Annals of Clinical Case Reports

Case Report
Published: 08 Jun, 2020

A Case Report: Dravet Syndrome in an Adult, It is never too late to Consider

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Abstract

"Dravet Syndrome (DS) is a severe form of epilepsy characterized by frequent, prolonged seizures often triggered by hyperthermia, developmental delay, speech impairment, ataxia, hypotonia, sleep disturbances, and other health problems". DS is associated with a mutation in the SCN1A gene in 80% to 90% of cases. The EEG in DS is usually non-specific, while the brain MRI is generally normal at onset. Sodium channel blocking Anti-Seizure Medications (ASM) exacerbates seizures in DS and should be avoided. About 80% of children with DS survive to adulthood, 92% of whom continue to have seizures. While the diagnosis of DS is easily made in early childhood, it can be challenging in older children and adults and missed in ~33% patients, at times misdiagnosed with common mimickers such as Lennox Gastuat Syndrome (LGS).

I present a 19-year-old female with intractable epilepsy and presumed LGS with seizure onset at three months of age, "multiple" and at times prolonged febrile seizures, worsening convulsions with sodium channel blocking ASM and cognitive limitations. A routine EEG showed diffuse slowing, while brain MRI was suggestive of right mesial temporal sclerosis. Genetic testing done revealed SCN1A pathogenic variant. Her ASMs were adjusted, leaving her with Zonisamide and Epidiolex and ~70% seizure reduction.

It is never too late to consider DS as well as other SCNIA related epilepsies; if found, it allows for optimal seizure management, a decrease in seizure burden, improving the social-economic dynamics of patients, caregivers, and the health care system.

Introduction

DS is among a spectrum of SCN1A seizure disorders that range from "simple febrile seizures and Generalized Epilepsy with Febrile Seizures plus (GEFS+) at the mild end to Dravet syndrome and Intractable Childhood Epilepsy with Generalized Tonic-Clonic Seizures (ICE-GTC) at the severe end [1-5]. DS is a specific early-life epilepsy that is believed to make up 33% to 90% of Seizure phenotypes on SCNIA seizures disorders [6] and with an incidence as high as 1 in 40,900 [7]. The classic presentation includes frequent, prolonged seizures often triggered by elevated body temperature beginning between 1 to 18 months, developmental delay, speech impairment, ataxia, hypotonia, sleep disturbances, and multiple comorbidities, including intellectual disability and behavioral problems. Approximately 80% to 90% of patients with DS have variants in the SCN1A gene, notable for encoding the a-1 submit of the neuronal voltage-gated sodium channel [3], however, when found in isolation, it does not endorse the diagnosis, nor does its absence exclude it. Early diagnosis of DS is crucial to the timely utilization of the best available treatments and avoiding exacerbating medications, costly and invasive testing, as well as futile therapies such as resective epilepsy surgery and giving closure for families, wondering about the cause of their loved one's condition. Despite a reasonably classic presentation, a 4.8-year delay in diagnosis has been reported [8]; with delays or misdiagnosis seen in as many as 33% of patients [4]. Patients may be presumed to have other syndromes such as LGS, leading to improper management. The highest priority in the management of DS is avoiding prolonged convulsive seizures and obtundation, which impact the developmental outcome and morbidity [9]. Seizure control is typically not achievable; however, seizures can be significantly reduced with appropriate treatment. Clobazam and valproic acid are considered first-line medications, while Stiripentol and topiramate second line. Other options include diet therapy, clonazepam, levetiracetam, and zonisamide, as well as Epidiolex. Sodium channel blocking agents such as Carbamazepine, oxcarbazepine, lamotrigine, phenytoin, and vigabatrin often exacerbate seizures and should be avoided. Surgical options, such as Vagus nerve stimulation and Callosotomy, may be considered in certain situations.

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Received Date: *16 May 2020*
Accepted Date: *04 Jun 2020*
Published Date: *08 Jun 2020*

Citation:
Wabulya A. A Case Report: Dravet Syndrome in an Adult, It is never too late to Consider. Ann Clin Case Rep. 2020; 5: 1846.

ISSN: 2474-1655

Case Presentation

A 19-year-old right-handed female with significant cognitive impairment, intractable epilepsy, and presumed Lennox Gastuat Syndrome referred for the management of her epilepsy.

The patient is a 35-Ex-weeker with "multiple" febrile convulsive seizures, delayed development, and a history of seizures in a brother. Seizures began at three months of age before prolonged status epilepticus ~3 h were seen at 18 months. She later developed afebrile seizures; the family insists on only one seizure type during which she becomes agitated, eye deviated to the right or left, extension of both legs and the right arm with flexion of the left arm followed by generalized tonic-clonic activity lasting about 1 to 2 minutes. There is associated tongue biting, urine incontinence, and 20 min to 40 min of postictal confusion. She had 4-5 seizures per month, results of a prior EEG are unknown, and a head CT scan was unremarkable. She was diagnosed with LGS and, despite several seizure medication trials, including but not limited to phenytoin, Oxcarbazepine, lamotrigine, Valproic acid, Zonisamide, Topiramate, and Phenobarbital seizure persisted. At the time she was seen at our center, she was taking Zonisamide/Depakote as well as Lamictal, the later used for at least 12 years. She had optimal levels of Lamictal, ranging from 3.5 to 8.1 mcg/mL and Depakote 33.0 to 164.6 mcg/mL from 2/28/2007 to 2/19/2019.

