

CANNABINOID HYPEREMESIS SYNDROME: A REVIEW OF THE LITERATURE

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SUMMARY

Background: Cannabinoid Hyperemesis Syndrome (CHS) is characterized by cyclic vomiting and compulsive need to take hot showers in the context of chronic cannabis use. Physicians' lack of knowledge of CHS often results in a diagnostic delay of several years. The purpose of this article is to describe CHS in order to enable physicians, and more particularly psychiatrists, to diagnose it as quickly as possible and thus avoid unnecessary additional invasive examinations.

Subjects and methods: Bibliographic search for scientific articles published between 2004 and 2019 in the Cochrane, Medline, PubMed, and Psycinfo databases. Key words used were "hyperemesis", "cannabis", "cannabinoid".

Results: CHS is associated with chronic cannabis use and typically manifests as incoercible cyclical vomiting, diffuse abdominal pain, and relief of symptoms by taking hot showers. Patients suffering from CHS generally visit emergency departments very regularly and undergo numerous additional examinations, both invasive and unnecessary. Since no organic cause can explain these symptoms, these patients are referred to the psychiatry department. The only curative treatment is the complete cessation of cannabis use.

Conclusion: CHS is an under-diagnosed pathology because it is little known to physicians. This syndrome has unique clinical characteristics. Early recognition of CHS avoids repeated visits to the emergency room and unnecessary follow-up examinations.

Key words: hyperemesis – cannabis - cannabinoid

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INTRODUCTION

Cannabis, extracted from the plant *Cannabis Sativa*, is the most widely used illicit drug in the world (Khattar & Routsolias 2018, Lu & Agito 2015). The main active substance in cannabis, responsible for psychotropic effects, is delta9-tetra-hydro-cannabinol (THC), which binds to the cannabinoid receptors CB1 and CB2 (Lu & Agito 2015). Numerous therapeutic properties of cannabis have been proven: analgesic, antiemetic, orexigenic, etc. This has led to its use in medicine in some indications, for example in nausea and vomiting induced by chemotherapy or in cachexia associated with AIDS (Khattar & Routsolias 2018, Lu & Agito 2015, Sun & Zimmerman 2013). However, many harmful effects are related to the chronic use of cannabis including increased risk of developing an anxiety and/or depression disorder, impaired cognitive performance, and amotivational syndrome. Chronic cannabis use was also correlated with the onset of a severe psychiatric disorder such as schizophrenia, particularly in people with pre-existing genetic susceptibility (Volkow et al. 2014). Another little-known adverse effect, often ignored by physicians, is the paradoxical proemetic effect that can occur in some chronic users. CHS was first described in Australia in 2004 by Allen et al. They reported a series of cases of 19 patients, chronic cannabis users, suffering from cyclic vomiting. These patients displayed a compulsive need to take hot showers to temporarily relieve their symptoms. It was also observed that the complete cessation of cannabis use led to the disappearance of symptoms, and on

resumption of consumption, these same symptoms reappeared. Since 2004, many cases of CHS worldwide have been described in the medical literature.

CHS typically occurs as recurrent episodes of nausea, vomiting, and abdominal pain. The cyclical and severe nature of these symptoms, as well as the lack of awareness of this syndrome by physicians, lead in these patients to repeated visits to emergency rooms, with numerous complementary invasive, costly, and unnecessary examinations. Without organic substrate, these patients may be referred to the psychiatry department for psychogenic vomiting, bulimia, or cyclic vomiting syndrome (Wallace et al. 2011). It is therefore important, in reference to a typical clinical picture, to evoke CHS and to make the link with cannabis use. In addition, with the increasing use of cannabis (recreational or medical) around the world, we may see an increase in cases of CHS in emergency rooms. The aim of this review is to inform physicians, and in particular psychiatrists, about this syndrome, which is little known and therefore under-diagnosed, in order to avoid further invasive examinations and to be able to properly care for patients as early as possible.

SUBJECTS AND METHODS

Literature review based on a bibliographic search of scientific articles published between 2004 and 2019 in the Cochrane, Medline, PubMed and Psycinfo databases. Key words used were "hyperemesis", "cannabis", "cannabinoid". All relevant publications (English and French) were selected.

RESULTS

Clinical description

CHS is a cyclical condition, occurring every week or month, characterised by asymptomatic intervals. Seventy percent of patients report more than seven episodes per year (Simonetto et al. 2012). This syndrome can be divided into three phases: prodromal, hyperemetic, and recovery (Allen et al. 2004, Lu & Agito 2015, Simonetto et al. 2012, Sun & Zimmerman 2013).

Prodromal phase

This phase precedes the acute phase of hyperemesis from several months to several years. It is characterized by morning sickness, abdominal discomfort, and fear of vomiting. Unlike eating disorders (anorexia, bulimia), eating habits remain normal with little or no weight loss. There is no compulsive need to take hot showers at this stage and patients tend to continue or even increase their cannabis use, hoping to alleviate their symptoms with the known antiemetic effect of the substance (Sun & Zimmerman 2013, Ukaigwe et al. 2014).

