Cannabis hyperemesis syndrome in type 1 diabetes: sheep in a wolf's clothing?

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Cannabis is the most commonly used illicit drug in New Zealand. New Zealand's use of cannabis peaked during lockdown, according to data published by the New Zealand Drug Foundation, making New Zealand's rate of use of cannabis the highest in the Western world. Evidence from longitudinal studies carried out in Dunedin and Christchurch indicates that by the age of 25, 80% of New Zealanders will have tried cannabis at least once,[1] and after adjustments for age and gender differences, Māori are reportedly twice as likely to use cannabis compared to non-Māori.[2] Chronic cannabis use is well-known to be associated with severe adverse health outcomes affecting mental health, cognition and respiratory and gastrointestinal systems.[1] Cannabis hyperemesis syndrome (CHS) is a condition that leads to recurrent episodes of vomiting and abdominal pain that occurs in long-term users of marijuana. Diabetic gastroparesis (DGp) affects about 40% of patients with type 1 diabetes and commonly occurs in people who have had diabetes for over ten years alongside other established microvascular complications.[3] Typical symptoms include early satiety, nausea, vomiting and weight loss, which result in frequent presentations to the emergency department (ED). The existing literature indicates that 10–30% of youth and young adults with type 1 diabetes report ever using cannabis.[4] Cyclical vomiting due to gastric dysmotility in diabetic patients who are also cannabis users is frequently misdiagnosed as DGp. Gastric emptying studies often cannot differentiate between the two conditions, as chronic cannabis use can result in varying degrees of delayed gastric emptying.[5] Autonomic dysfunction causing gastroparesis in type 1 diabetes is a devastating diagnosis. Traditional management strategies are generally unsatisfactory, and advanced treatment options like gastric neurostimulation are not readily available in many centres.

This case series will hopefully raise awareness about CHS among clinicians who frequently assess patients with type 1 diabetes presenting with cyclical vomiting and DKA.

Case 1

A 31-year-old Caucasian male presented to the emergency department with abdominal pain, vomiting and diarrhoea. His past medical history included a diagnosis of type 1 diabetes at the age of two and proliferative diabetic retinopathy. He was on a basal-bolus insulin regime and had an Hba1c in the range of 58–64mmol/mol. He had a history of 15 presentations to ED in the past nine years with recurrent vomiting, at times associated with DKA. His symptoms were attributed to gastroparesis secondary to long-standing diabetes. An upper gastrointestinal endoscopy, barium swallow, CT abdomen and gastric emptying study were all normal. He was a cannabis user but denied any association between smoking cannabis and his symptoms of cyclical vomiting. With good support from the dieticians and diabetes team, he completely stopped cannabis use in 2019. He did not present to ED with cyclical vomiting, and reported quick recovery from infrequent episodes, until this year, when he unfortunately restarted smoking cannabis. Cyclical vomiting recurred and the diagnosis of CHS was confirmed.

Case 2

38-year-old Māori woman with type 1 diabetes had multiple presentations to ED with vomiting and DKA. She had poorly

controlled diabetes for 28 years with a Hba1c of 112mmol/mol and a history of non-adherence to treatment. She had retinopathy, nephropathy and been labelled with DGp. She previously had normal upper-gastrointestinal endoscopy and abdomen X-rays. The gastric emptying study showed a long lag phase for gastric emptying and delayed initial emptying. Nasogastric tube feeding failed due to intolerance, and therefore she was treated with prokinetics and anti-emetics. During one of the presentations, a urine drug screen was requested, and the results were positive for cannabis. With the help of a multi-disciplinary team, she was educated on the adverse effects of cannabis use in type 1 diabetes and about the risks of DKA. This resulted in her successfully quitting cannabis, which helped improve compliance to treatment and dropped her Hba1c to 79mmol/L. Her symptoms resolved.

Case 3

28-year-old Caucasian woman had 20 presentations to ED in the past year with cyclical vomiting and abdominal pain. She was diagnosed with type 1 diabetes at age 17 and had variable control and compliance to treatment. Her Hba1c ranges between 64–70mmol/mol but there were no microvascular or macrovascular complications of diabetes. She also had a chronic history of anxiety and depression and was previously under the care of community mental health services. She smoked cannabis frequently to help improve her appetite and weight. Due to erratic eating habits (munchies) without bolusing, she often got ketoacidosis, which resulted in further weight loss. With support from gastroenterologists, she was treated with nasogastric feeding along with prokinetics, antidepressants (sertraline, quetiapine, mirtazapine and fluoxetine) and dietary modifications. This failed to achieve remission of symptoms, and she continued to present to ED with vomiting and DKA. A gastric emptying study demonstrated markedly delayed emptying consistent with moderate to severe gastroparesis. A trial of haloperidol was considered but not commenced due to the risk of previously reported suicidal ideations. Despite multiple attempts with heavy input from dieticians, gastroenterologists, psychiatrists and the diabetes team, she could not quit cannabis and remains significantly symptomatic with cyclical vomiting and severe mental health issues.

