A Case of Synthetic Cannabinoid (K2)-Induced Posterior Reversible Encephalopathy Syndrome (PRES)

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Patient: Female, 24-year-old
Final Diagnosis: K2 induced posterior reversible encephalopathy syndrome
Symptoms: Abnormal behavior • headache
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine • Toxicology

Objective: Unusual clinical course

Background: K2 is an artificially synthesized cannabinoid (SCB), manufactured as a non-consumption herbal incense but increasingly misused as a recreational drug. Posterior reversible encephalopathy syndrome (PRES) is a rare clinical and radiological entity characterized by brain edema, often in the setting of acute hypertension. Cases of PRES caused by recreational drug use have been reported in the literature.

Case Report: We report an unusual case of PRES after consumption of K2 in a 24-year-old healthy woman who presented with episodic agitation and altered mental status. Magnetic resonance imaging showed nonspecific subtle high T2/FLAIR (fluid-attenuated inversion recovery) signal intensities in the region of the posterior parietal and occipital cortices. Her extensive drug screen report was positive for K2. Her mental status improved over the course of 3 weeks and she had returned to her baseline at 3-month follow-up.

Conclusions: Our case highlights the importance of having a high clinical suspicion in patients presenting with altered mental status and a history of recreational drug use. K2 is not detected by routine urine drug testing, so a high level of clinical suspicion is required to request an extensive drug screen. It is important for the physician to counsel active synthetic cannabinoid users regarding these rare complications.

Keywords: Cannabinoids • Posterior Leukoencephalopathy Syndrome • Recreational Drug Use • Toxicology

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Background

K2, also colloquially called ‘Spice’, ‘Pot Pourri’, or ‘Mojo’, is the term for artificially engineered cannabinoids misused as psychedelic agents [1]. In 2016, among a cohort of college students, it was found that the weighted lifetime prevalence of K2 use at college entry was 7.6% [2]. Synthetic cannabinoids (SCBs) are increasingly gaining popularity as they are cheaper and are not detected by most standard drug screens [3]; therefore, its use is more common among low income individuals and high school and college students. K2 can be smoked using joints, pipes, and E-Cigarettes, or it can be brewed as a tea. While SCBs are often similar in their mechanism of action to natural marijuana, in vitro and in vivo studies have found that K2 functions as full agonists at cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CBR2), unlike (delta)9-THC, which is only a partial agonistic agent [4]. This has been postulated as the cause of the greater toxicity of K2 as compared to natural marijuana. We present the case of a young, healthy patient with no known comorbidities who developed posterior reversible encephalopathy syndrome (PRES) following ingestion of K2.

Case Report

Our patient was a 24-year-old woman brought by emergency medical service to the Emergency Department after an episode of abnormal behavior at home. Her mother reported that around 1:00 a.m., she found her daughter awake crying, clenching her teeth, and screaming incomprehensibly. She stated that her daughter had been experiencing such episodes intermittently over the past 3 days, along with vague, nonspecific, intermittent headaches. Her past medical and surgical histories were unremarkable. There was no significant family history of neurologic, psychiatric, or autoimmune conditions.

She was evaluated in the Emergency Department and was noted to have episodic agitation, with bouts of crying followed by blank staring. The patient had a pulse rate of 98 beats per minute, a temperature of 37.1°C, respiratory rate of 18 breaths per minute, and blood pressure of 114/76, and was saturating 98% on room air. On physical examination, the patient appeared anxious and drowsy. She was only oriented to place and time, and could follow simple commands. She had bilateral vesicular breathing on lung auscultation. Cardiac examination revealed normal S1 and S2 heart sound. Abdominal examination and neurological examination were unremarkable.

An initial computed tomography (CT) head was negative for any acute pathology, and a chest X-ray and a CT of the abdomen and pelvis were within normal limits. The complete cell count, electrolytes, creatinine, liver function test, creatine kinase, and ammonia blood test results were normal. Urinalysis revealed positive nitrites, leukocyte esterase, and bacteria. Her urine drug screen was positive for cannabinoids. Her initial investigation results are shown in Table 1.

