# Dravet syndrome: diverse seizure phenotypes with various triggers and developmental outcome- A case series from a LMIC

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## Abstract

Dravet syndrome (DS) is a severe childhood epilepsy characterised by drug-resistant seizures, developmental delays, and behavioural disturbances, often linked to de novo mutations in the SCN1A gene. This retrospective case series from Aga Khan University Hospital, Karachi, describes five patients with varying ages of seizure onset and difficult-to-control seizures despite conventional anti-seizure medications. Seizure types included focal clonic evolving into myoclonic, atonic, and generalised clonic seizures, with fever identified as a trigger in three cases. Developmental delays were universal, ranging from speech impairment to motor deficits. Behavioural issues such as aggression and autism spectrum traits were also observed. Treatment involved combinations of Valproic acid, Clobazam, Levetiracetam, Topiramate, and Cannabidiol, with varying responses. This study marks the first documented cases of DS in Pakistan, highlighting unique clinical manifestations and treatment challenges in this setting, thereby enhancing local understanding and management strategies for DS.

**Keywords:** Dravet syndrome, SCN1A mutation, Treatment-resistant epilepsy.

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## Introduction

Dravet syndrome (DS), also known as severe myoclonic epilepsy of infancy (SMEI), is a rare and severe form of childhood epilepsy. Initial seizures typically manifest as focal or generalised tonic-clonic, but can also include hemiclonic, focal impaired awareness, myoclonic, or absence seizures. Triggers such as fever, vaccination, or flashing lights may provoke seizures, though they can also occur spontaneously.[1,2] The predominant aetiology in DS is a de novo mutation in the SCN1A gene, affecting the alpha-1 subunit of the voltage-gated sodium channel.[3] While most cases are due to dominant mutations, rare instances of recessive mutations have been reported.[4] Development is typically normal before the onset of seizure, but delays and deficits in motor skills, language, and behaviour become evident afterwards.[3] Behavioural disturbances such as autism, ADHD, aggression, and irritability can accompany DS, along with EEG findings of generalised spike and polyspike waves.[2,5]

Despite its severity, documentation and understanding of DS in lower-middle-income countries like Pakistan remain limited, influencing diverse clinical presentations and treatment strategies. This study from Aga Khan University Hospital in Karachi highlights unique clinical features and contributes to broader insights into DS within the region.

## Case Series

This retrospective case series examined five patients with DS diagnosed at Aga Khan University Hospital in Karachi, Pakistan, in the paediatric neurology clinic. These patients, with drug-resistant epilepsy and developmental encephalopathy, underwent clinical assessments for evaluation and diagnosis. Five of the 18 patients exhibiting Dravet-like symptoms were confirmed to have DS through positive SCN1A mutations, while the remaining 13 showed no significant genetic findings. Blood samples from each indexed patient were drawn and outsourced to Invitae Genetics Lab in the USA for an epilepsy panel test, with the families covering the cost of genetic testing. No other epilepsy-related gene abnormalities, such as PCDH19, were detected in patients with Dravet-like profiles.

EEG Analysis: The conventional interictal EEG was typically performed at the onset of seizures, followed by additional EEGs to monitor changes. Information regarding ictal (during seizure) and interictal (between seizures) epileptiform activity was also considered.

Informed assent was taken from all patients' families to publish this case series.

**Case Number 1:** A seven-year-old boy presented in October 2017 with a history of seizures since he was three

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months old. Initial focal clonic seizures evolved into generalised clonic seizures. No specific triggers were identified. There was a positive family history of epilepsy, but no genetic diagnosis or workup was available. He was born full-term via C-section to non-consanguineous parents. EEG at the onset of seizure suggested mild cerebral encephalopathy; later EEG indicated a focal seizure disorder. No neuroimaging was available. Genetic testing revealed SCN1A pathogenic heterozygous variant p. Arg1407, creating a premature translational stop signal in the SCN1A gene and a variant of uncertain significance in TBC1D24 protein. Initial treatment included Phenobarbitone and Levetiracetam, followed by Valproic acid, Topiramate, and Clobazam. The patient has Unspecified Intellectual Disability (UID).

