

BRIEF COMMUNICATION

A case of acute cerebral ischemia following inhalation of a synthetic cannabinoid

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Objective. Synthetic cannabinoids are increasingly used in the United States as marijuana substitutes. However, reports of severe toxicity, resulting from their use, are limited. We present the case of acute cerebral infarction following synthetic cannabinoid inhalation. **Case report.** A 33-year-old man with no significant medical history presented at the emergency department with right-sided weakness and aphasia. He had smoked a synthetic cannabinoid (SC) product called “WTF” prior to the onset of symptoms. Physical examination showed right hemiparesis, dysarthria, and aphasia. Laboratory evaluation, electrocardiography, and computed tomography (CT) of the head were unremarkable. Following administration of intravenous tissue plasminogen activator, his symptoms improved. A repeat head CT showed acute infarction in the left insular cortex. His hypercoagulability panel was unremarkable, and the patient was discharged neurologically intact. Urine toxicology results were unremarkable. Analysis of the product by gas chromatography–mass spectrometry (GC–MS) procedure confirmed the presence of a synthetic cannabinoid known as XLR-11. **Conclusion.** XLR-11 has previously been associated with acute kidney injury in humans. However, there are no reports of it causing acute cerebral ischemic events. The close temporal association between XLR-11 inhalation and his stroke is concerning. Acute cerebral infarction may occur after XLR-11 use in healthy patients.

Keywords Synthetic cannabinoid; Ischemic stroke; XLR-11; JWH-018; Marijuana; Acute kidney injury

Introduction

Synthetic cannabinoids are increasingly used in the United States as novel psychoactive agents. These products are easily obtainable on the internet and at head shops (stores selling drug paraphernalia), generally sold in the form of chemical sprayed on plant materials and distributed as incense or potpourri.¹ Although structurally dissimilar from Δ^9 -tetrahydrocannabinol (Δ^9 -THC: the principal psychoactive component of marijuana), these synthetic compounds bind to CB1 cannabinoid receptors.² Unlike Δ^9 -THC that has only a partial agonist effect on the CB1 receptor, many of the synthetic cannabinoids are full agonists with higher potency.² Due to this desirable biological activity and the fact that they are usually not detected by common urine drug screening tests, synthetic cannabinoids are sold as marijuana substitutes.²

Regulation of synthetic cannabinoids is complicated because slight chemical structural modifications have historically allowed “street chemists” to evade analog provisions. Public health officials and other regulators continue to grapple for finding an appropriate solution to this ongoing problem. The Synthetic Drug Abuse Prevention Act of 2012 (SDAPA) is a recent regulation in the United States, which provides measures to classify most synthetic cannabinoids as regulated cannabimimetic drugs. However, there are instances where further regulatory action may be required to specifically list newly emerging synthetic cannabinoids as controlled cannabimimetics. It is not surprising that the lack of experience and quality control of these products raises concerns regarding their toxicities.³

Limited reports document seizures,^{3,4} supraventricular tachycardia,³ and acute myocardial infarction⁵ following synthetic cannabinoid use. Most recently, Freeman et al. reported on two young siblings, who developed ischemic strokes in close temporal relationship to JWH-018 use.⁶

We report a case of a 33-year-old man, who developed acute cerebral ischemia and infarction shortly following the use of the synthetic cannabinoid—XLR-11.

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Case details

A 33-year-old man with no significant medical history presented at the emergency department with right-sided weakness and aphasia. He had smoked two “joints” of a synthetic cannabinoid product labeled as “WTF” (Fig. 1) 10 min prior to the onset of symptoms. He denied any other drug use. His vital signs upon arrival were BP, 163/63 mmHg; pulse, 100/min; respiration, 16/min; oxygen saturation, 99% on room air; and afebrile. The patient was right-handed, and his initial physical examination was significant with right facial weakness/flattening of the right naso-labial fold, minor right hemiparesis, dysarthria, aphasia, and a mild right pronator drift. The National Institutes of Health Stroke Scale (NIHSS)⁷ score was 5. Initial chemistry and troponin I level were normal. Electrocardiography and a non-contrast head CT (Fig. 2a) were also unremarkable. His serum ethanol concentration was below the detection level (less than 10 mg/dL, Roche Ethanol Gen.2), and urine toxicology results were positive for opiates and negative for benzoylecgonine, cannabinoids, methadone, amphetamine, barbiturates, and benzodiazepines.

