CASE REPORT

Cannabinoid hyperemesis syndrome: a guide for the practising clinician

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SUMMARY

Cannabis is the most widely used illicit drug in the world. The medicinal value of cannabis as an antiemetic is well known by the medical fraternity. A less well-recognised entity is the potential for certain chronic users to develop hyperemesis. We describe the case of a young man who presented to us with features of cannabinoid hyperemesis syndrome. We review the current literature on this condition, its pathogenesis and management.

BACKGROUND

The adverse physical and psychological effects of cannabis are well documented. It is only recently that the effects of the world's most commonly abused drug on the gastrointestinal (GI) system have begun to be explored. One such adverse effect includes cannabinoid hyperemesis syndrome (CHS), which still remains an unfamiliar clinical entity among physicians worldwide. At the height of such curiosity sits the paradox of vomiting being caused by a substance most famously linked with its strong antiemetic properties. The mystery is further added to by the unexplained pathognomonic phenomenon of improvement of symptoms by compulsive hot bathing. Few clinicians are aware of this syndrome or its management. This comes at a time when illicit and medicinal cannabis and its compounds are being increasingly consumed by recreational users and patients alike. We describe a case of CHS and provide a literature review of this condition. We aim to promote recognition of the condition and to highlight the importance of patient education in its management.

CASE PRESENTATION

A previously healthy young Caucasian man was admitted to our hospital, with a 3-month history of intermittent profuse vomiting. Episodes of vomiting, which would occur roughly every 2 weeks and last up to 2 h, were accompanied by abdominal cramps, diaphoresis and loose stools. His vomiting could occur up to 20 times/day when symptomatic. He was asymptomatic between episodes. His symptoms were worse in the morning and were relieved by showering. He denied any mucous or per rectal bleeding. There was no relevant family history. Weight loss of up to 5 kg was reported during symptomatic periods. The patient had been smoking 1.5 g of cannabis per day regularly for the last 4 years. He consumed <10 units of alcohol per week. There were no features to suggest the presence of an eating disorder. His vital signs were

normal, with only mild generalised tenderness on abdominal examination. Haematological analysis was unremarkable except for mild leucocytosis ($12.3 \times 10^9/L$). All other investigations were negative (stool culture, coeliac screen, abdominal X-ray, upper and lower endoscopies with biopsies and CT of the head). Management involved the provision of intravenous fluids, antiemetics (metoclopramide) and liaison with the patient's general practitioner (GP) to refer him to community substance abuse services. On discharge, the patient continued to use cannabis and presented to the emergency department (ED) 3 days later with recurrence of his symptoms. He revealed a resolution of his symptoms following cannabis cessation and counselling, and remained asymptomatic at 6-week follow-up.

INVESTIGATIONS

Biochemical and haematological investigations were normal, except for mild leucocytosis (white cell count $12.3 \times 10^9/L$). Stool culture and coeliac screen were negative. Oesophagogastroduodenoscopy and flexible sigmoidoscopy investigations did not reveal any pathology, with normal D2, sigmoid and rectal biopsy results. Abdominal X-ray and CT of the head failed to show either a mechanical or intracranial cause, respectively. The above tests demonstrate the overinvestigation common to this condition; a strong history of symptoms synonymous with CHS may be all that is required to achieve its diagnosis. Obtaining biochemical tests of renal function is necessary to rule out acute renal failure, which has been shown to occur in these patients.^{1–5}

Causes for renal failure may be due to multiple episodes of vomiting, the dehydrating effects of repeated hot bathing and poor oral intake when symptomatic.¹ In cases where CHS is suspected but where the patient denies using cannabis, a urine toxicological screen may be useful to aid diagnosis of this condition. It must be noted that tests for urinary tetrahydrocannabinol (THC, the active compound in cannabis) will prove negative in instances where users have been taking synthetic cannabinoids, which are also capable of causing CHS. This highlights the need to ask about the precise form of the cannabinoid substance during history taking.

DIFFERENTIAL DIAGNOSIS

Following the exclusion of more sinister pathology, the main differential diagnoses includes CHS, cyclical vomiting syndrome (CVS) and psychogenic vomiting (PV). Diagnostically, there is a significant overlap between these conditions in that they all

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present with repeated bouts of vomiting. What distinguishes CHS from the former remains the pathognomonic behaviour of hot bathing and history of chronic cannabis use. According to the Rome criteria, a personal or family history of migraine or presence of psychological comorbidities tend to support a diagnosis of CVS.⁶ These features were all absent in our patient. Apart from vomiting, no other features of PV, which is thought to be a resurfacing of a childhood tendency to vomit, were present. Although the lower GI symptoms experienced by the patient are not common in CHS, these were more likely to represent the autonomic symptoms seen frequently in such patients. Misidentifying CHS for other vomiting syndromes holds the potential to perpetuate the problem, for which the only solution is cannabis cessation.

TREATMENT

The patient was treated with vigorous rehydration and antiemetics (metoclopramide), and was provided with cannabis cessation advice. His GP was asked to refer the patient to his local community substance abuse service. Six week gastroenterology outpatient follow-up was arranged for a review of his symptoms.

OUTCOME AND FOLLOW-UP

Telephone follow-up 4 weeks postadmission revealed that the patient had had a further ED admission 3 days after discharge, when he reported that he was still smoking cannabis. He attributed a lack of understanding of the association between his cannabis use and vomiting as the main reason for continuing to use the drug. Following appropriate information given about CHS, the patient ceased to take cannabis and remained asymptomatic at his 6-week clinic appointment.

