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Review

Cannabis Hyperemesis or Cyclic Vomiting- A Comparative Literature Review

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Abstract

Introduction: Gastrointestinal functional disorders are based on gut-brain axis dysfunction and have overlapping symptoms. This review demonstrates a diagnostic dilemma in the patients presenting with chronic cannabis use and hot bathing behavior, prompting a diagnosis of Cannabis hyperemesis syndrome (CHS). It highlights the lack of guidelines generally used for diagnosis and even the drawback of the Rome criterion with a requirement of improvement with cessation, which does not allow a diagnosis at the initial visit. Some patients get ultimately diagnosed with Cyclic vomiting syndrome (CVS) which is overlapping disorder often ignored in cannabis smokers. **Methods:** The authors reviewed databases including PubMed and Cochrane to look at reviews published in the last 5 years proposing guidelines for diagnosis, postulating shared pathophysiology based on animal/human studies and consolidated the treatment protocols. **Discussion:** The signs and symptoms of the diseases highly overlap. This occurs due to the internal endocannabinoid system with CB1 receptor stimulation leading to improvement in nausea but persistent use leading to possible contrary effects or receptor downregulation. Rome criterion, used for diagnosis and CVS includes acute stereotypical vomiting episodes with 3 episodes in a year and 2 in 6 months preceding diagnosis and relative symptom-free interval, supported by personal or family history of migraines whereas CHS has CVS-like episodes, cannabis use and improvement on cessation in criterion with hot showers as support. Thangam et al proposed a better criterion with at least one year of >4 times/week cannabis use and 6 months of cessation to allow washout. Lastly, treatment includes cannabis cessation, anti-emetics including ondansetron, and even aprepitant. Sumatriptan has been used as a good abortive agent as well. For maintenance of remission, coenzyme Q, tricyclic antidepressants and topiramate has shown promise. Lifestyle modifications and therapy are adjuvants. **Conclusion:** Gut brain axis is complex and leads to overlap in presentation and delayed diagnosis. Using defined criterion is the key for diagnosis and treatments though less studied have been postulated and can be used as per limited data available. The underlying case and review show the similarities and differences between cyclic vomiting and cannabis hyperemesis while touching upon pathogenesis and treatments. It also focuses on the prevalence of cannabis use in patients with cyclic vomiting and the role of the endocannabinoid system in the pathogenesis of both diseases.

Keywords: cannabis hyperemesis; cyclic vomiting; amitriptyline

Introduction

Cyclic Vomiting Syndrome (CVS) and Cannabis Hyperemesis Syndrome (CHS) are two functional gastrointestinal conditions characterized by recurrent episodes of severe nausea and vomiting. CVS has long been recognized as a functional gastrointestinal disorder, while CHS has emerged more recently in association with chronic cannabis use. Despite their apparent differences, emerging evidence suggests an intriguing overlap between these syndromes, hinting at a shared pathophysiological spectrum.

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CVS is marked by, episodes of intense nausea and vomiting, often accompanied by abdominal pain. The condition predominantly affects children but can persist into adulthood. Asymptomatic intervals follow episodes. CHS, in contrast, is linked to chronic cannabis use and manifests as cyclical episodes of severe nausea and vomiting. Individuals affected by CHS often find temporary relief in hot showers or baths. The pathophysiology of CHS is not fully understood, but it is believed to involve dysregulation of the endocannabinoid system, which might also play a role in the former.

Discussion and Literature Review

It is tough to differentiate between CHS and CVS. Generally, patients get an initial diagnosis made by hot showering behavior and cannabis use. Interestingly, no formal criterion is used for the diagnosis. 33% of patients were diagnosed with CHS based on marijuana use and intractable vomiting [1].

CHS has a Rome criterion for diagnosis and a separate, more refined criterion proposed by Thangam et al [2] as shown in Tables 1 and 2.