She was started on ceftriaxone for possible urinary tract infection and was admitted to the inpatient service for further evaluation. On day 4 of hospitalization, she became increasingly agitated and was found to be at risk of physical harm to herself and others. Haloperidol was given as needed for delirium and agitation.

She developed 1 episode of partial complex seizures with postictal confusion. Broad-spectrum antibiotics were initiated empirically for suspected meningococcal meningitis. A lumbar puncture was done, and cerebrospinal fluid (CSF) testing revealed 5 white blood cells, high glucose, normal proteins, negative bacterial antigens, cryptococcal antigen testing, Herpes simplex virus (HSV) PCR (polymerase chain reaction), and Cytomegalovirus (CMV) PCR (polymerase chain reaction) were normal. However, HSV PCR returned positive. Herpes simplex type 1 (HSV-1) PCR (polymerase chain reaction) returned positive.

Table 1. Initial laboratory investigation.

| Investigation                   | Value  | Reference range |
|----------------------------------|--------|-----------------|
| White blood cell (k/ul)          | 13.4   | 4.8-10.8        |
| Hemoglobin (g/dl)                | 12.6   | 12.0-16.0       |
| Hematocrit (%)                   | 39.6   | 42.0-51.0       |
| Platelet (k/ul)                  | 276    | 150-440         |
| Sodium (mEq/l)                   | 140    | 135-145         |
| Potassium (mEq/l)                | 3.9    | 3.5-5.0         |
| Bicarbonate (mEq/l)              | 23     | 24-30           |
| Chloride (mEq/l)                 | 106    | 98-108          |
| Glucose (mg/dl)                  | 107    | 70-120          |
| Blood urea nitrogen (mg/dl)      | 6      | 6-20            |
| Creatinine (mg/dl)               | 0.6    | 0.5-1.5         |
| Calcium (mg/dl)                  | 9.5    | 8.5-10.5        |
| Albumin, serum (g/dl)            | 4.7    | 3.4-4.8         |
| Total bilirubin (mg/dl)          | 0.7    | 0.2-1.2         |
| Conjugated bilirubin (mg/dl)     | 0.2    | 0.0-0.3         |
| Alkaline phosphatase (unit/l)    | 42     | 42-98           |
| Aspartate transaminase (unit/l)  | 17     | 9-36            |
| Alanine aminotransferase (unit/l)| 9      | 5-40            |
| Total protein, serum (g/dl)      | 7.1    | 6.0-8.5         |
| C reactive protein (mg/L)        | <5.00  | ≤5.00           |
(CMV) CSF PCR. Results of a work-up for other infectious diseases were negative, including testing for human immunodeficiency virus (HIV), hepatitis B, lyme disease, syphilis, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR. Blood and CSF cultures were negative, and antibiotics were discontinued. Antinuclear antibodies (ANA) were positive (1: 80) in a homogeneous nuclear pattern. Subsequent subse-
rologies were negative, and complement levels were normal.

She underwent an electroencephalogram, which was nonspecific and demonstrated bilateral slowing and disorganization of background rhythms suggestive of diffuse encephalopathy. MRI did not reveal any hemorrhage, masses, or recent infarcts. High T2/FLAIR signal intensities were seen in the regions of the parietal cortices, suggestive of PRES (Figure 1).

Given the MRI findings above, the acute onset of neurocognitive symptoms including headaches, seizures, confusion, nausea, and vomiting, and history of cannabinoid intake, without any clinical evidence of an infectious or autoimmune process, the diagnosis of posterior reversible encephalopathy syndrome was made. She was continued on levetiracetam for seizure prophylaxis and olanzapine as needed for agitation. Her extensive drug screen report was positive for K2. Her clinical condition improved after 3 weeks of inpatient hospitalization, and she was discharged home with outpatient neurology follow-up.

Three months after discharge, she reported feeling well and was getting ready to return to work. She also stated that she was no longer using cannabis and K2.

