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RESEARCH ARTICLE

DRAVET SYNDROME: AN ATYPICAL CASE REVEALED BY WHOLE EXOME SEQUENCING

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Abstract

Background: Dravet syndrome (DS) is a developmental and epileptic encephalopathy (DEE), caused in most cases by pathogenic variants in SCN1A, with seizure onset between 1 and 20 months of age.

Case presentation: We report a girl born to consanguineous parents, with a paternal family history of generalized epilepsy. Her development was normal until a first febrile, refractory status epilepticus at 3 years and 6 months. Over the following year she developed typical absence and generalized tonic-clonic seizures of increasing frequency and duration. An EEG recorded bilateral frontocentral spike-and-wave discharges predominating on the right; brain MRI was normal. Whole exome sequencing identified a heterozygous missense variant in SCN1A, NM_001165963.4:c.2839G>A (p.Val947Met), classified as pathogenic (class 5) by the diagnostic laboratory according to ACMG/AMP criteria. Seizures persisted on valproate monotherapy, then stopped after the stepwise introduction of clobazam, stiripentol and levetiracetam. She has remained seizure-free since the age of 4 years, with stable development and no cognitive, motor or behavioural deterioration after more than 12 months of follow-up (last visit at the age of 4 years and 5 months).

Conclusion: Late onset and preserved cognition place this case outside the ILAE 2022 mandatory criteria for DS, and the family history makes the genetic epilepsy with febrile seizures plus (GEFS+) spectrum the main differential. Seizure freedom since the age of 4 years without neurodevelopmental deterioration is consistent with a milder SCN1A phenotype, but longer follow-up is needed. Exome sequencing identified the cause, guided the choice of DS-specific treatment and the avoidance of sodium-channel blockers, and enabled family genetic counselling.

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Introduction:-

Dravet syndrome (DS) is a rare developmental and epileptic encephalopathy (DEE), in which both the seizures and the underlying genetic cause contribute to neurodevelopmental impairment [1,2]. It was first described in 1978 [3]. Seizures typically begin before the age of one year, are often triggered by fever, and are later followed by other seizure types, including myoclonic and atypical absence seizures [4]. The 2022 ILAE definition requires seizure onset between 1 and 20 months of age, drug-resistant epilepsy and intellectual impairment [1].

Developmental delay usually becomes evident after the age of two years. Affected children frequently have language difficulties, impaired motor coordination, behavioural disturbances and intellectual disability [4,5]. The incidence of DS is estimated at approximately 1 in 15,500 live births [6].

More than 85% of patients carry a pathogenic variant in SCN1A, located on chromosome 2q24.3 [7,8]. SCN1A encodes the alpha subunit of the voltage-gated sodium channel NaV1.1, which is predominantly expressed in inhibitory GABAergic interneurons. Loss of NaV1.1 function reduces inhibitory neurotransmission, which explains why DS is considered a channelopathy in which sodium-channel dysfunction causes both seizures and neurodevelopmental impairment [9]. SCN1A variants also cause milder phenotypes, notably the genetic epilepsy with febrile seizures plus (GEFS+) spectrum, in which members of the same family can show phenotypes ranging from simple febrile seizures to DS [8,10].

We report a girl with an SCN1A variant whose seizures began after the age of three years, with preserved cognition and a paternal family history of generalized epilepsy. This case illustrates the limits of the classical DS phenotype and the value of exome sequencing in atypical presentations.

Case Presentation:-

Patient Information:-

A girl, aged 4 years and 5 months at her last visit, was followed in the neurology department for generalized seizures. She was the second of two children born to consanguineous parents (the parents are second cousins once removed, i.e. sixth-degree relatives, with an expected inbreeding coefficient of 1/128 for the proband; Figure 1). Pregnancy and delivery were uneventful. Her father had generalized epilepsy since age 14, well controlled with treatment. One paternal uncle and one paternal aunt had had seizures that stopped in adolescence without medication, and several paternal cousins were affected (Figure 1).

No febrile or afebrile seizure was reported before the age of 3 years and 6 months, when she was admitted to the paediatric intensive care unit for a first febrile, refractory status epilepticus. Over the following year she developed typical absence seizures and generalized tonic-clonic seizures, which became progressively more frequent and longer. Her teacher recently reported mild academic difficulties, which the family had not noticed. The main events are summarized in Table 1.

