CME CREDIT ***EDUCATIONAL OBJECTIVE:*** Readers will consider the diagnosis of cannabinoid hyperemesis syndrome in chronic marijuana users who present with nausea and vomiting

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Cannabinoid hyperemesis syndrome: Marijuana is both antiemetic and proemetic

ABSTRACT

Although marijuana is sometimes used to treat chemotherapy-induced nausea and vomiting, when used long-term it can have a paradoxical hyperemetic effect known as cannabinoid hyperemesis syndrome. Knowledge of this phenomenon may reduce the ordering of unnecessary and expensive investigations, as well as inappropriate medical and surgical treatment in patients presenting with recurrent vomiting of unknown cause. This article reviews the pathophysiology, clinical presentation, diagnosis, and management of this emerging condition.

KEY POINTS

The prodromal phase is characterized by severe anxiety and agitation. Patients display a spectrum of autonomic symptoms such as sweating, flushing, constantly sipping water due to thirst, and colicky abdominal pain.

In the second phase, patients develop incapacitating nausea and vomiting that may occur without warning and is usually resistant to conventional antiemetics such as ondansetron and promethazine. During this phase, patients learn the immediate relieving effects of taking hot baths.

After 24 to 48 hours of conservative management, intravenous fluid replacement, and, most importantly, cessation of cannabis use, patients experience marked resolution of symptoms. The compulsive hot-bathing behavior subsides. However, eventually, patients go back to using marijuana, and the cycle of symptoms recurs.

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With the growing use of marijuana, reports have appeared of a newly recognized condition in long-term heavy users termed cannabinoid hyperemesis syndrome.[1]

This syndrome is interesting for at least two reasons. First, paradoxically, marijuana appears to have an emetic effect with chronic use, whereas it usually has the opposite effect and is used as an antiemetic in patients undergoing chemotherapy. Second, patients develop a compulsion to bathe or shower in extremely hot water to relieve the symptoms.

In this article, we review the pathophysiology, clinical presentation, diagnosis, and management of this emerging condition.

MARIJUANA USE ON THE RISE

Marijuana is the most widely used illicit drug worldwide. Although statistics on its use vary, a report from the Pew Research Center[2] stated that 49% of Americans say they have tried it. Several states now allow the use of marijuana for medicinal purposes, and Colorado and Washington have legalized it for recreational use. This marks a major turning point and may accelerate the slow-growing acceptance of marijuana use in the United States.

Marijuana has been used to treat HIV-associated anorexia and wasting, convulsions, glaucoma, headache, and chemotherapy-induced nausea and vomiting.[3–5]

Cannabinoid hyperemesis syndrome was first described in 2004 in South Australia.[1] Since its recognition, an increasing number of

TABLE 1

Proposed diagnostic criteria for cannabinoid hyperemesis syndrome

Essential feature
Long-term cannabis use

Major features
Severe cyclic nausea and vomiting
Resolution of symptoms with cannabis cessation
Relief of symptoms with hot showers and baths
Abdominal pain (epigastric and periumbilical)
Weekly use of marijuana

Supportive features
Age younger than 50
Weight loss greater than 5 kg
Morning predominance of symptoms
Normal bowel habits
Negative laboratory, radiographic, and endoscopic test results

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cases have been identified worldwide. However, there are still no population-based studies to estimate its exact prevalence.

THC is the principal psychoactive component in marijuana

THC PREVENTS VOMITING—AND CAUSES IT

Delta-9-tetrahydrocannabinol (THC) is the principal psychoactive component in marijuana.[6,7] There are two types of cannabinoid receptors in humans: CB1 and CB2. Both are found in the central nervous system and autonomic nervous system. Activation of CB1 receptors is responsible for the psychoactive effects of cannabinoids such as altered consciousness, euphoria, relaxation, perceptual disturbances, intensified sensory experiences, cognitive impairment, and increased reaction time. The physiologic role of CB2 is not known.

THC as an antiemetic

The antiemetic property of THC is not well understood but has been linked to activation of CB1 receptors found on the enteric plexus, presynaptic parasympathetic system, and central nervous system, particularly the cerebellum, hypothalamus, and vomiting center in the medulla.[1,8–12] Stimulation and blockade of CB1 receptors can inhibit and induce vomiting in a dose-dependent manner, implicating endogenous cannabinoids in emetic circuits.[12]

THC as a proemetic

The mechanism of the paradoxical hyperemetic effect of THC is unknown, but several concepts have been proposed.

