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Severe Hypophosphatemia in Adolescent Cannabis User

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Abstract

Cannabinoid hyperemesis syndrome (CHS) involves cyclical nausea, vomiting, and abdominal pain linked to use of cannabis with resolution of symptoms upon cessation of cannabinoids. Although electrolyte disturbances, fluid imbalances, and nutritional deficiencies are known complications of CHS in the setting of intractable vomiting, severe hypophosphatemia is a rare clinical phenomenon cited primarily in the adult literature. Pediatric cases are scarcer, thus the magnitude associated with our patient case describes an adolescent diagnosed with CHS complicated by recurrent severe hypophosphatemia. As cannabis accessibility and potential for abuse increase with the wave of legalization seen at the state level, clinician awareness is needed for such adverse entities related to cannabinoid toxicity.

Keywords

Cannabinoid, Toxicity, Hyperemesis

1. Introduction

Cannabis is the most prevalent illicit drug in the United States, particularly popular among adolescents due to its psychotropic attributes [1]. Despite the public's perception that cannabis is a harmless substance, serious adverse effects exist including impaired concentration, altered mood, memory loss, hyperemesis syndrome, and potential permanent sequelae on the developing brain [1]. Severe

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hypophosphatemia is a seldom and poorly understood complication associated with use of cannabis. Adults account for the majority of limited cases describing hypophosphatemia in the clinical setting of CHS. We present our experience with severe hypophosphatemia in an adolescent assessed with CHS.

