A New Pattern of Imaging Findings of the Brain in Synthetic Cannabis Toxicity

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Abstract — Increasing use of synthetic cannabis is resulting in increasing number of visits to emergency rooms due to intoxication. Many of its adverse effects are similar to natural cannabis, although synthetic cannabis has shown to result in greater toxicity. In addition to psychosis, cardiac arrhythmias, myocardial infarction, and seizures, cases of embolic stroke have been reported due to use of synthetic cannabis. However, to our knowledge, there have been no studies to date which report a symmetric pattern of abnormalities on CT and MRI imaging, as seen in our case, which do not correspond to a vascular territory and which cannot be explained by embolic phenomenon. The imaging findings of this case support the hypothesis that synthetic cannabis may result in direct neurotoxicity.

Keywords — brain, cannabis, K2, marijuana, MRI, spice, synthetic

INTRODUCTION

With higher affinity, the active psychoactive components of synthetic cannabis interact with the cannabinoid-1 receptor, the same receptor to which tetrahydrocannabinol (THC) binds, the active ingredient of natural cannabis.1,2 Due to the lack of effective detecting methods, wide availability, affordability, and marketing practice, the use of synthetic cannabis has been increasing.3,4 Typical urine drug screens will not detect synthetic cannabinoids effectively. Many of the adverse effects of synthetic cannabis are similar to those experienced by individuals consuming natural cannabis, although synthetic cannabis is mixed with other compounds which may result in greater toxicity than what is known to occur with natural cannabis.5 Several cases of damage to the central nervous system (CNS), namely embolic ischemic stroke, have been reported following the use of synthetic cannabis,6,7 a finding which has also been associated with natural cannabis.8 However, to our knowledge, there have been no studies to date which report a symmetric pattern of abnormalities on magnetic resonance imaging (MRI) which do not correspond to a vascular territory and which cannot be explained by embolic phenomenon after use of synthetic cannabis. Recognition of this pattern of brain imaging findings can be important in prompt diagnosis of patients with acute synthetic cannabis intoxication in an emergency setting. In addition, the mechanism of injury to the brain by cannabis remains unknown. There is suggestion that cannabis might have direct toxicity on the brain by causing mitochondrial dysfunction.9 The pattern of imaging findings seen in our case may provide support to a similar hypothesis for neurotoxicity induced by synthetic cannabis.

CASE PRESENTATION

The patient is a 50-year-old male who was found unresponsive by his girlfriend in the morning of presentation. En route to the hospital, the patient was given Naloxone. He was taken to an outside hospital at approximately 11:30 am where he was reported to be minimally responsive and have jaw clenching and left gaze preference. Of note, the patient was last seen normal the night before around 10:00 pm when he was smoking K2 synthetic marijuana. Computed tomography (CT) at the outside hospital showed decreased attenuation in the basal ganglia bilaterally but was otherwise unremarkable (Fig 1A). Vital signs and glucose were normal, and National Institutes of Health (NIH) stroke scale score was 18. Urine drug screen was negative. Specific screening for synthetic cannabinoid metabolites was not performed due to the lack of an effective detection method. The patient was loaded with Fosphenytoin for concern for possible seizure. He was then airlifted to our institution for further evaluation and treatment. In the Emergency Department, the patient remained minimally responsive and was noted to have persistent left gaze preference; however, jaw clenching was no longer appreciated. Vital signs and glucose remained normal, and the NIH stroke scale score improved to 9.

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Figure 1. Noncontrast CT (A) and CT angiography (B) of the head. Panel A is an axial noncontrast CT image of the head showing symmetric hypodensity and mild swelling in the basal ganglia. Panel B is a maximum intensity projection (MIP) image from the head CTA demonstrating normal intracranial and distal neck arteries.

Figure 2. MRI images of the brain. Panels A & B show symmetric FLAIR hyperintensities in: (A) the basal ganglia and (B) the hippocampi and cerebral peduncles. Panels C & D demonstrate symmetric restricted diffusion in the bilateral basal ganglia characterized by: (C) hyperintensity on diffusion weighted imaging (DWI) and (D) hypointensity on the apparent diffusion coefficient (ADC) map.

The patient has a past medical history of hypertension, traumatic brain injury secondary to motor vehicle collision in 1990, schizoaffective disorder, alcohol abuse, deep vein thrombosis treated with Rivaroxaban, and prior suicide attempt by overdosing on pills. There is no family history of stroke or seizures. The patient’s home medications include Losartan, Lamotrigine, Sertraline, Tamsulosin, and Levothyroxine. He is a daily cigarette smoker and also consumes alcohol. He admits to marijuana use but no other illicit drugs.

MRI of the brain was obtained soon after transfer due to concern for stroke. The MRI demonstrated symmetric diffusion restriction with associated hyperintensities on fluid attenuation inversion recovery (FLAIR) images within the bilateral basal ganglia, hippocampi, cerebral peduncles, posterior inferior cerebellar hemispheres, and posterior limb of internal capsule with a few punctate foci in the bilateral frontal cortices and the cerebellar vermis (Fig 2 and Fig 3). Clinical workup for embolic causes of stroke was negative, including a CT angiography (Fig 1B) and an echocardiogram.