**Case Number 2:** A 13-year-old girl presented in January 2018 with a history of seizures since she was three months old. Initial focal clonic and myoclonic seizures progressed to generalised tonic-clonic seizures. There was no positive family history of epilepsy. She was born full term via C-section to non-consanguineous parents. EEG results indicated mild encephalopathy and focal seizure disorder. No neuroimaging was available. Genetic testing identified a pathogenic variant of p. Lys 1737* that resulted in a premature translational stop signal in the SCN1A gene. The patient also reported mutations in AARS, FASN, and GABRD genes, but the associated variants were of uncertain significance. She is currently being treated with Clobazam, Valproic acid, and Levetiracetam, and has UID.

**Case Number 3:** A three-year-old boy presented in January 2023 with seizures since he was 3.5 months old, initially triggered by fever. Seizures included focal clonic, myoclonic, and generalised types. There was no positive family history of epilepsy. He was born at 37 weeks via Caesarean section following placenta previa, and the mother had hypothyroidism. The parents are non-consanguineous. EEG results showed intermittent bilateral frontotemporal sharp and slow waves. No neuroimaging was available. Genetic testing revealed a likely pathogenic SCN1A frameshift mutation (p. Asn1391fs*7) and a likely pathogenic RYR1 protein variant. Current treatments include Valproic acid, Topiramate, and Clobazam. The patient has a Global Developmental Delay (GDD).

**Case Number 4:** A nine-year-old girl presented in May 2023 with seizures since she was 1.7 years old, initially triggered by fever. There was a positive family history of epilepsy, but no genetic diagnosis or workup was available. She was born at 37 weeks via Caesarean section following placenta previa. There was no history of parents' consanguinity. Seizures progressed from focal clonic to generalised tonic-clonic. EEG results suggested mild cerebral encephalopathy with generalised spikes and slow waves. No neuroimaging was available. Genetic testing revealed a pathogenic variant, p. Val1390Met, which results in the replacement of valine with methionine at codon 1390 of the SCN1A protein. Treatment includes Valproic acid, Clobazam, and CBD. The patient has UID and aggressive behaviour.

**Case Number 5:** A six-year-old boy presented in December 2018 with febrile focal clonic seizures since he was one year old. Seizures included focal clonic, myoclonic, atonic, and head drops. There was no positive family history of epilepsy. He was born full term to consanguineous parents. EEG was initially normal but later showed bilateral frontocentral dominant high voltage with generalised spikes and slow waves. Neuroimaging was not available.

**Table:** Summary of the important findings of the five cases.

| Case Number | Type of seizure | Trigger for seizure | Mutation identified | Family history of epilepsy | Medications prescribed | Developmental outcome |
|---|---|---|---|---|---|---|
| Case Number 1 | Focal clonic which later developed into generalised clonic | None | SCNA1- p. Arg1407<br>TBC1D24 | Positive | Valproic acid, Topiramate, Nitrazepam | UID |
| Case Number 2 | Focal clonic, myoclonic which later developed into generalised clonic | None | SCNA1- p. Lys 1737*<br>AARS<br>FANS<br>GABRD | Negative | Clobazam, Valproic acid, Levetiracetam. | UID |
| Case Number 3 | Focal clonic, myoclonic, and generalised, later progressing to refractory epilepsy | High temperature | SCNA1- p. Asn1391fs*7<br>RYRA1 | Negative | Valproic acid, Clobazam, Topiramate | GDD<br>(DQ less than 70% of age) |
| Case Number 4 | Focal clonic which later developed into generalised clonic | High temperature | SCNA1- p. Val1390Met | Positive | Valproic acid, Clobazam, CBD | Unspecified Intellectual Disability with aggressive behaviour |
| Case Number 5 | Focal clonic, myoclonic, atonic, and head drops | High temperature | SCNA1-p. (Arg356*) | Negative | CBD, Valproic acid, and Clobazam | GDD with Autism spectrum disorder |

Abbreviations: DS: Dravet Syndrome; GDD: Global developmental delay; UID: Unspecified Intellectual Delay; CBD: Cannabidiol; GABA: Gamma-aminobutyric Acid.

Genetic testing revealed a pathogenic variant, which led to the following protein change p. (Arg356*) that resulted in a premature translational stop signal at codon 734 of the SCN1A protein. Treatment includes Valproic acid, Clonazepam, and CBD. The patient has Global Developmental Delays and autism spectrum disorder. The findings of the five cases have been summarised in Table.