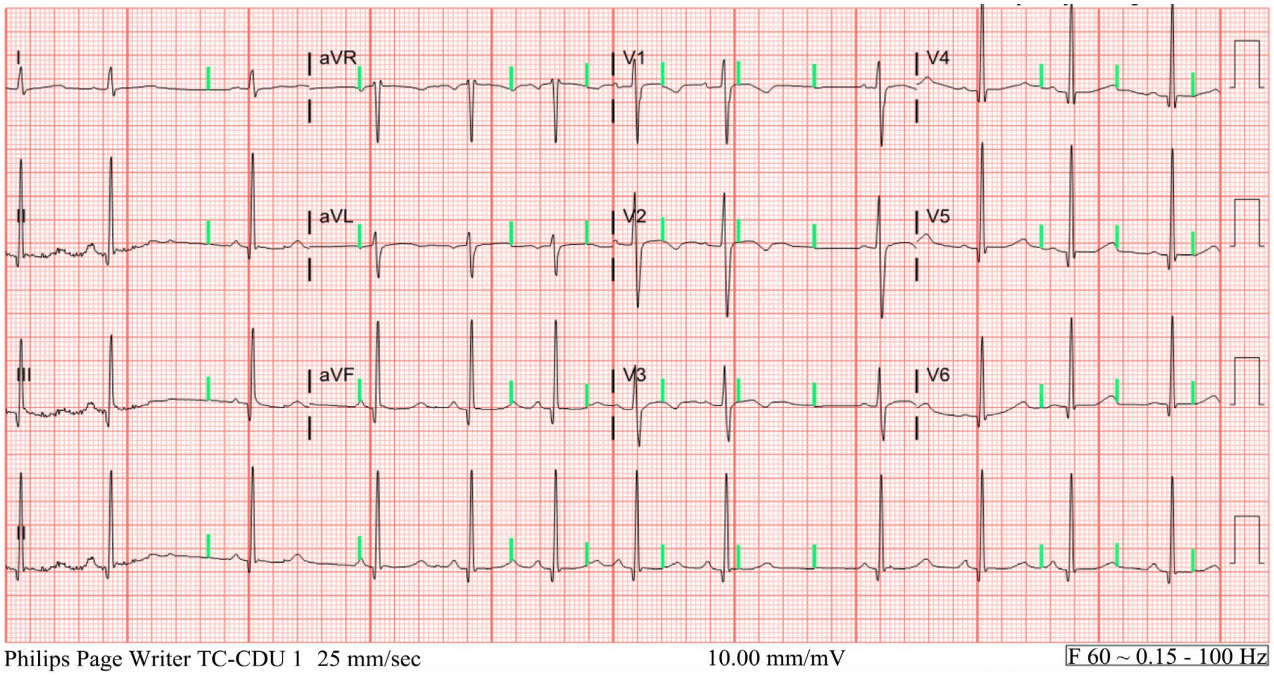
2. Case

A 17-year-old female with a history of anxiety, chronic cannabinoid use, and cyclical vomiting episodes was hospitalized on three separate occasions within a 3-week time frame resulting from a presentation of acute intractable vomiting and oral intolerance requiring intravenous fluids for risk of dehydration. Patient was accompanied by nausea and epigastric pain, and reported unintentional weight loss of 7 kg in the prior 3 weeks. Cannabis use started several years prior, consistently smoking a single joint twice per week up to the present time, and admitting to 5 days as the longest stretch without use. Onset of patterned vomiting episodes was nearly monthly with symptom-free interval periods coincide with onset 5 years ago. Prior evaluation done by Pediatric Gastroenterology involved laboratory studies and an esophagogastroduodenoscopy (EGD), results were all unremarkable and poor follow-up was nearly a year. Patient is also non-compliant with previous anxiolytics prescribed; anxiety is thought to stem from the death of her father as a young child.

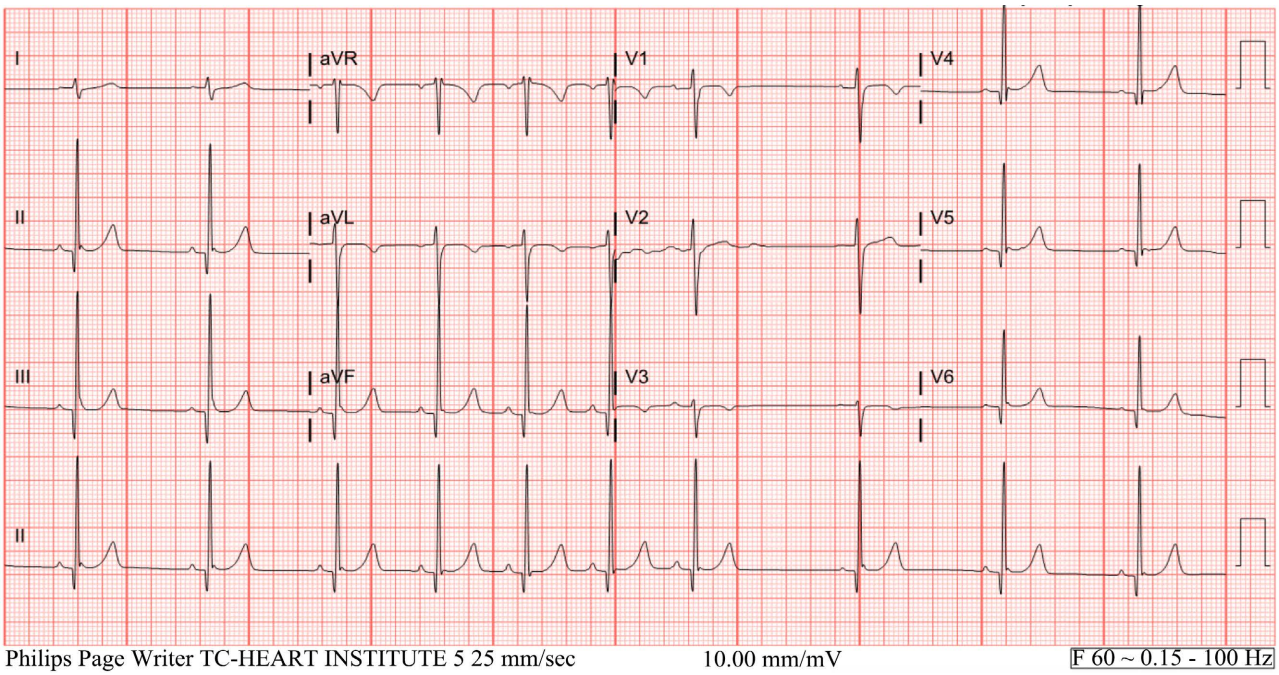
Clinical exam demonstrated vital signs within normal range, no hypertensive or tachycardia episodes, and absent signs of respiratory distress. Patient had met criteria for mild malnutrition on the basis of a BMI z-score of −1.62 and underlying alteration in gastrointestinal function related to chronic emesis. Laboratory studies to assess for electrolyte disturbances identified severe hypophosphatemia on two separate admissions within 3 weeks of one another, as detailed in **Table 1**. EKG changes showing prolonged QTc were seen on the patient's most recent admission (**Figure 1(a)**). Each episode of severe hypophosphatemia demonstrated a prompt response to administration of phosphate containing intravenous fluids with normalization of serum levels upon repeat serum levels performed 4 to 6 hours after supplementation. Other mild electrolyte abnormalities inclusive for hyponatremia and hypokalemia also normalized following fluid repletion, in addition to resolved EKG interval abnormalities on recent admission (**Figure 1(b)**). Urine studies collected on the second admission were positive for proteinuria, glucosuria, and high urine pH suggesting bicarbonaturia. Urine toxicology screen done on last admission was positive for cannabinoids. Diagnostic imaging (*i.e.* limited abdominal ultrasounds, abdominal x-rays) and esophagogastroduodenoscopy (EGD) were completed with no significant clinical findings.

