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Original article

Prognostic, Clinical, and Demographic Features in SCN1A Mutation-positive Dravet Syndrome

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Dravet syndrome typically manifests after the first year of life with prolonged febrile and afebrile seizures in previously developmentally normal children. The epilepsy is often refractory to standard anti-seizure medications, and by age two, most children develop epileptic encephalopathy. This retrospective study aimed to identify predictors of treatment response and developmental outcomes, as well as characterise demographic and clinical features in patients with SCN1A mutations. We reviewed clinical records of patients meeting Dravet syndrome diagnostic criteria, extracting data on demographics, clinical phenotype, and treatment history. Seventeen patients were included (male-to-female ratio 0.54:1; mean age 10.03 ± 5.8 years). All had normal birth histories, and 94.1% experienced their first seizure before six months of age, with fever as the precipitating factor in 70.6%. All patients had a history of prolonged seizures or status epilepticus. Initial interictal EEGs were normal in 76.5% during the first two years, and brain MRI was normal in 88.2%. While all children were developmentally normal before seizure onset, 76.5% later exhibited developmental delay and cognitive decline. Seizures worsened in 52.9% of patients when treated with phenobarbital, carbamazepine, lamotrigine, or vigabatrin (as mono- or polytherapy). After genetic confirmation, 94.1% received a combination of stiripentol, valproate, and clobazam, resulting in >50% seizure reduction in 88.2%. Dravet syndrome should be considered in children with refractory epilepsy, infantile-onset recurrent seizures (including febrile seizures/status epilepticus), and normal early development. Genetic testing enables early diagnosis and guides appropriate treatment, improving outcomes. However, no statistically significant predictors of treatment response or developmental outcomes were identified in this cohort.

Introduction

Since its first description in 1978, the clinical boundaries of Dravet syndrome (DS), additionally acknowledged as severe myoclonic epilepsy in infancy, have evolved significantly [1]. Since the discovery of the syndrome's primary genetic cause, SCN1A gene mutation, there has been an increase in diagnoses [2,3]. Dravet syndrome is one of the early recognised genetic epilepsies with a clear genotype-disease association. Before the widespread use of genetic testing, diagnosis of patients was based mainly on the clinical history patients presented with, involving early onset of convulsions, prolonged convulsions induced by infection or heat, multiple types, and later on global developmental impairment. Although Dravet syndrome incidence in the general population is 1:16,000–1:40,000 [15,16], it is low enough to be classified as rare.

This syndrome typically begins manifesting itself after the age of one year, accompanied by extended, afebrile, and febrile convulsions, and generalised clonic or hemiclonic epileptic convulsions in children with no pre-existing developmental issues. Myoclonic, focal, and atypical absence convulsions typically appear between the ages of 1 and 4 years. The seizures are usually refractory to standard anti-epileptic medication. Moreover, after the age of one year, affected patients develop what is known as an epileptic encephalopathy, which manifests as cognitive, behavioural, and motor impairment.

In Dravet syndrome, seizure types as status epilepticus could be life-threatening, and unexpected death in epilepsy can occur [4]. There is some evidence supporting specific treatment regimens for the epileptic seizures connected with Dravet syndrome [5-7].

As encephalopathy is associated with cognitive decline and permanent neurological impairment, it has been suggested that aggressively focused therapy should be commenced as soon as possible [8]. Most affected children (70–80%) have a mutation in the voltage-gated sodium channel type I alpha subunit gene, SCN1A. Latest scientific research suggests that the phenotype might be affected by the type of a mutation [9, 10,11]. However, it is not clear whether the developmental regression is primarily caused by genetic change, epileptic encephalopathy, or both [12]. Predictors for long-term developmental outcomes are not well known; however, several clinical variables, including age at seizure onset, suggest that early absences and myoclonus are

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associated with poorer developmental outcomes [13]. A retrospective report showed that vaccination-proximate children, who had seizure onset within 2 days after vaccination, exhibited earlier seizure onset, but the developmental outcome was not different between groups [14].
Until now, despite the prolonged course of the disease, not enough large studies have systematically examined the clinical, prognostic and demographic characteristics of the disease. This retrospective study was conducted to identify predictors of treatment response, developmental outcomes, and specific demographic and clinical features of patients with SCN1A gene mutation Dravet syndrome.