Chronic cannabis use can lead to down-regulation of CB1 receptors.[13] Simonetto et al[10] suggested that the central effects of long-term cannabis use on the hypothalamic-pituitary-adrenal axis may play a central role in the development of hyperemesis.[10]

Cannabinoids have a long half-life and are lipophilic.[1] When used infrequently, they prevent vomiting. But with chronic use, high concentrations of THC can accumulate in the body, including cerebral fat, and can cause severe nausea and vomiting.[8,9] This paradoxic hyperemesis was observed in people using intravenous crude marijuana extract.[7] The same response was also noted in ferrets injected with 2-arachidonoylglycerol, a potent cannabinoid agonist.[11]

Patients who experience hyperemesis from chronic cannabis use may also have a genetic variation in their hepatic drug-transforming enzymes that results in excessive levels of cannabis metabolites that promote emesis.[1,14]

Delayed gastric emptying has also been linked to the proemetic effect of THC. However, this association became controversial when a large case series study showed that only 30% of patients with cannabinoid hyperemesis syndrome had delayed emptying on gastric scintigraphy.[10]

It is also possible that excessive stimulation of cannabinoid receptors in the gut can cause diffuse splanchnic vasodilation and contribute to the abdominal pain.[13]

DIAGNOSING CANNABINOID HYPEREMESIS SYNDROME

Cannabinoid hyperemesis syndrome is a clinical diagnosis typically seen in young patients (under age 50) with a long history of marijuana use. They present with severe, cyclic nausea and vomiting and admit to compulsively taking extremely hot showers or baths. Most patients report using marijuana for more than

a year before developing episodes of severe vomiting. However, one study found that as many as 32% of patients had used it less than 1 year before experiencing symptoms.[10]

Other associated nonspecific symptoms are diaphoresis, bloating, abdominal discomfort, flushing, and weight loss. Symptoms are relieved with long, hot showers or baths and cessation of marijuana use. Taking a complete history is key to making the diagnosis.

In 2004, Allen et al[1] first defined cannabinoid hyperemesis as excessive marijuana use associated with cyclical vomiting and abdominal pain.[1] In 2012, Simonetto et al[10] proposed diagnostic criteria (**Table 1**). Although not yet validated, these criteria are based on the largest series of cases of cannabinoid hyperemesis syndrome to date (98 patients).[10]

THE THREE PHASES OF CANNABINOID HYPEREMESIS

The clinical presentation of cannabinoid hyperemesis syndrome can be divided into three phases: prodromal, vomiting, and resolution.

Prodromal phase

During this phase, patients often appear anxious and agitated and display a spectrum of autonomic symptoms such as sweating, flushing, and constantly sipping water due to thirst. They may sometimes have abdominal pain that is usually epigastric but may also be diffuse. Their symptoms are associated with severe nausea, usually early in the morning or when they see or smell food. Appetite and eating patterns remain normal. Compulsive hot bathing or showering is minimal at this phase.

Vomiting phase

In this next phase, patients experience incapacitating nausea and vomiting that may occur without warning and are resistant to conventional antiemetics such as ondansetron and promethazine.[14] However, patients eventually learn that hot baths or showers relieve the symptoms, and this behavior eventually becomes a compulsion. The higher the temperature of the water, the better the effect on symptoms.[1] Low-grade pyrexia, excessive thirst, orthostasis, abdominal tenderness, weight loss, and sometimes even superficial skin burns have been reported.[1,9,15–18]

Recovery phase

During the final phase of cannabinoid hyperemesis syndrome, most patients experience marked resolution of symptoms after 24 to 48 hours of conservative management (bowel rest until symptoms resolve, slowly advancing diet as tolerated, intravenous fluids, and electrolyte monitoring and repletion as necessary), and most importantly, cessation of cannabis use. However, the time from cessation of marijuana use to resolution of symptoms may be as long as 1 week to 1 month.[1,10,14] Patients begin to resume their normal diet and daily activities. The bathing-showering compulsion subsides, and patients regain lost weight after 3 to 6 months.[1]

In all case series and reports, resumption of cannabis use causes the symptoms to recur. This recurrence is compelling evidence that cannabis is the cause of the hyperemesis and should be part of the essential criteria for the diagnosis of cannabinoid hyperemesis syndrome.

WHY COMPULSIVE HOT BATHING?

The mechanism behind this unique characteristic of cannabinoid hyperemesis syndrome is not known. Several theories have been suggested, but no study has identified the exact explanation for this phenomenon.[1,9,10,13–15,17–31]

With chronic use, THC can accumulate in high concentrations in the body, including cerebral fat

One suggested mechanism is a response by the thermoregulatory center of the brain to the dose-dependent hypothermic effects of THC, or even a direct effect of CB1 receptor activation in the hypothalamus.[9] Cannabis toxicity could disrupt the equilibrium of satiety, thirst, digestive, and thermoregulatory systems of the hypothalamus, and this interference could resolve with hot bathing.[1]