Therapeutic management centered upon supportive measures involving intravenous fluids, acid suppression via a proton pump inhibitor (PPI), and an array of agents utilized for their specific properties to achieve a clinical response. Anti-psychotics (Haloperidol), benzodiazepines (Lorazepam), 5-HT3 receptor antagonists (Ondansetron), & antihistamines (Diphenhydramine) comprised the varied classes of medications prescribed at standard dosing. Tolerance to oral intake

was achieved at each discharge, with oral nutritional supplementation started to meet the patient's macro & micronutrient needs. Patient counseled extensively on the need to discontinue cannabinoids, however admitted to ongoing use between hospitalizations. Outpatient therapy and Adolescent Medicine follow-up



(a)



(b)

Figure 1. (a) Initial EKG demonstrating normal sinus rhythm with QTc prolongation (470 ms). (b) Repeat EKG displaying normal sinus rhythm with absent QTc prolongation (431 ms) nearly 24-hours following initial study with normalized potassium & no further ondansetron doses administered.

Table 1. Metabolic panel & electrolyte serum levels during admissions.

DOA	Admission #1									Admission #2			Admission #3	
	DOA#1	DOA#2		DOA#3		DOA#4	DOA#5	DOA#6		DOA#1	DOA#2	DOA#3	DOA#1	DOA#2
Na	136	137	138	135	135	136	133	135	135	130	134	134	138	138
K	3.4	3.1	3.2	2.9	3.0	3.3	3.1	3.0	3.6	3.2	3.9	3.7	3.3	3.9
Cl	105	106	109	105	103	107	100	105	105	98	105	105	102	109
CO_2	18	18	17	18	20	20	20	18	22	15	21	17	17	19
BUN	5	3	3	2	2	2	4	4	3	4	2	2	8	5
Cr	0.62	0.7	0.67	0.73	0.75	0.66	0.73	0.67	0.67	0.68	0.69	0.67	0.74	0.56
Ca	8.6	9.3	8.9	8.9	9.2	8.7	9.3	8.3	9.3	9.4	9.3	8.9	10.1	8.1
Gluc	110	108	105	93	118	99	93	102	96	103	95	92	193	86
Mg	1.6	1.6	1.7	1.6	1.4	1.5	1.5	-	1.9	1.8	2.0	1.9	1.5	2.0
Phos	2.7	**0.7**	**0.9**	2.7	3.5	3.5	3.1	-	-	3.1	4.0	2.9	**0.8**	3.9

*Normal laboratory range/units: Na (135 - 145 mEq/L), K (3.5 - 5.1 mEq/L), Cl (98 - 107 mEq/L), CO_2 (22 - 30 mEq/L), BUN (6 - 22 mg/dL), Cr (0.57 - 1.11 mg/dL), Ca (8.6 - 10.2 mg/dL), Gluc (70 - 105 mg/dL), Mg (1.6 - 2.6 mg/dL), Phos (2.3 - 4.7 mg/dL).
**DOA: Day of admission.

was arranged, medical therapy otherwise limited to continued acid suppression and consideration for starting a tricyclic antidepressant (*i.e.* Amitriptyline) if cyclical vomiting pattern persisted after stoppage of cannabis.