Other than her history of epilepsy and Intellectual disability, as well as a family history of epilepsy, she had not undergone surgical procedures, had no different reported family history, nor use of drugs, alcohol, or tobacco products. She lived home with her parents requiring full-time care.

On examination: Vital signs: Height 144.8 cm (4' 9"), weight 37.1 kg (81 lb. 12.8 oz), blood pressure 99/54 mmHg, and a pulse of 84 beats/min. The head was normocephalic and atraumatic; neck supple with no tenderness. Chest was clear to auscultation bilaterally. Cardiovascular: Regular rate and rhythm. The abdomen was soft, non-tender with normal bowel sounds.

She was awake, reaching for a book, flipping through pages, making noises without intelligible speech, and could not consistently follow commands. Pupils were equal reactive to light. She had reduced muscle tone; cortical thumb bilaterally left>right. Face grossly symmetric, moved all four extremities well, although she was unable to participate in dedicated muscle testing. Deep tendon reflexes were present in the bilateral upper and lower extremities with a slightly crouched, grossly stable gait.

Based on her history of seizure onset, response to medications, there was high suspicion for Dravet in this patient. Lamotrigine was tapered off alongside obtaining miscellaneous DNA testing, which later showed a pathogenic variant, in SCN1A; c.4224G>A (p. Trp1408*). She had diffuse slowing on a routine EEG while her brain MRI showed mild atrophy of the right hippocampus and associated FLAIR signal concerning for mesial temporal sclerosis.

The patient was cross titrated to Epidiolex and Zonisamide with significant improvement in seizures, four seizures in 3 months, as well as being more alert and interacting more with her environment. Her family has been pleased with the seizure control and quality of life.

Discussion

Dravet syndrome, a severe form of epilepsy with typical diagnostic criteria, confirmatory test, and proven effective therapies [1,2]. About 80% of children with DS survive to adulthood, with 92% of patients continuing to have seizures [4]. Diagnosing DS in older children and adults can be more challenging [1]; at times, patients misdiagnosed with conditions such as Lennox Gastuat Syndrome (LGS), genetic epilepsy with febrile seizures, focal epilepsies, myoclonic epilepsy in infancy among other [2]. A consensus panel suggests that "in young children as well as older previously undiagnosed children and adults if details of the early childhood history are not available, findings of persisting seizures, hyperthermia as a seizure trigger, seizure exacerbation with the use of sodium channel agents, intellectual disability, abnormalities on neurological examination, a crouched gait, hypotonia, incoordination, and impaired dexterity a diagnosis of Dravet syndrome should be considered" [2]. The presented patient had all items listed above, raising the suspicion on her initial evaluation even 17 years after seizure onset. The suspicion of Dravet syndrome should prompt adjustment of management, including genetic testing as feasibly possible, which may show a pathologic variant in SCNIA in 85% of patients with Dravet [3]. In the patient discussed, tested positive for this mutation, helping confirm the diagnosis. It should, however, be noted that a positive test in isolation does not confirm the diagnosis, nor does the absence of the mutation exclude it, as such clinical suspicion should still guide management [10,11].

Generally, the commonly used tests, notably EEG and brain imaging, do not have a "typical signature" in DS. The patient's brain MRI that was suggestive of right mesial temporal sclerosis could have easily led one to a different path, including continued use of sodium channel blocking seizure medication presumed the medication of choice in focal onset seizures; however, this finding insolation did not explain the patient's clinical presentation. It has also been previously reported that in Dravet syndrome, "brain MRI is typically normal but may show mild generalized atrophy and/or hippocampal sclerosis" [2]; the same authors note that the "EEG might show diffuse background slowing, often with multifocal and/or generalized interictal discharges."

Early diagnosis of DS is critical for initiating the appropriate treatment, avoiding unnecessary medical tests as well as seizure exacerbation if the wrong medication is used as well as providing an as giving closure to the patient's family [2]. In the US, the recommended anti-seizure medications include Clobazam and valproic acid as first-line; Stiripentol and topiramate second line while other options include diet therapy, clonazepam, levetiracetam, and zonisamide, Epidiolex, as well as neurostimulation and Callosotomy. It is well known that anti-seizure medications with sodium channel capabilities exacerbate seizures in DS and should be avoided. In the patient presented, her anti-seizure medications were adjusted, leaving her with zonisamide and Epidiolex and ~70% seizure reduction. While the long-term outlook is not likely for complete seizure control, the decrease is undoubtedly one can pursue.

Conclusion

Dravet syndrome is a severe form of epilepsy with typical diagnostic criteria; however, some patients will elude diagnosis for years or even decades. Health care providers need to be mindful of this possibility, given the management implications. It is never too late to make the right diagnosis and adjust management that could improve seizure control considerably as well as improving the social-economic dynamics of patients, caregivers, and the health care system.

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