Methods

This is a descriptive case series study. Clinical records for all patients with SCN1A gene mutation Dravet syndrome were reviewed to obtain the relevant information. The patients presented to the Neurology clinic at Tripoli Children's Hospital in the period from June 2003 up to the time of data collection, September 2024.
The relevant information includes sex, age, age at start of first seizure, history of prolonged febrile seizures, seizure semiology, factors precipitating the first seizure, history of epilepsy and febrile seizure in the family, the age at which development noted to be abnormal, developmental status, electroencephalographic findings, neuroradiological findings, medications, and medication response.
Cases that did not have an SCN1A gene mutation were not included in the study. This was done because these patients may have another diagnosis similar to SCN1A-related Dravet syndrome, like the X-linked protocadherin 19 (PCDH19) gene mutation. The data were coded and analysed using SPSS software. Mean, percentage, frequency and standard deviation were utilised to illustrate the data. Chi-square was used to identify the significant level of difference between categorised data; a P value < 0.05 was considered significant.

Results

A total of 17 patients who met the selection criteria were included in the study. 11 (64.7%) were female with a male-to-female ratio of 0.54:1. The mean age was 10.03 ± 5.8 years (range from 2 years to 24 years). All patients had a normal perinatal history, and a history of seizures in the family was present in 10/17 cases (58.8%). The characteristics of the patients are shown in Table 1.

Table 1. Phenotypic characteristics in SCN1A gene mutation Dravet syndrome (n = 17)

character	No.%	character	No.%
Gender(female)	**11(64.7)**	**developmental status**	
age	**10.03+- 5.8**	**normal/ mild learning disability**	**4(23.5)**
Age at first seizure		**moderate to severe learning disability**	**13(76.5)**
< 6 month	**16(94.1)**	**acquired autistic features**	
> 6 months < 1 year	**1(5.9)**	**yes**	**14(82.4)**
First seizure precipitating factor		**no**	**3(17.6)**
fever	**12(76.5)**	**ADHD**	
vaccination	**5(29.4)**	**yes**	**10(58.8)**
normal development before the start of the seizure	**17(100)**	**no**	**7(41.2)**
status epilepticus or prolonged seizure in the family	**17(100)**	**Interictal EEG findings in the first 2 years**	
history of seizure	**10(58.8)**	**normal**	**13(76.5)**

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Age at which development is noted to be abnormal		**generalised spike and wave**	**3(17.6)**
< 1 year	**5(29.4)**	**focal discharges**	**1(5.9)**
< 2 year	**11(64.7)**	**MRI findings**	
Acquired motor disorder		**normal**	**15(88.2)**
hypotonia	**4(23.5)**	**abnormal**	**2(11.8)**
spasticity	**1(5.9)**		
ataxia	**3(17.6)**		
spasticity and ataxia	**2(11.8)**		
nil	**7(41.2)**		

The first seizure happened within the first 6 months of life in 94.1% of children. The provoking factors for the first seizure were fever in 70.6% and vaccination in 29.4% of patients. Prolonged seizures with status epilepticus were present in all patients. 58.8% of patients presented with hemiclonic seizure type. Figure 1 shows seizure types during the disease course.

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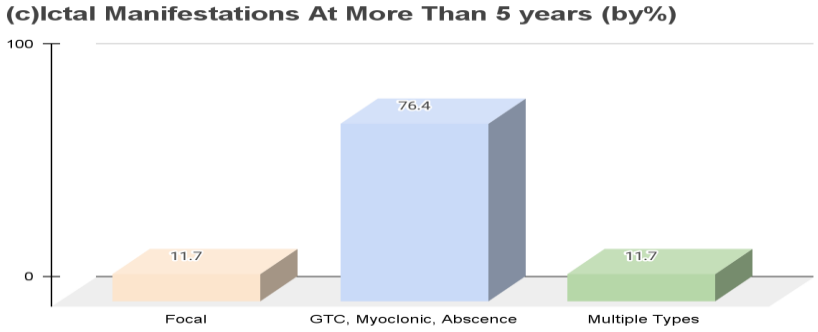

Figure 1: Seizure types during the disease course. (a) ictal manifestations at less than one year, (b) ictal manifestations at 1-5 years old, (c) ictal manifestations at more than 5 years old.

