Research Article

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Dravet Syndrome

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ABSTRACT

Introduction: Dravet Syndrome (DS) is a severe epileptic encephalopathy of childhood characterized by the presence of prolonged convulsive episodes that generate a great impact on the lives of patients and family members. The commonly identified etiology is a genetic mutation at the level of the SCN1A gene (voltage-gated sodium channel) associated with high rates of drug resistance, so the initial approach represents a challenge in the medical field.

Materials and methods: A systematic review of articles published from the year 2011 in high-impact journals that relevantly address the subject in question is carried out in order to provide the reader with updated general aspects.

Conclusion: Dravet Syndrome is considered a medical challenge, which is why, currently, early diagnosis should be prioritized, as well as control of the intensity and frequency of the convulsive episodes.

KEYWORDS: Encephalopathy; Genetic mutation; Drug resistance; challenge

INTRODUCTION

Dravet syndrome (DS) was first described in 1987 by Charlotte Dravet as Severe Myoclonic Epilepsy of Childhood and, later, in 1989 it was renamed with the name known to this day [1]. It is characterized as an early-onset complex epileptic entity that is associated with the appearance of seizures resistant to medical management, as well as cognitive and personality disorders. The International League Against Epilepsy (ILAE) classified DS as an

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epileptic encephalopathy, understood as a pathology in which the alteration of brain function is directly related to the presence of epileptiform episodes [2], however, this issue continues to be discussed at present since there is no definitive evidence of this relationship. Additionally, the ILAE defines the typical syndrome as "generalized and unilateral febrile and afebrile seizures, clonic or tonic-clonic that occur in the first year of life in an otherwise normal infant and are subsequently associated with myoclonus, atypical absences and partial seizures".

In 2001, the genetic basis of DS was described as a mutation in the SCN1A gene (voltage-gated sodium channel). This transformed the vision of the syndrome into a disease defined as channelopathy, in addition, it allowed us to understand the reason why some antiepileptic drugs such as carbamazepine or phenobarbital, due to their intrinsic mechanism of action, could worsen the frequency and duration of seizures. the seizures. Regarding the clinical evolution, it should be taken into account that patients frequently present a neurological delay that rapidly progresses to a severe disability manifested with ataxia, tremors, dysarthria and language impairment in addition to psychiatric disorders such as aggressiveness, agitation, obsession and hoarding behavior [3].

Evidenced seizures are usually drug-resistant, recurrent and of multiple types, therefore, taking into account that it has been possible to show that avoiding the presence of epileptic stages at an early age favors the neurological development of the population with this diagnosis, it is important to guarantee that all patients have a structured and clear rescue management that allows early care of parents at home [4]. Finally, it should be noted that medical management must be comprehensive, guaranteeing care not only for the minor but also for their family circle, since a significant incidence of depressive and anxious disorders was reported in caregivers [5].

METHODOLOGY

A systematic search of original articles, case reports and bibliographic reviews is carried out in databases including ScienceDirect, Pubmed, Elsevier, Scielo and Medline, as well as national and international libraries specialized in the subject matter. Search words such as: "Syndrome", "Dravet", "Myoclonic epilepsy", "Pediatrics" and "Encephalopathy" were used, obtaining approximately 10-40 results in Spanish and English, of which a total of 22 references were selected. bibliographies that were considered relevant for the development of this review article.

RESULTS AND DISCUSSION

Epidemiology

Epilepsy, being a frequent condition during the pediatric age, presents an incidence of 130/100,000 people during the first months of life and 40/100,000 people in the first decade 1,3). The prevalence of epilepsy is estimated between 2.7-40/1,000 people [3]. The figures reported are lower in developed countries compared to studies carried out in Africa, Latin America and Asia. The incidence of DS is estimated to be between 1/15,700 people in the United States and 1/40,900 people in the general population. For its part, taking into account that the ILAE classifies this syndrome as an Epileptic and Developmental Encephalopathy, a prevalence of 1/2,000 children are commented [1]. It has been shown that DS affects men and women in equal proportions and that the initial episode generally occurs during the first 12 months of life. Additionally, it is important to mention that patients have a higher mortality rate during childhood, with sudden death in epilepsy (SUDEP) and status epilepticus being the most common causes.6.