3. Discussion

Severe hypophosphatemia is seldom identified in CHS. Pediatric cases of this phenomenon encompass only a small case series of 3 adolescent-age patients with CHS [2]. Our patient met the Rome IV diagnostic checklist for CHS by fulfilling criteria for a minimum of 3 months & symptomatic onset ≥ 6 months before diagnosis, with stereotypical episodic vomiting resembling cyclical vomiting syndrome (CVS), presentation after prolonged excessive cannabis use, and relief of vomiting episodes by sustained cessation of cannabis use [3]. Urine toxicology is not necessary for diagnosis to support cannabis use elicited in patient history, but can be helpful to distinguish adherence to long-term abstinence and differentiate alternate diagnosis of CVS.

Hypophosphatemia may occur through several mechanisms such as decreased intake or absorption, increased excretion through the gastrointestinal tract or kidneys, or a transcellular shift from extracellular to intracellular as suspected in our patient with cannabinoid toxicity [4]. Absence of any clinical sequelae with such severe hypophosphatemia and rapidly normalizing serum phosphate levels further support ion redistribution as an explanation for our patient's clinical presentation.

Refeeding syndrome, catecholamine excess, and respiratory alkalosis encompass differentials leading to hypophosphatemia in a similar fashion [5]. No clinical features were suggestive in our patient for any of these conditions. The ab-

sence of diarrhea or findings to suggest malabsorption excluded excessive phosphorus loss via the gastrointestinal tract. Urinary phosphorus excretion was not measured at any admission or follow-up visit, neither was a parathyroid hormone (PTH) level obtained to exclude hyperparathyroidism.

Hypophosphatemia related to transient redistribution usually follows an asymptomatic course [5]. True phosphate depletion has significant clinical manifestations entailing ataxia, depressed myocardial contractility, diaphragmatic weakness, and rhabdomyolysis [5]. The patient's EKG abnormalities in the form of prolonged QTc cannot be attributed to hypophosphatemia. Such arrhythmic changes are likely multifactorial in the setting of hypokalemia, biochemical effects of cannabis itself, and use of QT-prolonging ondansetron [6].

Similar to CVS, patients with CHS encounter clinical phases, identified as prodromal, hyperemesis, and recovery phase [7]. Acute management of CHS entails intravenous hydration, correction of electrolyte abnormalities, and abortive therapy to relieve nausea, vomiting, & abdominal pain [7]. Intravenous ondansetron is the most common antiemetic given, though a systematic review found that conventional antiemetics alone are ineffective with refractory symptoms in CHS [7]. Newly emerging abortive treatment regimens include use of benzodiazepines, haloperidol, and topical capsaicin [8]. Mechanisms of these agents related to providing symptomatic relief in CHS are not clearly understood, but likely have involvement with the endocannabinoid network, central nervous system, & enteric nervous system [8]. Long-term management essentially involves complete cessation of cannabis use to abate relapsing episodes. Intravenous lorazepam and ondansetron were the most frequently used medications in our patient, diphenhydramine given for breakthrough symptoms, and haloperidol administered on one occasion in the emergency department setting. No particular single medication was identified as superior for abortive therapy, but it was evident that adjunctive therapy was needed to standard antiemetic in achieving symptom resolution. The short time intervals of relapsing symptoms warranting frequent hospitalizations had been attributed to likely cannabis reuse after discharge and exacerbation of the patient's known anxiety disorder.

4. Conclusion

As the landscape of cannabis legalization gives way to increase accessibility, heightened awareness by healthcare providers is required to identify potential serious adverse effects of cannabis toxicity. Despite its anomalous occurrence, consideration is warranted in CHS for electrolyte monitoring inclusive of serum phosphorus. Benefits lend to prevention of diagnostic delay of electrolyte disturbances like severe hypophosphatemia and opportunity for prompt repletion.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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