Case Report

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Emesis Ad Nauseum: A Case Report of Cannabinoid Hyperemesis Syndrome in Urgent Care

Urgent Message: Frequent cannabis use can lead to a syndrome characterized by severe and cyclical vomiting without other clear triggers. Termed "cannabinoid hyperemesis syndrome," this disorder is often refractory to conventional antiemetic pharmacotherapy.

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Abstract

Introduction: Cannabinoid hyperemesis syndrome (CHS) is increasingly recognized as a cause of cyclical vomiting.

Presentation: A 28-year-old man presented to urgent care (UC) with recurrent nausea and vomiting. He reported relief only when taking frequent, hot showers. He was noted to have multiple prior presentations for similar complaints in the previous 2 weeks.

Physical Examination: The patient was afebrile, normotensive, and had otherwise unremarkable vital signs other than mild tachycardia. He appeared uncomfortable, and his abdomen was mildly tender and without rebound or guarding. His abdomen was non-distended. He was observed to be frequently retching with only small amounts of clear gastric contents contained in an emesis bag.

Diagnosis: His previous work-up included unremarkable laboratory and imaging studies as well as a recent, normal esophagogastroduodenoscopy. A history of frequent use of cannabis was elicited. Felt to be the likely culprit for his presentation, cannabis cessation was advised. At the time of his UC presentation, the patient reported 5 days of abstinence from all cannabis and nicotine products.

Resolution: The patient was referred to the emergency department (ED) given his refractory nausea and vom-

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iting. With multimodal parenteral antiemetic therapy, the patient improved and was able to eventually tolerate oral (PO) fluids. He was discharged home from the ED with encouragement to continue to refrain from cannabis use.

Conclusion: Refractory nausea and vomiting is common in CHS. Nicotine withdrawal was felt to contribute to his nausea as well. Cessation of cannabis use will typically result in complete resolution of symptoms associated with CHS.

Introduction

Cannabinoid hyperemesis syndrome (CHS), which was first described in 2004, is "an episodic syndrome of cyclic vomiting in the context of the prolonged use of cannabis."[1-4] The diagnosis is challenging to make in the acute care setting as it is often a diagnosis of exclusion or, per 1 of the Rome IV diagnostic criteria for cyclic vomiting, by resolution of episodes of vomiting occurring with sustained cessation of cannabis use.[5] The pathophysiology of CHS is still debated, however, it is theorized that excessive, chronic stimulation of the cannabinoid receptors can affect vagal afferent regulation of the gastric motility and emptying leading to nausea and vomiting.[6]

Although CHS is increasingly recognized as an etiology for many presentations of recurrent vomiting and abdominal pain, delays in diagnosis are common, and the average time from onset of symptoms to diagnosis is 4.1 years.[3] Frequent cannabis use has increased dramatically in recent decades with current estimates citing over 50 million Americans engaging in at least annual cannabis use and one-third of using adults meeting criteria for cannabis use disorder.[7,8] Additionally, with widespread decriminalization of cannabis in the United States, the average potency (ie, delta-9-tetrahydrocannibinol [THC] content) of cannabis has more than doubled over the past 30 years.[9] This combination of wider spread use of more potent cannabis, coupled with increasing clinician awareness of the condition, has led to a marked increase in diagnoses of CHS in recent years.[10]

Patients afflicted with CHS are more frequently male and will report symptomatic relief from hot baths or showers. Cannabis is a weak antiemetic at low doses, and patients may report symptomatic relief with infrequent use. Coupled commonly with psychological and/or physical dependence, patients often reject the possibility of cannabis as the culprit for their symptoms, leading to continued cannabis use in many cases.[1-4]

Cannabinoid hyperemesis syndrome is considered a subset of the cyclical vomiting syndrome (CVS). Of note, many patients with non-CHS CVS report symptomatic relief with cannabis (although use typically postdates the onset of symptoms), and 48% of patients with CVS report relief with hot showers irrespective of cannabis use.[2,11] Diagnostic criteria for CHS are proposed by expert consensus (**Table 1**), however it can occur with any duration of cannabis use, and the response to cannabis cessation is unable to be evaluated in the acute setting.[2,6]

Clinical Presentation

A 28-year-old man presented to UC with diffuse abdominal pain, nausea and non-bloody, non-bilious vomiting for 3 days. He was discharged from the emergency department (ED) just before this episode occurred. His UC presentation was the 4th in 2 weeks for the same symptoms. He had no other chronic medical or psychiatric conditions. He reported cannabis use 5 days prior to this presentation and had previously been using THC-containing products daily. He also had a 10-pack per-year history of cigarette use. He also reported no tobacco use over the prior 5 days due to his vomiting. His abdominal pain began in the epigastric region and progressed to radiation to the back and lower abdomen. He reported some relief with hot showers at home.