The so-called "cutaneous steal" syndrome has also been proposed, in which cutaneous vasodilation caused by hot water decreases the blood volume available for the splanchnic circulation thought to be responsible for the abdominal pain and vomiting.[13] The compulsive hot bathing may also be a response by the brain to the anxiety or psychological stress induced by severe nausea and vomiting.[14]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cannabinoid hyperemesis syndrome includes mainly cyclic vomiting syndrome and psychogenic vomit-

ing. A careful history is useful, as is ruling out medication-induced reactions, toxins, pregnancy, and gastrointestinal, neurologic, metabolic, and endocrine causes. All three of these vomiting syndromes can present with a cyclic pattern of nausea and vomiting. Cannabis use is common in all three and so is not helpful in differentiating them. But the characteristic compulsive hot bathing and showering is unique and pathognomonic of cannabinoid hyperemesis syndrome.[32]

Endoscopic examination may reveal esophagitis and gastritis from severe bouts of retching.[26]

Cyclic vomiting syndrome

The Rome III criteria for the diagnosis of cyclic vomiting syndrome include three or more stereotypic episodes of acute-onset nausea and vomiting lasting less than 1 week, alternating with intervals of completely normal health. The criteria should be fulfilled for the previous 3 months with symptom onset at least 6 months before diagnosis.[33]

In a series of 17 patients with adult-onset cyclic vomiting syndrome,[18] the average age at onset was 30, and 13 (76%) of the patients were women. Fifteen (88%) of the patients experienced a prodrome or aura of abdominal pain or headache, and in this group, a trigger such as emotional stress and infection could also be identified in 9 (60%).

In all case series and reports, resuming cannabis use caused the symptoms to recur

Unlike in cannabinoid hyperemesis syndrome, most patients with cyclic vomiting syndrome have a family history of migraine headache, and the prevalence of psychological stressors is high.[31] Also, patients with cannabinoid hyperemesis syndrome do not respond to medications that usually abort migraine episodes,[15] whereas patients with cyclic vomiting syndrome, especially those who have a family history of migraines, may respond to antimigraine medications such as triptans. There is evidence of clinical psychological overlap between cyclic vomiting syndrome, abdominal migraine, and migraine headaches. Some authors recommend antimigraine therapy even in the absence of a family or personal history of migraine if, after a careful history and physical examination, the diagnosis of cyclic vomiting syndrome seems likely. Moreover, nonmedical management such as sleep, dark rooms, and quiet environment are not as effective in cannabinoid hyperemesis syndrome as they are in cyclic vomiting syndrome.[18]

Psychogenic vomiting

Psychogenic vomiting is classically defined as vomiting caused by psychological mechanisms without any obvious organic cause.[13] It occurs most commonly in patients with major depressive disorder or conversion disorder.[34] The mechanism appears to be a combination of past organic or gastrointestinal functional abnormalities and emotional problems, and multiple patterns of vomiting can occur. Most of these patients can be treated with behavioral therapy, antidepressant drug therapy, and supportive psychotherapy.[34,35]

ASKING A SERIES OF QUESTIONS

Most patients with cannabinoid hyperemesis syndrome have a history of frequent visits to emergency departments or clinics for persistent nausea and vomiting, and they may have undergone extensive diagnostic workups to exclude structural, inflammatory, infectious, and functional diseases of the bowel.[23,24]

To prevent unnecessary testing and use of healthcare resources, Wallace et al[32] proposed an algorithm to help guide clinicians in diagnosing and treating patients with suspected cannabinoid hyperemesis syndrome. A patient presenting with severe nausea and vomiting should prompt a series of questions:

Do the signs and symptoms suggest a severe underlying medical cause? If so, this should be pursued.

Do symptoms improve while taking a hot shower or bath? If not, pursue an appropriate diagnostic evaluation and treatment for conditions other than cannabinoid hyperemesis syndrome.

Is the bathing compulsive? If not, consider other diagnoses, but remain suspicious about cannabinoid hyperemesis syndrome.

Does the patient currently use cannabis daily or almost daily, and has the patient done so for at least the past year? If the patient denies using cannabis, a urine drug screen for THC may be useful. If the patient admits to use, a presumptive diagnosis of cannabinoid hyperemesis syndrome can be made.

