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Dravet Syndrome – Clinical and Developmental Characteristics: A Case Report

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Case report

Abstract

Introduction: Dravet syndrome is a rare, genetically determined epilepsy and epileptic encephalopathy primarily caused by a loss-of-function mutation in the SCN1A gene, also associated with autism spectrum disorder. Following birth, patients have typical neurodevelopment, but the regression of cognitive, motor and speech abilities become noticeable after the onset of seizures.

Aims and case report: We report on the case of a five-year-old girl with characteristic clinical features of Dravet syndrome, detailing her basic clinical and developmental characteristics, disease course and treatment. The first seizure occured at four months of age, coinciding with increased body temperature, and by the end of first year she developed recurrent seizures. While the baseline electroencephagram was nomal, follow-up examinations revealed continuous high-amplitude and sharp, multifocal spike waves. During her second year of life, significant delay in psychomotor development became apparent. The Bayley-III scale was used to assess psychomotor development in cognition area, comprehension and quality of speech, as well as fine and gross motor skills. The results indicated that her cognitive abilities corresponded to those of an eight-month-old child, while her motor skills were at the level of an 18-month-old. Notable gait impairment was observed, with a wide-based crouch gait. The patient was also diagnosed with an autism spectrum disorder.

Conclusion: Although rare, Dravet syndrome is an important differential diagnosis in children presenting with early-onset epilepsy and progressive developmental delays. It is essential to evaluate patients for common comorbidities, such as autism, gait disorders, and intellectual disability, important determinants of patients' quality of life.

Keywords: Dravet syndrome, epilepsy, autism spectrum disorder, developmental delay

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1. Introduction

Dravet syndrome (DS) is a rare developmental and epileptic encephalopathy, with an estimated incidence ranging from 1:15,500 (Juandó-Prats et al., 2021) to 1:40,000 live births (Anwar et al., 2019). Signs of DS usually appear in the first year of life, most often between the fourth and eighth month, in a previously healthy child with typical development. This syndrome is characterised by frequent prolonged seizures and recurrent status epilepticus. Comorbidities include moderate to severe intellectual disability, sleep abnormalities, motor disorders, and autism spectrum disorder (ASD) (Clayton et al., 2022). Additional DS manifestations may include autonomic neuropathy, ataxia, sleep and feeding problems, and a high rate of sudden unexplained death (Anwar et al., 2019; Skluzsacek et al., 2011). The typical presentation of DS is generalised clonic seizures provoked by elevated body temperature caused by infections or routine immunisation. Seizures are often drug-resistant (Gao et al., 2023). Many children require 24-hour care, and mortality before adulthood is estimated at 15 to 20% (Skluzsacek et al., 2011). In 80 to 90% of DS patients, de novo mutations of the SCN1A gene encoding the voltage-gated sodium channel NaV1.1 subunit are believed to be causative (Yadav et al., 2022). At the time of onset, diagnosis may be challenging, as magnetic resonance imaging (MRI) is typically unremarkable, and the electroencephalography (EEG) finding is nonspecific at first (Kapoor et al., 2021). In this paper, we report on the case of a five-year-old girl diagnosed with DS and highlight her basic clinical and developmental characteristics, course and treatment strategies. The aim of this case report is to increase awareness of the complexity of DS manifestations and emphasise the need for multidisciplinary approach in DS management.

