Resolution of Cannabinoid Hyperemesis Syndrome with Benzodiazepines: A Case Series

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ABSTRACT: **Background:** Cannabinoid hyperemesis syndrome (CHS) is under-recognized by clinicians. It is characterized by nausea, severe abdominal pain, and cyclical vomiting in the context of chronic cannabis use. Oral benzodiazepine is a proposed treatment for CHS. It decreases activation of Cannabinoid Type 1 Receptor (CB1) in the frontal cortex, has a sedative and hypnotic effect and reduces the anticipation of nausea and vomiting. These effects on the central nervous system (CNS) might explain its beneficial antiemetic effect for this syndrome.

Objectives: To increase the index of suspicion for CHS, a unique syndrome that requires a unique treatment with benzodiazepines and not antiemetics.

Methods: We describe a series of four patients with documented cannabis use, who were admitted to an internal medicine department of Meir Medical Center due to symptoms consistent with abdominal pain, nausea, and vomiting. They were initially treated with conventional antiemetics and proton pump inhibitors without response. Intensive investigations were conducted to exclude common and sometimes urgent gastrointestinal or CNS syndromes.

Results: After excluding urgent gastrointestinal and CNS origins for the vomiting, we suspected CHS. All four patients experienced similar symptoms and failure of conventional treatment with antiemetics and proton pump inhibitors. They experienced relief after administration of benzodiazepines.

Conclusions: A high index of suspicion for CHS allows for rapid, appropriate treatment with benzodiazepines, which in turn may lead to cessation of the debilitating symptoms caused by this syndrome.

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KEY WORDS: abdominal pain, benzodiazepines, cannabis, cannabis hyperemesis syndrome (CHS), hydrotherapy

Cannabinoid hyperemesis syndrome (CHS) is a common, yet under-recognized clinical syndrome of chronic cannabis users [1-3]. It is characterized by nausea, severe abdominal pain, and cyclical vomiting. Other characteristics include age younger than 50 years, more than 5 kg weight loss, morning predominance, normal bowel habits, negative laboratory, radiographic, and endoscopic workup [1,3,4].

The syndrome consists of three stages:

1. Prodrome: Symptoms of nausea, anorexia, and vague abdominal discomfort precede the acute vomiting and last from a few weeks to several months
2. Hyperemesis: Usually lasts for a few hours but may continue for days, accompanied by acute emesis and severe abdominal pain
3. Recovery: Following cessation of cannabis ingestion, may last for several days; consists of resolution of all symptoms and return to a state of general well-being [1]

Proposed etiologies of CHS include toxic accumulation of cannabinoid metabolites due to genetic variation, override of the enteric proemetic effect of cannabis over its central nervous system (CNS)-mediated antiemetic effect and increased activation of the hypothalamic-pituitary-adrenal axis (HPA) [1]. A distinguishing feature of this syndrome is the relief of symptoms following hot showers. This action might be attributed to several molecular and neurohumoral effects. The main feature of hydrotherapy (> 43°C) is activation of transient receptor potential vanilloid 1, both cutaneously and in the CNS, resulting in a decrease in nociceptive pain. Other effects of hydrotherapy include reversal of hypothalamic cannabinoid-induced hypothermia, decrease in HPA and sympathetic nervous system activation, cutaneous steal syndrome, and effects on various polypeptides, including somatostatin [5].

Highly regared evidence for pharmacologic treatment therapy of CHS is extremely limited. So far, only a few medications have been effective [6]. These include capsaicin [7], haloperidol [8-10], and benzodiazepines [6]. Although the prevalence of CHS is very high among daily and weekly cannabis users, the syndrome is under-diagnosed to a surprising degree for various reasons, including the paradoxical use of cannabis for treatment of nausea and vomiting, the stigma associated with cannabis use, and the illegal status of cannabis in many regions, which leads to under-reporting of use [3]. Cannabis use in Israel has been increasing over the past 10 years. Reports indicate that as much as 27% of the population over the age of 18 uses cannabis at least once per year. This figure increases up to 37.5% among people ages 18 to 40 years [11]. This report presents a series of four cases of CHS successfully treated with benzodiazepines at the department of internal medicine.

PATIENTS AND METHODS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethics committee of Meir Medical Center, Kfar Saba, Israel. All participants provided verbal informed consent prior to data collection.

The patients described in this study were admitted to the Internal Medicine Department B at Meir Medical Center from April 2017 through April 2018, after they arrived at the emergency department (ED) with complaints of abdominal pain, nausea, and vomiting. The patients confirmed chronic long-term cannabis use and had cyclical vomiting that failed other outpatient antiemetics. They underwent intensive investigations to exclude gastrointestinal and CNS origins for the symptoms. The patients displayed compulsive bathing behavior during their hospitalization. After the diagnosis was established, all patients were treated, according to the latest guidelines [3,6], with resolution of their presenting symptoms. The cases were reviewed in April and May 2018.

RESULTS

We present four cases with a newly-established diagnosis of CHS. A brief description of each case follows and all are summarized in Table 1.