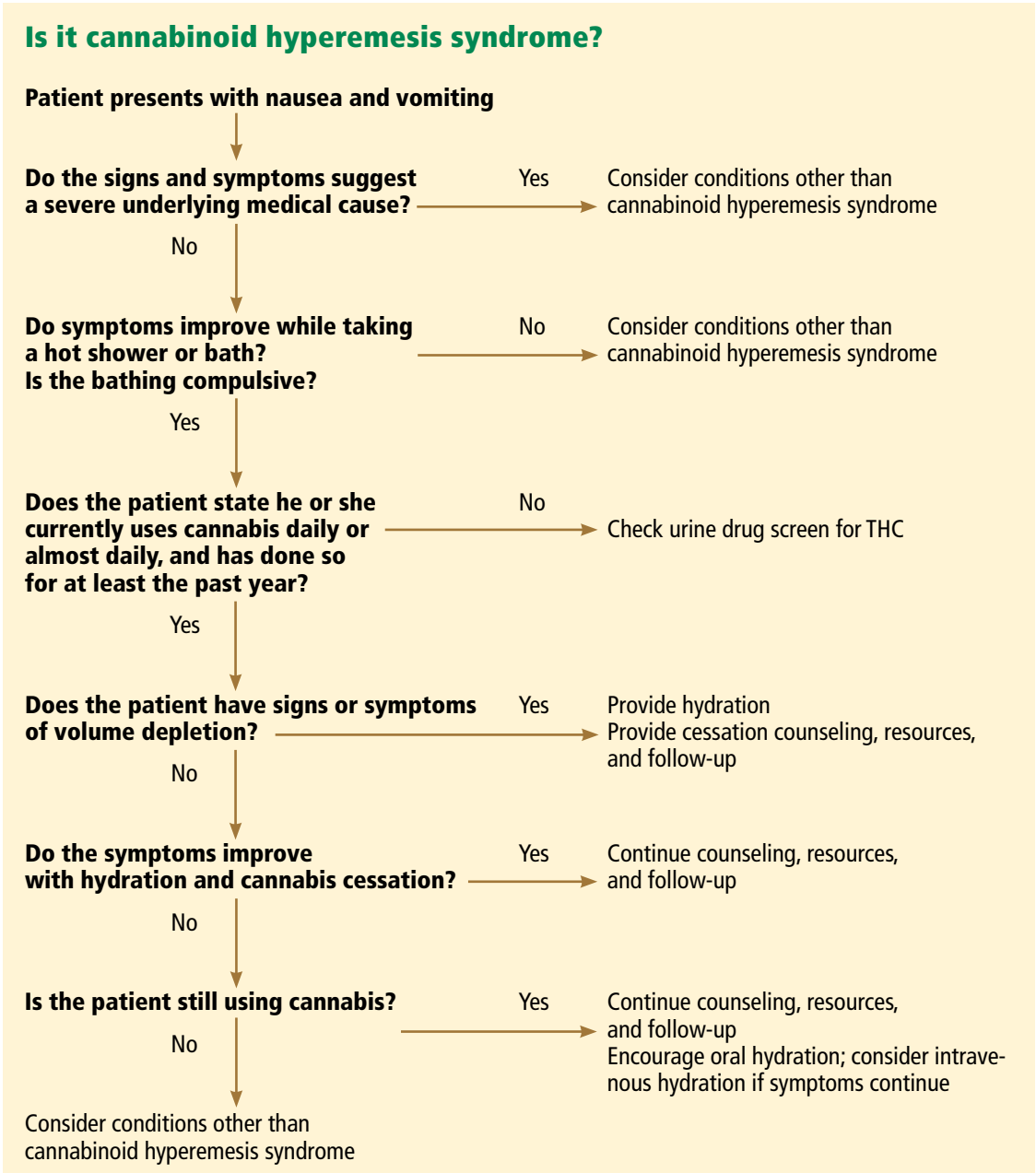

FIGURE 1

Does the patient have signs or symptoms of volume depletion, or is the patient unable to tolerate oral hydration? Encourage oral hydration or provide intravenous hydration, and provide cannabis cessation counseling.

Do the symptoms improve? If yes, great! Provide cessation counseling, resources, and follow-up. If not:

Is the patient still using cannabis? If not, it is time to rethink the diagnosis.

Treatment in the acute setting is supportive and includes intravenous hydration and correction of electrolytes. Conventional antiemetics such as ondansetron, metoclopramide, prochlorperazine, and promethazine have not been effective in relieving hyperemesis.[9,12,14] This implies that the mechanism of emesis likely does not involve dopaminer-

gic and serotonin pathways in the central and autonomic nervous systems.

Cessation of cannabis use is key for long-term resolution of symptoms. Efforts should be made to provide counseling and encourage patients to stop using the drug entirely (**Figure 1**).

SOMETHING TO THINK ABOUT

With the high prevalence of chronic cannabis abuse and the recent legalization of recreational marijuana use, we will all likely encounter a patient with cannabinoid hyperemesis. With adequate knowledge of this phenomenon, we can avoid unnecessary workups and inappropriate medical and surgical treatment in patients presenting with recurrent vomiting of unknown cause. The diagnosis can easily be made by simply asking for a history of chronic marijuana use and symptoms related to cannabinoid hyperemesis syndrome, such as relief of symptoms with hot baths or showers and with marijuana cessation.

Conservative management and fluid resuscitation is important in the acute setting, but cessation of marijuana use and follow-up counseling are the key components for treating patients with cannabinoid hyperemesis syndrome and for preventing recurrence.

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