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Case Report

Dravet syndrome an unusual cause of atypical febrile seizure: a case report

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ABSTRACT

Dravet syndrome is a rare refractory epileptic encephalopathy with an underlying genetic basis. It presents with recurrent febrile seizures in infancy. Though development is normal in infancy, neurodevelopmental delay and neurologic disability begin after the onset of seizure at the age of around 2-4 years. The outcome can be improved by early diagnosis (genetic testing for SCN1A gene) and timely treatment. In this case report we are presenting a 3-year-old female child with recurrent refractory epilepsy associated with fever and was diagnosed with Dravet syndrome.

Keywords: Dravet syndrome, Pediatric epilepsy, Refractory epilepsy, Encephalopathy

INTRODUCTION

Dravet syndrome (DS) was first described by Charlotte Dravet in 1978 as severe myoclonic epilepsy of infancy (SMEI), which was later renamed Dravet syndrome (DS) in 1989. It is a rare genetic, early-onset epilepsy syndrome characterized by intractable epilepsy and neurodevelopmental delays. It affects males and females with equal preponderance with an incidence of 1 in 15,700 to 1 in 40,000 live births.[1-3] Dravet syndrome is characterized by multiple different types of seizures (including tonic-clonic, hemiclonic, generalized clonic, focal impaired awareness, myoclonic, and absence seizures), which are refractory, neurodevelopmental delay and neurologic disability that begin after the onset of the seizure, and cognitive and motor system dysfunction persisting into adulthood. Mutations in the voltage-gated sodium channel alpha-1 subunit (SCN1A) gene have been identified in approximately 70-80% of patients with Dravet syndrome. More than 1,000 variants have been identified in the SCN1A gene, making it the most clinically relevant gene in epilepsy. Mizuguchi et al defined Acute encephalopathy (AE) as a generic term for acute brain dysfunction that is usually preceded by infection. In children with Dravet syndrome, acute encephalopathy has occasionally been reported in the literature.[4-8] The International League Against Epilepsy (ILAE) classified the Dravet syndrome as an epileptic syndrome as it is associated with a rare and devastating form of epilepsy.[9-13]

The diagnosis of Dravet syndrome can be confirmed by mutations within the SCN1A gene in genetic testing. The prognosis of Dravet syndrome is poor with severe epileptic seizures and cognitive impairment, with a significant mortality rate.[14] Long-term developmental outcomes of the DS child can be improved by early diagnosis and by reducing the seizure burden. As this is a rare disease with important implications arising from early diagnosis, management, and parent education we decided to present this case as it will be useful for pediatricians and pediatric epileptologists in this region. Due care was taken for ethical issues by taking parental consent and ensuring that the institute has no objection to publishing this case report.

CASE REPORT

A 3-year-old female child was admitted to the pediatric intensive care unit (PICU) with recurrent abnormal body movements associated with fever for 1 day. Similar episodes were present in the last two years associated with fever and the first episode at 7 months of age for which she was treated outside. This time she was referred to our institute. She was the firstborn child to nonconsanguineous parents. The mother's age at conception was 25 years. On examination at admission, she was nonresponsive to stimuli with stiffening, and abnormal movement of both upper and lower limbs. She had no rashes, petechiae, purpura or bruises, icterus, or dehydration.

Physical examination revealed a pulse rate of 154 beats per minute, respiratory rate of 30 breaths per minute, blood pressure of 88/56 mmHg, temperature of 101.2 Fahrenheit, and oxygen saturation of 99% on room air. CNS examination found microcephaly and other systemic examinations were normal. She was admitted to the Pediatric intensive care unit (PICU) with a diagnosis of status epilepticus with global developmental delay and was treated with midazolam immediately. Seizures were difficult to control and required multiple antiepileptic drugs. All routine investigations including CSF examination, EEG, and MRI Brain showed normal results. The child was investigated for drug-resistant genetic epileptic encephalopathy syndrome. SCN1A mutation turned out to be positive for Dravet syndrome.