CASE 1

A 21-year-old male with a medical history of recurrent abdominal pain and cyclic vomiting for the past 2.5 years was admitted to our department. He was not taking any prescription medication. During that period, he had been admitted to the intensive care unit with a diagnosis of Boerhaave syndrome (spontaneous perforation of the esophagus resulting from a sudden increase in intraesophageal pressure combined with negative intrathoracic pressure) due to severe recurrent vomiting. He received conservative therapy that consisted of fasting, oxygenation, and monitoring but no surgical interventions.

He arrived at the ED presenting with nausea, vomiting, and epigastric pain that began a week before his current admission. He also reported an unintentional weight loss of more than 5 kg in the past few months. Laboratory and imaging studies that included abdominal X-ray, abdominal ultrasound, and both chest and abdominal computed topography (CT), were all negative, including an esophagogastroduodenoscopy that was conducted in 2017. Various antiemetic drugs had no effect on his current symptoms. Two days after his current hospital admission, he confessed to weekly marijuana use for the past 3 years. After receiving two doses of 0.5 mg clonazepam per os (PO), 8 hours apart, his symptoms resolved completely in less than 24 hours.

CASE 2

A 24-year-old male with a medical history of attention deficit hyperactivity disorder presented to our department. He was not taking any prescription medication. He had experienced recurrent nausea, abdominal pain, and cyclical vomiting lasting for the past 6 months. He also reported an unintentional weight loss of more than 5 kg during that period. Laboratory and imaging studies, which included abdominal X-ray, abdominal ultrasound, and chest and abdominal CT, were all negative. On further anamnesis, he reported using "Nice Guy" (synthetic marijuana). After receiving a single dose of 0.5 mg clonazepam PO, his symptoms resolved in less than 24 hours.

CASE 3

A 31-year-old female with a 10-year medical history of recurrent abdominal pain and vomiting was admitted to our department. She began using cannabis on daily basis about the time her symptoms first appeared. During this period, she visited her family physician regularly and was prescribed metoclopramide (antiemetic) due to these chronic debilitating symptoms. She was examined by a gastroenterologist on several occasions, with no diagnosis. Laboratory and imaging studies, including abdominal X-ray, abdominal ultrasound, and abdominal CT

Table 1. Summary of case reports

Case	Age, years	Gender	Co-morbidities	Frequency of marijuana use	ED visits/admissions within one year of index	Previously failed treatment
1	21	Male	Boerhaave syndrome	Weekly	7/7	Metoclopramide IV Ranitidine IV Perfalgan IV
2	23	Male	Attention deficit hypersensitivity disorder	Weekly	1/1	Metoclopramide IV Ranitidine IV Perfalgan IV
3	31	Female	Hemorrhoids Hirsutism	Daily	5/4	Metoclopramide IV Ondansetron IV Ranitidine IV Perfalgan IV
4	40	Male	Fibromyalgia | Disc herniations | Multiple suicide attempts S/P Total hip replacement | S/P Atrial septal defect repair	Daily	1/1	Metoclopramide IV

ED = emergency department, IV = intravenous

were all negative, including an esophagogastroduodenoscopy in 2017. On admission, the patient was treated with various antiemetic drugs, including metoclopramide, ranitidine, ondansetron, and perfalgan IV with little to no effect on her symptoms. After receiving a single dose 0.5 mg clonazepam PO, her symptoms resolved in less than 24 hours.

CASE 4

A 40-year-old male with fibromyalgia, borderline personality disorder, and a history of several suicide attempts arrived at our department. He also had chronic back pain due to herniations of several discs. He was prescribed 30 g of medicinal marijuana for chronic pain and he bought an additional 20 g monthly. He had a 2-month history of recurrent abdominal pain and vomiting. At admission, he reported using marijuana daily for more than 10 years. After receiving two doses of 0.5 mg clonazepam PO, 8 hours apart, his symptoms completely resolved in less than 12 hours.

While hospitalized, all patients took long, hot showers 6 to 12 times per day and reported symptomatic relief and/or resolution of symptoms after each shower.

DISCUSSION

For centuries, cannabis has been the most widely-used drug for both recreational and therapeutic purposes worldwide [12]. Its therapeutic effects include antiemesis, appetite stimulation, and pain control. Delta-9-tetrahydrocannabino is the main active ingredient in cannabis. It binds to cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors in human tissue. CB1 receptors are located primarily in the CNS, whereas CB2 receptors are mainly found in the peripheral nervous system, most notably in the digestive system.

CHS is a common yet under-recognized clinical syndrome of cyclical vomiting related to long-term cannabis use, which primarily affects adults under the age of 50 [1-4]. Although the exact mechanism of CHS remains unclear, proposed etiologies indicate genetic, metabolic, and environmental variations that might enhance the proemetic effect of cannabis. This result is mainly regulated through CB2 receptors, and eventually overrides the CNS-mediated antiemetic effects, mainly regulated through CB1 receptors, to promote emesis. Prior to the diagnosis of CHS, patients often endure years of potentially debilitating symptoms on a cyclical basis. These patients, typically, arrive frequently at healthcare facilities with similar symptoms and receive multiple diagnostic tests and invasive procedures, but they do not receive a clear diagnosis or effective treatment plan [1]. The current study included four patients who were first diagnosed with CHS during their hospitalization.