Table 1

Rome criterion for CHS
Stereotypical episodic vomiting resembling (CVS) in terms of onset, duration, and frequency
Presentation after prolonged, excessive cannabis use
Relief of vomiting episodes by sustained cessation of cannabis use
Supportive remarks:
May be associated with pathologic bathing behavior (prolonged hot baths or showers)
Criteria fulfilled for the last 3 months, symptom onset at least 6 months before diagnosis

Table 2

Criterion per Thangam et al	
Clinical features	Stereotypical episodic vomiting resembling CVS in terms of onset, and frequency ≥3 episodes a year
Cannabis-use patterns	Duration of use >1 y preceding onset of symptoms Frequency of use >4 times a week on average
Cannabis cessation	Resolution of symptoms should follow a period of cessation from cannabis for a minimum of 6 mo or at least equal to a duration that spans three typical cycles in an individual patient

Table 3

Rome criterion for CVS

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Stereotypical episodes of vomiting regarding onset (acute) and duration (less than 1 week)
At least three discrete episodes in the prior year and two episodes in the past 6 months, occurring at least 1 week apart
Absence of vomiting between episodes, but other milder symptoms can be present between cycles
Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
Supportive remark- History or family history of migraine headaches

The former includes episodes of vomiting resembling CVS in duration and onset; secondly, cannabis use; and lastly, improvement with cessation. Hot showers were supporting evidence. It had to start 6 months before diagnosis and meet the criterion for 3 months. Limitations of this criterion include no mention of the duration of onset of cannabis use and duration of cessation. The criterion by Thangam et al is more detailed with 3 episodes needed in a year, one year of cannabis use >4 times in a week, and a minimum of one year or 2-3 cycles of cessation to make the diagnosis. It is always important for cannabis use to predate symptom onset. A prolonged 2- to 3-month elimination period due to lipophilic storage of cannabis chronic use. This duration of time may still be insufficient as restoration of cannabinoid receptor function may take even longer. Thus, a minimum of three typical cycles or 6-12 months is needed to determine whether cessation results in symptom resolution.

Hot showers, even though thought to be diagnostic, only hold a supportive role in diagnosis. Moreover, in studies, up to 10% of patients did not demonstrate showering behavior, whereas in another, half of patients with CVS had similar behavior compared to three fourths with cannabis use [3,4].

Patients might start smoking marijuana as a measure of relief from the vomiting. This sparks contrast to the concept of CHS. This can be partially explained by the pathophysiology behind the role of cannabis in nausea and vomiting. The endocannabinoid system has CB1R and CB2R, with the former being more prominent [5]. Stimulation of the receptor with endocannabinoids throughout the central and peripheral nervous system, especially vagal nuclei, decreases emesis, and it has been seen that antagonism of these receptors has been shown to induce vomiting [5–7]. Endocannabinoids and even cannabis, which is a major component in marijuana, have agonistic activity on these receptors. Hence, it is responsible for anti-emetic effects. It has been postulated that a bimodal effect of marijuana might exist, especially at higher doses. Another observation is that the downregulation of CB1R with increasing doses and developing tolerance might play a key [8].

Cannabinoid hyperemesis shares symptomatology with cyclical vomiting syndrome. It is more common in men likely due to more cannabis use. The role of the endocannabinoid system has been seen in cyclic vomiting as well. This suggests that CHS is a subset of CVS rather than being a separate entity. This overlap has led to confusion in diagnosing patients with one or the other. Hospital studies have shown that one-third of patients admitted with nausea and vomiting were diagnosed with CHS but only 7% of them met the Rome criterion [9]. It is interesting to note that the odds of cannabis use in CVS is three-fold since the legalization of cannabis use [10], hinting towards a spectrum of disease with CVS and CHD at ends, where some patients with CVS, without any cannabinoid use, are entirely based on environmental and genetic factors. The other end is cannabis-induced ECS pathway dysregulation triggering the CVS subset called CHS. Triggering CVS by cannabis without meeting the full criterion for CHS lies somewhere in the spectrum as well. The association can also be attributed to the initial anti-emetic effects of cannabis.

Therapies that are beneficial as preventative in CVS have shown efficacy in CHS. These therapies include amitriptyline. It is a first-line preventative treatment for migraines. Migraine headaches are very strongly associated with the CVS/CHS spectrum of diseases, with migraine seen in at least first

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or second-degree relatives. It is unclear if the management of migraine controls the symptoms of CVS. CVS spectrum is also closely associated with psychiatric disorders [11]. Many CVS patients exhibit autonomic dysregulation, including postural tachycardia or orthostatic hypotension [12].