2. Case Report

A five-year-old girl (born in 2019; height 115 cm; body mass 24.1 kg) was hospitalised for the first time at the age of four months at a pediatric clinic in Serbia due to the first episode of generalised convulsions. At the time of the onset of the first convulsions, she had a respiratory infection and an increased body temperature of 38.7°C. During her one-week stay at the hospital, she was treated with antibiotics and analgesics, with a diagnosis of febrile convulsions (ICD-10 code R56.0). Four months after this event, the patient developed a prolonged episode of generalised tonic-clonic convulsions, this time while afebrile. This seizure was terminated with parenteral lorazepam in a pediatric facility. Family history was negative for epilepsy and neurodevelopmental disorders. Laboratory analysis and electrocardiogram were unremarkable, as well as MRI and EEG. Evidence of developmental regression was observed during the second year of life, when the diagnosis of DS was confirmed by clinical exome sequencing indicating the existence of the SCN1A gene variant c. 1028+5G>C. Over the following years, seizure pattern typically included absence seizures at awakening and focal motor seizures during sleep, while generalised clonic seizures occurred up to twice a month, most often with elevated body temperature (e.g. during the evening bath). The repeated EEG started showing continuous, high-amplitude and sharp, multifocal spike waves. Antiseizure medications were initiated and gradually increased to target dose of 0.4 mg/kg/day clobazam divided in two daily doses and 30 mg/kg/day valproate divided in two daily doses; medications were well-tolerated and initially led to reduction of seizure frequency. The procedure in case of a seizure was explained to the parents, and they were advised about the ketogenic diet and ways to avoid the seizure triggers (preventive measures of using a cooling vest at higher air temperatures, wearing sunglasses in case of visual hypersensitivity, as well as the home use of benzodiazepines to prevent occurrence of status epilepticus). Escalating stiripentol therapy was considered but was not indicated at the time of the last assessment. In the last series of examinations, the Bayley-III scale (Bayley, 2005) was used to assess the psychomotor development of children aged 16 days to 42 months and 15 days. The girl's achievement in cognition, comprehension and quality of speech, as well as fine and gross motor skills, were assessed. Intentionally, a scale corresponding to a younger age than the one the patient currently belongs to was applied to obtain information about the girl's real current developmental status. In this way, it was determined exactly in which developmental stage the child is, in which stage she is "stuck" and from which developmental point the stimulating treatment should start (in relation to the abilities reached), regardless of age. The assessment concluded that the area of cognition corresponds to the age of a child of 8 months, speech comprehension corresponds to the achievement of a child of 14 months, the quality of speech corresponds to the development of a child of 7 months, fine motor skills remain developmentally linked to the achievement of 17 months, and gross motor skills to 18 months. The neurological examination revealed no focal neurological deficit but delayed motor development with lack of fine motor hand skills, and wide-based ataxic gait (Figure 1 and 2). The patient was also diagnosed with ASD (Gilliam Autism Rating Scale - Third Edition, GARS-3) (Gilliam, 2014). An individual stimulating-developmental treatment was applied to the girl, which aimed to raise the quality of abilities in all developmental areas: fine motor, gross motor, cognition and speech understanding. Both parents of the girl gave their written consent for the presentation of her case on the paper. It was explained to them that they could withdraw their consent at any time, until the paper was sent to the journal for peer review, but this did not happen, because the parents also felt that it was worth presenting this case to the readership.

Fig. 1: Ataxic gait with elements of crouch gait in a girl with Dravet syndrome. Walking with occasional help from another person

Fig. 2: Palmer supinate grasp, still without a "pincher grasp"

3. Discussion

Our patient presented with distinctive clinical phenotype of DS comprising infantile onset of epilepsy followed by motor and cognitive developmental delay at the beginning of the second year of life, leading to the diagnosis of DS confirmed with genetic testing. In addition, she had features of well-described comorbidities of DS, intellectual disability, ASD and gait impairment. The genetic basis of this debilitating disease comprising loss-of-function in Nav1.1 channels, results in severely impaired sodium current and action potential firing in the brain, leading to imbalance between excitation and inhibition, hyperexcitability and seizures, and subsequent neuronal damage.

Epilepsy in our patient was characterizsed by several types of seizures, including generalised tonic-clonic seizures, absence seizures, and focal motor seizures., occasionally complicated with prolonged seizures and status epilepticus, occurring both in febrile and afebrile state. As anti-seizure medications usually have limited effectiveness, every effort should be made to minimise their triggers and to control the seizures as much as possible.

Stiripentol, valproate, benzodiazepine, and topiramate are among the drugs thought to help reduce the frequency and severity of seisures., and cannabidiol, fenfluramine, and bromides are among the newer drugs to control seizures in people with DS (Yadav et al., 2022). Carbamazepine, oxcarbazepine, lamotrigine and phenytoin are contraindicated and may worsen seizures in people with DS (Gao et al., 2023). The typical cognitive and motor developmental delay appeared after the normal initial development, following onset of seizures. In the majority of children with DS older than 2 years, motor development is delayed and is more pronounced with age (Verheyen et al., 2019). Fifty-eight to as many as 100% of DS patients have intellectual disability, extending from mild to profound (Ouss et al., 2018). Patients with DS have heterogenous neuropsychological phenotypes, with some patients demonstrating global impairment while others have a discordant neuropsychological profile, often with worse nonverbal than verbal performance (Ouss et al., 2018; Brown et al., 2020). Hyperactivity and inattention are the most frequently reported behavioural problems (Brown et al., 2020).

ASD has been reported in as many as two-thirds of formally assessed children with DS (Reilly et al., 2024). Although highly relevant for patients' quality of life, ASD is generally underrecognised in this population, possibly due to a relative preservation of the social skills observed in some patients, indicating a

specific ASD profile (Ouss et al., 2018). (Reilly et al., 2024). Mutation in the SCN1A gene has been linked to ASD and is being considered as an ASD candidate gene (Ding et al., 2021). While ASD and intellectual disability persist in adulthood of DS patients, epilepsy and hyperactivity often subside (Berkvens et al., 2015).

A variety of gait disorders has been reported in patients with DS, with ataxic and crouch gait being the most reported gait pattern (Wyers et al., 2019). Besides changes in cerebellar cells, gait abnormalities in DS can be secondary to various skeletal malalignments which are usually evident in the second decade of life (Rodda et al., 2012). Gait alterations have a significant impact on mobility and independence of the patients.

