoclonic Epilepsy of Infancy. Epilepsia. 1990;31(4):397–400.
4. Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, *et*

al. Incidence of dravet syndrome in a US population. Pediatrics. 2015;136(5):e1310–5.
5. Dravet C. Dravet syndrome history. Dev Med Child Neurol. 2011;53(SUPPL. 2):1–6.
6. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, *et al.* ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512–21.
7. Bureau M, Bernardina BD. Electroencephalographic characteristics of Dravet syndrome. Epilepsia. 2011;52(SUPPL. 2):13–23.
8. Zuberi SM, Brunklaus A, Birch R, Reavey E, Duncan J, Forbes GH. Genotype-phenotype associations in SCN1A-related epilepsies. Neurology. 2011 Feb 15;76(7):594-600.
9. Margherita Mancardi M, Striano P, Gennaro E, Madia F, Paravidino R, Scapolan S, *et al*. Familial occurrence of febrile seizures and epilepsy in severe myoclonic epilepsy of infancy (SMEI) patients with SCN1A mutations. Epilepsia. 2006;47(10):1629–35.
10. 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 [Internet]. 2017;68:18-34.e3.
11. Caraballo RH, Fejerman N. Dravet syndrome: A study of 53 patients. Epilepsy Res. 2006;70(SUPPL.)1:S231-8.
12. Rosander C, Hallböök T. Dravet syndrome in Sweden: A population-based study. Dev Med Child Neurol. 2015;57(7):628–33.
13. Anwar A, Saleem S, Patel UK, Arumaithurai K, Malik P. Dravet Syndrome: An Overview. Cureus. 2019;11(6):1–11.
14. Djémié T, Weckhuysen S, Von Spiczak S, Carvill GL, Jaehn J, Anttonen AK, *et al.* Pitfalls in genetic testing: The story of missed SCN1A mutations. Mol Genet Genomic Med. 2016;4(4):457–64.
15. Wheless JW, Fulton SP, Mudigoudar BD. Dravet Syndrome: A Review of Current Management. Pediatr Neurol [Internet]. 2020;107:28–40.
16. Striano P, Mancardi MM, Biancheri R, Madia F, Gennaro E, Paravidino R, *et al.* Brain MRI findings in severe myoclonic epilepsy in infancy and genotype-phenotype correlations. Epilepsia. 2007;48(6):1092–6.
17. Siegler Z, Barsi P, Neuwirth M, Jerney J, Kassay M, Janszky J, *et al*. Hippocampal sclerosis in severe myoclonic epilepsy in infancy: A retrospective MRI study. Epilepsia. 2005;46(5):704–8.
18. Ziobro J, Eschbach K, Sullivan JE, Knupp KG. Current Treatment Strategies and Future Treatment Options for Dravet Syndrome. Curr Treat Options Neurol. 2018 Oct 13;20(12):52.
19. Specchio N, Balestri M, Trivisano M, Japaridze N, Striano P, Carotenuto A, *et al.* Electroencephalographic features in Dravet syndrome: Five-year follow-up study in 22 patients. J Child Neurol. 2012;27(4):439–44.
20. Cross JH, Caraballo RH, Nabbout R, Vigevano F, Guerrini R, Lagae L. Dravet syndrome: Treatment options and management of prolonged seizures. Epilepsia. 2019;60(S3):S39–48.
21. Kröll-Seger J, Portilla P, Dulac O, Chiron C. Topiramate in the treatment of highly refractory patients with dravet syndrome. Neuropediatrics. 2006;37(6):325–9.
22. Fariba K, Saadabadi A. Topiramate. [Updated 2020 Mar 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020.
23. Wheless JW, Fulton SP, Mudigoudar BD. Dravet Syndrome: A Review of Current Management. Pediatr Neurol [Internet]. 2020;107:28–40.
24. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, *et al.* Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. N Engl J Med. 2017;376(21):2011–20.
25. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, *et al.* Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet [Internet]. 2019;394(10216):2243–54.
26. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, *et al.* Fenfluramine for Treatment-Resistant Seizures in Patients with Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2020;77(3):300–8.
27. Hsiao J, Yuan TY, Tsai MS, Lu CY, Lin YC, Lee ML, *et al.* Upregulation of Haploinsufficient Gene Expression in the Brain by Targeting a Long Non-coding RNA Improves Seizure Phenotype in a Model of Dravet Syndrome. EBioMedicine. 2016;9:257–77.
28. Ragona F, Brazzo D, Giorgi I De, Morbi M, Freri E, Teutonico F, *et al.* Dravet syndrome: Early clinical manifestations and cognitive outcome in 37 Italian patients. Brain Dev [Internet]. 2010;32(1):71–7.
29. Skluzacek J V., Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: The IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia. 2011;52(SUPPL. 2):95–101.
30. Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, *et al.* Mortality in Dravet syndrome. Epilepsy Res [Internet]. 2016;128:43–7.
31. Shmuely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: A review. Epilepsy Behav [Internet]. 2016;64:69–74.

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