So, the other end of the spectrum, CVS, is diagnosed with its own Rome criterion with acute onset of at least three episodes in the last year with two in 6 months, at least one week apart, absence in between episodes, and supported by personal and family history of migraines. It is important to rule out other causes necessitating a full workup with CBC, Liver and Kidney function, Lipase, CT abdomen and pelvis, RUQ ultrasound, and EGD. EGD helps rule out volvulus which can present with severe retching and vomiting but might mislead with pre-existing gastritis or ulcer [13]. Gastric emptying study is generally normal in the patients [14].

CVS progresses from a prodrome characterized by nausea, hot or cold slashes for one to two days followed by a week-long vomiting occurring 1 to 6 times/hour, persisting as retching with patients trying to induce vomiting even if the stomach has been completely emptied [15]. Patients have abdominal pain in three-fourths of the cases; migraines might present during these days [15]. Then patients start tolerating food, and emesis halts, followed by a period of normalcy.

Once the organic diagnosis is ruled out and CVS is diagnosed, severity should be established. Mild disease involves<4 episodes/year brief episodes <2 days and quick recovery. It improved with abortive therapy including triptans, ondansetron and antihistamines. On the other hand, severe episodes include one of >4 eps/day, longer episodes >2 days and longer recovery requiring prophylactic treatment [13].

For now, the cornerstone of prophylactic treatment, anti-epileptics, most notably TCA derives evidence based on current studies. Hejazi et al demonstrated a marked reduction in the number of CVS episodes from 17 to 3, in the duration of a CVS episode from 6 to 2 days in an OL study of 46 patients [16]. Kumar et al. had similar positive results [17]. The mean effective dose in adults is 75-100 mg daily, but most studies use 10 mg - 25 mg. It can be titrated per patient response [17].

Topiramate is an alternative prophylactic medication. Studies show that topiramate is effective in preventing migraine headaches, with limited evidence. One major pediatric study with topiramate found that 81% remission, 13% showed at least ≥50% reduction in the number of episodes, and only 6% did not respond [18]. Topiramate at 25 mg daily with up-titration by 25 mg each week to a target dose of 100 mg daily is recommended.

Other antiepileptics including zonisamide or levetiracetam as prophylactic therapy in CVS have shown complete response in one-fourth and partial response in the rest of the patients [19]. Dosages are similar to anti-epileptic doses with titration per patient response [19].

Enzyme Q10 (Co-Q10), a part of the mitochondrial respiratory chain has shown efficacy in migraine prophylaxis. The prophylactic treatment of CVS with Co-Q10 showed overall efficacy of 68%, in a survey in patients with CVS [20].

Abortive medications include ondansetron, aprepitant, and triptans. Ondansetron is a selective 5-HT3 receptor antagonist on the vagus peripherally and centrally in the chemoreceptor trigger zone (CTZ) [13].

Based upon low-quality evidence in children, aprepitant as a potentially effective agent was proposed by Thangam et al [13]. The recommendation was based on a study on children and adolescents where they received 125 mg during prodrome followed by 80 mg daily for 2 days. At 52-week follow-up, the regimen significantly reduced the duration of episodes from 5 days to 1 day, the amount of emesis from 9 to 4 times per hour, and the number of hospital admissions from 9 to 2.5 [21].

For sumatriptan, the efficacy appears to diminish after the first 60 minutes. A dosage of 20 mg nasal or 6 mg subcutaneous is recommended. If there is no response or inadequate response, repeat dose can be administered as early as 2 hours. This has been proposed for CVS is needed, making it an abdominal migraine-like entity [13,22].

Lastly, CVS occurs due to altered brain-gut interaction, often triggered by stressors and lifestyle modifications, including diet patterns, activity and therapy might help [23].

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Conclusion

In patients with functional gastrointestinal disorders, the Rome criterion is the backbone for diagnosis. Diagnosing based on common features like bot baths has led to misdiagnosis in patients with either CHS or CVS. Despite the problem with the diagnosis, pathophysiology, and medical therapy are similar and tailored on a case-to-case basis. Cannabis cessation is always recommended even in patients who claim to have started it for improvement. CHS and CVS appear to be on a spectrum with patients distributed at different points during presentation.

This series has previously been submitted as a letter to the editor prior to the full manuscript. [24] creation.

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