His blood pressure spontaneously normalized in repeat measurement, prompting administration of tissue plasminogen activator. Over the next 60 minutes, his NIHSS score had improved to 3, with an almost complete resolution of his neurological findings. Dysarthria had completely resolved, and his motor strength improved to 5/5 throughout the body. This left him with only a mild right facial weakness and a right pronator drift. A repeat head CT, performed the next day, showed acute infarction in the left insular cortex (Fig. 2b). A lipid panel, coagulation panel, hemoglobin A1c, and hypercoagulability panel including antithrombin III activity, protein C activity, protein S activity, and lupus anticoagulant were all within normal limits as was 48 h of continuous cardiac monitoring that failed to show any arrhythmias. Over the course of 3 days in the hospital, his neurological findings completely resolved and the patient requested to be discharged prior to completion of his

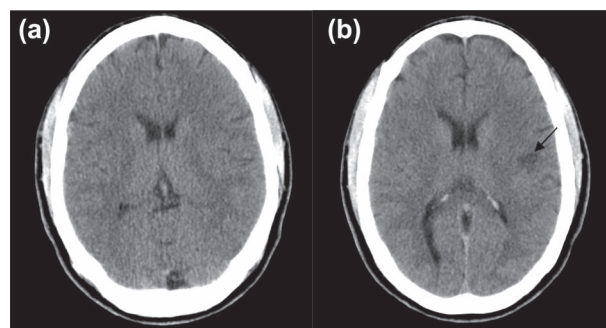


Fig. 2. (a) Non-contrast CT scan of the head upon arrival pre-tPA (tissue plasminogen activator). (b) Non-contrast CT taken the next day. Acute infarction in the left insular cortex is observed (arrow).

evaluation. He was discharged home on daily aspirin with an outpatient follow-up at the neurology clinic to obtain a brain MRI and echocardiography. The patient was also advised to stop using any synthetic cannabinoids. Unfortunately, he did not follow up for any of the recommended additional testing.

The actual product that he bought was tested using gas chromatography–mass spectrometry (GC–MS) at the Center for Drug Detection and Response (Little Rock, Arkansas). Validated GC–MS results confirmed the presence of synthetic cannabinoid—XLR-11 or 1-(5-fluoropentyl)-1H-indol-3-yl (2,2,3,3-tetramethylcyclopropyl)methanone. Toxicological testing of blood and urine samples collected approximately 1 h post inhalation was performed using a liquid chromatography tandem mass spectrometry assay previously validated for synthetic cannabinoids.^{8–10} Interestingly, neither the parent drug nor the predicted hydroxylated metabolite of XLR-11 were detected.

Discussion

While speculative, there are several pharmacokinetic, metabolic, and chemical examples that may explain the negative finding of this patient’s biological specimen. For example,

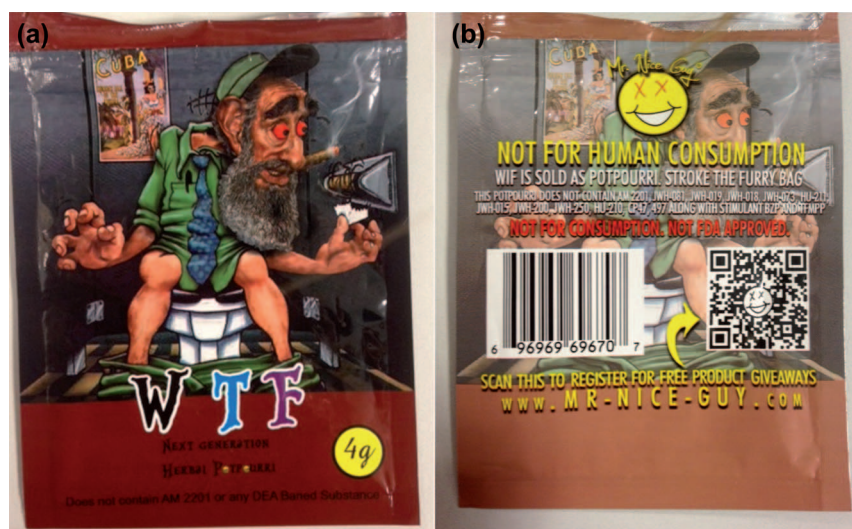


Fig. 1. Front (a) and back (b) view of the SC product package, “WTF,” that the patient brought.

XLR-11 may have a rapid half-life and/or may be rapidly metabolized to unidentified metabolites.

Some authors suggest that cases of cerebral ischemia associated with the use of synthetic cannabinoid could be due to the regular use of marijuana and genetic predisposition.^{6,11} The patient described in this report did not have any significant stroke risk factors, such as tobacco smoking history, marijuana smoking history, family history of stroke, cardiac dysrhythmias, or hypercoagulability, and his urine toxicology was negative for THC, supporting that he neither had recent nor chronic use of marijuana. The primary factor contributing to stroke in this case was the recent use of the synthetic cannabinoid—XLR-11. However, the possibility of other unidentified contaminants cannot be eliminated. Analysis of widely available products has shown that there is a complete lack of quality control during the manufacture of synthetic cannabinoid products, and that cannabinoid doses and ingredients vary between lots and even between the same package.¹²

XLR-11 has previously been associated with acute kidney injury in humans.¹³ However, there are no reports of XLR-11 causing acute cerebral ischemic events. The etiology of acute kidney injury is not clear, but it can be postulated that vasoconstriction causes decreased perfusion to both the kidney and the brain.

A history of synthetic cannabinoid use should be considered when young patients with low risks present with stroke symptoms.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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