Management of the Psychiatric Manifestations in Dravet Syndrome

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Dravet syndrome is a rare autosomal recessive genetic epileptic encephalopathy[1] first described in 1978. Its incidence is estimated to be 1 in 40,000.[2] Prior to 1989, this syndrome was known as epilepsy with polymorphic seizures, polymorphic epilepsy in infancy, or severe myoclonic epilepsy in infancy. It is primarily caused by de novo mutations of the *SCN1A* gene encoding a neuronal voltage-activated sodium channel. It is broadly known to present with intellectual disability,[3] behavioral problems, and severe refractory seizures.[4] Its unique genetics[5] with mutations in the gene encoding the α1 subunit of the voltage-gated sodium channel[6] and neurodevelopmental profile[7] have inspired research to delve into understanding the disorder and its treatment options.

There is often normal cognitive development during the first year of life, but it later slows down, and if drug-resistant epilepsy is associated, a loss of acquired milestones may occur. Autistic traits are widely reported[8,9] in Dravet syndrome and has been estimated to be present in up to 61% of patients.[10] Treatment is primarily guided by pediatric neurologists, and, hence, the epilepsy aspect of the condition has been widely researched due to its drug resistance. The cognitive and behavioral aspects of Dravet syndrome also contribute significantly to the overall quality of life in these patients.[11] In this case report, we focus on the management of neurodevelopmental and psychiatric symptoms of Dravet syndrome, which is a common association but not yet published in the current research on this disorder.

Case Report

The patient was a 6-year-old girl with a genetically confirmed diagnosis of Dravet syndrome (mutation of *SCN1A* gene in exon 15 was detected of variant c2853G > C p. Glu951Asp) who was under the care of a pediatric neurologist for intellectual disability and drug-resistant epilepsy. The child first experienced fever-triggered generalized seizures at 4 months of age after the third dose of a primary vaccination. During infancy, she had fever-triggered seizures but subsequently started to have afebrile generalized seizures and myoclonic jerks. During the follow-up assessments, significant behavioral and neurodevelopmental issues were identified. She was referred to the specialized child psychiatry services for evaluation of her academic problems, aggression, social difficulties, and defiant behavior.

During the evaluation, she rarely smiled and avoided eye contact. Her speech was repetitive and suggestive of delayed language development and echolalia (a scripted speech with less reciprocity). She had sleeping difficulties, decreased attention span, social engagement issues, sensory problems (particularly her preference of clothes), and repetitive behavior (hand flapping). She often had temper tantrums and aggressive outbursts at home and in social settings. Her parents had a consanguineous marriage, and her aunt also had a psychiatric history, the specifics of which were unknown. She had been enrolled in a special school, with multidisciplinary input from special educators and speech and occupational therapists. The patient lived with her mother, father, elder sister, and first relatives (paternal aunt, uncle, and 2 cousins). A formal assessment with the Wechsler Intelligence Scale for Children[12] and the Childhood Autism Rating Scale[13] was conducted, and the patient scored 62 and 29, respectively. Besides Dravet syndrome, she met the clinical criteria for autism spectrum disorder (ASD), intellectual disability, social pragmatic language disorder, and attention-deficit/hyperactivity disorder (ADHD) combined type.

The pediatric neurologist stabilized the patient's epilepsy (1 febrile seizure every 3 months, afebrile seizure once every 6 months, myoclonus was controlled) on the regimen of topiramate 5 mg/kg/d and clobazam 0.5 mg/kg/d. Prior to this regimen, she had failed to respond to sodium valproate, levetiracetam, ethosuximide, potassium bromide, and a ketogenic diet (stiripentol, cannabis oil, and fenfluramine are not approved in India and hence could not be used). The patient also had a trial of risperidone for her aggression and behavioral problems without appropriate response. After the initial evaluation by the child psychiatry team, a low dose of aripiprazole 1.25 mg was added to her treatment regimen to address the mood and irritability symptoms. Melatonin 3 mg was recommended to the family to help with sleep initiation, and education about sleep hygiene was provided to the parents. We also liaised with her school to work on her learning and educational difficulties. At 6-month

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Prim Care Companion CNS Disord 2022;24(1):21cr02940

To cite: Gupta M, Jain V, Khurana P. Management of the psychiatric manifestations in Dravet syndrome. *Prim Care Companion CNS Disord.* 2022;24(1):21cr02940.