Hyperemetic phase

This phase usually lasts 24 to 48 hours. It is characterized by severe incoercible nausea and vomiting (up to five times per hour) (Galli et al. 2011). These symptoms are resistant to conventional antiemetic treatments. In the majority of cases, mild, diffuse abdominal pain is present. During this phase, the compulsive need to take hot showers to temporarily relieve the symptoms is observed. This relief is temperature-dependent: the hotter the water, the more effective it is and patients sometimes burn themselves (Cuppens et al. 2016, Khattar & Routsolias 2018, Lu & Agito 2015, Sun & Zimmerman 2013). Patients have decreased appetite and weight loss is seen in 83 percent of patients (Simonetto et al. 2012). During this hyperemesis phase, patients often visit the emergency department where they recorded as slightly dehydrated, but patients generally remain hemodynamically stable (Galli et al. 2011). They undergo numerous examinations (imageries, endoscopies, etc.) usually revealing negative cases. However, esogastroduodenoscopy reveals gastritis and esophagitis (Chen & McCarron 2013).

Recovery phase

This phase begins when cannabis use is stopped. The symptoms resolve within a few days. The patient regains normal eating habits and the compulsive need to take hot showers disappears. Symptoms recur when the patient resumes consumption.

Diagnosis

A patient presenting to the emergency department with severe nausea and vomiting should first be subjected to a thorough history and clinical examination to rule out any significant medical cause, such as pancreatitis, intestinal obstruction/perforation, or pregnancy

(Chen & McCarron 2013). Basic biology (ionogram, hemogram, liver function, amylase, lipase, beta HCG), urinary toxicology, and standard abdominal radiography are recommended as the initial examination (Chen & McCarron 2013).

In order to facilitate the diagnosis of CHS, Simonetto et al. developed a series of clinical criteria in 2012 after carrying out a study (the largest at present) on a series of cases of 98 patients, spanning a period of five years. First, the mandatory criterion for diagnosis of CHS is prolonged use of cannabis. The duration of cannabis use before the onset of symptoms varies widely, but most patients develop CHS within one to five years of initiating cannabis use (Simonetto et al. 2012). Next, Simonetto et al. proposed a series of major criteria:

- severe cyclical nausea and vomiting;
- resolution of symptoms upon stopping cannabis use;
- symptomatic relief by taking hot showers;
- abdominal, epigastric, or periumbilical pain;
- weekly cannabis use.

Finally, minor criteria:

- age less than 50 years;
- weight loss >5 kg;
- morning predominance of symptoms;
- normal intestinal transit;
- negative laboratory, radiological, and endoscopic tests.

Differential diagnoses

The main diagnoses for patients presenting with cyclic nausea and vomiting are CHS, migraine headaches, hyperemesis gravidarum, Addison's disease, bulimia, psychogenic vomiting, and cyclic vomiting syndrome (CVS) (Bajgoric et al. 2015, Lu & Agito 2015, Wallace et al. 2011). These last two diagnoses are the most confusing with CHS; only a precise anamnesis will distinguish them. CVS is typically characterized by psychological stressors and a family history of migraine, with no specific link to substance use (Bajgoric et al. 2015, Chen & McCarron 2013, Wallace et al. 2011). Psychogenic vomiting is generally associated with a psychiatric diagnosis, such as an anxiety disorder, a depressive episode, or a factitious disorder (Chen & McCarron 2013, Lu & Agito 2015). For CHS, pathognomonic elements guiding the diagnosis are compulsive taking of hot showers and prolonged cannabis use (Bajgoric et al. 2015).

Pathophysiological elements

Cannabis contains more than 500 different chemical components, about 100 of which have a cannabinoid structure (Lafaye et al. 2017). The three main cannabinoids found in cannabis are delta9-tetra-hydro-cannabinol (THC), cannabidiol (CBD), and cannabigerol (CBG). THC is the main active substance responsible for the

psychotropic effects of cannabis. Cannabinoids are extremely lipophilic substances with a very long half-life. They easily cross the blood-brain barrier and accumulate in body fat (Lu & Agito 2015).

Cannabis is an ancestral plant that has been used for hundreds of years, so it is surprising that CHS has only been identified since 2004. Increasing THC concentrations in current cannabis plants may explain this paradox (Schreck et al. 2018).

Two cannabinoid receptors have been identified: CB1 and CB2 (Lu & Agito 2015). The CB1 receptor is found primarily in the central nervous system and the enteric nervous system (Simonetto et al. 2012). Our knowledge of the CB2 receptor is more limited. It is primarily present in immune cells and its activation plays a role in the inhibition of intestinal inflammation, visceral pain, and intestinal motility (Galli et al. 2011).

