Case Report

Beyond Seizures: Exploring Cannabidiol in Dravet Syndrome

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ABSTRACT

Dravet Syndrome (DS) is a historically severe epileptic and developmental encephalopathy forming uncontrolled seizures with stimuli, other neurological deficits, including cognitive and motor function impairment. This work demonstrates two case studies of infants suffering from DS that are complicated by recurrent infections and developmental delays. Early genetic evaluation, especially SCN1A testing, was important for diagnosis and therapy. Both infants presented periodic prolonged febrile seizures as well, thus exposed to a range of anti-seizure drugs which include Levetiracetam, Sodium Valproate and Topiramate. In addition to this, Cannabidiol (CBD) was included in their regimen and proved effective in term of seizure control where other therapies were not effective. Somnolence, gastrointestinal upset and elevated liver enzyme levels necessitated caution in usage. Also, management of patients involved several disciplines: neurologic, genetic and developmental care as well as control of infections. However, patients were able to achieve some level of stabilization with early interventions such as physiotherapy and nutritional interventions despite the persistent developmental challenges. Based on the unmet clinical needs in controlling seizures in DS disorders, CBD is appropriate, but caring for the patients should be enduring and additional research is needed on the optimal doses in children.

Keywords: Cannabidiol, Dravet syndrome, Pediatric patient, SCN1A Mutation.

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INTRODUCTION

Dravet syndrome (DS) is a severe epileptic and developmental encephalopathy that impairs the quality of life for patients and their families by causing drug-resistant seizures and cognitive impairment.[1] Dravet syndrome is a type of epilepsy that starts in infants or very young children and it is usually provoked by fever related seizures. It is defined as refractive epilepsy with a myriad of seizure types including, tonic clonic, myoclonic and absence seizures, associated with delayed development, speech and motor challenges. It is prevalent in about 1 in every 15,700 to 1 in 40,000 live births and affects equally boys and girls. In most cases the cause is an alteration within the SCN1A gene which causes continuous effects in cognition and motor functions that alter into adulthood.[2,3]

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Dravet Syndrome, along with other developmental and epileptic encephalopathies, presents complexities in its management, particularly since some medications for seizure control can aggravate seizures. Early diagnosis is crucial for patients to get the right treatment. .

Cannabidiol, otherwise known as CBD, is a non-psychoactive ingredient from the cannabis plant that raises interest as a possible therapeutic agent for Dravet Syndrome (DS). The FDA's endorsement of Epidiolex suggests great potential in this respect. However, most studies to date tend to assess specific parameters such as seizure reduction and safety rather than offer an overall assessment of the effectiveness of such treatment in DS management.[4] Sodium channel blocking Anti-Seizure Medications (ASM) should be avoided in this because it exacerbates seizure.[5]

However, a systematic review and network meta-analysis were conducted involving three add-on treatments for Dravet Syndrome: stiripentol, fenfluramine and cannabidiol. The results suggested that stiripentol and fenfluramine both reduced the seizure frequency and were superior to cannabidiol. According to Xia D *et al*., the initial therapy for seizures in patients with Dravet syndrome should be the administration of Stiripentol while fenfluramine (0.4 mg/kg/day) can be incorporated in the treatment as a second-line option. Other treatment regimens can be adopted within the context of management of Dravet syndrome, although their effectiveness may differ from one patient to another and thus help in making clinically appropriate choices to improve the management of Dravet syndrome.[6]

CLINICAL PRESENTATION

Case No: 1

A male infant aged 11 months diagnosed with Dravet syndrome presented with bronchopneumonia and febrile status epilepticus following 1 hr of fever, cough and convulsions staged over three days. The patient's seizures were characterized as left hemiclonic with secondary generalization. Whole exome sequencing suggested channelopathy or SCN1A gene mutations and the patient's family history was positive for febrile seizures. Clinical examination revealed the patient during an active seizure and the neurological examination was otherwise unremarkable with normal muscle tone, deep tendon reflexes +2 and downgoing plantar reflex. Auxiliary investigations demonstrated the following results: aspartate Aminotransferase (AST) level 73 U/L, Alanine aminotransferase (ALT) level 16 U/L which was within the normal range and C-Reactive Protein level (CRP) 6.8 mg/L showing the presence of inflammation. The patient was suffering From bronchopneumonia, febrile status epilepticus and had Dravet syndrome. His seizures were initially managed with intravenous levetiracetam which was followed by sodium valproate and higher doses of topiramate for more effective seizure control. Along with these medications, he was put on intravenous Cefoperazone-Sulbactam for bronchopneumonia, oxygen therapy, Levosalbutamol and Budesonide via nebulization and paracetamol for fever. The patient demonstrated improvement throughout the hospital stay, controlling his seizures and stabilizing his respiratory problems. After being released from the hospital, he was put on an anti-seizure medication regimen that included phenobarbitone (30 mg, 1 1/2 tablets at night), cannabidiol (0.7 mL BD), sodium valproate (5 mL BD), levetiracetam (2.5 mL BD) and topiramate (25 mg, 1/2 tab BD). Levosalbutamol and Budesonide were nebulized every 6 hr for six days, along with Cefuroxime Axetil (125 mg, 2.5 mL TID), Deriphyllin (2.5 mL QID) and other treatments for bronchopneumonia. The patient was instructed to follow up with both the pediatric neurology OPD and the pediatric OPD.