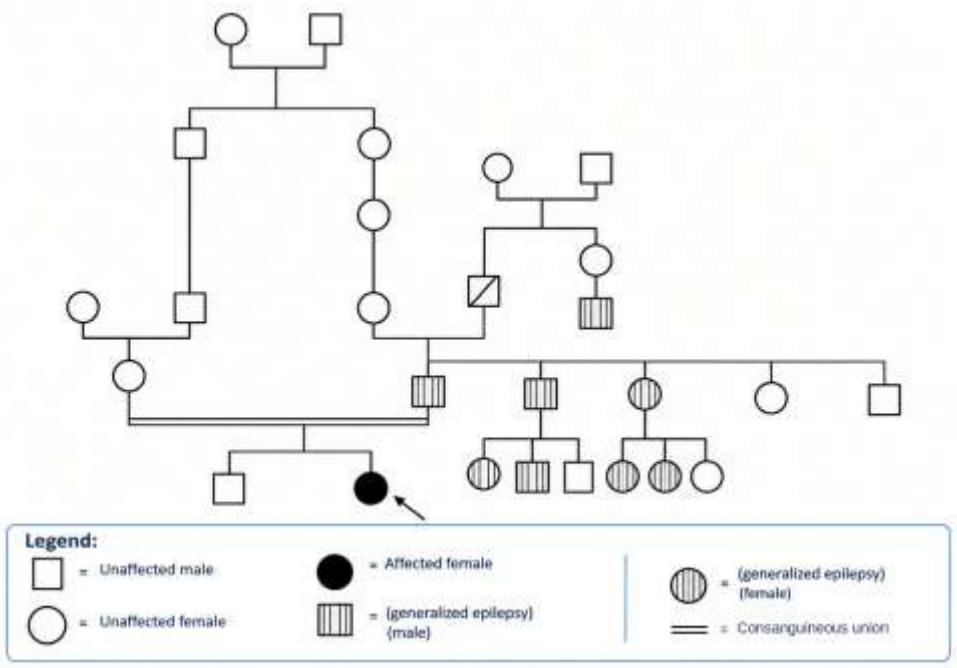


Figure 1. Pedigree of the family. Generalized epilepsy is transmitted vertically on the paternal side (father, paternal uncle and aunt, paternal cousins, and a first cousin of the father), a pattern consistent with autosomal dominant inheritance with variable expressivity. The double line indicates the consanguineous union of the proband's parents. The proband is indicated by the arrow.

Clinical Examination:
The patient was conscious and in good general condition. Weight, height and head circumference at birth and at assessment were within normal ranges. Neurological examination was normal, and psychomotor development had been normal up to that point.

Investigations:
Two electroencephalograms (EEGs) were performed. The first, at the time of diagnosis (3 years and 6 months), was normal. The second, at 3 years and 9 months, after three months of evolution, showed a normal background with numerous bilateral frontocentral spike-and-wave discharges predominating on the right (Figure 2). Brain magnetic resonance imaging (MRI) was normal. Standard laboratory tests showed no abnormality.



Figure 2: EEG of the patient. Normal background activity with frequent bilateral frontocentral spike-and-wave discharges, predominant over the right hemisphere.

Table 1. Clinical timeline.

Age	Event	Investigations / treatment
Birth to 3 y 6 mo	Normal development; no seizure reported	—
3 y 6 mo	First febrile, refractory status epilepticus; PICU admission	Emergency treatment
3 y 6 mo to 4 y	Typical absence and generalized tonic-clonic seizures, increasing in frequency and duration	Sodium valproate 30 mg/kg/day in three doses
3 y 6 mo – 3 y 9 mo	Diagnostic assessment in neurology	EEG 1 at 3 y 6 mo (normal); EEG 2 at 3 y 9 mo (bilateral frontocentral spike-and-wave); normal MRI; normal standard laboratory tests; whole exome sequencing
Before 4 y	Seizures persist despite valproate	Add-on clobazam, stiripentol and levetiracetam (clobazam 0.5–1 mg/kg/day, then stiripentol 50 mg/kg/day, then levetiracetam 40–60 mg/kg/day)
4 y	Last seizure; seizure-free thereafter on the four-drug regimen	Clinical review
4 y 5 mo (last visit)	Seizure-free for 5 months; no cognitive, motor or behavioural deterioration	Normal neurological examination; ongoing neurology and genetics follow-up

Molecular Genetic Analysis:
Given the febrile status epilepticus, the seizure course and the family history, a genetic aetiology was suspected and DS was the leading hypothesis. After genomic DNA extraction from peripheral blood, whole exome sequencing was performed. The analysis identified a heterozygous missense variant in SCN1A: NM_001165963.4:c.2839G>A, p.(Val947Met). The variant is absent or extremely rare in gnomAD v4 (2 of 1,461,888 exome alleles; no homozygote), is predicted to be deleterious by in silico tools (REVEL 0.90; CADD 28; AlphaMissense 0.97), and is reported in ClinVar (Variation ID 206788) with conflicting classifications. It was classified as pathogenic (class 5) by the diagnostic laboratory according to the ACMG/AMP guidelines [11]. Targeted testing of the father is in progress.