The exact pathophysiological mechanism of CHS remains unknown. Various hypotheses have been proposed to explain the development of this syndrome, the main ones of which are described here:

- Activation of central CB1 receptors is believed to be responsible for many of the known clinical effects of cannabis: altered cognitive function (memory, attention), euphoria, relaxation, appetite stimulation, analgesia, and an antiemetic effect (Lapoint et al. 2018, Lu & Agito 2015). In particular, the antiemetic action of cannabis could be explained by stimulation of CB1 receptors in the vomiting centre in the brain stem (Sun & Zimmerman 2013). However, over-stimulation of peripheral CB1 receptors (in the enteric nervous system) could create a potent proemetic effect, outweighing the antiemetic effect mediated by the central nervous system (Schreck et al. 2018).
- Prolonged use of cannabis leads to the down regulation of CB1 receptors, causing a proemetic effect (Lu & Agito 2015).
- Another hypothesis suggested is that genetic variation in some individuals in cannabinoid-metabolizing liver enzymes causes toxic accumulation of metabolites (Lu & Agito 2015, Schreck et al. 2018, Sun & Zimmerman 2013).
- Activation of central CB1 receptors could also disrupt the hypothalamic-pituitary axis and play a role in the development of CHS (Simonetto et al. 2012, Sun & Zimmerman 2013). Prolonged cannabis use could break the balance of the satiety, thirst, and digestion systems, and thermoregulation of the hypothalamus (Sun & Zimmerman 2013).

Two main hypotheses have been formulated to explain the relieve of symptoms by taking hot showers:

- Cannabinoids are believed to act on central CB1 receptors located in the preoptic area near the thermoregulatory centre located in the hypothalamus and cause hypothermia. Hot showers would temporarily restore this thermoregulatory dysfunction (Patterson et al. 2010, Simonetto et al. 2012).

- Symptoms of CHS could be explained by cannabinoid-induced vasodilation of blood vessels in the digestive tract. For example, hot showers, causing skin vasodilation, could divert blood flow from the digestive tract to the periphery, thereby relieving symptoms (Patterson et al. 2010).

Management of the acute phase of hyperemesis

Management of the acute phase of hyperemesis relies essentially on supportive measures: intravenous hydration, electrolyte disorders correction (Bajgoric et al. 2015, Khattar & Routsolias 2018). Administration of traditional antiemetics to relieve the symptoms of CHS is generally ineffective (Khattar & Routsolias 2018), unlike CVS (Desjardins & Stheneur 2016).

In the medical literature, various alternative treatments have been tried with some success. Several case reports describe the effectiveness of the following medications:

- Topical capsaicin (Dezieck et al. 2017, Graham et al. 2017);
- Haloperidol (Inayat et al. 2017, Jones & Abernathy 2016, Witsil & Mycyk 2017);
- Propranolol (Richards & Dutczak 2017);
- Lorazepam (Khattar & Routsolias 2018). Prescribing benzodiazepines, however, must be used on a reduced basis given the potential for abuse in a population already known to be substance-dependent (Bajgoric et al. 2015, Sun & Zimmerman 2013).

Opioids are sometimes prescribed to relieve CHS-associated abdominal pain, but are not effective and should be used with caution as they may increase symptoms (Bajgoric et al. 2015, Galli et al. 2011, Khattar & Routsolias 2018). Given the frequency of acute-phase CHS-associated esophagitis and gastritis, the use of proton pump inhibitors is recommended until vomiting is stopped (Galli et al. 2011, Rehman et al. 2019).

The most effective symptomatic treatment during the hyperemesis phase is taking hot showers (Desjardins & Stheneur 2016).

Recidivism prevention

Currently, the only effective treatment to prevent recidivism is the complete cessation of cannabis use. CHS symptoms usually resolve spontaneously in the days following cessation of the substance and these same symptoms reappear when consumption resumes. It seems essential to educate the patient about this risk and to reassure him / her about the complete disappearance of the symptoms after stopping cannabis (Galli et al. 2011, Lapoint et al. 2018). Various studies have shown the benefit of cognitive-behavioural therapies and motivational interviewing to help the patient with the cannabis withdrawal process (Cuppens et al. 2016, Galli et al. 2011).

DISCUSSION

CHS is an under-recognized and under-diagnosed medical condition, related to long-term cannabis use. The clinical diagnostic criteria proposed can be useful for diagnosing CHS. The treatment during the hyperemetic phase includes prevention of dehydration, vomiting cessation and relief of abdominal pain. It's also important to educate the patient about the link between CHS symptoms and cannabis. The only curative treatment is the complete cessation of cannabis use. The pathophysiologic mechanism underlying CHS appears to be very complex. It is also important to note that most chronic cannabis users will not develop this syndrome. Additional studies are needed to understand the full extent of this disorder, the exact pathophysiology and to identify risk factors, the prevalence, an optimal pharmacotherapy.

CONCLUSION

CHS, whose pathophysiology is uncertain, is a recently described medical condition and, therefore, little known to physicians. This syndrome has unique clinical characteristics. It should be considered in patients with severe cyclic vomiting associated with chronic cannabis use. The pathognomonic sign guiding the diagnosis is the compulsive need to take hot showers. With increasing cannabis use worldwide, we can expect an increase in cases of CHS in emergency rooms. Early diagnosis reduces the costs and morbidity associated with unnecessary follow-up examinations.

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Contribution of individual authors:

Eleonore Deceuninck & Denis Jacques jointly conceived and designed the study, and completed data acquisition, analysis and interpretation.

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