On further examination after regaining consciousness, she was found to have global developmental delay with the most affected domain being speech and language, she recognized her mother and was able to speak disyllables only. She was not able to speak words as per his age. She had delayed motor development; she was not able to perform motor activities appropriate for her age. She attained walking without support at 2 years 6 months of age. Anthropometry revealed 12 kg weight, 102 cm height, and 44 cm head circumference, of which head circumference was lower than expected and found to be microcephaly. The ophthalmological examination was normal. Her cranial nerves were intact. There were no signs of meningeal irritation. Motor and sensory System examination was found normal. Other systemic examinations were normal.

Laboratory investigations revealed hemoglobin 12 g%, packed cell volume 32.9%, total red blood cell count of 498,000 cells/mm3, total leukocyte count 4800 cells/mm3 with neutrophils 46%, lymphocytes 44%, monocytes 7%, eosinophil 3%, basophil 0%, platelets 356,000 cells/mm3, urea 5.8 mmol/l, creatinine 0.5 mg/dl, Na+143 meq/l, K+ 3.9 meq/l, total protein 70 g/l, and albumin 49 g/l. Her random blood glucose was 110 mg/dl, and her calcium level was 9.6 mg/dl. C-reactive protein (CRP) latex was negative. Blood culture had no growth of microorganisms after 72 hours. Cerebrospinal fluid (CSF) analysis showed a total leukocyte count of 5 cells/mm3, and protein, and glucose levels were within the normal range. Urine analysis was normal. Interictal electroencephalography (EEG) was done twice before this admission during wakefulness and showed no significant findings. However, EEG recording in our hospital found epileptiform discharges in the form of frontal dominant rhythmic activity lasting <3secs. Magnetic resonance imaging (MRI) of the brain was normal (Figure 1). Genetic analysis showed SCN1A gene mutation.

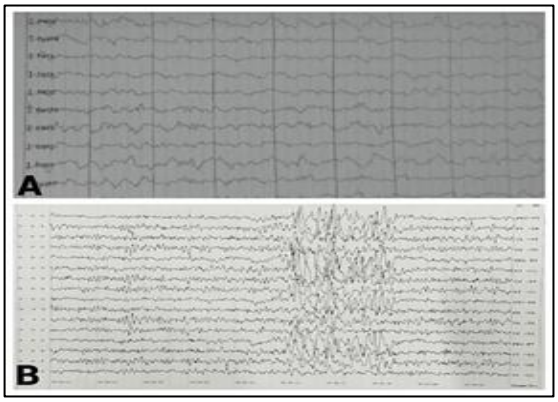


Figure 1: EEG traces (A) Normal and (B) Epileptiform discharges in the form of frontal dominant rhythmic activity lasting <3secs (present case).

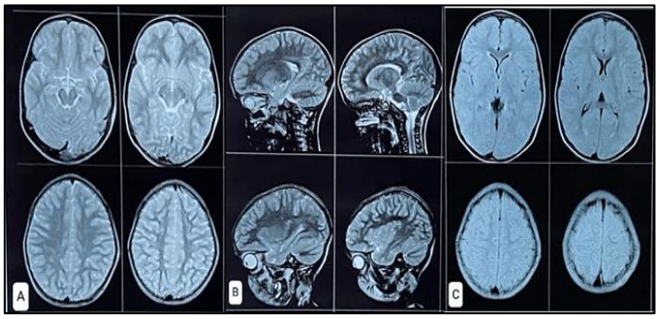
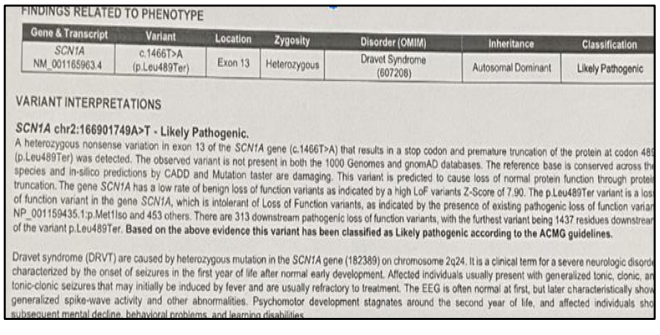


Figure 2: (A) Axial section and (B) Sagittal section T 2 weighted MRI images and (C) T2 flair showing normal brain.



