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CASE REPORT/CASO CLÍNICO

Cannabinoid Hyperemesis Syndrome: The Missed Diagnosis
Síndrome da Hiperemese por Canabinóides: O Diagnóstico Esquecido

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Abstract
Cannabis is the most cultivated and abused illicit drug worldwide. Paradoxically to the antiemetic properties attributed to cannabis, a relatively new cannabinoid hyperemesis syndrome (CHS) started to be recognized and is characterized by cyclic vomiting that are interspaced by asymptomatic phases.
We present a case of a 36-year-old woman who repeatedly presented to the emergency room with cyclic vomiting that alleviated with hot showers. She was a long-term cannabis user and the diagnosis was only established several years later after the onset of symptoms. The diagnostic work up was unremarkable, and the only effective treatment was cannabis cessation. Hot bathing behavior is a key characteristic of this syndrome.
CHS is a new clinical condition that should be considered in a setting of recurrent and intractable vomiting in patients with a history of cannabis use.

Resumo
O canábis é a substância ilícita mais cultivada e consumida em todo o mundo. Paradoxalmente às propriedades antieméticas atribuídas ao canábis, a síndrome de hiperemese por canabinóides (SHC) começou a ser reconhecido e é caracterizado por episódios de vómitos cíclicos espaçados por períodos assintomáticos.
Apresentamos o caso de uma mulher de 36 anos com múltiplos recursos ao serviço de urgência por vómitos persistentes que aliviavam com banhos quentes. Tinha história de consumos de canabinóides desde longa data e o diagnóstico de SHC só foi estabelecido após vários anos. O estudo complementar não revelou alterações e o único tratamento eficaz foi a cessação dos consumos. O recurso a banhos quentes é uma característica central deste quadro clínico.
A SHC é uma entidade clínica que deve ser considerada em contexto de vómitos recorrentes difíceis de tratar em doentes com história de consumos de canábis.

Keywords: Baths; Cannabinoids/adverse effects; Marijuana Abuse/complications; Syndrome; Vomiting/chemically induced

Palavras-chave: Abuso de Marijuana/complicações; Banhos; Canabinóides/efeitos adversos; Síndrome; Vómito/induzido quimicamente

INTRODUCTION

According to the World Health Organization, Cannabis is the most abused illicit drug, being consumed by over 147 million people worldwide. Its use has been growing especially in North America, western Europe and Australia.[1] In fact, only in European Union (EU) around 91.2 million adults with an age span between 15 and 64 years are estimated to have used cannabinoids at least once during

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their lives. Regarding the frequency of its consumption, 1% of adults in EU consume cannabis on a daily or near-daily basis, being the prevalence significantly higher in young people aged below 35 years. Aligned with this data, the cases related to cannabinoids use disorder entering to treatment for the first time increased 76% between 2006 and 2017.[2,3] Portugal figures follow this trend with cannabis ranking first as the most used psychotropic substance.[4]
Cannabis has been credited with some medical properties showing efficacy in reducing nausea and vomiting during chemotherapy treatment, enhancing appetite and weight gain and improving chronic pain.[5,6] Paradoxically to the antiemetic properties attributed to cannabis, a syndrome characterized by cyclic vomiting episodes in long term cannabis users started to be recognized. The first report describing cannabinoid yperemesis syndrome was published in 2004 by Allen *et al*, giving account of a series of patients observed for persistent vomiting alleviated by hot showering, a core behavior exhibited by the patients in the acute phase of the illness.[7]
However, most of the people presenting this syndrome remain without a diagnosis for several years and it is therefore extremely important that clinicians are aware of the existence of this condition. Given the growing use of cannabis, the purpose of this report is to provide a better understanding of CHS and draw readers attention to its recognition.

CASE REPORT

We report the case of a 36-year-old woman who was sent to the psychiatry outpatient clinic after recurring multiples times to the Emergency Room (ER) with gastrointestinal complains.
For the last 14 years, the patient kept coming to the hospital emergency department presenting with persisting vomiting associated with abdominal pain and nausea. There were no complains of chills, fever, diarrhea, palpitations, thoracic pain, loss of conscience and genitourinary tract symptoms. She had a history of cannabis consumption since she was 16 years old and used the substance almost on a daily basis. She denied using other illicit drugs.
She admitted spending a significant amount of time taking hot water showers at home, stating that this behavior was the only way to mitigate the symptoms. In fact, even during the observations in the ER, she was frequently found in the bathroom showering. The patient described to have experienced numerous similar episodes before in an intermittently fashion. Each episode would start 7 days prior seeking medical attention.
Regarding her past medical history, she had no other chronic medical conditions and allergies. She had been admitted twice into the psychiatry ward after two of these episodes due to psychomotor agitation and anxiety causing familiar distress. She was diagnosed with dysfunctional personality traits and medicated with venlafaxine and quetiapine with poor therapeutic adhesion.
Physical examination was unremarkable with the exception of the mild epigastric tenderness the patient complained during abdominal palpation and mild dehydration. Often, the laboratory values revealed electrolyte imbalances such as hypokalemia and positive urine testing for cannabinoids.
Reviewing the previous workup records, the patient was submitted to an extensive diagnosis investigation including imagiology and laboratory exams. Abdominal radiography and ultrasonography were normal. Other analytic results extending to complete blood count, liver function, amylase, lipase, thyroid hormones, viral serologies and urinalysis were unremarkable.
During these episodes the patient remained under observation in the ER. Supportive treatment with fluid therapy and antiemetic agents like metoclopramide and ondansetron were given in the acute phase and abstinence of cannabis consumption was advised.
Cannabinoid hyperemesis syndrome was only pointed out as the diagnosis for this patient 6 years after the first time she went to ER with this clinical picture.