Discussion

Most systemic effects of K2 ingestion are the result of its full agonist effect on CB1R and CB2R [5]. CB1Rs are abundant in many regions of the brain, while CB2Rs are concentrated in the hippocampus and ventral tegmental area, and regulate the dopaminergic pathway [6,7]. One of the postulated mechanisms of PRES caused by K2 consumption is activation of CB receptors, which leads to acute inhibition of synaptic neurotransmitter release in the brain [8]. Patients with K2 toxicity can present with vomiting, headache, chest pain, tachycardia, inability to speak, memory loss, numbness, seizures, stroke, hallucinations, paranoia, anxiety attacks, aggressive behavior, and suicidal ideation [7]. In severe cases, K2 intoxication can lead to cardiac arrest [9] and acute liver failure [10]. Our patient experienced episodic agitation, altered mental status, and partial complex seizures with post-ictal confusion.

PRES is a clinico-radiologic disorder characterized by symptoms of headaches, seizures, visual disturbances, and altered mental status, with the finding of white matter vasogenic edema of the posterior occipital and parietal lobes. PRES is often triggered by elevated blood pressure and the associated cerebral vascular damage and interstitial extravasation. Blood pressure plays a pivotal role in the pathogenesis of toxin-mediated PRES. A possible mechanism is the cerebral vasoconstriction causing infarcts in the brain, failure of cerebral autoregulation with edema, and endothelial damage with blood-brain barrier disruption. It is believed that the rapid rise in blood pressure is more important than the blood pressure itself [11,12]. Our case demonstrates that PRES syndrome can occur in patients without hypertension; therefore, the possibility of PRES should not be dismissed in normotensive patients.

PRES can also manifest in patients who are normotensive at presentation. Immunosuppressive or immunomodulatory therapies have also been implicated in the causation of PRES. In a large case series, it was shown that half of the patients with PRES had a history of immunosuppressive medication intake [13]. There is no direct connection between the serum levels of immunosuppressive medication and the development of PRES [14]. Few cases of PRES are related to consumption of alcohol [15], cocaine [16], mephedrone [17], kratom [18], and K2 [3] have been reported in the literature. We report the second case of PRES caused by consumption of K2.

Radiological abnormalities of PRES are often apparent on CT but are best described by MRI [19,20]. The typical findings of
PRES include bilateral areas of white matter edema in the posterior cerebral hemispheres, especially the parieto-occipital regions. The presence of vasogenic edema has been linked with worse clinical outcomes but not with the severity of presentation [21]. Our patient had nonspecific subtle high T2/FLAIR signal intensities in the regions of the posterior parietal and occipital cortices.

PRES should be promptly recognized, as it is reversible with appropriate management. There are no clinical studies on the management of PRES, and most of the current recommendations are based on observational data and focus on blood pressure control. In a patient presenting with a hypertensive emergency, the initial goal should be to lower diastolic blood pressure to 100-105 mmHg within 2-6 h, with maximum initial fall not exceeding 25% [22]. For patients with hypertension without end-organ damage, blood pressure-lowering guidelines are the same as described for hypertensive emergencies. Aggressive blood pressure-lowering should be avoided because it can lead to complications. Seizures can occur in PRES, and antiepileptic treatment has been used in selected patients [23]. Immunosuppressive therapy should be decreased or discontinued in patients with PRES [24]. Steroids have been used in the treatment of PRES, but they are not routinely recommended due to the associated risk of hypertension, which can worsen PRES [25]. Supportive care is the standard of care for patients presenting with PRES. Our patient clinically improved with supportive care.

Delayed diagnosis and treatment can lead to irreversible neurological deficit and death [26]. It is vital to have a low threshold for suspecting PRES based on clinical presentation, as neuro-imaging lags behind the clinical progression. In hypertension or toxin/drug-associated PRES, the effective therapy is the withdrawal of the drug, control of blood pressure, and antiseizure medication. In most cases, the syndrome is fully reversible within days to weeks [27]. According to a retrospective review, recurrence of PRES was seen in 4% of patients [28]. On rare occasions, some patients develop epilepsy after recovering from PRES [29]. Our patient did not develop epilepsy after recovering from PRES.

Conclusions

Our case highlights the importance of having a high clinical suspicion in patients presenting with altered mental status and a history of recreational drug use. K2 is not detected by routine urine drug testing, so a high level of clinical suspicion is required to request an extensive drug screen. It is important for the physician to counsel active synthetic cannabinoid users regarding these rare complications.

Declaration of figures’ Authenticity

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