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Case Report

A Case of Synthetic Cannabinoid Induced Ischemic Stroke in a 20-Year-Old Female

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Abstract

Synthetic cannabinoids, also known as "K2" or "spice", refer to a recreational drug that is chemically synthesized and becoming more frequently abused. Although many of the symptoms from acute intoxication of synthetic cannabinoids are similar to marijuana, there are additional adverse effects that are unique to the synthetic cannabinoids. We present a patient who presented to the hospital with acute encephalopathy/amnestic episode for 1-day duration and symptoms of abulia. An extensive workup in the hospital for common causes of acute encephalopathy came negative, but an MRI ended up showing findings consistent with acute ischemic stroke of the right caudate nucleus. Acute ischemic stroke has been described in the literature as an adverse effect from synthetic cannabinoids, but the mechanism of causing stroke is currently unclear. Physicians should be alerted to the potential adverse effects of synthetic cannabinoids and should consider synthetic cannabinoids as an etiology in patients presenting with symptoms consistent with an acute ischemic stroke.

Introduction

There are over 60+ cannabinoids found in marijuana (including THC, CBD, CBN, etc.) that each have their own distinct pharmacology [1]. The main physiologic effects of synthetic cannabinoids are similar to that of marijuana, including tachycardia, increased appetite, conjunctival injection, increased appetite, nystagmus, ataxia, etc. [1]. Synthetic cannabinoids differ from natural cannabinoids found in marijuana by having a slightly different chemical structure, but generally still bind to similar receptors with varying affinities [2]. Synthetic cannabinoids initially emerged as a way to avoid legal restrictions and drug detection, as they will not show up in urine drug tests [2]. Synthetic cannabinoids can also contain impurities that have been imparted from the synthesizing process that may add to their unique adverse effects. Additionally, synthetic cannabinoids can sometimes be mixed with other herbs that may have different physiological effects. It is impossible to know what proportion or mixture of herbs/synthetic cannabinoids are present in any given preparation without chemical testing of the sample. Generally synthetic cannabinoids have varying agonistic activity at the Cannabinoid Receptors (CB) and may have other effects on serotonin, NMDA, and dopamine receptors [2]. Because of the variety of multiple different active ingredients in synthetic cannabinoids, there is a heterogenous range of clinical symptoms that patients can present with. Some clinical manifestations that have been reported include agitation, coma, toxic psychosis, rhabdomyolysis, acute kidney injury, tachycardia, vomiting, agitation, hallucinations, hyperthermia, seizures, and ischemic stroke [3,4]. Our case describes a 20-year-old female who presented with signs of disorientation-confusion with abulia after smoking synthetic cannabinoids and who was subsequently diagnosed with an ischemic stroke.

Case Presentation

Our case begins with a 20-year-old female with no significant past medical history who presented to our emergency department with altered mental status. The patient had attended a county fair one day prior to admission and admitted to smoking marijuana with some friends at the event. She had smoked marijuana before, but this time, she admitted to using synthetic marijuana that a friend had brought to the event. Within a few hours of smoking the synthetic marijuana, the patient started experiencing profound memory loss and cognitive dysfunction that persisted throughout the day and continued into the following day. One day after the patient continued to experience this profound memory loss, the patient was brought in to our emergency department by her parents who were concerned that the patient was "not acting like herself".

On arrival, the patient was found to be tachycardic with a pulse of 116, blood pressure of 128/85, and temperature of 101.3 F. The patient had impaired memory with poor recall and insight in the events taking place in the last few days. Initially, the patient was alert and oriented to person and place. She was oriented to the current year, but had difficulty naming the current day/month. The patient was noted to also have an increased response-time to questioning and poor short term recall which was significantly different from her baseline level per her parents. The patient otherwise had no other focal neurologic deficits from a comprehensive neurologic exam. The patient's neck was supple and Kernig/Brudzinski's sign were both negative. Furthermore, the patient denied any other symptoms and denies headache, blurry vision, chest pain, shortness, abdominal pain, nausea/vomiting, constipation/diarrhea, fevers/chills, or dysuria (Figure 1).