Case No: 2

An 8-month-old girl was referred to Al Shifa Hospital to undergo neurological and genetic workups after she developed a fever with several over fived provoked hemiclonic seizures. On admission, she was placed on intravenous anti-epileptic drugs which consisted of levetiracetam (200 mg IV BD), sodium valproate (150 mg IV TDS), meropenem (150 mg IV TID) which was given for respiratory issues and other supportive measures such as nebulization therapy. The physician also ordered WES to rule out any genetic condition and performed an EEG for monitoring. At the time of discharge, she was given several medications, including sodium valproate syrup (4 mL), lamotrigine syrup (2 mL), paracetamol syrup (120 mg/5 mL) and 2 mL syrup levosalbutamol for respiratory aid as well as budesonide (0.5 mL), hypertonic saline (3 mL with 2.7% NaCl) and continued with the anti-epileptic drugs. Midazolam nasal spray (0.5 mg 1 puff) was added in case of any breakthrough seizures. Three months later, she was brought back with a presumed genetic diagnosis of infantile far-up with intractable varicella due to motor vegetative degeneration. The patient arrived with a 104°F high-grade fever and varicella-like vesicular pustules all over her body. Concerns were expressed on her developmental state in addition to her varicella since she showed notable delays in motor, mental and social milestones, despite having just learned how to stand up straight.

The patient received intravenous acyclovir and acyclovir ointment for the varicella infection at the time of admission. Syrups for Levosalbutamol, Sodium Valproate, Cannabdiol and Paracetamol were among the other drugs. Additionally, syrup Phenargan and ocular drops Tobramycin were given. Acyclovir ointment, syrups Cefuroxime Axetil and Phenargan, calcium and iron drops and other supportive treatments were given to the patient before they were discharged. For a period of sixty days, the calcium and iron supplements were recommended in order to support nutritional status. The patient was admitted in order to treat the varicella infection and an underlying developmental delay that was thought to be a result of a larger genetic condition.

The management strategy addressed both the long-term developmental issues and the acute infection. Upon clinical examination, the throat appeared normal. Initial laboratory tests revealed a platelet count of 136,000/cu.mm, a lymphocyte count of 62% and a hemoglobin level of 9.2 g/dL. After further testing, the platelet count dropped to 115,000/cu.mm and the lymphocyte count increased to 64%, resulting in a hemoglobin level of 9.2 g/dL. A hematocrit of 33.7%, an MCV of 77.8 fL and an RBC count of 3.81 million/cu.mm were among the other results. The Platelet Crit (PCT) was 0.08%, the PDW was 15.2 fL and the monocyte count was 0%. At 54 U/L, the ALT level was found to be high.

DISCUSSION

Dravet syndrome is a serious condition that affects development and causes severe seizures. These seizures are often resistant to medication and the condition can also lead to cognitive issues. This significantly impacts the quality of life for both patients and their families. This is a case series that highlights complexities in the clinical management of two children with genetic epileptic encephalopathies complicated by recurrent seizures, infections and developmental delays. Both cases would therefore underscore the importance of integrated, multidisciplinary approaches to the management of neurological, genetic and infectious complications in infants. Genetic mutations in genes such as SCN1A, often implicated in Dravet syndrome, can help confirm the diagnosis and guide targeted therapies, which was confirmed in both patients based on whole exome sequencing test.[1] Wirrell EC recommends genetic testing in developmentally normal children by 2-15 months of age after single prolonged seizure or status epilepticus, especially postvaccination or after fever. Testing should be supported at any age in recurrent seizures either with or without fever. Both patients an 11-month-old male and an 8-month-old female with suspected Dravet syndromepresented with prolonged, recurrent seizures, primarily triggered by febrile illnesses. Febrile status epilepticus, as seen in the first patient and frequent hemiclonic seizures, as in the second case, are hallmark features of genetic epilepsies like Dravet syndrome. Early genetic testing and ongoing monitoring with MRI and EEG are crucial for tracking the progression of the condition.

