Dravet Syndrome: an atypical case revealed by whole exome sequencing.

Abstract:

Dravet syndrome is a rare, early-onset, drug-resistant developmental and epileptic encephalopathy that typically manifests during the first months of life. We report the case of a girl aged 4 years and 5 months who was referred to the neurology department for epileptic seizures. Clinical findings, electroencephalographic features, and molecular analysis confirmed the diagnosis of Dravet syndrome associated with a variant in the SCN1A gene (c.2839G>A [p.Val947Met]). This case is noteworthy because of its relatively milder clinical presentation and unusually late age at presentation.

Key words:-Dravet syndrome, childhood epilepsy, SCN1A gene.

1. INTRODUCTION:

Dravet syndrome (DS) is a rare, early-onset epilepsy associated with neurodevelopmental impairment [1]. It was first described in 1978 [2] and is characterized by seizures that typically begin before the age of one year and are often triggered by fever. As the disease progresses, children may develop various seizure types, including atypical absence seizures and myoclonic seizures [3].

The syndrome is associated with developmental delay, which generally becomes evident after the age of two years. Affected children frequently experience language difficulties, impaired motor coordination, and behavioral disturbances, and may develop intellectual disability [4]. Its prevalence is estimated at approximately 1 in 15,500 live births [5].

More than 85% of patients carry pathogenic variants in the SCN1A gene (SCN1A-positive Dravet syndrome), which encodes the α-subunit of the voltage-gated sodium channel NaV1.1, predominantly expressed in inhibitory GABAergic interneurons [6,7]. Impaired function of this channel may lead to reduced GABAergic inhibitory neurotransmission, thereby contributing to the pathophysiology of the disease. Dravet syndrome is therefore considered a channelopathy, as sodium channel dysfunction contributes not only to epileptic seizures but also to the associated neurodevelopmental impairment [8].

We report the case of a patient with Dravet syndrome associated with an SCN1A gene variant. The case is noteworthy for its relatively mild clinical presentation and later age at presentation compared with the typical clinical course of the syndrome.

2. CASE PRESENTATION:

Patient Information

A 4-year-and-5-month-old girl, born to consanguineous parents, was the second child in a family of two children. Her family history was notable for epilepsy: her father had been followed for generalized epilepsy since the age of

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14 years, which was well controlled with treatment. In addition, one paternal uncle and two paternal aunts had been seizure-free since adolescence without medication (Figure 1). The pregnancy and delivery were uneventful.

The patient was referred for evaluation of generalized epileptic seizures, including absence seizures and tonic-clonic seizures, which had been occurring for approximately one year. The seizures had progressively worsened, becoming more frequent and longer in duration. Recently, mild academic difficulties had been reported by her teacher, although these had not been noticed by the family.

At the age of 3 years and 6 months, the patient had been admitted to the intensive care unit for an initial episode of status epilepticus in the context of fever.