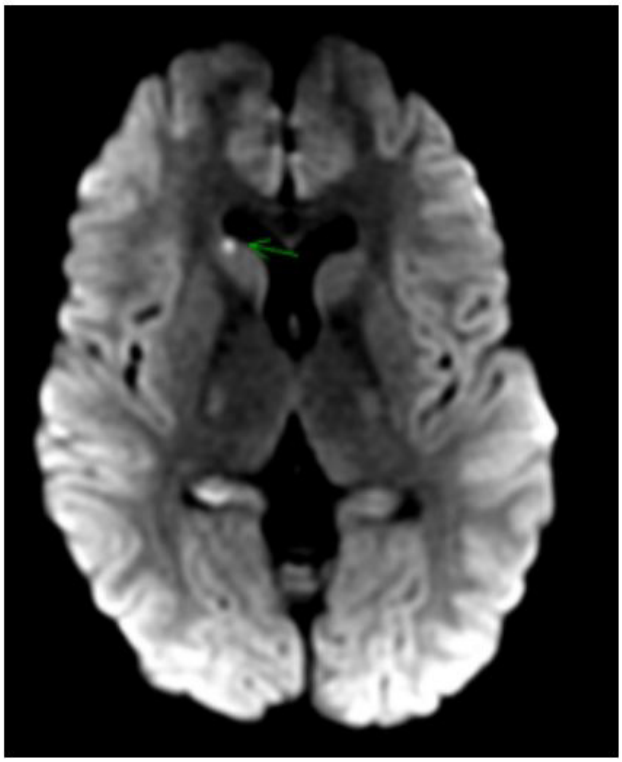

Figure 1: Axial Slice of MRI of the head showing a punctuate opacity on diffusion weighted imaging in the right caudate nucleus.

A CBC and CMP were obtained which was significant for absence of leukocytosis, AST of 96 units/liters, ALT of 70 units/liter, and a total Alkaline Phosphatase of 136 units/liter. An EKG showed normal sinus rhythm with no evidence of ST/T changes, but an initial troponin was found to be elevated at 0.129. Other labs obtained at the time were significant for an elevated Creatine Kinase of 626 units/liter, mildly elevated CRP, normal ammonia level, normal TSH/free T4, and normal INR/PTT. The patient's elevated troponins in the absence of chest pain and a normal EKG were thought to be likely secondary to demand ischemia. Additionally, serial troponins obtained 6 hours apart showed a downward trend from .129 to .056 to < .015. A urine toxicology screen came back positive for only marijuana. A noncontrast CT of the head showed no evidence of any acute intracranial process and no evidence of a bleed. A lumbar puncture was also obtained due to the patient's presentation with a fever and altered mental status. The lumbar puncture elicited a clear, colorless fluid with 1 WBC, 1 RBC, glucose of 58, and total protein of 21, which ruled out meningitis. A MRI, however, revealed small punctuate opacities in the right head and body of the caudate nucleus on diffusion-weighted imaging without definite low ADC concerning for an acute ischemic stroke. A GRE sequence was not performed. While the DWI and ADC did not correlate with each other, a diagnosis of ischemic stroke was made based on the patient's symptoms, exclusion of secondary causes, and her compatible signs/symptoms with the area of infarct involved on DWI. The patient was not a candidate for tPA and a full work up for secondary causes of stroke including TEE for PFO/intracardic thrombus, carotid ultrasound, prothrombin mutation, protein C/S activity, Factor V Leiden, and antiphospholipid antibodies were negative. A CT angiogram of the head and neck showed no evidence of cerebral vascular disease. HSV-1/2 PCR, HIV, and a MonoSpot were also obtained during her hospitalization and were found to be negative.

Throughout the patient's hospital stay, the patient was noticed to have an increased latency period to answering questions and a blunted emotional response. When the patient was told about her diagnosis of ischemic stroke and other laboratory abnormalities, there was a blunted emotional reaction from the patient and her response was generally nonchalant. Per the patient's family, her behavioral symptoms were vastly different from her baseline prior to the onset of her current symptoms (Figure 2).