Physical Exam Findings

On presentation to UC, his heart rate was 112 beats per minute, but the remainder of his vital signs were normal. On examination, the patient seemed uncomfortable but non-toxic. His abdominal exam showed minimal tenderness in the epigastric region without rebound or guarding. He was non-distended with normal bowel tones and no palpable abdominal masses.

Table 1. Diagnostic Criteria for Cannabinoid Hyperemesis Syndrome

Clinical features	3 or more vomiting episodes annually
Cannabis use	Duration of use more than 1 year before onset of symptoms, frequency of use more than 4 times per week
Cannabis cessation	Resolution of symptoms after a period of abstinence from cannabis use for at least 6 months, or at least equal to the total duration of 3 typical vomiting cycles

Urgent Care Management

The patient initially presented to UC for the visit outlined above. In urgent care, he had a point-of-care basic metabolic panel which was entirely normal, including potassium, creatinine, and glucose values. A urine dipstick was normal except for 1+ ketones. He was administered intravenous promethazine and 1 liter of normal saline. On reassessment, his tachycardia had improved but he continued to vomit.

Differential Diagnoses and Medical Decision Making

The first visit during this patient's 2-week episode of repeated vomiting was to the local ED. A broad differential diagnosis was considered for his severe nausea and vomiting including pancreatitis, bowel obstruction, gallstone disease, and infectious enteritis. At that visit, he had normal labs including a complete blood count, metabolic panel, liver panel, and lipase. A right upper quadrant ultrasound and contrast enhanced computed tomography (CT) of the abdomen revealed no concerning abnormalities. In the ED, he was treated with intravenous (IV) droperidol and 1liter of Lactated Ringer's. He was tolerating oral (PO) liquids after his work-up in the ED and was able to be discharged home.

One week later, he presented to the same ED again for the same complaints. At the time, he reported ongoing daily THC use. Laboratory tests were repeated and were again normal. His electrocardiogram (ECG) showed QT interval 460 ms at that visit. He was treated with IV ondansetron and promethazine as well intramuscular trimethobenzamide for his persistent symptoms.

Given his refractory symptoms despite multimodal use of antiemetics, he was admitted to the hospital where his ongoing treatment included a nicotine patch, topical capsaicin applied to the abdomen 3 times daily, and IV pantoprazole, metoclopramide, and diazepam. During the hospitalization he had a normal esophagogastroduodenoscopy (EGD) and was transitioned to oral antiemetics on day 2. He was informed of the clinical suspicion for CHS and committed to abstinence from cannabis and tobacco. He was discharged with a prescription for oral omeprazole and ondansetron.

Two days later, he represented the ED with the same complaint. He again had an unremarkable laboratory work-up and an ECG without QT prolongation. His symptoms improved with 1 dose of intravenous droperidol at that visit, and he was again discharged. He ultimately presented the following day to UC for the visit discussed.

Final Diagnosis

Given refractory symptoms in UC after IV fluids and promethazine, he was referred again to the ED. In the ED, the patient again was given a nicotine patch. However, there was a delay in obtaining IV access, and 1 hour after receiving the nicotine patch, the patient's nausea improved without antiemetics. Eight hours later, without any antiemetic treatment, he was tolerating a soft diet and was discharged with a diagnosis of CHS complicated by nicotine withdrawal.

Disposition and Patient Perspective

At 24 hour follow-up, the patient continued nicotine replacement therapy and reported he was asymptomatic. He denied vomiting or requiring antiemetics at home to manage his nausea. He planned to follow-up with his primary care provider in the next week.

Discussion

Acute vomiting caries a broad differential diagnosis. However, in cases of recurrent episodes of vomiting, while having an initially broad differential is important, inquiries about cannabis use can be a critically important aspect of history gathering to determine if CHS may be the etiology. Laboratory studies (particularly liver function tests and lipase) and a urine pregnancy test (in female patients) can be helpful initially in assessing for biliary disease, pancreatitis, and hyperemesis gravidarum, respectively. Imaging studies such as right upper quadrant ultrasound and/or CT of the abdomen can prove useful for identification of alternate pathology. A metabolic panel is prudent in prolonged episodes to screen for sequalae of vomiting (eg, electrolyte derangements, hypoglycemia, starvation ketoacidosis, acute kidney injury, etc).[1,2] As this is a recurrent issue for patients, referral to a gastroenterologist for consideration of EGD is reasonable, however, there are no formal recommendations that all patients undergo EGD as part of their work-up.[3,11] When EGDs are performed during or shortly after a vomiting episode, epiphenomena like gastritis, esophagitis, or Mallory-Weiss tears may be sequalae and not causal.[6,11]