The patient was treated with supportive care for 10 days and discharged to rehabilitation with improved condition (awake, alert, but still confused). Aspirin was added to his list of home medications.

DISCUSSION

The toxic effects of synthetic marijuana on the brain have not been extensively studied to date. In particular, there is sparse data available in terms of MRI findings in patients with acute synthetic marijuana toxicity. A few case reports have been published which show diffusion restriction in a large vascular territory or in an embolic pattern. For example, a 28-year-old previously healthy female who presented with slurred speech and left-sided hemiplegia was found to have multiple embolic strokes in the right middle cerebral artery territory on MRI. Another study described two cases of a 22-year-old woman and a 26-year-old woman who presented with stroke-like symptoms hours after synthetic cannabis use. Both of these women were found to have large acute infarctions in the right middle cerebral artery territory. A different study described two young healthy siblings, ages 19 and 26, who presented with acute stroke-like symptoms following synthetic cannabis use, and both were found to have emboli in the left middle cerebral artery. However, no studies to date have shown a symmetric pattern of diffusion restriction affecting multiple parts of the brain as seen in our case, a pattern that does not correspond to a single vascular territory and cannot be explained by embolic phenomenon. Diffuse hypoxic and ischemic brain injury is a possibility, however, unlikely given the negative evaluations and his clinical condition at admission. Recognition of this pattern of imaging findings can be vital in prompt diagnosis of synthetic cannabis intoxication, an increasingly important emergency problem.

The mechanism of this type of CNS injury is unknown. For natural cannabis, recent publications suggest a combination of direct neurotoxicity and cerebral hypoxia/
ischemia related to cannabis-induced vasoconstriction. Studies have found that tetrahydrocannabinol, the main psychoactive component of cannabis, increases oxidative stress and induces cerebral mitochondrial dysfunction. Specifically, THC has been shown to decrease maximal oxidative capacity, decrease mitochondrial coupling, and increase hydrogen peroxide production. The limitation of our report was that specific screening to detect synthetic cannabinoid metabolites was not performed due to the lack of an effective detection method. Our correlation was based on the provided history of very recent synthetic cannabis use and the lack of other findings to explain the imaging characteristics. In addition, the precise chemical composition of synthetic cannabis is unknown and, in fact, may vary from product to product; however, several key components have been identified. The compounds JWH-018, CP-47,497, and JWH-073 were commonly found in many of the preparations and have been categorized as schedule I substances under the Controlled Substances Act in 2011. Unlike THC, which is a partial agonist of the CB-1 receptor, these synthetic cannabinoids are full agonists with high affinity. Several other toxic contaminants have been identified in various preparations of synthetic cannabis and include, but are not limited to, fatty acids and their esters, amide fatty acids, plant-derived substances, preservatives such as benzyl benzoate, additives such as alpha-tocopherol, and vitamin E. The addition of beta-2 agonists has been reported and may account for some of the sympathomimetic adverse effects. Given that the production of synthetic cannabis is not regulated, manufacturers do not list the entire chemical composition of their product on the label, making it difficult to pinpoint the exact compound resulting in toxicity.

REFERENCES


Figure 3. DWI images of the brain. Only DWI images are displayed to show the unique symmetric pattern of restricted diffusion. The FLAIR images (not shown) demonstrated corresponding hyperintensities in the DWI bright areas.


**Questions (please choose one single answer):**

1. Synthetic cannabinoids are increasingly a health problem because:
   A. They are marketed as safe and legal alternatives to natural cannabis.
   B. They are inexpensive and easily accessible to young people.
   C. They are not commonly detected in typical urine drug screens.
   D. They are labeled “not for human consumption” to mask their intended purpose.
   E. All of above.

2. Synthetic marijuana products are sold under the following names, except:
   A. K2
   B. Spice
   C. Fake Weed
   D. Black Rock
   E. Moon Rocks

3. Which of the following are potential side effects of synthetic cannabis?
   A. Agitation, confusion, hallucinations, and psychosis
   B. Seizures
   C. Myocardial infarction
   D. Ischemic stroke due to embolic events
   E. All of the above

4. What is the mechanism of action of synthetic cannabinoids?
   A. Agonist of the cannabinoid-1 receptor
   B. Antagonist of the cannabinoid-1 receptor
   C. Agonist of the THC receptor
   D. Antagonist of the THC receptor

5. What is a proposed mechanism for the potential neurotoxicity caused by cannabis ingestion?
   A. Inhibition of norepinephrine release
   B. Induction of inflammatory cascade
   C. Induction of mitochondrial dysfunction
   D. Increased GABA transmission

Correct answer: 1: E; 2: D; 3: E; 4: A; 5: C