Etiology

DS is a genetic disease in which about 85% of those affected have detected the presence of a mutation at the level of the SCN1A gene that codes for the a-1 subunit of the type 1 voltage-gated sodium channel (Nav 1.1). These mutations are located on chromosome 2q24 and more than 90% of them are de novo [6,7] however, recent data suggest that the remaining percentage could correspond to families with gamete mutations or mosaicisms. SCN1A mutations and impaired NAV 1.1 lead to dysfunction of GABAergic inhibitory neurons in the neocortex and hippocampus [8,9] which leads to a general imbalance in neuronal inhibition/excitation and finally, to a process of net overexcitation that leads to the appearance of seizures. It is important to take into account that in about 20% of people diagnosed with DS, no mutation could be identified in the SCN1A gene and that this type of alteration can also occur in other less severe epilepsies, so the clinicopathological correlation It's fundamental. Additionally, in less than 20% of the reported cases, damage has been identified in other genes called "imitators" such as PCDH19, GABRG2, CHD2, HCN1, STXBP1, GABRA1 and SCN1B, which are included in various commercial genetic panels [10].

Clinical Presentation

The clinical manifestations of DS, as previously mentioned, can be variable, however, the main symptoms are refractory seizures, developmental delay, cognitive impairment, and motor dysfunction. In order to facilitate the understanding of the pathology, as well as its diagnosis, three evolutionary stages have been identified based on the specific characteristics of the patient according to their age.

Initial phase: Generally, the first seizure episode is evident between five and eight months of age [3] associated or not to a trigger factor such as fever, infection, vaccination or even bathing. This first seizure is characterized by presenting prolonged focal or generalized tonic-clonic activity with extension studies such as normal brain magnetic resonance imaging and electroencephalogram with limited or no initial changes [3,10]. Some variability in the mode of onset of seizures has been reported as up to 61% of them may be afebrile and 49% of them exceed twenty minutes in duration. Additionally, some caregivers have reported the presence of isolated episodes of focal myoclonic jerks' days before the formal onset of the first seizure [2]. This first episode is generally considered accidental, which is why investigations are rarely carried out or medical management is instituted; however, other seizures later become evident that are associated with slow development, which makes the condition characteristic [11,12].

Worsening phase: During the first five years of life, patients present various types of seizures, among which are myoclonic, atypical absence seizures, and focal seizures [10]. However, characteristically the events will be found to be more frequent but less prolonged than the initial ones. In this age group, the main triggers will be fever, stress, excitement and particularly flashes of light [2]. In half of the patients a slowing of the electroencephalographic activity can be observed while, in the other half, the activity is frankly slow and disorganized. In addition, abnormalities defined as spike or polyspike waves and photoparoxysmal response could be found [10,13]. At this stage, alterations in neurological and language development become evident, manifesting the presence of ataxia associated with hyperactivity, inattention and excessive impulsivity [14].

Stabilization phase: After five years of age, patients usually present a period of stability in which the interictal time increases and the duration of the seizures decreases with some persistence of generalized or focal tonic-clonic episodes [10]. Additionally, at this stage cognitive and language alterations become more visible with progressive worsening of non-convulsive comorbidities such as mental retardation and ataxia. About 15% of patients present sudden death during sleep.

Comorbidities: Over time, many DS patients develop various comorbidities resulting from underlying channelopathy, recurrent seizures, and side effects of polypharmacy (fifteen). The Dravet Syndrome Foundation in 2016 (16) conducted the largest survey of parents and caregivers to date seeking to identify the top concerns of caregivers, as well as the approximate frequency of comorbidities of the syndrome beyond seizures. A total of 256 responses representing patients ranging in age from 9 months to 32 years with a group median of 7-10 years were included in this project. Table 1 shows that sleep disorders, communication disorders, mobilization disorders, and finally, what is understood as metabolic maintenance, are the most commonly related.