## Discussion

This case series report five cases of Dravet syndrome (DS), a severe developmental and epileptic encephalopathy characterised by diverse seizure patterns, cognitive deterioration, and motor and behavioural abnormalities.[5] Initial seizures typically occur between five and eight months of age, though in the present case series, DS manifested before five months in three instances and at one and 1.7 years in two others.[6] This observation underscores the variable age presentations in the timeline of DS onset, which differ from the established literature. Primary seizure types include hemi-clonic and generalised tonic-clonic seizures, with additional types such as myoclonic, atypical absence, focal, tonic, and atonic seizures. All cases initially presented with focal clonic seizures, a finding that contrasts with the broader diversity of typically emphasised initial seizure patterns. Additionally, two patients also had myoclonic seizures. Patients displayed generalised tonic-clonic seizures, which decreased in adulthood and often occurred nocturnally; this finding is also new and adds further nuance to the existing reports.[7] Cognitive decline usually begins around the second year, affecting language development, leading to intellectual disability, and learning difficulties.[8] One study noted cognitive disabilities in 33 children, with 21 also exhibiting behavioural disorders.[9] The current cases showed developmental setbacks like speech difficulties, communication obstacles, sporadic aggressive behaviour, UID in three cases, and GDD in two. These findings provide additional specificity to the cognitive and behavioural manifestations associated with DS, something that is quite scarcely reported in the past literature.

The diagnosis of DS is supported clinically by the mutation in the sodium channel genes, especially SCN1A, which encodes for voltage-gated sodium channel, crucial for neuronal excitability.[10] In addition to SCN1A, in one of the current patients, mutations in GABRD, AARS, and FASN were noted. These genes have been associated with a few epileptic disorders; however, their exact association in DS is uncertain.[11,12] On the other hand, other genes, for example, PCH19 and STXBP1, have been implicated in Dravet-like phenotypes, underscoring the genetic heterogeneity of DS.[13] In LMICs, where genetic testing may be limited due to a lack of resources, identification of these genes could help guide diagnosis and treatment in a cost-effective and targetted manner.

However, it is important to note that the major difference in such syndromes comes from the management in resource-limited settings like Pakistan. In such countries, the goal of managing DS is to decrease seizure frequency, prevent prolonged seizures, and mitigate the adverse effects of anti-seizure medications.[6] The typical treatment begins with Valproic acid, which increases gamma-aminobutyric acid (GABA) levels, followed by Clobazam, enhancing GABA's effect on GABA-A receptors. Stiripentol increases GABAergic transmission and inhibits certain enzymes, while Fenfluramine boosts serotonin release. Topiramate blocks sodium channels and modulates GABA activity, and CBD—a third-line option—affects various receptors and ion channels. Often, a combination of these drugs is necessary for better seizure control due to ineffectiveness and side effects when used alone.[14] In the current study, two cases showed uncontrolled seizures with Valproic acid and Clobazam alone, prompting the addition of CBD. However, specific anti-seizure drugs, particularly sodium channel blockers like Carbamazepine, should be avoided as they can worsen seizures and increase their frequency. This was also observed in the present cases where Carbamazepine exacerbated seizures. New genetic therapies for DS are advancing, such as delivering healthy SCN1A genes to replace mutated ones, using antisense oligonucleotides to boost the expression of functional SCN1A alleles, and employing CRISPR/Cas9 for direct correction of genetic mutations.[15] However, in managing conditions such as DS, the scarcity of resources and the cost of these therapies and pharmaceutical medications should also be considered, which often impact outcomes and contribute to further discoveries.

## Conclusion

This case series highlights the broad clinical presentation and genetic profiles of Dravet syndrome (DS), emphasizing how diagnosis and management can be achieved in a resource-limited setting. Due to limited access to advanced therapies, optimal seizure control is hindered, further stressing treatment disparities in LMICs. To improve DS outcomes in such areas, early diagnosis, genetic testing, and multidisciplinary care are crucial.

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**AA & SSBZ:** Data acquisition, interpretation, drafting, final approval and agreement to be accountable for all aspects of the work.

**PC:** Concept, design, revision, final approval and agreement to be accountable for all aspects of the work.