To share: https://doi.org/10.4088/PCC.21cr02940

follow-up, her parents reported improved mood and decreased aggression in home and social settings. However, her attention span and hyperactivity continued to affect her academics. The family was reluctant to start an additional psychopharmacologic agent for the residual ADHD symptoms. The primary team also recommended individual psychotherapy, behavioral therapy, and occupational therapy. These interventions significantly improved her attention span, behavioral issues, and academic performance, as well as the overall quality of life of the family.

Discussion

The treatment of cognitive and psychiatric symptoms in patients with a rare genetic syndrome[14] like Dravet syndrome has been a challenge. These patients initially present with serious neurologic conditions like epilepsy to the specialized medical center, while other comorbid conditions are often overlooked. Families fail to follow up when they are referred to a mental health professional after their primary medical condition is stabilized. However, due to significant impairments associated with comorbid disorders, non–psychiatrist clinicians often end up treating these conditions. Antiepileptic agents have adverse behavioral effects,[15] as do benzodiazepines, which are associated with paradoxical[16] disinhibition. Without mental health evaluation and psychometric testing, these patients receive empirical treatment for psychiatric symptoms. Due to the complex nature of behavioral presentations,[17] ADHD symptoms are often treated mostly with psychopharmacologic agents like clonidine and methylphenidate, sometimes prescribed by nonpsychiatrist clinicians. In a few cases, these patients do partially respond, which further impedes access to specialized mental health services. The irritability associated with ASD[18] symptomatology and hyperactivity[19] has ambiguity in its nosology and often leads to the dilemma of whether to treat one or both symptom clusters. Due to significant caregiver distress, patient education is critical to address these symptoms.

Stimulants[20] and selective serotonin reuptake inhibitor[21] antidepressants are associated with mixed evidence, including worsening of symptoms in select patients. US Food and Drug Administration–approved medications for irritability associated with ASD are not used for many reasons. Many clinicians are concerned about the risk of second-generation antipsychotics lowering the seizure threshold. Often the use of the word *antipsychotic* for classification has negative connotations, as well as side effects including metabolic syndrome and weight gain. However, after careful assessment and family education, low-dose second-generation antipsychotics may be a good option for these patients. Aripiprazole has a unique partial agonist dopaminergic (D2) property and serotonergic receptor (5-HT_{2A})[22] activity and functions selectively at the cellular level. It is a dopamine agonist at low levels and an antagonist at higher doses.[23] Its serotonin 5-HT_{2A} receptor antagonism is lower compared to risperidone, which along with partial D2 agonist actions reduces the likelihood of extrapyramidal side effects and tardive dyskinesia. Aripiprazole's moderate affinity on histaminergic receptors is the reason for less sedation and weight gain.[24] A National Institute of Mental Health–funded study on biomarkers in autism of aripiprazole and risperidone treatment found no statistically significant differences in efficacy and other outcome measures in a 10-week trial.[25] However, a statistically significant increase in prolactin levels was seen with risperidone, which may be of concern for select patients including females. Weight gain occurrence was also more common with risperidone, but differences were nonsignificant at the end of the trial.[25] A careful review of the profiles, side effects, and tolerability data of these approved psychopharmacologic agents matched with the patient's impairments and needs would be an appropriate step.

Conclusion

Dravet syndrome presents with myriad and complex symptoms with impairments in social and academic domains and significant caregiver distress. Due to recent changes in cost-effective genetic testing, including whole genomic sequencing, diagnosis has been more accurate. It is observed that these patients first receive interventions for intractable epilepsy, but the treatment for psychiatric manifestations is overlooked or not reported in the empirical studies. In the last decade, there has been more evidence of ASD-like symptoms in patients with Dravet syndrome. In our patient, co-occurring mental health symptoms and diagnosis could be identified with psychiatric evaluations and assessment. These patients and families may benefit from psychoeducation about these disorders and specialized neurodevelopmental mental health services. Interventions including psychopharmacology and other behavioral treatment have a role in addressing the overall morbidity associated with Dravet syndrome. We recommend more funding and research in understanding and treatment of the psychiatric and behavioral presentations of Dravet syndrome.

Published online: January 6, 2022.
Potential conflicts of interest: None.
Funding/support: None.
Additional information: Patient information has been de-identified to protect anonymity.

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