At present, approved DS treatments are symptomatic, but there is a potential for disease-modifying therapy by targeting underlying NaV1.1 channelopathy. Even though evidence-based treatment strategies have so far failed to significantly change or improve the outcome of the clinical picture in DS (Brunklaus, 2019), it is very important to work on the rehabilitation of compromised cognitive, behavioural, motor, communication and social skills (Nabbout et al., 2019). Targeted gene therapies promise to provide more effective personalised treatments but remain in its early stages (Fan et al., 2023).

In children with DS, due to constant regression of the motor domain, the implementation of encouraging individual development and rehabilitation treatment is advised. One of the possible explanations for their positive effects on functional status in patients with epilepsy is that motor exercise strengthens mechanisms of neuronal protection related to biochemical and structural changes, which have an inhibitory effect on excessive electrical activity (Carrizosa-Moog et al., 2018). It is believed that during exercise, epileptic discharges can be reduced or even disappear (Carrizzosa-Moog et al., 2018), and that it is possible to contribute to the preservation of bone mass that can be reduced due to antiepileptic drugs (Arida et al., 2013).

The DS is associated with substantial impact on individuals, their families, and healthcare system. The primary drivers of quality of life in DS cases include seizure severity, cognition, and motor and behavioral problems (Sullivan et al., 2022). With social and economic burden of the disease, DS have a very comprehensive negative impact on caregiver and family functioning (Brown et al., 2020; Sullivan et al., 2022).

4. Conclusion

We presented a case of a five-year-old girl with typical clinical features of genetically confirmed DS. Professionals working with children's developmental delay should be aware of this important although rare disease, characterised by early-onset epilepsy and delay in cognitive, motor and speech development. Notably, patients often present with additional features such as ASD, gait disturbances and skeletomuscular disorders. In conclusion, patients with DS present with complex and still intractable clinical phenotype which is often challenging to manage. The main goal of treating people with DS is to modify the difficulties caused by this severe condition and to ensure the maximum neurodevelopmental outcome with minimal deficits. The characteristics of patients with DS, comorbidities, and the availability of pharmacological and non-pharmacological therapy should guide the treatment.

Conflict of interests

The authors have no conflicts of interest to declare.

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5. References

Anwar, A., Saleem, S., Patel, U. K., Arumaithurai, K., & Malik, P. (2019). Dravet syndrome: An overview. Cureus, 11(6), e5006. https://doi.org/10.7759/cureus.5006.

Arida, R. M., de Almeida, A. C. G., Cavalheiro, E. A., & Scorzza, F. A. (2013). Experimental and clinical findings from physical exercise as complementary therapy for epilepsy. Epilepsy & Behavior, 26(3), 273-278. https://doi.org/10.1016/j.yebeh.2012.07.025

Bayley, N. (2005). Bayley Scales of Infant and Toddler Development, third edition (Bayley-III®). San Antonio, TX: Psychological Corporation. https://doi.org/10.1037/t14978-000

Berkvens, J. J., Veugen, I., Veendrick-Meekes, M. J., Snoeijen-Schouwenaars, F. M., Schelhaas, H. J., Willemsen, M. H., Tan, I. Y., & Aldenkamp, A. P. (2015). Autism and behavior in adult patients with Dravet syndrome (DS). Epilepsy & Behavior, 47, 11-16. https://doi.org/10.1016/j.yebeh.2015.04.057

Brown, A., Arpone, M., Schneider, A. L., Micallef, S., Anderson, V. A., & Scheffer, I. E. (2020). Cognitive, behavioral, and social functioning in children and adults with Dravet syndrome. Epilepsy & Behavior, 112, 107319. https://doi.org/10.1016/j.yebeh.2020.107319

Brunklaus, A. (2019). Dravet syndrome – Time to consider the burden beyond the disease. European Journal of Paediatric Neurology, 23(3), 344. https://doi.org/10.1016/j.ejpn.2019.05.006

Carrizzosa-Moog, J., Ladino, L. D., Benjumea-Cuartas, V., Orozzco-Hernándezz, J. P., Castrillón-Velilla, D. M., Rizzvi, S., & Téllezz-ZZenteno, J. F. (2018). Epilepsy, physical activity and sports: A narrative review. Canadian Journal of

Neurological Sciences, 45(6), 624-632. https://doi.org/10.1017/cjn.2018.340

Clayton, L. M., Williams, E., Balestrini, S., & Sisodiya, S. M. (2022). Case report: Dravet syndrome, feeding difficulties and gastrostomy. Frontiers in Neurology, 13, 993906. https://doi.org/10.3389/fneur.2022.993906