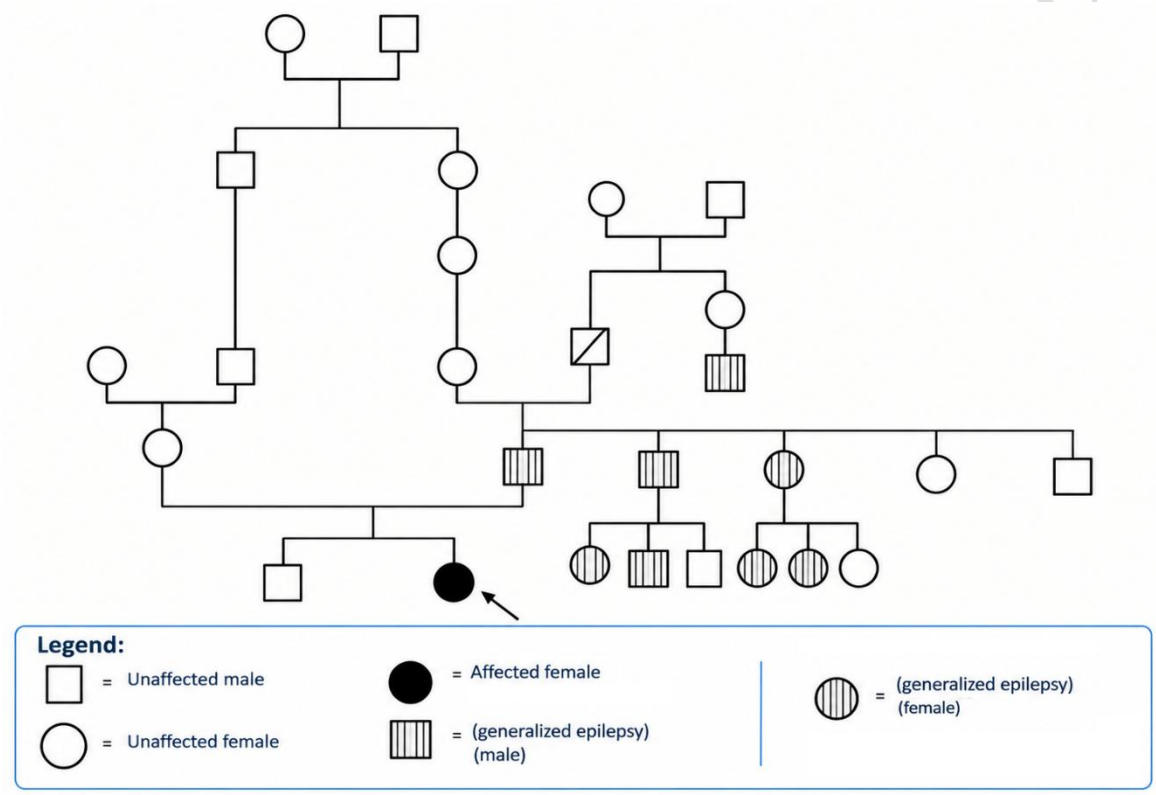


Figure 1. Pedigree chart illustrating the familial distribution of generalized epilepsy

Clinical Examination

On examination, the patient was conscious and in good general condition. Her anthropometric measurements at birth and at the time of assessment, including weight, height, and head circumference, were within normal ranges. Her psychomotor development had also been normal up to that point.

Ancillary Investigations

The patient underwent two electroencephalograms (EEGs). The first, performed during the interictal period, was normal. The second, performed during the ictal period, showed normal background activity with numerous bilateral frontocentral spike-and-wave discharges, predominantly on the right side, potentially consistent with an epileptic encephalopathy (Figure 2).Brain magnetic resonance imaging (MRI) was normal. A comprehensive laboratory workup revealed no significant abnormalities.



Figure 2: Patient's EEG

Molecular Genetic Analysis

In view of the clinical and paraclinical findings, a genetic etiology was suspected, with Dravet syndrome considered the leading diagnostic hypothesis. The patient subsequently underwent molecular genetic testing targeting the SCN1A gene.

Following genomic DNA extraction, whole-exome sequencing was performed. The analysis identified a heterozygous missense variant in the SCN1A gene: c.2839G>A (p.Val947Met).

Therapeutic Management

The patient was initially treated with sodium valproate at a dose of 30 mg/kg/day, administered in three divided doses. Her treatment was subsequently adjusted, and she is currently receiving a combination of sodium valproate (Depakine), levetiracetam, clobazam, and stiripentol.

Follow-up

The seizures progressively increased in frequency, occurring at increasingly shorter intervals despite treatment. However, the clinical course improved over the following six months with the introduction of a four-drug regimen, and the patient is currently seizure-free.From a cognitive perspective, no cognitive delay has been reported to

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date.The patient remains under regular medical follow-up by a neurologist and a clinical geneticist to monitor her general health, growth, and psychomotor development and to detect the possible emergence of additional manifestations, including behavioral disturbances, motor coordination difficulties, learning disabilities, language difficulties, or potential spinal deformities.

