Open Journal of
Clinical & Medical
Case Reports

Volume 7 (2021)
Issue 13

ISSN: 2379-1039

Cannabis hyperemesis syndrome with major depressive disorder treated with intramuscular haloperidol and behavioral supported substance cessation aid

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Abstract

We report on a 21-year-old male patient with Attention-Deficit Hyperactivity Disorder (ADHD), Major Depressive Disorder (MDD), and chronic daily marijuana smoker who had three consecutive visits to the Emergency Department (ED) for symptoms of Cannabis Hyperemesis Syndrome (CHS) including abdominal pain, nausea, vomiting, and diarrhea. During his first visit, typical antiemetics were effective in resolving his symptoms; however, he returned a second and third time to the ED for the same symptoms following repeated marijuana use which were relieved by an intramuscular injection of haloperidol. The patient's past medical history of MDD and ADHD paired with recurrent use of marijuana against medical advice demonstrate the importance of behavioral health modification and support with cannabis cessation. Because of the patient's pre-existing comorbid psychiatric conditions, the patient should be monitored and educated on symptoms of cannabis withdrawal as this may increase anxiety, depression, and agitation.

Keywords

cannabis hyperemesis syndrome; marijuana; cannabis; major depressive disorder; haloperidol.

Abbreviations

CHS: Cannabis-induced hyperemesis; ED: Emergency department; MDD: Major depressive disorder; ADHD: Attention-deficit hyperactivity disorder.

Introduction

Cannabis is the most used illicit substance worldwide. Cannabis is often used clinically for its antiemetic effects in treating chemotherapy-induced nausea, cyclic vomiting syndrome, and anorexia [1,2]. With the legalization and increased use of cannabis, the prevalence of cannabis-induced hyperemesis (CHS) has risen more recently. CHS is typically a diagnosis of exclusion and has been recognized as a medical diagno-

sis since 2004 [3]. Paradoxically, CHS often mimics cyclic vomiting syndrome and is characterized by the following symptoms: persistent nausea, cyclic vomiting, abdominal discomfort, and compulsive hot-water bathing behavior [4]. Sometimes, CHS has presented with chronic abdominal myofascial pain within the musculature [5]. Currently, the criterion for CHS is lacking. There is some evidence that supports the biphasic presentation of CHS including low cannabis doses associated with antiemetic effects and high doses eliciting hyperemesis [6]. Russo, et al. reports five genomic mutations with a possible etiological role in CHS symptoms [4]. The current treatment for CHS is similar to cyclic vomiting syndrome. Traditional antiemetics are associated with treatment failure; thus, CHS requires the use of benzodiazepines or antipsychotics despite the lack of data-driven clinical data [7]. Oftentimes, CHS will require inpatient treatment for electrolyte imbalance, dehydration, possible upper gastrointestinal tract injury, and acute renal failure [8]. According to Moye-Dickerson, et al., seven case reports support the benefit of using IV haloperidol to manage acute CHS [9]. Hot hydrotherapy has also been seen to provide short-term symptomatic relief of acute CHS [8]. In other cases, dopamine antagonists and topical capsaicin cream have exhibited symptomatic relief of CHS in an outpatient setting [10]. We present a case of CHS that improved significantly after treatment with haloperidol, famotidine, iopamidol, and 0.9% sodium chloride in the Emergency Department (ED).