Table 1: Frequency of comorbidities reported in the DSF survey.

Category	Affair	n/n (%)	Category	Affair	n/n (%)
Sleep	Sleep disorders	85%	Growth, endocrine and metabolism	Change in body temperature	88%
	nocturnal seizures	77%		lack of sweating	67%
	Insomnia	71%		Stunted growth	39%
	premature awakening	62%		Appetite disturbance	68%
Orthopedics/ Movement	gait disorders	75%	Communication problems	delayed language	84%
	hypotonia	72%		Aphasia	70%
	Ataxia	65%		Difficult to understand language	70%

DIAGNOSIS

The early diagnosis of DS is of vital importance since, as previously mentioned, it has been shown that assertively established management has a positive impact on the neurological and behavioral development of patients, as well as on the quality of life, without However, a multicenter study conducted in the United States documented a median time from seizure onset to definitive diagnosis of 4.8 years (fifteen). The reality is that there are currently limited data in the literature on the guidelines that should be used for the diagnosis and management of the pathology, however, it must be taken into account that suspicion is generated from the clinical manifestations evidenced by Therefore, according to the ILAE, there are a series of characteristics, mentioned in Table 2, that must be taken into account to confirm the presence or not of the disease.

Table 2: Clinical characteristics determined by the ILAE in the diagnosis of Dravet syndrome.

Family history of epilepsy or febrile seizures
Normal development before seizure onset
Seizure before one year of age
Electroencephalogram with generalized spike and polyspike waves
Pleomorphic epilepsy
Focal abnormalities or early photosensitivity
Psychomotor retardation after 24 months
Exacerbation of seizures with increased body temperature
Appearance of ataxia, pyramidal signs, or interictal myoclonus after the onset of psychomotor impairment

Regarding extension studies, it should be noted that in most cases the nuclear magnetic resonance and the electroencephalogram are without reported alterations, however, few investigations have carefully documented the evolution of these parameters over time. In 2011, in a study carried out in 22 children with DS during the first five years after diagnosis, it was found that 27% presented slowing of the fundus in the electroencephalographic tracing after 6 months, 64% focal or multifocal epileptiform discharges and 41% photoparoxysmal response [15-17]. For its part, in magnetic resonance imaging, a study carried out in Italy in 2014 showed that, of 120 patients with a confirmed diagnosis, only four had malformations of cortical development, while another study from 2013 concluded that, of 18 patients, 7 had hippocampal sclerosis or loss of gray and white matter definition, however, this is not standardized data [18]. Finally, it is important to mention that the techniques used for the diagnosis of DS have evolved drastically in recent years, including small-scale tools such as fluorescence in situ to multigene panels, clinical exome sequencing, and chromosomal microarrays [19]. However, the reality is that due to limited cost coverage for medical care, the performance of these procedures is limited.

DIFFERENTIAL DIAGNOSIS

Since the first convulsive episode of DS is usually associated with the presence of fever, it is vitally important to mention that it must be differentiated in a timely and rapid manner from febrile seizures frequently seen in the pediatric population. For this, the characteristics of the pathology must be taken into account, such as that the first event always occurs before one year of age, the type of seizure is clonic and often unilateral instead of generalized and tonic and, finally, the episodes seizures tend to be longer and more frequent [2]. Additionally, the reported temperatures are not usually that high. On the other hand, there are other childhood epileptic encephalopathies that must be taken into account when making the diagnosis. In Table 3. Some examples of pathologies can be clearly observed, as well as their main characteristics.

Table 3: Differential diagnoses of Dravet syndrome.