3. Discussion

Dravet syndrome (DS), formerly known as severe myoclonic epilepsy of infancy (SMEI), is currently classified as a developmental and epileptic encephalopathy (DEE), as it leads not only to seizures but also to neurodevelopmental impairment [1]. Dravet syndrome typically presents with focal or generalized convulsive seizures in otherwise healthy infants.Across published studies, the age at seizure onset generally ranges from 5 to 8 months, with an upper limit of approximately 18 months [9,10]. In contrast, the first seizure in our patient occurred after the age of 3 years, representing an atypical feature of the syndrome.Seizures vary considerably among children in terms of type, severity, frequency, and duration. Initial seizures are generally triggered by elevated body temperature, including fever or environmental heat. Other reported triggers include infections, visual stimuli, noise, emotional stress, and physical overexertion [3–5]. The initial seizures are often generalized tonic-clonic seizures or hemiconvulsions and may progress to status epilepticus. Myoclonic seizures generally emerge around the age of 2 years [11,12].Children may also develop episodes of obtundation, focal seizures, and atypical absence seizures (AAS). Typical absence seizures and infantile spasms are not characteristic of Dravet syndrome. Overall, seizure frequency tends to increase during the first decade of life, after which it may stabilize or even decrease during adolescence and adulthood [11,13–17].Myoclonic and atypical absence seizures tend to decrease further in frequency and may even disappear in adulthood [14–18].In adults with Dravet syndrome, convulsive seizures tend to occur predominantly during sleep, although they may also occur during daytime naps. These seizures may have generalized or focal onset, most commonly originating in the frontal region [13,16,17,19]. Akiyama et al. reported nocturnal seizures in 19 of 31 adults with Dravet syndrome (61%) [16]. Other studies involving adults have not reported the frequency of individual seizure types. Status epilepticus occurs more frequently in children aged from birth to 5 years than in adults.In our patient, the mother reported no fever-associated paroxysmal events before the age of 2 years and 5 months, when the patient experienced an initial, refractory episode of status epilepticus. This episode required admission to the pediatric intensive care unit until clinical stabilization.EEG findings, both ictal and interictal, vary according to age. Most interictal EEG recordings are normal during the first year of life. From the second year onward, generalized spike-and-wave or polyspike-and-wave discharges, as well as focal or multifocal epileptiform abnormalities, are observed in approximately half of children and in 75% of adolescents and adults [20,21]. Several studies have specifically investigated EEG characteristics in children with Dravet syndrome.Although neuroimaging studies in patients with Dravet syndrome remain relatively limited across age groups, most reported findings are normal [22–25]. However, hippocampal sclerosis has been described in some patients [26–28].

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In our patient, EEG revealed normal background activity with numerous bilateral frontocentral spike-and-wave discharges, predominantly on the right side, potentially consistent with an epileptic encephalopathy. Brain MRI was normal.

Dravet syndrome is generally inherited in an autosomal dominant manner; however, approximately 90% of causative genetic variants arise de novo [29]. Approximately 85% of cases are associated with pathogenic variants in the SCN1A gene, which encodes the voltage-gated sodium channel NaV1.1. Dysfunction of this channel contributes to seizure development and may also be associated with behavioral abnormalities, hyperactivity, social interaction deficits, and cognitive impairment [30].

According to the literature, the presence of an SCN1A variant in a patient with developmental and epileptic encephalopathy does not necessarily establish a diagnosis of Dravet syndrome [31]. Furthermore, Dravet-like phenotypes may be associated with variants in several other genes, including PCDH19, SCN2A, SCN8A, SCN9A, SCN1B, GABRA1, GABRG2, GABRB3, STXBP1, HCN1, CHD2, and KCNA2 [32,33].In our patient, genomic DNA was extracted, followed by whole-exome sequencing. The analysis identified a heterozygous missense variant in the SCN1A gene, c.2839G>A (p.Val947Met). According to the American College of Medical Genetics and Genomics (ACMG) criteria, this variant was classified as pathogenic (Class 5). The SCN1A gene is associated with the phenotypes listed in OMIM as Dravet syndrome (OMIM 607208) and generalized epilepsy with febrile seizures plus type 2 (OMIM 604403), both inherited in an autosomal dominant manner.