Ding, J., Li, X., Tian, H., Wang, L., Guo, B., Wang, Y., Li, W., Wang, F., & Sun, T. (2021). SCN1A mutation-beyond Dravet syndrome: A systematic review and narrative synthesis. Frontiers in Neurology, 12, 743726. https://doi.org/10.3389/fneur.2021.743726

Fan, H. C., Yang, M. T., Lin, L. C., Chiang, K. L., & Chen, C. M. (2023). Clinical and genetic features of Dravet syndrome: A prime example of the role of precision medicine in genetic epilepsy. International Journal of Molecular Sciences, 25(1), 31. https://doi.org/10.3390/ijms25010031

Gao, C., Pielas, M., Jiao, F., Mei, D., Wang, X., Kotulska, K., & Jozzwiak, S. (2023). Epilepsy in Dravet syndrome – current and future therapeutic opportunities. Journal of Clinical Medicine, 12(7), 2532. https://doi.org/10.3390/jcm12072532

Juandó-Prats, C., James, E., Bilder, D. A., McNair, L., Kenneally, N., Helfer, J., Huang, N., Vila, M. C., Sullivan, J., Wirrell, E., & Rico, S. (2021). DRAVET ENGAGE. Parent caregivers of children with Dravet syndrome: Perspectives, needs, and opportunities for clinical research. Epilepsy & Behavior, 122, 108198. https://doi.org/10.1016/j.yebeh.2021.108198.

Kapoor, D., Anand, A., Sharma, S., Mukherjee, S. B., Marini, C., Mei, D., Chopra, S. S., & Chettali, A. M. (2021). Dravet syndrome: A case series. The Indian Journal of Pediatrics, 88, 82. https://doi.org/10.1007/s12098-020-03383-zz

Nabbout, R., Auvin, S., Chiron, C., Thiele, E., Cross, H., Scheffer, I. E., ... & Bennett, B. (2019). Perception of impact of Dravet syndrome on children and caregivers in multiple countries: looking beyond seizsures. Developmental Medicine & Child Neurology, 61(10), 1229-1236. https://doi.org/10.1111/dmcn.14186

Yadav, R., Shah, S., Bhandari, B., Marasini, K., Mandal, P., Murarka, H., Pandey, A. K., & Sharma Paudel, B. (2022). Patient with Dravet syndrome: A case report. Clinical Case Reports, 10(5), e05840. https://doi.org/10.1002/ccr3.5840

Reilly, C., Bjurulf, B., & Hallböök, T. (2024). Autism and attention-deficit/hyperactivity disorder in children with Dravet syndrome: A population-based study. Developmental Medicine & Child Neurology, 66(11), 1457-1465. https://doi.org/10.1111/dmcn.15937

Rodda, J. M., Scheffer, I. E., McMahon, J. M., Berkovic, S. F., & Graham, H. K. (2012). Progressive gait deterioration in adolescents with Dravet syndrome. Archives of Neurology, 69(7), 873-878. https://doi.org/10.1001/archneurol.2011.3275

Skluzzacek, J. V., Watts, K. P., Parsy, O., Wical, B., & Camfield, P. (2011). Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia, 52, 95-101. https://doi.org/10.1111/j.1528-1167.2011.03012.x.

Sullivan, J., Deighton, A. M., Vila, M. C., Szzabo, S. M., Maru, B., Gofshteyn, J. S., James, E. S., Rico, S., & ZZuberi, S. M. (2022). The clinical, economic, and humanistic burden of Dravet syndrome - A systematic literature review. Epilepsy & Behavior, 130, 108661. https://doi.org/10.1016/j.yebeh.2022.108661

Verheyen, K., Verbecque, E., Ceulemans, B., Schoonjans, A. S., Van De Walle, P., & Hallemans, A. (2019). Motor development in children with Dravet syndrome. Developmental Medicine and Child Neurology, 61(8), 950-956. https://doi.org/10.1111/dmcn.14147

Wyers, L., Van de Walle, P., Hoornweg, A., Tepes Bobescu, I., Verheyen, K., Ceulemans, B., Schoonjans, A. S., Desloovere, K., & Hallemans, A. (2019). Gait deviations in patients with Dravet syndrome: A systematic review. European Journal of Paediatric Neurology, 23(3), 357-367. https://doi.org/10.1016/j.ejpn.2019.03.003

Ouss, L., Leunen, D., Laschet, J., Chemaly, N., Barcia, G., Losito, E. M., Aouidad, A., Barrault, ZZ., Desguerre, I., Breuillard, D., & Nabbout, R. (2018). Autism spectrum disorder and cognitive profile in children with Dravet syndrome: Delineation of a specific phenotype. Epilepsia Open, 4(1), 40-53. https://doi.org/10.1002/epi4.12281

Gilliam, J. E. (2014). Gilliam Autism Rating Scale–third edition (GARS-3). Austin, TX: Pro-Ed.