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A Rare Case of Cannabinoid Hyperemesis Syndrome Secondary to Cannabidiol for Refractory Epilepsy

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Abstract: Cannabinoid hyperemesis syndrome (CHS) is associated with tetrahydrocannabinol, and rarely has been reported with cannabidiol. Cannabidiol is used in treatment-refractory epilepsy. This is a case of a pediatric patient with Lennox-Gastaut syndrome on cannabidiol, who was started on the ketogenic diet with significant seizure reduction. However, within 6 months he developed monthly bouts of severe emesis unresponsive to conventional anti-emetic therapy. Based on the stereotypical nature of his vomiting episodes, CHS was suspected. Cannabidiol was discontinued and within 2 months his emesis resolved. He has had no increase in seizure frequency or hospitalizations for emesis since cannabidiol was discontinued nearly 1 year ago. This is the first case of CHS secondary to cannabidiol for refractory epilepsy reported in the literature. We review the mechanism by which cannabidiol is believed to reduce seizures and be both anti- and pro-emetic, mainly through interactions with cannabinoid receptors and transient receptor channels.

Key Words: cannabidiol, ketogenic diet, refractory epilepsy, vomiting

INTRODUCTION

Cannabinoid hyperemesis syndrome (CHS) is defined by the Rome IV criteria as stereotypical episodic vomiting that presents after prolonged, excessive cannabis use, with relief of vomiting episodes by sustained cessation of cannabis use. At least 3 episodes must occur over the preceding year for diagnosis, with 2 episodes occurring at least 1 week apart over the preceding 6 months (1). CHS has been primarily associated with tetrahydrocannabinol, the main psychoactive compound of cannabis, and rarely with cannabidiol, which has no abuse potential (2).

In 2018 the U.S. Food and Drug Administration approved the first drug containing a purified substance derived from marijuana, namely cannabidiol, for the treatment of Lennox-Gastaut and Dravet syndromes in patients 2 years of age and older (3). This decision was made following multiple clinical trials demonstrating that cannabidiol decreases monthly frequency of seizures in children and adults with these syndromes (4). Although the anti-seizure mechanism is not entirely understood, cannabidiol is believed to modulate neuronal hyperexcitability mainly through interactions with cannabinoid receptors (CB_1 and CB_2) as well as transient receptor potential (TRP) channels (5,6). The ketogenic diet, a high-fat, low-carbohydrate diet, is an alternative treatment for medically refractory epilepsy that likely works through production of ketone bodies and restriction of glycolysis (7).

Here, we present a patient with Lennox-Gastaut syndrome on the ketogenic diet and cannabidiol, among other medications, who developed recurrent bouts of hyperemesis resulting in multiple hospitalizations. This is the first reported case of CHS secondary to cannabidiol for refractory epilepsy in the literature.

CASE REPORT

Our patient was born at 35 weeks by cesarian section due to maternal preeclampsia. He grew and developed with no medical issues until he was 6 years old. He then acutely developed altered mental status and status epilepticus and was admitted to an outside hospital, where he remained in a deep state of unconsciousness for 6 weeks. He was ultimately diagnosed with autoimmune encephalitis by brain biopsy. Treatment involved high-dose steroids and monthly cyclophosphamide infusions, to which he initially responded.

Eight months after completing cyclophosphamide infusions, his seizures recurred, and he developmentally regressed. He was started on multiple anti-epileptic drugs over the ensuing years, including cannabidiol 15 mg/kg/d when he was eleven years old. He also underwent placement of a gastrostomy tube in the setting of global developmental delay. Due to emesis with bolus feedings, he was switched to continuous feeds. Despite titration and multiple changes of his anti-epileptic drugs, he continued to have frequent breakthrough seizures. He was referred to our Pediatric Gastroenterology department when he was 13 years old for initiation of the ketogenic diet.

Following initiation of the ketogenic diet, he was noted to have a significant reduction in seizure frequency from an average of 15 per day to 2 to 5 seizures per day. However, over the next 6 months, he had 5 episodes of severe bouts of emesis lasting 24 to 48 hours, each separated by approximately 1 month. Follow-up electroencephalography demonstrated no change in his baseline seizure frequency.

We initially recommended empiric treatment of constipation, which did not reduce the frequency of his vomiting episodes. We subsequently ordered a liquid gastric emptying scan, which was delayed according to our hospital's protocol (31% retention at 2.5 hours). Due to the stereotypical nature of his vomiting episodes, the diagnosis of cyclic vomiting syndrome was also explored. An endoscopy was deferred due to anesthesia considerations for patients with epilepsy.

He was evaluated by a motility specialist at our center who refined our patient's diagnosis to CHS based on his chronic use of cannabidiol. Cannabidiol was weaned off. He had 1 mild vomiting attack during weaning, and his episodes of emesis completely resolved 2 months after cannabidiol was discontinued. He has had no increase in seizure frequency and has not required inpatient hospitalization for emesis since cannabidiol was discontinued nearly 1 year ago. He continues to receive the ketogenic diet with good tolerance.

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DISCUSSION

Cannabinoids are CB_1 and CB_2 receptor agonists, which are predominantly located in the brain, and are believed to produce anti-seizure and anti-emetic effects when activated. However, chronic exposure to cannabis leads to desensitization and decreased density of CB_1 and CB_2 receptors, therefore resulting in a pro-emetic effect (8). Cannabinoids are also agonists of TRP channels. When ligand concentration is high, TRP is anti-emetic, and when ligand concentration is low, TRP is pro-emetic. Chronic cannabis use leads to downregulation of TRP channels, which results in an increase in nausea and vomiting. Moreover, extreme stimulation of TRP can be pro-emetic. As cannabinoids are highly lipophilic and accumulate in adipose tissue, patients with chronic use accumulate cannabis in their body fat over time. Eventually, sufficiently high concentrations may be achieved to stimulate TRP channels to their emetic threshold (9). In several clinical trials, the most common adverse events in patients on cannabidiol included diarrhea, loss of appetite, and less commonly vomiting. The likelihood of severe adverse events increased in patients on higher doses of cannabidiol (ie, 20 mg/kg/d compared with 10 mg/kg/d), and in patients with longer use of cannabidiol (ie, median of 48 weeks compared with 12 weeks) (10).

Treatment of CHS primarily involves cessation of cannabis use. Topical capsaicin has been hypothesized to abort CHS symptoms through activation of the TRP vanilloid-1 receptor. Benzodiazepines, tricyclic antidepressants, and standard anti-emetic therapy have been reported to have variable efficacy in CHS (1,11).

Our patient's diagnosis of CHS was a difficult one to make. In retrospect, he had likely accumulated cannabis in his adipose tissue over the 2 years, he was on cannabidiol. Moreover, due to the highly lipophilic nature of cannabis, initiation of the ketogenic diet may have resulted in attainment of plasma concentrations high enough to induce a pro-emetic effect. This case highlights the importance of considering the diagnosis of CHS in patients with both chronic use of tetrahydrocannabinol and cannabidiol. Moreover, in patients with treatment-refractory epilepsy, consideration may be given to stopping cannabidiol after prolonged use, particularly with initiation of a ketogenic diet.

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