Benzodiazepines are one of few classes of drugs that are effective for the treatment of CHS [6]. Clonazepam is a benzodiazepine whose main mechanism of action is through the enhancement of gamma-aminobutyric acid activity, which is the major inhibitory neurotransmitter in the CNS. This mechanism causes both a sedative/hypnotic effect and also reduces anticipation of nausea and vomiting [13]. In addition, benzodiazepines decrease activation of the CB1 receptor in the frontal cortex; thus, enhancing its antiemetic effect [14]. All patients in this report obtained complete symptomatic relief and were discharged within 24 hours after receiving clonazepam, as other supportive, antiemetic therapy failed to improve their condition.

Despite the worldwide increase in cannabis use, CHS remains underdiagnosed and undertreated. Benzodiazepines are a group of highly potent, commonly used psychoactive drugs, whose antiemetic effects are an efficient solution for the relief of CHS symptoms. Although this study included a small number of patients, all were successfully treated with complete resolution of their symptoms. The only way to prevent recurrence is to refrain from cannabinoid use, but efficient symptom management with benzodiazepines could decrease hospital admissions and reduce unnecessary testing, overall costs, and severe life-threatening complications of the profuse vomiting, such as Boerhaave syndrome and severe metabolic complications including hypokalemia, alkalosis-contraction, dehydration, hypovolemic shock, and cardiac events. Future research should focus on the benefits of benzodiazepines and other high potency antiemetics such as haloperidol and capsaicin.

Limitations to this case series include the small sample size, medical co-morbidities, and lack of an objective means of measuring long-term positive outcomes.

CONCLUSIONS

CHS is a unique, underestimated entity that responds poorly to standard antiemetic treatment. Physicians of different disciplines, especially those working in EDs, internists, neurologists, psychiatrists, and those working in treatment with narcotics should have a high level of suspicion and be able to recognize this syndrome promptly. In the setting of chronic cannabis use, delay is dangerous and even potentially life-threatening. Early and appropriate treatment with benzodiazepines may terminate the hyperemesis and prevent severe complications and extensive, unnecessary investigations.

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Capsule

Exome sequencing of 20,791 cases of type 2 diabetes and 24,440 controls

Protein-coding genetic variants that strongly affect disease risk can yield relevant clues to disease pathogenesis. **Flannnick** and co-authors reported exome-sequencing analyses of 20,791 individuals with type 2 diabetes (T2D) and 24,440 non-diabetic control participants from five ancestries. The authors identified gene-level associations of rare variants (with minor allele frequencies of less than 0.5%) in four genes at exome-wide significance, including a series of more than 30 *SLC30A8* alleles that conveys protection against T2D, and in 12 gene sets, including those corresponding to T2D drug targets (P = 6.1 × 10–3) and candidate genes from knockout mice (P = 5.2 × 10–3). Within the study, the strongest T2D gene-level signals for rare variants explain a maximum of 25% of the heritability of the strongest common single-variant signals, and the gene-level effect sizes of the rare variants observed in established T2D drug targets will require 75,000–185,000 sequenced cases to achieve exome-wide significance. The authors proposed a method to interpret these modest rare-variant associations and to incorporate these associations into future target or gene prioritization efforts.

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Capsule

Preference phenotypes in support of shared decision-making at point-of-care for patients with rheumatoid arthritis: a proof-of-concept study

In this proof-of-concept study, Hsiao et al. evaluated whether a value clarification tool enabling patients to view a set of rheumatoid arthritis (RA) treatment preference phenotypes could be used to support shared decision-making at the point-of-care. The authors conducted a pretest/post-test study. English-speaking patients with RA presenting to their scheduled outpatient visits were asked to participate. Visits for patients with active RA were transcribed. Shared decision-making components were measured using a quantitative coding scheme based on an established model of shared decision-making. Forty-six visits were included in the pretest and 40 in the post-test phases. Providers offered more disease-modifying antirheumatic drugs (DMARDs) (two or more) in the post-test visits (60%) compared to the pretest visits (47.8%). Overall, more patients vocalized their values and/or preferences in the post-test visits compared to the pretest visits for treatment escalation decisions including a choice of one new DMARD (90.9% vs. 56.3%), 2 or more new DMARDs (95.8% vs. 86.4%), as well as prednisone (87.5% vs. 66.7%). Providers were also more likely to base their recommendations on patient values and/or preferences in the post test (100% of six visits) than the pretest (64.3% of 14 visits) phases during visits in which a recommendation was made. The mean length of the visit was 29.9 ± 11.6 minutes and 25.1 ± 10.7 minutes in the pretest and post-test phases, respectively.

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