Obtaining an ECG is prudent as the risk of fatal arrhythmia increases with electrolyte derangements experienced from decreased PO intake (eg, hypokalemia, hypomagnesemia) and the cumulative effect of QT interval prolonging effects of most antiemetics.[1,4,12] Referral to the ED is generally warranted for patients with significant dehydration, known or suspected electrolyte derangements, marked QT interval prolongation, or refractory nausea impairing adequate PO intake. Clinicians should evaluate for the rare but real possibility of esophageal tear and rupture as well and refer patients

Table 2. Common Antiemetics [11,14-17]

Class	Name	Adverse Effects	Takeaway Points
5-HT3-RA			
	Ondansetron (IM, IV, PO, ODT)	Constipation, dose-dependent QTc prolongation, dizziness, drowsiness, headache	ODT formulation effective and tolerable by most patients.
Anticholinergic			
	Scopolamine (Transdermal)	Dry mouth, dizziness, sedation, visual disturbances.	Slow onset of action. Transdermal delivery for outpatient use. Caution in elderly.
Antihistamine			
	Diphenhydramine (IM, IV, PO)	Constipation, dizziness, drowsiness, dry mouth, sedation, visual disturbances, urinary retention	Highly sedating; May reduce akathisia associated with D2-RAs.
	Doxylamine (PO)		
	Meclizine (PO)		Available OTC.
	Promethazine (IM, IV, PO, PR)		Highly sedating; Achieves D2-RA at IV doses; be mindful of EPS, QTc prolongation (unlikely to progress to arrhythmia). Rectal formulation useful for breakthrough vomiting and widely available for outpatient use.
Benzamide (D2-RA, 5-HT3/4-RA)			
	Metoclopramide (IM, IV, PO)	ADR, agitation, akathisia,* dizziness, dose-dependent QTc prolongation, EPS, headache, insomnia, TD (black box warning)	Promotility agent; helpful for gastric emptying. Avoid if concern for bowel obstruction.
	Trimethobenzamide (IM, PO)		Does not prolong QTc.
Benzodiazepines			
	Diazepam (IM, IV, PO)	Sedation, addictive, paradoxical agitation in older adults	Typically reserved for inpatient use.
	Lorazepam (IM, IV, PO)		
Butyrophenones (D2-RA)			
	Droperidol (IM, IV)	Dose-dependent QTc prolongation, ADR, akathisia,* EPS, TD	Greatest efficacy as single agents in CHS.
Haloperidol (IM, IV)			
Phenothiazines (D2-RA)			
	Prochlorperazine (IM, IV, PO)	ADR, akathisia,* drug-induced leukopenia, NMS (rare), TD	
	Chlorpromazine (IM, IV, PO)		
Glucocorticoids			
	Dexamethasone (IM, IV, PO)	Anal pruritus (doses › 20 mg),* hyperactivity, hyperglycemia, gastritis	

** Occurrence more common with rapid infusion or push doses.*
5-HT-RA = 5-hydroxytryptamine receptor antagonism; ADR = acute dystonic reaction; D2-RA = dopamine 2 receptor antagonism; EPS = extrapyramidal symptoms; IM = intramuscular; IV = intravenous; NMS = neuroleptic malignant syndrome; ODT = oral disintegrating tablet; OTC = over the counter; PO = oral; PR = rectal; QTc = QT interval; TD = tardive dyskinesia.

to the ED for evaluation when such complications are suspected.[13]

The patient presented had recently had an extensive work-up prior to presentation to UC, ruling out conditions like appendicitis, bowel obstruction, cholecystitis, cholelithiasis, pancreatitis, urolithiasis, and inflammatory bowel disease. Other diagnoses which may present similarly include gastroesophageal reflux disease, functional dyspepsia, porphyria, diabetic ketoacidosis, and Addison's disease. Neuroimaging is advised for patients with localizing neurologic systems or other features consistent with elevated intracranial pressure, which can produce severe vomiting.[2]

Recommendations for treatment of acute vomiting episodes associated with CHS should be managed with antiemetics (**Table 2**), oral and/or IV rehydration, opioid sparing analgesia, and electrolyte repletion if indicated.[1-4] Butyrophenone agents such as droperidol and haloperidol have proven uniquely effective in ED settings for management of vomiting associated with CHS and are the recommended first-line antiemetics (if available).[1,2,4] Limited evidence also supports the efficacy of ondansetron, metoclopramide, and promethazine for the management of nausea in episodes of CHS as well.[1,2,4] Topical capsaicin may be offered as an adjunct treatment, especially if previously efficacious in managing vomiting episodes. Localized burning sensation is reported by 4.8% to 17.8% of patients, but resolves with medication removal.[1,14]

