

## Clinical Vignettes

# Running Out of Options: Rhabdomyolysis Associated with Cannabis Hyperemesis Syndrome

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Cannabis hyperemesis syndrome (CHS) is a condition in which some patients with long-term, frequent use of cannabis paradoxically develop recurrent episodes of nausea and vomiting. The pathophysiology underlying this condition is poorly understood, as is the explanation for its common association with patients' discovery that hot-water bathing alleviates symptoms. We describe the case of a 24-year-old male with daily marijuana use and a history of CHS who was found to have rhabdomyolysis induced by a period of 15 h of continuous jogging after he discovered that this activity helped to alleviate his symptoms. To our knowledge, this is the first reported case of exercise-alleviated CHS symptoms, and we propose that this case provides support to the theory of redistribution of enteric blood flow as the mechanism behind the learned hot-water bathing behavior seen so commonly in CHS.

**KEY WORDS:** cannabis hyperemesis syndrome; cannabis; hyperemesis; rhabdomyolysis; hot water; adverse drug effect.

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## INTRODUCTION

Cannabis is one of the most commonly used recreational drugs. The lifetime cumulative prevalence of cannabis use in the USA is 43%, and attitudes toward its use are rapidly changing.<sup>1</sup> Seven states and the District of Columbia have passed measures legalizing recreational cannabis use, and another 19 states have laws legalizing cannabis use in some form.<sup>2</sup> While cannabis is often used medically for its antiemetic properties, long-term cannabis use is associated with recurrent episodes of severe nausea, vomiting, and abdominal cramping in some patients. Though only first described in 2004, cannabis hyperemesis syndrome (CHS) and affected patients' characteristic compulsive hot showering or bathing behavior has been well documented.<sup>3–6</sup> The physiologic cause of CHS remains poorly understood, and the mechanism of relief of symptoms that patients receive from hot water bathing and showering is even less well understood.<sup>7</sup>

## CASE

A 24-year-old male with recurrent episodes of intractable nausea and vomiting presented with 5 days of nausea, vomiting, and abdominal cramping. He had been admitted to the hospital with the same symptoms 3 days prior. During that hospitalization, he stated that his daily marijuana use helped control his symptoms. Similar to previous encounters, his symptoms resolved within 24 h after treatment with intravenous fluids, ondansetron, and metaclopramide. He spent the majority of the hospitalization taking hot showers and had to be asked by staff to come out for assessments. He was discharged and counseled about the role marijuana was playing in his symptoms and the importance of abstaining from its use.

When he returned home, he resumed his typical marijuana use, and his symptoms of nausea, vomiting, and abdominal cramping soon returned. These symptoms were not relieved by the ondansetron prescribed on discharge from the hospital. After nearly 2 days of continuous symptoms, he returned to the emergency department.

He had been suffering from these recurrent episodes of nausea, vomiting, and abdominal pain for the past 4 years and had required 25 emergency department visits and 6 hospitalizations over that period of time. He had previously undergone an extensive evaluation, including abdominal radiographs, ultrasounds, and computed tomography as well as an upper endoscopy and a gastric emptying study, the results of which had all been normal and unrevealing. Based on the negative evaluation and his history of extensive cannabis use, he was diagnosed with CHS.

On physical examination in the emergency room, the patient was standing, holding onto the rail of the stretcher, and running in place. The physician had cared for him on many previous occasions and had never seen him exhibit this type of behavior. His heart rate was 110 beats per minute and respiratory rate was 22 breaths per minute. The remainder of the physical examination was normal.

Initial laboratory studies revealed a normal complete blood count and basic metabolic panel, elevated AST (2600 U/l, normal <70 U/l) and ALT (931 U/l, normal <45 U/l) with normal alkaline phosphatase and bilirubin. A workup for acute hepatitis was performed, including a toxicology screen, acetaminophen level, viral hepatitis serologies, ceruloplasmin,

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iron studies, and liver ultrasound with Dopplers; all tests were normal and unrevealing. Due to this isolated transaminase elevation and the patient's unusual behavior, a creatine kinase (CK) level was obtained and was markedly elevated at 39,610 U/l (normal <300 U/l). With the otherwise negative workup, the transaminitis was attributed to rhabdomyolysis.<sup>8</sup>

When asked why he was running in place, the patient stated that he had a limited hot water supply in his apartment and had to share the bathroom with family so was unable to spend all day in the shower. However, he had discovered the previous day that when he started running his symptoms very quickly improved. He had been jogging nearly non-stop for the past 15 h. He also admitted to some lower extremity soreness and the realization that he had been running "more than he can handle."

The patient was admitted to the hospital for exercise-induced rhabdomyolysis and treated with aggressive intravenous hydration. His symptoms again resolved within 24 h of nausea control, abstinence from marijuana, and frequent hot showers in the hospital. He did not feel compelled to run when his symptoms were under control. His CK levels trended down over the next 4 days, and his renal function remained normal. His AST and ALT trended down as well over the course of his hospitalization and returned to normal after discharge.

Since discharge, the patient has continued to use exercise as a means of alleviating his symptoms when he smokes marijuana and has since had several other presentations for the same symptoms with milder CK elevations and without transaminase elevations. In between presentations, his CK levels fully returned to baseline.