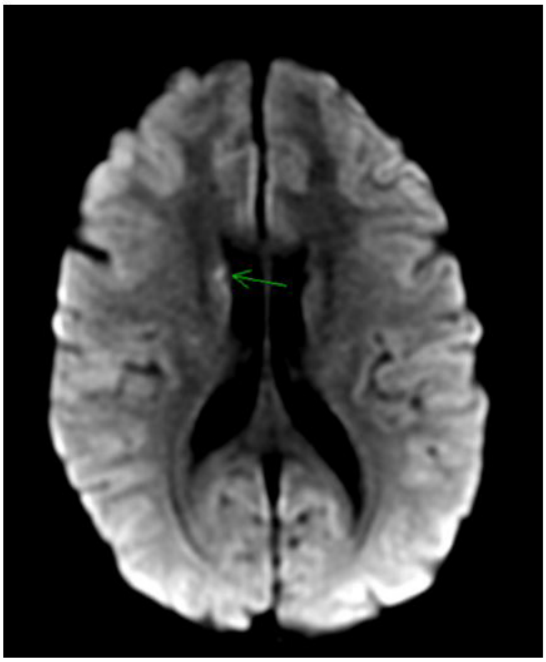

Figure 2: Axial Slice of MRI of the head showing a punctuate opacity on diffusion weighted imaging in the right caudate nucleus.

During the patient's hospital course, it was found that her liver function tests started to increase. Her AST rose from 95 units/L to a peak of 201 units/L and her ALT rose from 70 units/L to a peak of 166 units/L at day 3 before slowly down trending to normal limits. A liver ultrasound was obtained which showed a normal liver span with homogenous echogenicity. HIV, Hepatitis profile, anti-mitochondrial antibodies, ANA, c-ANCA, p-ANCA were all within normal limits. Her anti-smooth antibodies were found to be mildly elevated at 35 units, but the patient did not meet criteria for autoimmune hepatitis. The patient's memory and cognition improved mildly over the course of her hospitalization, but the patient never got back to her baseline cognition/memory level. Because the patient's stroke was deemed to be secondary to synthetic cannabinoids, it was thought that her best prophylaxis would be abstinence from further synthetic cannabinoids. The patient was still placed on temporary low dose aspirin for secondary stroke prophylaxis until follow up with outpatient neurology for further management and changes. The patient was scheduled to follow up with cardiology for long term cardiac monitoring to screen for atrial fibrillation/flutter, even though she was deemed to be low risk and there was no evidence of any arrhythmia on telemetry during her entire hospitalization stay. The patient, however, never followed up with neurology or cardiology after she was discharged.

Discussion

Cerebral infarction associated with synthetic marijuana has been described in the literature before and is considered to be a rare adverse effect [3]. The mechanism is currently unclear, but may be due to a reversible vasoconstrictive process, which has even been proposed in a case of marijuana induced ischemic stroke [5]. The most studied cannabinoids found in marijuana have predominantly vasodilatory properties, but there have been various cannabinoids found with vasoconstrictive properties [6]. Synthetic cannabinoids mimic the endogenous pharmacologic effects of natural cannabinoids found in marijuana but are structurally different. Thus, it is possible that these structurally different analogues have varying pharmacologic effects on different receptors. One study on the vascular activity of various cannabinoids illustrated that while most cannabinoids have vasodilatory properties, many cannabinoids had vasoconstrictve properties secondary to activation of prostanoid receptors [6]. The study further concluded that the direct vascular effects of cannabinoids can vary depending on the cannabinoid involved and the vascular bed it was being applied to. Another case report presented a patient who presented with a K2-induced STEMI [4], which further bolsters the theory that different preparations of synthetic cannabinoids have varying vasoconstrictive effects in different vascular beds. A similar case was described from our very own facility in the past, where a young patient with no risk factors presented with marijuana induced coronary vasospasm. It is possible that our patient's synthetic cannabinoid preparation may have had pharmacologic properties that were predominantly vasoconstrictive to certain parts of her cerebral vasculature resulting in an ischemic stroke. The varying affinities for different receptors due to the structural differences of synthetic cannabinoids would also explain why the synthetic cannabinoids are associated with their own unique toxicities and adverse effects. It can be concluded that certain strains/preparations of synthetic cannabinoids can have vasoconstrictive properties that can induce vasoconstriction of cerebral arteries resulting in an ischemic stroke. The reversibility and duration of the cerebral vasoconstriction could be based on the half-life/elimination of the active substances. The reversibility of this phenomenon could also explain why there was no evidence of cerebral artery disease on our patient's CT angiography of the head and neck, which was taken on her 3rd day of hospitalization.

Another postulated theory for an ischemic stroke secondary to synthetic cannabinoids is thought to be secondary to a cardioembolic event from a cardiac arrhythmia [4]. However, this is generally thought to result from chronic use of synthetic marijuana which could result in multiple short run episodes of tachyarrhythmias and predispose the patient to thrombus formation. Though our patient was tachycardic on initial presentation, it is worth mentioning that she was in sinus rhythm on arrival and throughout her stay.