Discussion

Cannabis hyperemesis syndrome, once thought to be a rare condition, is becoming increasingly common due to the widespread availability of cannabis and a favourable public opinion about its healing effects on various medical conditions. Allen and colleagues reported the first published case series of CHS in Australia in 2004, which were followed by several other published case reports. The true prevalence of CHS in New Zealand is primarily unknown due to most cases often being misdiagnosed or not brought to medical attention. It may also be possible that some clinicians and cannabis users have not heard of CHS as a clinical entity and remain unaware of the diagnostic criteria and treatment options. Given the recent political shift for legalisation of cannabis in New Zealand, there is a renewed interest in understanding CHS.

CHS is an important differential diagnosis of cyclical vomiting syndrome. It should be considered in all cannabis users presenting with recurrent symptoms of abdominal pain, weight loss, intractable vomiting and compulsive bathing. Some studies report an average duration of 16 years of regular marijuana use before developing emesis symptoms.[6] In contrast, one study reported the development of an acute illness with multisystem involvement after a single injection of crude marijuana extract.[7]

The mechanism by which cannabis induces hyperemesis is currently unknown, which adds to the complexity of diagnosis. It is hard to fathom how a drug that is often used to treat intractable nausea can also cause such severe vomiting. A recent review has explored numerous potential explanations regarding various pharmacokinetic and pharmacodynamic factors of cannabinoids.[5] Tetrahydrocannabinol (THC), which is lipophilic with its widespread distribution, tends to sequester in fat and contributes to its long half-life and thus potential toxicity.[8] Another proposed explanation is that, in susceptible individuals, the pro-emetic effect of cannabis on the gut (eg, delayed gastric emptying) overrides its anti-emetic CNS

properties.[6] This hypothesis is supported by the demonstration of delayed gastric emptying on gastric emptying scintigraphy in some cases.[7]

CHS is typically characterised by a prodrome of early morning nausea and abdominal discomfort, during which patients may increase cannabis use to relieve nausea. A hyperemetic phase follows with intense and persistent vomiting, significant weight loss and compulsive warm bathing behaviour to alleviate symptoms. If complete cessation of cannabis is achieved, a recovery phase follows with a total resolution of symptoms within 12 hours to three weeks, and a normal eating pattern resumes.[9]

In 2009, Sontineni proposed initial diagnostic criteria for CHS, which Simonetto modified later, in 2012.[10] This was followed by many authors suggesting diagnostic criteria with varying degrees of overlap, which has resulted in inconsistency with the diagnosis. A recent systematic review summarises the published diagnostic criteria and proposes an individualised diagnostic approach that may increase sensitivity in identifying CHS patients.[11] Rome IV Diagnostic Criteria is widely used to assist in diagnosing CHS but is under-utilised in patients with diabetes.

1. Criteria fulfilled for the last three months with symptom onset at least six months prior to diagnosis and may be associated with pathologic bathing behaviour (prolonged hot baths or showers).
2. Stereotypical episodic vomiting resembling cyclic vomiting syndrome (CVS) in terms of onset, duration and frequency.
3. Presentation after prolonged excessive cannabis use.
4. Relief of vomiting episodes by sustained cessation of cannabis use.

Although a definitive duration of cannabis use is not well described, the diagnosis must be made in the setting of habitual cannabis use even if using for less than a year.[10]

Abstinence from cannabis has been shown to completely resolve symptoms of CHS in several studies.[10,12] In an emergency setting, the initial step is to exclude other conditions causing cyclical vomiting, including hyperemesis gravidarum, Addison's disease, DKA and psychogenic vomiting. If there is a history of cannabis use and the patient meets Rome IV criteria, a diagnosis of CHS can be made and rehydration should be commenced in a calm environment. Studies on the effectiveness of supportive therapy in the care of CHS patients are limited; however, intravenous antiemetics like ondansetron and topical capsaicin have been traditionally used to control symptoms in the acute phase.

Off-label use of haloperidol is proposed as a rescue medication in the acute treatment of CHS in multiple published case reports. A recent randomised triple-blinded crossover trial identified low-dose intravenous haloperidol (0.05mg/kg) superior to intravenous ondansetron 8mg in the emergency treatment of CHS.[13] Once acute treatment is completed, a multi-disciplinary team input consisting of endocrinologists, gastroenterologists, dieticians, addiction services and a mental health team is essential to provide adequate support to such patients in order to maintain abstinence.

Conclusion

The above cases demonstrate the challenges faced by clinicians when trying to differentiate between two extremely similar conditions causing cyclical vomiting syndrome, cannabis hyperemesis syndrome and diabetic gastroparesis. CHS, if recognised, is a potentially reversible condition with cessation of use, as demonstrated in the first two cases, and should be considered before embarking on unnecessary and expensive investigations. Moreover, patients are erroneously made to believe that they have DGp, thus failing to acknowledge their cannabis addiction, which is a significant step towards education and de-addiction strategies. This case series might prompt clinicians to undertake a urine drug screen for all diabetic patients presenting with cyclical vomiting with or without DKA and use Rome IV criteria to reach the diagnosis of CHS. Further research in this field is needed to develop a better diagnostic tool to help distinguish between the two conditions, which in turn may facilitate quick and effective rehabilitation of patients.

Competing interests:
Nil.

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URL:
www.nzma.org.nz/journal-articles/cannabis-hyperemesis-syndrome-in-type-1-diabetes-sheep-in-a-wolfs-clothing

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