Molecular testing was subsequently requested for the patient's father to determine whether the variant was inherited or had arisen de novo.

Seizures in Dravet syndrome are generally resistant to antiseizure medications (ASMs) and to several other therapeutic approaches, including the ketogenic diet and neurostimulation [34–36]. According to the literature available in January 2021, first-line pharmacological treatment included valproic acid and clobazam. When this combination proved insufficient, stiripentol was used in combination with valproic acid and/or clobazam [34–37].Topiramate and the ketogenic diet have also been used as second-line therapeutic options [34,35].Third-line treatments include levetiracetam, clonazepam, zonisamide, ethosuximide for absence seizures, phenobarbital, and neuromodulation [34]. Cannabidiol has also been approved for the treatment of Dravet syndrome, and several studies have demonstrated its efficacy in reducing seizure frequency in children and adolescents [38,39]. Fenfluramine has likewise received approval from the US Food and Drug Administration (FDA) for the treatment of patients with Dravet syndrome.Caring for a child with Dravet syndrome places a substantial psychosocial and emotional burden on the entire family. Management therefore requires a multidisciplinary approach involving various healthcare professionals, including physicians, nurses, physiotherapists, psychologists, and speech-language therapists [40].

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4. Conclusion

Dravet syndrome is a rare, early-onset developmental and epileptic encephalopathy characterized by seizures that are often resistant to treatment and typically begin during the first year of life. Our patient, whose diagnosis was supported by molecular analysis, presented with several atypical features, including a later age at seizure onset and a relatively milder clinical presentation, with a favorable response to combination therapy. This case highlights the importance of considering genetic testing in patients with atypical epilepsy presentations and emphasizes the value of correlating molecular findings with clinical features.

References

1. Scheffer, I.E., Berkovic, S., Capovilla, G., Connolly, M.B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G.W., Mosh´e, S.L., Nordli, D.R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y.H., Zuberi, S.M., 2017. ILAE classification of the epilepsies: position paper of the ILAE Commission for classification and terminology. Epilepsia 58, 512–521.
2. Dravet, C., 1978. Les ´epilepsies graves de l′ enfant. Vie Med. 8, 543–548.
3. Dravet, C., 2011. The core Dravet syndrome phenotype. Epilepsia 52 (Suppl 2), 3–9.
4. Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. Epilepsy Res 2016;128:43–7.
5. Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: A prospective population-based national cohort. Brain 2019;142:2303–18.
6. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68:1327–32.
7. Scheffer IE, Nabbout R. SCN1A-related phenotypes: Epilepsy and beyond. Epilepsia 2019;60:S17–24.
8. Brunklaus A, Zuberi SM. Dravet syndrome - From epileptic encephalopathy to channelopathy. Epilepsia 2014;55:979–84.
9. Daniel L. Hurst, Severe myoclonic epilepsy of infancy, Pediatric Neurology 1987 ;3 ; 269-272.
10. Jennifer A. Kearney, Anna K. Wiste, Ulrich Stephani, Michelle M. Trudeau, Anne Siegel, Rajesh RamachandranNair, et al. Recurrent De Novo Mutations of SCN1A in Severe Myoclonic Epilepsy of Infancy, Pediatric Neurology, 2006;34; 116-120.
11. Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011.
12. Commission on classification and terminology of the international league against epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989:289–99.
13. Genton P, Velizarova R, Dravet, Dravet C. Syndrome: the long-term outcome. Epilepsia 2011.
14. Jansen FE, et al. Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. Neurology 2006.
15. Rilstone JJ, Coelho FM, Minassian BA, Andrade DM. Dravet syndrome: seizure control and gait in adults with different SCN1A mutations. Epilepsia 2012.
16. Akiyama M, Kobayashi K, Yoshinaga H, Ohtsuka Y. A long-term follow-up study of Dravet syndrome up to adulthood. Epilepsia 2010.
17. Takayama R, et al. Long-term course of Dravet syndrome: a study from an epilepsy center in Japan. Epilepsia 2014.
18. Fasano A, Borlot F, Lang AE, Andrade DM. Antecollis and levodopa-responsive parkinsonism are late features of dravet syndrome. Neurology 2014.