Therapeutic Management:
Sodium valproate was started at 30 mg/kg/day in three divided doses, as recommended first-line therapy [5]. Because seizures persisted, clobazam (starting at 0.2–0.3 mg/kg/day and titrated to 0.5–1 mg/kg/day in two divided doses) and then stiripentol (starting at 20 mg/kg/day and titrated to 50 mg/kg/day in two to three divided doses with meals) were added, in line with consensus recommendations for DS [5]. Levetiracetam (starting at 20 mg/kg/day and titrated to 40–60 mg/kg/day in two divided doses) completed the regimen. Sodium-channel blockers (carbamazepine, oxcarbazepine, lamotrigine, phenytoin) were avoided once SCN1A involvement was suspected.

Follow-up: Seizures increased in frequency on valproate monotherapy. After introduction of the four-drug regimen, the clinical course improved and the patient became seizure-free from the age of 4 years. At the last visit, at the age of 4 years and 5 months, after a total follow-up of more than 12 months, she had been seizure-free for 5 months, with no status epilepticus and no emergency admission. Her development has remained stable, with no cognitive, motor, language or behavioural deterioration, and a normal neurological examination. Treatment was well tolerated. She remains under regular follow-up by a neurologist and a clinical geneticist to monitor growth and development and to detect behavioural disturbances, motor coordination difficulties, learning or language difficulties, and spinal deformities.

Discussion:-

Age at onset. Dravet syndrome, formerly called severe myoclonic epilepsy of infancy, typically presents with prolonged febrile hemiclonic or generalized convulsive seizures in previously healthy infants. Seizure onset usually occurs between 5 and 8 months, with an upper limit of about 18 months [12,13]. The 2022 ILAE criteria make onset between 1 and 20 months mandatory and treat onset at 15–20 months as an alert [1]. Our patient had her first seizure, a febrile refractory status epilepticus, at 3 years and 6 months. This is the main atypical feature of the case and the reason why we describe it as Dravet-like rather than as classical DS.

Seizure types and course. First seizures are usually triggered by fever or environmental heat; infections, visual stimuli, noise, emotional stress and overexertion are other triggers [4,5]. Initial seizures are often generalized tonic-clonic or hemiclonic and may evolve into status epilepticus. Myoclonic seizures generally appear around the age of two years [4,14], followed by obtundation, focal seizures and atypical absences. Typical absences and epileptic spasms are not characteristic of DS [1,4]. Seizure frequency tends to increase during the first decade and then stabilizes or decreases; myoclonic and atypical absence seizures may disappear in adulthood [15–17]. In adults, convulsive seizures occur mainly during sleep; Akiyama et al. reported nocturnal seizures in 19 of 31 adults (61%) [18,19]. Our patient had typical absence seizures, which are not characteristic of DS, and generalized tonic-clonic seizures with a febrile status epilepticus as the first event, but no myoclonic seizures so far.

EEG and imaging. Interictal EEG is usually normal during the first year of life. From the second year onwards, generalized spike-and-wave or polyspike-and-wave discharges, or focal and multifocal abnormalities, are found in about half of children and in 75% of adolescents and adults [20,21]. Brain MRI is normal in most patients [22,23], although hippocampal sclerosis has been reported [24–26]. In our patient, EEG showed bilateral frontocentral spike-and-wave discharges predominating on the right, with a normal background, and MRI was normal. These findings are compatible with SCN1A-related epilepsy but not specific to DS.