In both instances, the utilization of various antiepileptic drugs played a significant role in controlling the occurrence of seizures and avoiding the sequelae of other neurological complications. Valproic acid is among the first treatment choices in patients with Dravet syndrome. Clobazam is also recommended either as the first or second adjuvant antiepileptic drug. For caregivers, pharmaceutical-grade cannabidiol may be recommended as a first or second line therapy for these patients, however, the doctors remain divided on this use.[7] In both cases, levetiracetam and sodium valproate were important in the management of seizures, both of which were effective for focal and generalized onset seizures. For infants, broad-spectrum levetiracetam is preferred over sodium valproate-which, albeit effective, has serious hepatic and hematological side effects that require close monitoring.[8,9] The situation surrounding the use of topiramate and the addition of phenobarbitone and cannabidiol in the male patient highlights the difficulties faced in managing epilepsy syndromes because of the tendency of recurrent seizures which requires often, several antiepileptic drugs. There is still much debate regarding the use of topiramate for infants afflicted with Dravet syndrome.[9] It has been revealed through studies that the incorporation of cannabidiol of clinical form into the current anti-epileptic medications, seek to improve the management of seizures specifically prolonged seizures found in Dravet syndrome with a resulting median reduction in motor seizure frequency of 36.5% over a month during which the study was conducted.[10] The differences in types of CBD, dosage and dosing regimen within the studies points to further research in optimising the treatment regimens. The findings are encouraging, however, the high frequency of off-target adverse effects such as drowsiness, digestive problems, elevated liver enzymes occasionally, carry a risk of escalation.[11] The female patient demonstrated that breakthrough seizures can be effectively rescued using midazolam spray, thus providing an effective strategy to combat an acute seizure activity episode outside of treatment institution. Both patients faced infections that exacerbated their neurological states, with the male patient suffering from febrile status epilepticus secondary to bronchopneumonia and the female patient suffering from chicken pox, which complicates the situation in those who are neurologically compromised and have a low immunity. In children suffering from genetic epilepsy syndromes, infections are commonplace because of immune compromise, prolonged exposure to medications and compromised ventilation. If untreated infections are present, they can instigate or aggravate seizure activity resulting to such undesirable consequences.[12]

The initiation of early antibiotic therapy (Cefoperazone-Sulbactam for pneumonia in the male patient) and antiviral therapy (Acyclovir for varicella in the female patient) was an important aspect of controlling

the infections and preventing the development of complications. Supportive respiratory care consisting of nebulization and bronchodilator therapy was instrumental in the stabilization of both patients. Both patients experienced severe secondary impairment due to their genetic siezures disabling syndromes that are complicated. The male patient sustained some gross motor functionality but has progressive neurological deficits, while the female patient is characterized by severe developmental delays and muscle wasting that denotes an extensive genetic syndrome. Though nutritional supplements were utilized, progress in development is still not achievable. Correct the treatment shall be targeted preventive developmental therapy, physical rehabilitation as well as ortho and or nutrition. Both patients presented with similar laboratory deficiencies including anaemia, thrombocytopenia hepatic enzymes raised therefore there is a risk with the use of Valproate due to its known hepatotoxic properties. The male patient was discharged after stabilization on the eight day post admission with improvement documented on subsequent follow up. The female patient improved and was also discharged on the fifth day with the follow up visit planned for six days after discharge.

CONCLUSION

Cannabidiol (CBD) has garnered favorable attention in the medical world and has been proven reliable in treating the refractory types of seizures that are witnessed in Dravet Syndrome. In the cases presented, the incorporation of CBD into treatment has demonstrated enhanced seizure control in patients whose baseline seizures remained uncontrolled despite adequate therapy with conventional doses of Levetiracetam, Sodium Valproate and Topiramate. The clinical research backing up the claim of CBD's usefulness in seizure control for bending over episodes is effusive. However, it must be used with care especially because of possible adverse effects such as drowsiness, gastrointestinal distress and raised liver transaminases. This case series demonstrates how essential it is to adopt a multidisciplinary strategy in the management of complicated genetic epilepsies and how long CBD treatment is necessary in such patients. More studies should be conducted to help in the standardization of the treatment regimen and elucidation of dosing in patients with Dravet syndrome of less than 18 years.

SUMMARY

The severe epilepsy known as Dravet Syndrome (DS) is characterized by cognitive impairment, developmental delays and seizures. Early genetic testing for SCN1A mutations directed treatment in two baby cases. Seizures continued even after using many anti-seizure medications until Cannabidiol (CBD) was introduced, which greatly improved control. It was crucial to provide multidisciplinary treatment that included developmental support and infection control. CBD worked well for resistant seizures, but more studies on dosage and customized treatment are required.

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CONFLICT OF INTEREST

The Authors declare that there is no conflict of interest regarding the publication of this case series.

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