Syndrome	Dravet Syndrome	Othahara Syndrome	West's Syndrome	Lennox-Gastaut Syndrome	Landau-Kleffnner Syndrome
Starting age	1-12 months	1-3 months	4-6 months	10 days-9 years	18 months-3 years
Seizure type	Focal to generalized tonic clonic, absence seizures	Absence, tonic/clonic, myoclonic, partial and complex seizures	Epileptic Spasms	Focal, myoclonic-atonic and myoclonic	Generalized tonic-clonic
EEG findings	May be normal or show abnormal theta activity between 4-5 Hz above the vertex	Burst pattern and suppression during the awake and sleep stage	Hypsarrhythmia	Sharp multifocal waves, sharp Rolandic waves	Paroxysmal changes and little or no language development

TREATMENT

Complete control of SD is usually not achieved (fifteen) Therefore, currently and in order to reduce the mortality and neurological deterioration figures, the priority is to avoid as much as possible the appearance of prolonged convulsive crises. As a general recommendation, there are three fundamental pillars that must be taken into account when establishing medical management: anticonvulsant drugs, the ketogenic diet and, finally, surgical interventions.

Drugs

Valproate or clobazam are defined as first-line drugs for the management of DS (10) and, according to the 2017 North American Consensus Panel(twenty), are given in combination with stiripentol or topiramate if seizures remain refractory. Ethosuximide, levetiracetam, clonazepam, zonisamide, and phenobarbital are recognized as third-line agents [19]. In June 2018, the US Food and Drug Administration (FDA) approved the use of Epidiolex (cannabidiol) for the treatment of DS and Lennox-Gastaut Syndrome [3]. This drug has agonist activity at the cannabinoid 1 and 2 receptor, demonstrating an anticonvulsant effect that has been supported by several long-term open-label studies that comment on tolerability and efficacy of the drug in a median duration of 38-39 weeks. This has generated important expectations in patients and relatives regarding the possibility of achieving better medical control. The most common side effects in pharmacological management are drowsiness, decreased appetite, agitation, weight loss, nausea, and tremors.

Ketogenic Diet

It is a diet rich in fat, low in carbohydrates and adequate in protein that has been studied as an adjunctive management of refractory epilepsy since the 20th century (twenty-one). Its mechanism of action is based on the hypothesis that increasing fat metabolism increases acetoacetic acid (ketone body), which is the main molecule involved in the reduction of convulsive episodes in mice [20]. This technique is contraindicated in patients with pancreatitis, liver failure, or fat metabolism disorders; however, it is an important factor to take into account when considering the medical management of patients with DS, since studies have demonstrated up to 50% reduction in seizures in 40% of reported cases within the first three months [21].

Surgical Interventions

Options for surgical management of patients with DS are limited, however, the FDA has approved deep brain stimulation and vagus nerve stimulation as treatment for recurrent seizures. Additionally, the use of other surgical options such as temporary lobectomy and callosotomy of the body can be performed only in those cases in which therapeutic failure has been proven with other medical management techniques, always considering the risk/benefit ratio.

Forecast

Life expectancy is not well defined; however, studies have been carried out that show that approximately 10-20% of these patients die before the age of 10. Additionally, it has been established that the two most common reasons for premature mortality would be SUDEP and status epilepticus.

The International League of Action against Dravet Syndrome Epilepsy (IDEA league) carried out a study in which it used a population of 833 already diagnosed patients, among which 31 died before the age of 10, with a mean age of death of 4.6. years. In addition to the above, through this study it was possible to observe that 61.2% of the patients died due to SUDEP, 32.2% due to status epilepticus and the remaining 6.8%, which corresponded to two patients, due to ketoacidosis or an accident [22]. Regarding mental prognosis, a prospective study of 37 patients demonstrated that reducing the appearance of epileptic states at an early age has a positive impact on neurological compromise. For this reason, it is vitally important to train parents on the initial care of convulsive episodes, as well as the timely response of medical personnel in emergency care.

CONCLUSION

DS is a distinctive, early-onset epilepsy that must be effectively diagnosed through its clinical presentation, imaging studies, and genetic testing. The priority should be seizure control, as well as management of status epilepticus through anticonvulsant medications, a ketogenic diet, and sometimes, if necessary, surgical

intervention. It is a pathology with a high percentage of early death as well as comorbidities related to its origin and management, therefore, DS continues to be a challenge for clinicians who must, at all times, individualize the patient's medical condition in order to offer appropriate therapy and reduce the occurrence of complications.

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