## DISCUSSION

Cannabis, with its key psychoactive ingredient tetrahydrocannabinol (THC), is well known for its antiemetic and appetite-stimulant properties. The mechanism behind these effects as well as the psychoactive effects that lead to recreational use is facilitated by its partial agonism of endogenous CB1 and CB2 receptors found primarily throughout the central nervous system.<sup>9</sup> CHS was first described by Allen in 2004<sup>3</sup> and in numerous case reports since. Many of these have confirmed the common symptoms of recurrent episodes of severe nausea and vomiting in patients who smoke marijuana frequently and their characteristic relief from these symptoms with the learned behavior of compulsive bathing or showering in hot water.<sup>3, 4, 10</sup> Proposed diagnostic criteria for CHS include major criteria of severe cyclic nausea and vomiting, resolution with cannabis cessation, relief of symptoms with hot baths or showers, epigastric or periumbilical abdominal pain, marijuana use (at least weekly), and supportive features of age <50 years, weight loss more than 5 kg, morning predominance of symptoms, normal bowel habits, and negative laboratory, radiographic, and endoscopic test results all in the setting of chronic cannabis use.<sup>10</sup>

The mechanism behind the paradoxical development of hyperemesis in patients with CHS remains poorly understood. Proposed mechanisms include pharmacokinetic factors such as THC's long half-life and high lipid solubility, the effect of lipid-soluble compounds other than THC present in cannabis, as well as pharmacodynamics factors. Patients suffering from CHS may also have predisposing genetic factors such as variation in the metabolism or clearance of THC, thereby leading to accumulation of emetogenic metabolites or cannabinoid withdrawal. A commonly cited mechanism for hyperemesis involves the dysregulation of body temperature due to the high number of CB1 receptors in the medial preoptic/anterior hypothalamic area, the primary thermosensitive site of the central nervous system, leading to autonomic dysregulation and vomiting.<sup>3, 5, 9</sup>

Hot-water bathing is a key feature of CHS occurring in as many as 91% of patients.<sup>5</sup> This is a learned behavior that often is not present with the first few episodes of the condition but later develops as patients discover that their symptoms resolve within minutes of exposure to hot water and return soon after withdrawal from the hot water. As in this patient, case reports describe patients bathing for hours at a time and many times per day.<sup>3</sup> The mechanism by which hot water bathing or showering improves symptoms remains unknown, though two proposed mechanisms have been commonly cited.

The first and most often cited mechanism is that compulsive bathing behavior may alleviate symptoms through the normalization of temperature.<sup>3, 5, 9, 10</sup> In rodent models, large doses of cannabinoids have been shown to cause hypothermia; however, at lower human-relevant doses, hypothermia does not occur. At usual doses, THC causes core temperature elevation but also reduces skin temperature. Hot water bathing would help increase blood flow to the skin and thus help dissipate heat.<sup>9</sup> How the dysregulation of temperature causes CHS symptoms is not entirely clear, though autonomic dysregulation has been cited.<sup>3</sup>

More recently, another mechanism has been proposed. In addition to the central nervous system, CB1 and CB2 receptors are found throughout the enteric nerves and on the presynaptic ganglia of the parasympathetic system, and activation of these receptors causes vasodilation in sepsis and late-stage cirrhosis.<sup>11</sup> Thus, the symptoms of CHS could be related to this vasodilation, and the relief of symptoms from hot water bathing may be due to redistribution of blood flow from the gut to the skin in what has been called "cutaneous steal syndrome."<sup>7, 11</sup> The immediate relief of symptoms that this patient experienced while running seems to give support to this second hypothesis as redistribution of blood flow to the musculature during exercise would act in the same way as hot-water bathing. Interestingly, when Patterson et al.,<sup>7</sup> first proposed this cutaneous steal syndrome, they did so by citing the previously known redistribution of blood flow from the splanchnic circulation to muscle, which has been demonstrated during exercise.<sup>12</sup>

We are unaware of previously reported cases of CHS symptoms alleviated by exercise or of CHS with concurrent exercise-induced rhabdomyolysis. One recent report described a case of hyperemesis and rhabdomyolysis after a patient used a synthetic cannabinoid product, but this was non-exertional rhabdomyolysis and a different compound.<sup>13</sup> We believe that this patient's learned behavior of alleviation of CHS symptoms with strenuous exercise gives additional support to the hypothesis of redistribution of blood flow from the gut as the mechanism behind the hot-water bathing learned behavior characteristic of CHS. Clinicians should ask patients with CHS about their exercise habits and have a high index of suspicion for exercise-associated injuries and conditions, such as rhabdomyolysis.

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**Key Points:** Exercise can relieve symptoms of cannabis hyperemesis syndrome (CHS), which can include symptoms such as severe nausea, vomiting, and abdominal cramping. Much like the compulsive hot water bathing and showering behavior characteristic of CHS, exercise used to relieve symptoms can become a compulsion and can lead to potentially dangerous complications such as rhabdomyolysis. Exercise-alleviated symptom relief gives support to the theory that redistribution of blood flow away from the gut may be the mechanism responsible for relief of symptoms with hot water bathing and showering in CHS.

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