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Case Report

Recurrent Hospitalization for Cannabinoid Hyperemesis Syndrome in an Adolescent

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1. Abstract

Cannabis use is a widely debated topic in current media, however there is still little known about the effects of long-term cannabis use in pediatric patients. In this nearly two-year-long case, we describe an adolescent male with multiple hospital admissions for complications associated with chronic daily use of highly concentrated cannabis in the setting of key clinical characteristics of cannabinoid hyperemesis syndrome (CHS). Additionally, we review current literature regarding trends of cannabis use, treatment of CHS, and suggest future areas for research.

2. Abbreviations: CHS: Cannabinoid Hyperemesis Syndrome, ED: Emergency Department, CT: Computed tomography, WBC: White Blood Cell

3. Introduction

Cannabinoids are the most widely used psychoactive substances by adolescents in the United States. Recreational use of marijuana is reported by as many as 13.5% of eighth graders nationwide, 30.7% of tenth graders, and 45% of twelfth graders. Furthermore, one in seventeen twelfth graders report daily marijuana use. [1] Though traditionally noted for their antiemetic properties, cannabinoids have been linked to a clinical syndrome characterized by abdominal pain, excessive hot water bathing, and recurrent, intractable vomiting that was first described in adults in South Australia in 2004. [2] Though there are many and varied case reports of CHS in the adult literature, there have been very few pediatric cases reported. Here we present a complicated case in a male adolescent in which we describe multiple hospitalizations and consistently recurring, previously unreported clinical features which are likely attributable to CHS.

4. Case Report

A 16-year-old male with history of major depressive disorder and attention deficit hyperactivity disorder presented to an outside ED with four days of recurrent episodes of nausea and vomiting associated with weight loss and decreased appetite. He was transferred to our facility due to chest pain and shortness of breath attributed to pneumomediastinum identified on chest radiograph. The patient reported at least 2 years of daily use of "wax" marijuana which he smoked to maintain a constant "high" from morning to night.

On admission the patient continued with nausea and intractable non-bilious, non-bloody vomiting. Vital signs were reassuring with normal oxygen saturation. Physical exam was notable for crepitus over his upper left anterior chest wall, but normal breath sounds and work of breathing. The abdomen was soft and non-distended but generally tender to palpation. Lab values including lipase were normal except for white blood cell count of 23.5 bil/L and slightly low sodium and chloride. Chest x-ray (Figure 1) showed mediastinal air and CT scan of the chest, abdomen, and pelvis confirmed pneumomediastinum with subcutaneous air, and ruled out intestinal obstruction. His symptoms were unresponsive to typical antiemetics such as ondansetron and promethazine, but he reported significant relief with hot water bathing. Based on his chronic cannabis use and symptoms he was diagnosed with CHS. Due

[&]**Author Contributions:** Kimberly DeLeon, Julie Pham, These authors have contributed equally to this article.

to persistent symptoms, he was started on haloperidol after which he experienced relief. Neuropsychology and social work were consulted, and it was recommended that he seek drug rehabilitation and continue with outpatient psychology. He was discharged home but would go on to have multiple further encounters.

In total, over the course of approximately 18 months he presented eight times to various EDs reporting the same symptoms: nausea, abdominal pain, and vomiting associated with cannabis wax use. Five of these eight ED visits resulted in hospital admission for a total of 23 hospital days. Recurring clinical findings were: pneumomediastinum, leukocytosis (as high as 30.5 bil/L), hypertension, hypokalemia, and hypochloremia. He was treated with ondansetron and promethazine at least once during each visit with negligible benefit. He did not tolerate a trial of topical capsaicin. He was given haloperidol on three separate visits with reported improvement each time. He underwent a total of three abdominal CT scans, two ultrasounds, and numerous x-rays. He received intravenous antibiotics on two occasions presumably related to leukocytosis. Of note, on his last visit to the ED, his CHS was triggered by a single use of cannabis after 4 months of abstinence. Upon phone interview with the patient's legal guardian, he has been symptom free for 8 months since he quit using cannabis. A summary of the patient's experience with CHS can be found in (Table 1).

Figure 1: Chest radiograph of our patient with cannabinoid hyperemesis syndrome demonstrating a pneumomediastinum.

Table 1: Key features of this case report.

Table 1: Summary of two-year experience with cannabis hyperemesis	
Age of Cannabis Hyperemesis Syndrome diagnosis	16 y.o.
Number of Emergency Department visits	8
Number of days admitted in total	23
Range of leukocytosis	12.0-30.5
Range of hypokalemia	2.9-3.5
Number of visits ondansetron was prescribed	8/8
Number of times promethazine was prescribed	8/8
Number of times haloperidol was administered	3/8
Number of visits diagnosed with pneumomediastinum	3/8

5. Discussion

Changing policies regarding legalization indicate that marijuana use is becoming overall more accepted in our society. As of the writing of this manuscript, thirty states and the District of Columbia have laws legalizing cannabis in some form, and eight states have broadly legalized cannabis for recreational use. As marijuana and cannabinoids become more accessible in the United States, the rate of cannabis abuse may increase not only in adult patients, but also within the pediatric population. The Drug Abuse Warning Network estimated that in 2011, about 13 percent of the 456,000 drug related emergency department visits in which cannabis use was implicated involved children between the ages 12 and 17. [3] Despite this high rate of cannabis related visits, we have found only two cases reported in the pediatric literature. [4,5] Ours is the first to link CHS with pneumomediastinum, leukocytosis, and hypokalemia, and is unique in the number of documented encounters and duration of follow-up.