The initial interictal EEG findings in the first and second year of age were normal in 76.5% and specified as generalised wave and spike in 17.6% of cases, and focal/multifocal EEG discharges in 5.9% of patients. MRI brain imaging was normal in 88.2% of patients, while MRI abnormalities were present in 11.8% of patients and were reported as nonspecific atrophic changes and mild periventricular leukomalacia in 5.9% of each. All patients had normal development before the start of convulsions. Unfortunately, this was followed by a developmental delay and a cognitive decline in 76.5% of patients after the start of convulsions. Most patients developed behavioural issues, notably autistic (82.4 %) and ADHD (58.8%) features at follow-up. Initial anti-seizure treatments are illustrated in Table 2.

Table 2: Initial medication frequency

Initial ASM	**Frequency(%)**
Valproate	**8(47.1)**
Clobazam	**7(41.1)**
Phenobarbitone	**5(29.4)**
Topiramate	**5(29.4)**
Levetiracetam	**4(23.5)**
Carbamazepine	**3(17.6)**
Lamotrigine	**3(17.6)**

The most frequently used ASMS were valproate (n = 8, 47.1%), Clobazam (n = 7, 41.2%), and Topiramate (n = 5, 29.4%). 52.9% of patients experienced worsening seizures following the administration of Phenobarbital, Carbamazepine, Lamotrigine, or Vigabatrin as monotherapy or in combination. After confirmation of the diagnosis of Dravet syndrome by genetic testing, a combination of Clobazam, Valproate, and Stiripentol is currently being used in 94.1% of patients. 88.2% of patients showed an improvement, and more than 50% of them experienced a reduction of convulsions; Table 3 shows the response to medications.

Table 3: Frequency of medication responses

Medication reported to have reduced seizure frequency	**No.(%)**
Valproate	**11(64.7)**
Clobazam	**1(5.9)**
Levetiracetam	**3(17.6)**

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Topiramate	**2(11.8)**
Medication reported to have aggravated seizure frequency	**No.(%)**
Phenobarbitone	**7(41.2)**
Carbamazepine	**7(41.2)**
Lamotrigine	**3(17.6)**
Vigabatrin	**1(5.9)**

Discussion

In our study, out of 17 patients, females were more affected than males, accounting for 64.7% of the children with a male-to-female ratio of 0.54:1; this finding was inconsistent with recent figures acquired from a broad parent survey [17]. Sixteen (94.1%) children presented with their first seizure within the first 6 months of age. The mean age at first seizure was 5.19 months, in a study of SCN1A mutation by Cetica et al., usually, patients who had their first seizure after 12 months of age did not develop Dravet syndrome [18]. The most common trigger for first seizures was high temperature, accounting for 70.6% of the cases, while vaccination was the second most common trigger, accounting for 29.4% of children.

The above-mentioned finding was in accordance with the study by Caraballo et al, who reported in 75.5% of their cases that the first seizure was associated with febrile illness, while vaccination accounted for 24.5% of children [19]. Vaccine-triggered seizures were noted in 27% of patients with Dravet syndrome in a study by Tro-Baumann et al, study [20].

In our study, the seizure trigger factor itself did not affect the developmental outcome, which is in line with a previous report [21]. This supports the argument that patients carrying an SCN1A gene mutation are doomed to develop the syndrome, which can be caused by a group of factors like fever, vaccination/illness or both. However, the type of the trigger will not affect developmental outcome and does not appear to be responsible for the later encephalopathy.

It is mentioned in [22] that in approximately 25% of cases, a family history of epilepsy or febrile seizures was a positive finding. This is the same with our findings, where we show that 58.8% of patients had a family history of convulsions. Many types of seizure semiology appear by 2 years of age and may involve generalised myoclonus, focal, and atypical absences [23]. As in previous studies, we noticed several seizure types, including generalised tonic, focal seizures, myoclonic jerks, and atypical absence seizures.