FINDINGS RELATED TO PHENOTYPE

Gene & Transcript	Variant	Location	Zygosity	Disorder (OMIM)	Inheritance	Classification
SCN1A NM_001165963.4	c.1466T>A (p.Leu489Ter)	Exon 13	Heterozygous	Dravet Syndrome (607208)	Autosomal Dominant	Likely Pathogenic

VARIANT INTERPRETATIONS

***SCN1A* chr2:166901749A>T - Likely Pathogenic.**

A heterozygous nonsense variation in exon 13 of the *SCN1A* gene (c.1466T>A) that results in a stop codon and premature truncation of the protein at codon 48 (p.Leu489Ter) was detected. The observed variant is not present in both the 1000 Genomes and gnomAD databases. The reference base is conserved across th species and in-silico predictions by CADD and Mutation taster are damaging. This variant is predicted to cause loss of normal protein function through protei truncation. The gene *SCN1A* has a low rate of benign loss of function variants as indicated by a high LoF variants Z-Score of 7.90. The p.Leu489Ter variant is a los of function variant in the gene *SCN1A*, which is intolerant of Loss of Function variants, as indicated by the presence of existing pathogenic loss of function varian NP_001159435.1:p.Met1Iso and 453 others. There are 313 downstream pathogenic loss of function variants, with the furthest variant being 1437 residues downstrean of the variant p.Leu489Ter. **Based on the above evidence this variant has been classified as Likely pathogenic according to the ACMG guidelines.**

Dravet syndrome (DRVT) are caused by heterozygous mutation in the *SCN1A* gene (182389) on chromosome 2q24. It is a clinical term for a severe neurologic disord characterized by the onset of seizures in the first year of life after normal early development. Affected individuals usually present with generalized tonic, clonic, ar tonic-clonic seizures that may initially be induced by fever and are usually refractory to treatment. The EEG is often normal at first, but later characteristically show generalized spike-wave activity and other abnormalities. Psychomotor development stagnates around the second year of life, and affected individuals sho subsequent mental decline, behavioral problems, and learning disabilities.

Figure 3: Variant interpretation findings relayed to Dravet syndrome phenotype in the present case.

The girl is the firstborn child of non-consanguineous parents. Her mother did not smoke, consume alcohol, or use illicit or teratogenic drugs during the period of gestation. She had undergone all necessary antenatal examination visits. The child was born at term following normal vaginal delivery. She cried immediately after birth. Her birth weight and head circumference were normal and appropriate for gestational age. She was discharged following evaluation and had no immediate neonatal complications. The mother and father were 25 and 30 years old, respectively, at the time of gestation. She has been fully immunized according to the National immunization schedule. The patient had the first episode of seizure at 7 months of age. She used to have up to ten episodes of seizures per day during febrile illnesses. She was on Levetiracetam and regular follow-ups since then. Her developmental milestones were normal till 10 months of age. Later, she had a delay in attaining age-appropriate milestones. Seizures were difficult to control and required multiple antiepileptic drugs. The child was investigated for drug-resistant genetic epileptic encephalopathy syndrome. SCN1A mutation turned out to be positive for Dravet syndrome. She was diagnosed with Dravet syndrome. Following this, she was managed with, levetiracetam, clobazam, sodium valproate, and per rectal paracetamol.

DISCUSSION

As per the Dravet Syndrome Foundation and other medical bodies, the diagnostic criteria for this condition should include several symptoms. Onset of seizures in the first year of life in an otherwise healthy infant. The average age of onset is 5.2 months. Initial seizures that are typically prolonged and are generalized or unilateral. Presence of other seizure types (i.e., myoclonic seizures, tonic-clonic or hemi convulsive seizures). Seizures associated with fever due to illness or vaccinations, Seizures induced by prolonged exposure to warm temperatures. Seizures in response to strong lighting, photosensitivity or certain visual patterns, initially normal EEGs and later EEGs with slowing and severe generalized polyspikes. Normal initial development followed by slow development during the first few years of life. Some degree of hypotonia, Unstable and crouched gait and balance issues. Ankle pronation and flat feet and/or development of a crouched gait with age. In older children and adults, persisting seizures, which may or may not be prolonged. Status epilepticus becomes less frequent with time and may not be apparent by young adulthood. MRI may be normal or show mild generalized atrophy and/or hippocampal sclerosis. Two or more seizures with or without fever before 1 year of age; two or more seizures lasting longer than 10 minutes; failure to respond to first-line antiepileptic drug therapy with continued seizures after 2 years of age.[15,16] In our patient, several of the above-mentioned features were present.