DISCUSSION

The term CHS was first coined by Allen *et al.*,⁷ when he described a case series of nine chronic cannabis users who all displayed a cyclical vomiting-like illness. Since then, there has been debate as to whether such cases belong to a subset of patients whose primary condition is CVS, or whether they represent a separate clinical entity altogether.⁸ This diagnostic overlap arises from the fact that 53% of patients with CVS were also found to use cannabis.⁹ There is still a paucity of literature around CHS, which, given the prevalence of cannabis use worldwide, makes us wonder whether frank underdiagnosis exists.⁸ Lack of physician awareness and diagnostic confusion can lead to patients self-medicating with cannabis, resulting in a vicious cycle.

DIAGNOSIS

Sontineni proposes diagnostic criteria that include the essential feature of chronic cannabis use and major features of: recurrent nausea and vomiting that resolve after cannabis cessation, relief of symptoms with hot bathing, abdominal pain and weekly marijuana use.¹⁰ Supportive criteria have been suggested by Simonetto *et al.*,¹¹ and include: age <50 years, weight loss of >5 kg, morning predominance of symptoms, normal bowel habits, and negative laboratory, radiographic and endoscopic test results. Simonetto *et al.*¹¹ go further by characterising the abdominal pain, which is often reported to be periumbilical or epigastric, and colicky or crampy in nature. Over-investigation and unnecessary exposure to ionising radiation is common in these patients.¹² This is exacerbated by their frequent attendance to the ED. We propose that the lower GI symptoms experienced by the patient may have been the consequence of an

autonomic response and as such should not deter a diagnosis of CHS. A dominance of lower GI symptoms or clear features synonymous with a lower GI pathology would make CHS increasingly unlikely, however.

PATHOPHYSIOLOGY

Hyperemesis

There have been several proposed theories to explain how a drug renowned for its antiemetic effect causes hyperemesis. These stem from our pre-existing knowledge of cannabinoid receptors (CB1 and CB2); CB1 receptors are concentrated in the central nervous system (CNS) and the enteric nervous system, while CB2 receptors are found mainly in glial cells, where they may have an immunomodulatory role.⁸ Over-riding of THC action on CNS receptors by its effect on the gut has been the most widely used theory to explain the hyperemesis response in CHS.¹³ The hypothesised net effect is reduced GI motility and emesis. It has been proposed that the long half-life and lipophilic nature of THC may explain hyperemesis in susceptible individuals in whom toxic levels accumulate.⁷

Relief by hot water bathing

Theories to explain the learned behaviour of hot water bathing have included anatomical and more elaborate explanations. It is known that the endocannabinoid system plays a role in the modulation of neuroendocrine function by way of CB1 receptors in the hypothalamus pituitary–adrenal axis.¹⁴ Proposed direct CB1 activation by THC in the hypothalamus is one mechanism of explaining core body temperature changes.¹³ The ‘cutaneous steal syndrome’ proposes that bathing in warm water diverts the blood from the gut to the skin, thus remedying the symptoms of hyperemesis.¹³

MANAGEMENT

Beyond the treatment of the complications of recurrent vomiting, which necessitate fluid resuscitation, the management of CHS is poorly understood. Greatest symptomatic relief is achieved by hot bathing, which is often impractical, and the effects of which are short lived. Antiemetics, although not discouraged, have not shown great efficacy in CHS.¹⁰ Opioids should be used with caution due to their own ability to cause emesis. Benzodiazepines, such as lorazepam, may be of potential benefit in the treatment of CHS.⁷ This drug class may have the ability to avert cannabis withdrawal syndrome, reduce psychological cravings and improve appetite in those patients with strongly conditioned food aversion.^{7 15} We suggest a cautious and limited approach to the prescribing of benzodiazepines in view of their misuse potential in a patient cohort already known to misuse an illicit substance. Weight should be monitored in patients with CHS and enteral feeding considered in severe cases. The ubiquitous finding that most of the symptoms of CHS resolve after 3–4 days is testimony to the importance of cannabis cessation in its management. This is further supported by a widely reported return of symptoms on re-establishment of cannabis use. Admission to hospital itself can act as a treatment method, as patients are unavoidably abstinent from cannabis during this period. Prevention of relapse may require challenging misconceptions about the antiemetic effects of cannabis and reiterating the high relapse rates if patients return to their previous activity.^{16 17} This may be achieved most effectively by the referral of patients with CHS to community substance abuse services. Under such settings, urinary drug screening may be of benefit in monitoring patients’ abstinence from cannabis and correlating this with their clinical course.⁷

FURTHER RESEARCH

Greater understanding of the endocannabinoid system in humans is needed to aid our understanding of the pathophysiology of this condition. More robust studies are needed and should include a greater follow-up of patients diagnosed with CHS. A lack of epidemiological data on the incidence and prevalence of CHS among chronic cannabis smokers may reflect an under-reporting of this condition.⁸ Conversely, genetic polymorphisms in P450 enzymes responsible for cannabinoid metabolism could explain the rarity of the condition despite widespread cannabis use.¹⁸ Lastly, crude cannabis is constituted of over 60 compounds. It is therefore incorrect to assume that THC alone is responsible for hyperemesis, and further analysis may be required.

Learning points

- Greater physician awareness of cannabinoid hyperemesis syndrome can expedite its diagnosis, avoid over investigation and improve the doctor-patient relationship.
- Taking a comprehensive drug history in all patients presenting with abdominal symptoms is essential.
- Cannabis smoking cessation advice, with adequate explanation of the drugs ability to cause hyperemesis, is key to its management.
- Early referral to substance abuse services can help reduce relapse among this difficult to treat cohort of patients.

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