DISCUSSION

Cannabis is a complex plant that contains over 400 chemical compounds, including at least 144 unique products known as cannabinoids.[8,9] One of the major substances produced is Δ9-tetrahydrocannabinol (THC), which is responsible for the psychoactive effects of feeling high pursued by its users, but also for other disagreeable effects like psychosis and impairment of cognitive performance. THC exerts its effects by activating the endocannabinoid system that on its turn has two receptors known as CB1 and CB2. CB1 is located in the central and peripheral nervous system and the stimulation of the latter causes vasodilation and decrease gastric emptiness.[10] CB2 receptors can be found in immune cells and are involved in immunomodulation by inhibiting inflammation, visceral pain, and intestinal motility.[11]
THC demonstrated to have antiemetic properties mediated by activation of CB1 receptors in myenteric plexus and dorsal-vagal complex in the medulla.[12] Nevertheless, CHB brings evidence for its paradoxical emetic effects, leading to the elaboration of some explicative hypothesis over the years. One of them states that as cannabis is a very lipophilic substance, it accumulates in fat tissue for long periods. During times of stress or food deprivation, lipolysis release THC which produces a reintoxification effect that may contribute to CHB in sensitive subjects.[13]
Since just a small percentage of long term cannabis users develop CHS, genetic polymorphisms in the cytochrome P450 enzymes might be responsible for the higher rate of emetic metabolites in these individuals.[11]
Alongside with THC, other two non-psychotropic cannabinoids present in cannabis may contribute for the development of CHS. They are cannabidiol (CBD) that in high doses enhance vomiting and cannabigerol (CBG) that antagonize CB1 and 5-HT1A receptors contributing to emesis.[11]
Cannabinoids also showed to influence gastrointestinal and colonic dysmotility and THC exerts an inhibitory

action on gastric emptying through inhibition of intrinsic cholinergic mechanisms in peripheral myenteric system. This peripheral action can override the central actions of THC and producing vomiting.[12,14]

The stimulation of CB1 receptors in the hypothalamus and pituitary gland helps to modulate the hypothalamic--pituitary axe. THC produces a hypothermic effect that is amplified by the action of CBD that upregulate CB1 receptors in the hypothalamus.[11] These mechanisms may contribute to understand why patients with CHS show the compulsive bathing behavior.

Concerning the diagnosis, Sorensen et al made a systematic review and identified the major characteristics of CHS as severe cyclic vomiting (100%), abdominal pain (85.1%), weekly use of cannabis (97.4%), consumption of cannabis for over a year (74.8%), resolution of the symptoms after cannabis cessation (96.8%), temporary symptomatic relieve with compulsive hot showers (92.3%) and age less than 50 at time of evaluation (100%) . 92% of the patients evaluated met at least three of the latter criteria. The diagnosis of CHS is made with a mean delay of 4.1 years after the beginning of the symptoms.[15]

The only treatment that showed efficacy is cannabis cessation. In the acute phase, supportive treatment including intravenous fluids should be provided if there is volume depletion and renal failure or electrolytic imbalances. Application of topic capsaicin on the abdomen may relieve the symptoms, and this effect is exerted by activation of TRVP-1 receptors producing a heat sensation. Haloperidol was used successfully in some reports. Opioids are not recommended as they might aggravated the nausea.[11,16]

The acute phase usually resolves in 48 hours, but relapse is likely to occur if the patient resumes cannabis use.[11]

The case presented here is paradigmatic of the delay until the recognition CHS in a long-term cannabis user with multiples recurrences to ER with cyclic vomiting. Moreover, the patient went to extensive non conclusive diagnostic workups, showing that CHS is still underdiagnosed.

CONCLUSION

Since the use of cannabis is growing and new medical indications are being considered it is important to pay attention to the paradoxical effects of cannabis and study its underlying pathophysiology.

Responsabilidades Éticas

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