Case Description

First visit: The patient is a 21-year-old male with a past medical history of Attention-Deficit Hyperactivity Disorder (ADHD) and Major Depressive Disorder (MDD) who is a self-reported chronic daily marijuana smoker for the last 3 years who presented to the ED for abdominal pain, nausea, vomiting, and diarrhea for the past 4 days. He reported intake of an unspecified large amount of alcohol 3 days prior. The following morning, the patient had persistent nausea and vomiting and presented to the ED on day 3. His symptoms became worse with solid and liquid intake, stating that it makes him gag and vomit. He has since ceased any drinking or eating. The patient described the vomiting substance as grossly undigested/digested food at the onset which gradually became retch-like/bilious in character. The patient denied any associated hematemesis or coffee ground colored emesis. He also complained of epigastric pain, described as constant achy pain with episodes of cramping just prior to episodes of vomiting. He complained of feeling dehydrated and feeling more fatigued than usual. The patient denied any associated bloody stool, black-colored stool, or tarry appearing stool. He also denied any associated back pain, dysuria, hematuria, urinary frequency, nausea, vomiting, diarrhea, or constipation. He had no history of abdominal surgery or any recent trauma. He denied any history of colitis, diverticulitis, Crohn's disease, or peptic ulcer disease. The patient was taking Dextroamphetamine-Amphetamine 20 mg PO BID for ADHD and escitalopram 20 mg PO for MDD. Vitals were stable. On exam, he appeared fatigued without overt distress. His abdomen was soft with mild discomfort to palpation at the epigastric region. Bowel sounds were present and normal throughout, no organomegaly or masses appreciated, no rebound or guarding appreciated diffusely, negative Murphy's/McBurney's sign. There was no abdominal distension, no bruising, or sign of trauma noted. At that time, the following were differential diagnoses: gastritis, pancreatitis, dehydration, and electrolyte imbalance. After the initial assessment, CMP, CBC, lipase, rapid COVID-19, urine drug screen, EKG, cardiac monitoring, and abdomen/chest x-rays were ordered. Ondansetron 4mg IV push and sodium chloride 0.9% 2000 mL IV bolus were administered. All lab work-up and imaging were unremarkable, except for elevated

WBC count. His urine toxicology screening was positive for cannabis and negative for other illicit substances. The patient later reported much less discomfort and tolerated applesauce and juice without vomiting. A diagnosis of nausea, vomiting, and dehydration were made. He was discharged with instructions to drink plenty of fluids, maintain a balanced diet, avoid marijuana, caffeine and alcohol, and plan to follow up with his primary care doctor and gastroenterologist.

Second visit: The patient returned the following day to the ED due to persistent vomiting in the morning. Of note, the patient disclosed smoking marijuana the previous night. He stated he has had approximately 30+ episodes of vomiting and dry heaving since the morning. He denied any chest pain, dizziness, recent illness, or sick contact. He was also awake, alert, oriented x4, and hemodynamically stable. He admitted to abdominal pain, nausea, vomiting, without diarrhea or constipation. On the physical exam, he appeared comfortable. His abdomen was soft, supple, non-distended with mild generalized tenderness to palpation. His bowel sounds were present and hyperactive. At this point, there was a concern for electrolyte imbalance due to persistent vomiting and suspected cannabis-induced hyperemesis. Basic blood work including CMP and CBC was repeated. The patient was given sodium chloride 0.9% 1000mL IV bolus and haloperidol 5 mg IM instead of ondansetron. His blood work was within normal limits after medication administration and monitoring. He passed a PO challenge with water, crackers, and applesauce. During the visit, the physician emphasized the importance of marijuana cessation and follow-up with his primary care physician. The patient was diagnosed with acute vomiting and cannabis abuse.

Third visit: Five days after his last discharge, the patient returned to the ED with nausea and vomiting. He stated he had some discomfort in his upper abdominal area, denied any fever or frank abdominal pain. The patient stated his symptoms returned last night. His father reported that the patient continued to smoke cannabis regularly despite telling staff that he stopped smoking since his last visit to the ED. The patient was told that his symptoms are likely due to his marijuana use but stated that he feels better when he smokes marijuana. He admitted to abdominal pain, nausea, vomiting, without diarrhea or constipation. On the physical exam, the patient's abdomen was soft, supple, non-distended with mild epigastric tenderness to palpation. Basic blood work including CMP and CBC was obtained. The CMP revealed elevated liver enzymes compared to previous visits. He was given famotidine 20 mg/2 mL IV, haloperidol 2 mg IM, 61% iopamidol 100 mL, and sodium chloride 0.9% 1000 mL IV bolus. An abdominal CT was ordered as this was his third visit to the ED for the same symptoms. The results showed scattered sigmoid diverticulosis; however, this finding is unlikely to be the cause of his chief complaint. An ultrasound on his upper right quadrant was performed due to his elevated liver function tests: results were normal. Two hours after initial treatment, the patient's symptoms had significantly improved, and he was able to tolerate PO liquids without issue. The patient was counseled extensively on his marijuana abuse in reference to his symptoms. The physician also counseled him on supportive care including a liquid diet and advancing as tolerated the same day. The patient and his father were counseled on outpatient follow-up. The patient was cooperative and comfortable with the plan.