Genetic findings and role of exome sequencing. About 85% of DS cases are caused by SCN1A variants, and around 90% of these arise de novo [7]. NaV1.1 dysfunction contributes to seizures and to behavioural problems, hyperactivity, social deficits and cognitive impairment [27]. However, an SCN1A variant in a child with epilepsy does not by itself establish a diagnosis of DS [28]. Conversely, Dravet-like phenotypes can be caused by variants in other genes, including PCDH19, SCN2A, SCN8A, SCN1B, GABRA1, GABRG2, STXBP1, HCN1, CHD2 and KCNA2 [29,30]. Exome sequencing is therefore well suited to atypical presentations, where a single-gene test may be too narrow and a panel may miss rarer causes. A prediction model combining age at onset and an SCN1A variant score can help distinguish DS from milder SCN1A-related epilepsies [31]. In our patient, exome sequencing identified the heterozygous missense variant c.2839G>A, p.(Val947Met), classified as pathogenic (class 5) by the diagnostic laboratory. SCN1A is associated in OMIM with DS (#607208) and with GEFS+ type 2 (#604403), both autosomal dominant. A preliminary report of this case was presented as a poster at a scientific congress in 2025.

Family history and differential diagnosis. The paternal pedigree shows generalized epilepsy over two generations, with seizures that remitted in adolescence in two relatives (a paternal uncle and aunt). This pattern is typical of GEFS+, an autosomal dominant condition with incomplete penetrance and wide intrafamilial variability [10]. Three findings in our patient fit the GEFS+ spectrum better than classical DS: onset after 20 months, preserved cognition with no deterioration at the last visit (at 4 years and 5 months), and a family history of milder epilepsy. Others fit DS: a febrile refractory status epilepticus, worsening seizures over one year, and the need for DS-specific polytherapy. Testing the father will help resolve this. If he carries the variant, the case would represent a severe phenotype within a GEFS+ family, and segregation in the affected relatives would add PP1 evidence. If the variant is de novo, PS2 would apply and paternal epilepsy would be coincidental. Parental consanguinity does not influence the inheritance of this dominant variant. Long-term follow-up of cognition is essential, since intellectual impairment in DS may only become apparent after the age of two to five years [4,5].

Treatment. Seizures in DS are usually resistant to antiseizure medications and to other approaches such as the ketogenic diet and neurostimulation [32–35]. The 2022 international consensus considers valproate, clobazam, stiripentol and fenfluramine as first- or second-line maintenance therapies, with cannabidiol as a later option [5]. Cannabidiol reduced convulsive seizures in a randomized trial, with sustained benefit in an expanded-access programme [36,37], and fenfluramine reduced convulsive seizure frequency in a placebo-controlled trial [38]. Sodium-channel blockers such as carbamazepine, oxcarbazepine, lamotrigine and phenytoin may worsen seizures and should be avoided [5,32]. Our patient's regimen (valproate, clobazam, stiripentol and levetiracetam) follows this approach. Her favourable course, with sustained seizure freedom and no neurodevelopmental deterioration over

more than 12 months, is consistent with a milder SCN1A phenotype and contrasts with the progressive cognitive decline usually seen in DS during early childhood [4,5]. Caring for a child with DS places a heavy psychosocial burden on the family, which calls for multidisciplinary management involving physicians, nurses, physiotherapists, psychologists and speech-language therapists [39].

Conclusion:-

This patient carries an SCN1A variant and has a Dravet-like epilepsy with three atypical features: onset after the age of three years, preserved cognition, and a paternal family history of generalized epilepsy. These features fall outside the ILAE 2022 mandatory criteria for DS and point to the GEFS+ spectrum as the main differential. Exome sequencing established the genetic cause, guided the choice of DS-specific therapy and the avoidance of sodium-channel blockers, and enabled genetic counselling of the family. After more than 12 months of follow-up, the patient remains seizure-free with stable development and no deterioration. Genetic testing should be considered in febrile status epilepticus beyond infancy, and molecular findings should always be interpreted together with the clinical course.

Consent for publication:

Written informed consent for publication of clinical data, the pedigree and the EEG was obtained from the patient's legal guardians.

Prior presentation:

This case was previously presented as a poster communication at a scientific congress in 2025, and the abstract was published in the European Journal of Human Genetics conference abstracts. The present report adds additional follow-up, during which the patient remained clinically stable, with no intellectual disability and no new neurological sign.

Conflict of Interest:

None of the authors has any conflict of interest to declare. The authors confirm that they have read the journal policies regarding publication ethics and affirm that this case report complies with these guidelines.

Author Contributions:

Oussama Cherkaoui Rhazouani contributed to the collection of the patient's medical records, patient follow-up, manuscript drafting, and editing. Kenza Dafir contributed to the supervision of the manuscript. All authors read and approved the final version of the manuscript.

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