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19. Cheah CS, et al. Specific deletion of NaV1.1 sodium channels in inhibitory interneurons causes seizures and premature death in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A 2012.
20. (Connolly MB. Dravet syndrome: diagnosis and long-term course. Can J Neurol Sci 2016.
21. (Lee HF, Chi CS, Tsai CR, Chen CH, Wang CC. Electroencephalographic features of patients with SCN1A-positive dravet syndrome. Brain Dev 2015.
22. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012.
23. Haginoya K, et al. [18 F]fluorodeoxyglucose-positron emission tomography study of genetically confirmed patients with Dravet syndrome. Epilepsy Res 2018.
24. Wirrell EC. Treatment of Dravet syndrome. Can J Neurol Sci 2016.
25. Mancardi M, et al. Brain MRI Findings in severe myoclonic epilepsy in infancy and genotype-phenotype correlations. Epilepsia 2007; 48:1092–6.
26. 26.Tiefes AM, et al. Mesial temporal sclerosis in SCN1A-Related epilepsy: two longterm EEG case studies. Clin EEG Neurosci2019;50:267–72.
27. Van Poppel K, et al. Mesial temporal sclerosis in a cohort of children with SCN1A gene mutation. 2021. https://doi.org/10.1177/0883073811435325.
28. 28.Barba C, et al. Co-occurring malformations of cortical development and SCN1A gene mutations. Epilepsia 2014;55:1009–19.
29. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68:1327–32.]
30. Bender AC, Morse RP, Scott RC, Holmes GL, Lenck-Santini PP. SCN1A mutations in Dravet syndrome: impact of interneuron dysfunction on neural networks and cognitive outcome. Epilepsy Behav 2012;23(3):177–86.] [Steel D, Symonds J, Zuberi S, Brunklaus A. Dravet syndrome and its mimics: beyond SCN1A. Epilepsia 2017;58:1807–16
31. Sadleir L.G. Mountier E.I. Gill D. Davis S. Joshi C. DeVile C. et al. Not all SCN1A epileptic encephalopathies are Dravet syndrome: Early profound Thr226Met phenotype. Neurology. 2017; 89: 1035-1042
32. Steel D, Symonds J, Zuberi S, Brunklaus A. Dravet syndrome and its mimics: beyond SCN1A. Epilepsia 2017;58:1807–16
33. Lindy AS, Stosser M, Butler E, Downtain-Pickersgill C, Shanmugham A, Retterer K, et al. Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. Epilepsia 2018;59:1062–71.
34. 34.Wirrell EC, et al. Optimizing the diagnosis and management of dravet syndrome: recommendations from a north american consensus panel. Pediatr Neurol 2017;68: 18–34.
35. Cross JH, et al. Dravet syndrome: treatment options and management of prolonged seizures. Epilepsia 2019;60:S39–48.
36. Knupp KG, Wirrell EC. Treatment strategies for dravet syndrome. CNS Drugs 2018.
37. Wallace A, Wirrell E, Kenney-Jung DL. Pharmacotherapy for dravet syndrome. Pediatr Drugs 2016.
38. Devinsky O, et al. Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. N Engl J Med 2017.
39. Laux LC, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatmentresistant Lennox-Gastaut syndrome or Dravet syndrome: expanded access program results. Epilepsy Res 2019.
40. Jan Domaradzki, Dariusz Walkowiak. Emotional experiences of family caregivers of children with Dravet syndrome.epilepsy and behavior 2023 ;142.

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