Clinical Findings

First Visit			
Serum Test	***Value***	***Serum Test***	***Value***
Sodium	139 mmol/L	Hemoglobin	16.7 g/dL
Potassium	4.1 mmol/L	Hematocrit	50.3%
Chloride	104 mmol/L	WBC	11.2 x10^9/L
Bicarbonate	24 mmol/L	Platelets	266 x10^9/L
BUN	14.0 mg/dL	ALT	15 IU/L
Creatinine	0.97 mg/dL	AST	14 IU/L
Glucose	105 mg/dL		
Lipase	22 UI/L		
Second Visit			
Serum Test	***Value***	***Serum Test***	***Value***
Sodium	140 mmol/L	Hemoglobin	16.4 g/dL
Potassium	3.8 mmol/L	Hematocrit	48.4%
Chloride	103 mmol/L	WBC	8.5 x10^9/L
Bicarbonate	22 mmol/L	Platelets	275 x10^9/L
BUN	11.0 mg/dL	ALT	13 IU/L
Creatinine	0.88 mg/dL	AST	16 IU/L
Glucose	119 mg/dL		
Third Visit			
Serum Test	***Value***	***Serum Test***	***Value***
Sodium	136 mmol/L	Hemoglobin	16.5 g/dL
Potassium	3.7 mmol/L	Hematocrit	47.5%
Chloride	101 mmol/L	WBC	10.0 x10^9/L
Bicarbonate	24 mmol/L	Platelets	308 x10^9/L
BUN	15.0 mg/dL	ALT	21 IU/L
Creatinine	0.89 mg/dL	AST	20 IU/L
Glucose	115 mg/dL		
Lipase	22 UI/L		

Therapeutic Intervention

Emergency department visit	Treatment
#1	Ondansetron 4mg IV @ 1103 Sodium chloride 0.9% 2000mL IV @ 1103
#2	Haloperidol 5mg IM @1154 Sodium chloride 0.9% 1000mL IV @ 1154
#3	Haloperidol 2mg IM @ 0920 Sodium chloride 0.9% 1000mL IV @ 0920 Famotidine 20mg IV @ 0921 Iopamidol 100mL IV @1039

Discussion

CHS has been recognized clinically for nearly twenty years, yet few advancements into the criteria for clinical diagnosis, pathophysiology, and specific risk factors have been made. Here we highlight the need for further investigation into the condition and the high importance of behavioral interventions such as marijuana cessation, addiction treatment, cognitive-behavioral therapy, and monitoring for withdrawal symptoms.

CHS is often confused with CVS due to its similar presentation; however, CHS is considered a subset of CVS according to Venketasan, et al [2]. Most research on CHS remains miscellaneous and limited to follow-up making it difficult to discern whether chronic cannabis use is contributory, a clinical association with CVS, or exacerbation of symptoms in patients who are predisposed to develop CVS [8]. The Rome IV Criteria is used in patients with symptoms of recurrent abdominal pain and/or altered bowel habits for at least 6 months. According to this criteria, the following symptoms are suggestive of CHS: (1) episodic vomiting resembling CVS in terms of onset, duration, and frequency, (2) presentation after prolonged use of cannabis, and (3) relief of vomiting episodes upon cessation of cannabis use. According to this criteria, our patient had CHS. It's been reported that mutations in genes *COMT, CYP2C9, DRD2, TRPV1,* and *ABCA1* affect neurotransmitters, endocannabinoid system, and the cytochrome P450 complex related to cannabinoid metabolism [4]. It is clear cannabis abuse disrupts the normal operation of the endocannabinoid system. One possible mechanism of disruption is Δ9-THC exposure leading to desensitization of CB-1 gabaergic effects which usually cause hypothermia, analgesia, and intestinal hypomotility [10]. Another suggested mechanism is unusual stimulation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system [8]. It could be considered as a gut-brain axis disorder [12].