Our patient developed a seizure at the age of 7 months while the first seizure usually occurs between five and eight months of age with normal physical and psychomotor development at the time of onset of seizures in infants with DS.[16] The most common type of seizure during the first year of life in DS is the febrile tonic-clonic seizure, but some patients may have cyclonic and dyscognitive seizures.[17] Often seizures are prolonged and may lead to status epilepticus. The precipitating factors for seizures in the first year of life are fever/illness, immunization, and bathing.[18] With advancing age, the child may have a multitude of seizure types, with fever, emotional stress, flashes of light, or overexertion as precipitating factors for seizures. Subsequently, the child with DS will develop hypotonia, ataxia, incoordination, pyramidal signs, dysautonomia events, cognitive impairment, and behavioral disturbances like attention deficit hyperactivity or autistic traits.[19-21]

There is a natural tendency to reduce epileptic seizures in late childhood and adulthood. Therefore, the clinical course can be divided into three phases. The seizure phase (up to 12 months) is associated with fever, while psychomotor development is normal. The worsening phase with emerging new types of seizures such as myoclonic, atypical absence, and focal seizures (between 1 to 5 years of age), and the psychomotor developmental delay becomes apparent around the second year of life. The stabilization phase is the one in which motor disabilities such as crouching, choreoathetosis, pyramidal signs, and Parkinson's syndrome are observed (before 10 years of age). Our patient had SCN1A gene mutation (located on chromosome 2q24) which is the most common mutation seen in approximately 80% of patients with DS. Among them, the common genomic abnormalities in the SCN1A gene are truncating mutations (40%), missense mutations (40%), nonsense mutations, and splice site changes. Other genetic mutations observed in patients with DS are PCDH19, SCN1B, SCN2A, GABRA1, STXBP1, CDH2, and rarely HCN1, KCNA2, and GABRG2.[22-25] During the early phases of the disease, EEG is usually normal, but as the child grows, it may show abnormalities like slowing of background activity and poly-spike or generalized spike-wave pattern. MRI of the brain is normal at initial presentation but rarely it can demonstrate enlarged ventricles with cerebral atrophy as seen in our case.[26] Our patient had the presentation of DS with infantile-onset (7 months of age) generalized tonic-clonic seizure and status epilepticus. She had a normal early developmental profile and after seizure onset, she had a developmental delay. Autonomic manifestations like urinary incontinence can occur in DS.

Despite the fact that anti-seizure medications have limited efficacy, every effort should be made to minimize seizure triggers and control seizures and status epilepticus. Valproate, Benzodiazepine, and Topiramate are among the drugs that can help to reduce the frequency of seizures and severity of the disease. Newer drugs available for the management of seizures in patients with DS are cannabidiol, fenfluramine, and bromides.[27] Along

with medication, other measures like controlling infections, and body temperature variations have also been shown to decrease the frequency of seizures and severity of the disease. In selected patients, ketogenic diet and neuromodulation may be of help but still, pharmacologic therapy remains the mainstay of treatment in patients with DS. Among different anti-epileptic drugs sodium channel blockers like carbamazepine, phenytoin, and their analogues should be avoided as these drugs have the potential to worsen the seizure in DS patients.[28] Routine immunization should not be withheld in children with DS. It is worth noting that due to the misdiagnosis of DS, many patients are undertreated and do not get the standard treatment.

As polypharmacy is required in most patients with DS, practitioners must be aware of drug-drug interactions in order to recognize and manage them properly. Practitioners should also be familiar with therapeutic drug monitoring and pharmacokinetic characteristics of the drugs as they help in dealing with practical problems such as variations in serum concentrations of anti-epileptic drugs which may lead to increased side effects or therapeutic failure which may necessitate dose modifications.[29]

CONCLUSION

Dravet syndrome (DS) is a rare refractory epileptic encephalopathy that may present with atypical febrile seizures with developmental delay. Early diagnosis by genetic testing, predicting the prognosis, awareness of the mortality risk, and selection of appropriate antiepileptic drugs are important as early seizure control contributes to improvement in neurodevelopmental outcomes and cognitive status.

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