As in other studies, we show that 76.5% of the initial EEG is normal. But, abnormalities become clear with recurrent convulsions. The abnormalities include generalised, focal, or multifocal epileptiform changes, like multifocal spikes, spike and waves, polyspike and wave discharges, and a slowing of background activity [24].

In a recent review paper [25] containing 58 brain MRIs of patients with DS, 22.4% showed abnormal findings consistent with cortical brain atrophy, cerebellar atrophy, hippocampal sclerosis, focal cortical dysplasia, and ventricular enlargement. While recurrent, prolonged convulsion in infancy is the hallmark of Dravet syndrome, it is surprising that hippocampal changes on brain MRI are not seen more frequently. There is good clinical evidence to show that prolonged febrile seizures can result in acute hippocampal injury. In general, it remains unclear as to how many of those children will develop mesial temporal sclerosis in the future [26]. It remains unclear if the atrophic changes are caused by the underlying channelopathy.

Overall, MRI abnormalities could not be a predictor of a worse developmental outcome. This is in agreement with the findings of this study, as 88.2% of the MRI results were reported as normal. Frequent abnormalities that appear after seizure onset involve gait abnormalities, gait abnormalities, and behavioural disturbances revealed as ADHD or autistic traits. A study by Li et al [27] suggests that nearly 25% of the patients with DS had autism, and almost 95% of them showed intellectual disability. Also, previous work shows that two-thirds of patients with Dravet syndrome scored in the abnormal range (>90th percentile) of 'hyperactivity/inattention,' and one-third in the abnormal range for 'conduct problems' [28]; this correlates with the current study indicating that ADHD was present in 58.5%, autism was found in 82.4 % of children, and developmental delay and cognitive incline in 76.5% of patients after the start of disease.

Many independent predictors for developmental outcomes in Dravet syndrome have been found. The earlier the developmental delay was identified, the worse the outcome appeared to be, suggesting that a significant genetic change presents early and becomes clearer with time. In this study, 64.7% of patients showed developmental delay before the age of two. Similarly, the presence of a motor disorder indicated a worse

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outcome. Animal models have clearly demonstrated the important role Nav1.1 plays in the function of cerebellar Purkinje cells and that significant SCN1A mutations can result in a motor disorder [29]. Therefore, the presence of a motor disorder may reflect a higher disease burden in that patient, although in our study, such a correlation was not observed.

Therapeutic approaches in DS have undergone huge changes in the last years and are currently advancing toward more patient-based treatment. The medications which were recently accepted for the treatment of Dravet syndrome include Fenfluramine, Stiripentol, and Cannabidiol. Stiripentol inhibits CYP450 isoenzymes, which leads to an increase in the concentration of other anti-seizure medications, including Clobazam [30]. As an add-on therapy to VPA and CLB, Stiripentol was exhibited to reduce seizure frequency in two randomised, placebo-controlled trials[31, 32]. This is consistent with our study, where 88.2% of patients showed a response with more than a 50% reduction in seizures after the administration of valproic acid, Stiripentol, and Clobazam.

Even though levetiracetam and phenobarbital are often used in infants due to ease of use and safety profiles, these medications are less likely to be beneficial in Dravet syndrome. Sodium channel blockers like Carbamazepine or Lamotrigine were administered in this study before establishing a genetic diagnosis. The result was an increased seizure frequency, which correlates with previous reports that showed that said blockers aggravate myoclonic and generalised clonic seizures as well as status epilepticus [33], and are now known to correlate with a worse developmental outcome [34].

Conclusion

DS diagnosis should be considered in children with refractory epilepsy, onset in infancy with recurrent febrile seizures, or febrile status epilepticus with normal perinatal history and development before the onset of seizures. Genetic testing allows early identification of the disease and affects the selection of antiepileptic drugs, and hence the outcome.

We couldn't identify any statistically significant predictors of treatment response or developmental outcomes in our patients.

Conflicts of Interest. Nil.

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