The largest CHS case series to date included 98 patients aged twenty years and older. The authors' analysis of patient characteristics, radiological, laboratory, and endoscopic results led to the development of major and minor supportive features for the diagnosis for CHS (outlined in Table 2). [6] Although no consistent laboratory or radiological findings were suggested in these criteria, our patient's experience revealed three consistently recurring clinical and laboratory findings which we propose are secondary complications of his CHS: pneumomediastinum, leukocytosis, and low potassium.

Table 2: Key clinical criteria for the diagnosis of Cannabis Hyperemesis Syndrome as previously reported in the literature.

Table 2: Proposed Clinical Criteria for Cannabinoid Hyperemesis Syndrome [2]
Essential for Diagnosis
Long- term cannabis use
Major Features
Severe Cyclic nausea and vomiting
Resolution with cannabis cessation
Relief of symptoms with hot showers or baths
Abdominal pain, epigastric, or periumbilical
Weekly use of marijuana
Supportive Features
Age less than 50 y
Weight loss of >5kg
Morning predominance of symptoms
Normal bowel habits
Negative Laboratory, radiographic, and endoscopic test results

Multiple authors have reported a link between pneumomediastinum and vomiting. [7-10] Forceful contraction of the abdominal muscles against a closed glottis leads to increase intra-alveolar pressure and alveolar leak into the mediastinal cavity via the bronchovascular trunks and lymphatics. [7] Vomiting has been reported as the initiating event in up to 38% of patients diagnosed with spontaneous pneumomediastinum. [10] Pneumomediastinum generally occurs in younger patients most likely due to their undeveloped mediastinum, in contrast to the mostly fibrosed mediastinum of the elderly. [11] Since patients with CHS tend to be younger and the vomiting can be severe, we hypothesize that these patients are at higher risk for pneumomediastinum. We recommend that providers should obtain a good history for symptoms suggesting pneumomediastinum and have a low threshold for further imaging to diagnose pneumomediastinum in patients that present with CHS and chest pain. We also recommend that providers who care for adolescents presenting with vomiting induced pneumomediastinum should obtain a good cannabis use history in order to identify possible cases of CHS.

A 2015 report outlines cannabinoid suppressive effects on T-cell function, but no direct effect was noted on the total WBC count. [12] The Mayo CHS case series of 98 patients reported complete

blood cell counts were normal in the majority of their patients. [6] However, our patient was consistently documented to have leukocytosis with each presentation- at one point as high as 30.5 bil/L. We found at least one other CHS case report which also identified leukocytosis. [13] Leukocytosis in our patient was significant not only in its recurrence, but also in prompting unnecessary antibiotic use. The mechanism of this leukocytosis is unclear but may be related to a stress response and white blood cell demargination in the setting of intractable vomiting. We suggest further investigation in order to more fully characterize any relationship between CHS and leukocytosis.

Low levels of potassium in CHS maybe caused by a combination of acute and chronic mechanisms. First, potassium balance within the body is maintained by excretion versus intake which is disrupted with acute cannabis hyperemesis. [14] Second, cannabis smokers may have baseline hypokalemia in contrast to non-smokers. [15] And third, vomiting leads to metabolic alkalosis and increased aldosterone release both of which result in increased renal potassium loss. This chronic loss of urinary potassium with marijuana use, coupled with decreased intake and renal losses due to the cyclic vomiting of CHS, leads to acute mild to moderate hypokalemia.

In addition to secondary complications of CHS, we identified a number of unnecessary or ineffective treatments that are worth highlighting. In almost every published case of CHS, patients are treated with common antiemetics such as ondansetron and promethazine with negligible relief. Due to the risk of side effects and lack of any benefit, these drugs likely should not be used to treat CHS. [16-19] In contrast to the above medication failures, our patient was noted to have marked improvement with haloperidol which has previously been shown to be effective in lessening symptoms associated with CHS especially in cases treated in the ED. [20-21] Stage 4 trials comparing haloperidol to ondansetron in CHS are currently underway in adults. [22]

In addition to ineffective antiemetics, our patient received unnecessary intravenous antibiotics on two separate occasions due to elevated white blood cell count in the setting of abdominal pain and vomiting. It is unclear how many patients with CHS have leukocytosis, and further studies are needed to define this relationship, but our patient's experience suggests that antibiotics should not be administered unless other signs and symptoms of infection are present.

6. Conclusion

Marijuana use and legalization has become increasingly accepted in American society. Despite widespread use, little is known about the detrimental effects of cannabis use in adolescents. Given the high rate of marijuana use in high school aged children, medical providers especially in ED and inpatient settings should be aware of cannabinoid hyperemesis syndrome and its possible complications in order to appropriately evaluate and treat these patients. Typical antiemetics are ineffective for symptom control. The only widely accepted treatment for symptoms is hot bathing, but haloperidol may also be effective. More research is needed to further define diagnostic criteria, acute and long-term management of this condition.

7. Table of Contents Summary

As changing legislation leads to increased adolescent access to cannabinoid products, proper identification and management of Cannabinoid Hyperemesis Syndrome by providers caring for pediatric patients is increasingly important.

8. What's Known on This Subject

Cannabinoid hyperemesis syndrome is a well described entity in adults triggered by chronic regular cannabis use. The syndrome is characterized by abdominal pain, severe nausea and vomiting, and improvement with hot water bathing. Traditional anti-emetics are generally ineffective. Termination of marijuana use is the only known effective treatment.

9. What This Study Adds

This report is the longest-term pediatric case to date. It is also the first to suggest a link between cannabinoid hyperemesis syndrome and certain secondary complications including pneumomediastinum and leukocytosis.

10. Consent

The patient's legal guardian gave informed consent for this information to be presented.

11. Conflict of Interest: The authors have no conflicts of interest relevant to this article to disclose

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