For pain, ketorolac or acetaminophen are reasonable options, while guidelines and best evidence suggest that opioids should be avoided given the chronic nature of the condition and their potential to worsen nausea.[2,4] Intravenous fluids containing dextrose are preferred for rehydration, which can mitigate nausea associated with ketosis from inadequate PO intake.[6]

The risk of QT interval prolongation or progression to fatal arrythmia is low with most antiemetics at routine doses.[15-18] While patients with CHS are typically younger and less often on simultaneous therapy with other pro-dysrhythmic cardiac medications, they often require multiple IV antiemetic agents and at higher than standard doses to control vomiting. In 1 study of CHS patients, a potassium less than 3.0 mmol/L was the only predictor of QTc prolongation greater than 500 msec.[19] Cardiac monitoring may be reserved for patients with a higher risk of arrhythmia: age ≥65 years, female sex, hypokalemia, or use of concomitant QT prolonging medications.[12] Scopolamine patches, trimethobenzamide, and dexamethasone do not prolong the QT interval at routine doses, however their efficacy in CHS has not been evaluated specifically.[15] Benzodiazepines are unlikely to prolong the QT interval, but their sedative effects and propensity for abuse/dependence limit utility in the outpatient setting.[4]

Extrapyramidal side effects (EPS) are not uncommon with dopamine antagonizing agents. The risk of EPS is higher in patients concurrently treated with antipsychotics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and/or serotonin-norepinephrine reuptake inhibitors.[16,17] Acute dystonic reactions and akathisia are often relieved with antimuscarinic agents (benztropine) or diphenhydramine. Although rare, laryngeal and pharyngeal dystonic reactions can be airway threatening emergencies.[16,17]

Several treatments for prophylaxis have been proposed for CVS and may be helpful in CHS. Tricyclic antidepressants (eg, amitriptyline) have shown efficacy in the long-term management of CHS and cannabis withdrawal symptoms. Amitriptyline can be started at 25 mg nightly and titrated weekly to the minimal effective dose of 75 to 100 mg.[3,11] In addition to tricyclic antidepressants, beta blockers, topiramate, and levetiracetam are also used, however, the need for close monitoring and titration may preclude their use in the acute care setting.[1,3,6,11]

This patient presented in this case demonstrated several suggestive features of CHS, including episodes associated with regular cannabis use and symptomatic relief with hot showers. Like many patients with CHS, multiple diagnostic tests were ordered to rule out alternative pathology. Refractory symptoms are common in CHS; patients have high hospital admission rates and prolonged ED lengths of stay, and often receive multiple diagnostic studies.[20]

Nicotine exposure is known to induce nausea and motion sickness in nicotine naïve individuals.[21] However, chronic nicotine exposure leads to reduced sensitivity of central nervous system nicotine receptors, which provides some emetogenic and nociceptive defense following anesthesia and surgery.[22,23] Chronic nicotine exposure may increase the threshold for nausea by causing a relative decrease in functional acetylcholine, similar to the anticholinergic and antimuscarinic actions of antiemetics.[22,23] Beyond the nicotine patches the patient received, there is no objective evidence that nicotine withdrawal significantly contributed to refractory symptoms, considering the expected convalescence from a CHS episode. Practically, concurrent cannabis and nicotine use is common, and cessation from both should be encouraged.[24]

Ethics Statement

The patient was unable to be contacted because of being lost to follow-up (phone number no longer in service), and therefore demographics and some details of the case were changed to protect patient anonymity and confidentiality.

Takeaway Points

- CHS is a syndrome of episodic cyclical vomiting that can occur with any duration of cannabis use and improves with cannabis cessation. Given the criterion of improvement with cannabis cessation and CHS being a diagnosis of exclusion, UC providers should exercise caution making an initial diagnosis of CHS.
- CHS symptoms are typically refractory to traditional doses of antiemetics.
- Vomiting can occur due to nicotine withdrawal and is best managed with nicotine replacement therapy.
- Patients with refractory vomiting may require ED referral for electrolyte repletion, cardiac monitoring, or management of refractory symptoms (ie, inability to tolerate PO fluids). Additionally, in patients with severe vomiting without an established diagnosis of CHS, ED referral for exclusion of alternative etiologies is prudent.
- Concurrent cannabis and nicotine (including electronic delivery systems) use is common, and cessation of both should be encouraged. ■

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