Intravenous haloperidol has been reported as the wonder drug to cure the symptoms of CHS although there are hardly any studies reporting the efficacy and long-term side effects [7]. In this case, the initial treatment was ondansetron 4mg IV. Our patient did get symptom relief, however, intramuscular haloperidol with 2 mg IM and 5 mg IM was also effective in relieving his symptoms on his second and third visit, respectively. Comparing the effectiveness of intramuscular vs. intravenous administration is another area of research that has not yet been explored.

Cannabinoids act on central CB-1 receptors in the central nervous system, leading to the nausea and vomiting associated with CHS [13]. Jones, et al. reported haloperidol (unspecified route of administration) as the preferred treatment and prevention of CHS when the use of other antiemetics (e.g., promethazine, prochlorperazine, ondansetron, omeprazole, and lorazepam) are ineffective in symptom relief [14]. The effectiveness of haloperidol may be due to its action on D2 receptors in the brain which effectively blocks the chemoreceptor trigger zone [15]. There appears to be an association with CB-1 and dopamine signaling in recent animal studies, which may also explain the effectiveness of haloperidol in treating CHS [13]. Ultimately, the most effective way to relieve CHS is smoking cessation. Without smoking cessation, it is likely the CHS episodes will reoccur.

Substance cessation in chronic users typically requires a multifactorial approach [16]. One of the major pillars of treatment for our patient was the emphasis on marijuana cessation and the sharing of

resources available to support his transition from daily marijuana use. This is where addiction treatment, cognitive-behavioral therapy, and monitoring for withdrawal symptoms become particularly important.

The patient had pre-existing psychiatric conditions of MDD and ADHD depression. He disclosed to providers that he uses marijuana because it makes him "feel better." His three-year history of daily marijuana use also puts him at a higher risk of experiencing cannabis withdrawal symptoms. Hasin, et al. highlighted how prevalent withdrawal symptoms are among chronic users: 44% of users experienced ≥ two cannabis withdrawal symptoms, while 34% experienced ≥ three symptoms [17]. The study found the most reported symptoms of cannabis withdrawal were fatigue, hypersomnia, yawning, psychomotor retardation, anxiety, and depressed mood. Of note, these symptoms were associated with significant distress/impairment ($p < 0.01$).

Because of our patient's MDD and self-medication with cannabis, the providers believed monitoring for withdrawal symptoms were of high importance. Notable symptoms to watch for because of his medical history would be changes in anxiety, depression, aggression, sleep, and appetite changes. Symptoms of marijuana withdrawal need to be detangled from those of psychiatric disorders as cannabis has been shown to induce psychiatric disorders with either use or cessation [18]. For this reason, multifactorial approaches to treating and monitoring patients with co-existing psychiatric and marijuana use disorders should be developed and implemented in treating such patients with CHS.

Conclusion

There is a need for genetic analysis to confirm the correlation between specific mutations and CHS. Large-scale placebo-controlled trials are necessary to confirm haloperidol's beneficial role in treating patients with CHS symptoms. Future studies should emphasize cannabis-use patterns (e.g., cannabis potency, antecedent duration, frequency of use) and accurate phenotyping and genotyping of patients with CVS and CHS. In addition to symptomatic relief and medical stabilization, long-term treatment of CHS should include behavioral modifications of smoking cessation with aid from cognitive-behavioral therapy, addiction resources, and regular appointments. All patients should be monitored for psychological symptoms of cannabis withdrawal, especially those with co-existing psychiatric disorders.

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Manuscript Information: Received: August 06, 2021; Accepted: September 23, 2021; Published: September 30, 2021

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Citation: Ho A, Kanzaki L, Bell K, Manna D. Case report: Cannabis hyperemesis syndrome with major depressive disorder treated with intramuscular haloperidol and behavioral supported substance cessation aid. Open J Clin Med Case Rep. 2021; 1795.