Our patient's presentation is also atypical for ischemic stroke. Ischemic stroke is usually associated with a focal neurologic deficit and rarely presents with signs of altered mental status

alone. Altered mental status is considered to be a nontraditional finding, especially when there is a lack of focal neurologic deficits [7]. One study found that women were more likely to experience nontraditional symptoms when compared to men with altered mental status being a predominant symptom [7]. Additionally, during the patient's hospitalization, the patient had symptoms that were consistent with abulia. Abulia is defined as a lack of will or initiative. Symptoms of abulia can include decrease in will, poverty of behavior/speech, lack of initiative, loss of emotional responses, psychomotor slowing, and prolonged speech latency [8]. Our patient was noticed to have decreased cognition, a blunted emotional response, anhedonia, and a prolonged speech latency period which was consistent with symptoms of abulia.

Infarctions involving the caudate nucleus have been known to give symptoms of memory loss, impaired cognition, and abulia related symptoms. Ischemic strokes involving the caudate nucleus are relatively rare and diseases that affect the caudate are usually neurodegenerative in nature [9]. In one study examining clinical symptoms of patients with unilateral caudate infarcts, confusion-disorientation, abulia, dysarthria, and upper facial motor weakness were common with behavioral and cognitive abnormalities being the most prominent clinical features [9]. Willed behavior (including symptoms consistent with abulia) is thought to result from a complex neural circuit involving the anterior thalamus, caudate nucleus, globus pallidus, and internal capsule [10]. Injury to any of these structures can derail the neural circuit of willed behavior and give clinical manifestations consistent with abulia. Our patient's symptoms of impaired cognition, anhedonia, increased speech latency time, and blunted emotional response were consistent with the findings on the MRI of a unilateral ischemic stroke of the right caudate nucleus.

Synthetic cannabinoids also carry a number of adverse effects that are unique and rarely seen in marijuana use. Some of the clinical manifestations that have been reported include agitation, coma, toxic psychosis, rhabdomyolysis, acute kidney injury, liver toxicity, tachycardia, vomiting, agitation, hallucinations, hyperthermia, seizures, and ischemic stroke [4]. Our patient came in with tachycardia and hyperthermia without any source of infection. It has been postulated that the hyperthermia could be a manifestation of rhabdomyolysis [4], but additionally could have been a central hyperthermia secondary to her ischemic stroke. Hepatotoxicity is also a potential adverse effect of synthetic cannabinoids, but is usually more potent in cases where patients have ingested synthetic cannabinoids. Our patient's AST and ALT were also elevated on arrival and peaked at day 3 of her hospitalization before slowly trending down. Impurities that are instilled in synthetic cannabinoids during the manufacturing process can also contribute to a number of adverse effects as well.

Our patient was diagnosed with an acute stroke and was instructed that her best secondary prevention would be to avoid any further substance use. The patient was still discharged on low dose aspirin for secondary stroke prophylaxis temporarily until further follow up with an outpatient neurologist. The aspirin was unlikely to be beneficial in our patient's case as her stroke was deemed to be drug induced, but due to current lack of recommendations/guidelines for synthetic cannabinoid induced stroke and the low side effect profile of aspirin, it was deemed that this would be the best course of action until further risk stratification done with a neurology follow up. The patient was also set to follow up with cardiology for further cardiac monitoring for an underlying arrhythmia, however the patient never followed up with neurology or cardiology [11].

Conclusion

Synthetic Cannabinoids have a significant amount of serious adverse effects compared to regular marijuana. Our patient smoked synthetic cannabinoids and experienced an amnestic episode followed by disorientation and symptoms consistent with abulia before arriving at our emergency department. The patient was later found to have evidence on MRI of an acute ischemic stroke. Ischemic stroke secondary to synthetic marijuana use has been described in the literature, but currently there is poor insight on the pathophysiologic mechanisms that are involved. We propose that ischemic stroke from synthetic marijuana may be due to reversible vasoconstrictive properties. This case highlights a rare presentation of an adverse effect from synthetic cannabinoids as well as a rare presentation of an acute ischemic stroke. Physicians should consider ischemic stroke as an etiologic agent in patients presenting with a history of synthetic cannabinoid use.

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