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HEMORRHAGIC STROKE FOLLOWING USE OF THE SYNTHETIC MARIJUANA "SPICE"

The association between the street drug spice (K-2 or herbal incense), a synthetic marijuana, and intracranial hemorrhage (ICH) has not yet been described, but it has with acute ischemic stroke (AIS),¹ seizure, and myocardial infarction.² Two young patients (31 and 25 years old) independently presented to our hospital with subarachnoid hemorrhage (SAH) after spice inhalation. The first also had 2 large intraparenchymal hemorrhages (IPH); the other also had AIS. Both were previously healthy without hypertension, coagulopathy, bleeding diathesis, thrombocytopenia, intracranial aneurysm,

arteriovenous malformation, connective tissue disease, or anticoagulant/antiplatelet medication use.

Case reports. *Case 1.* A 31-year-old man had a generalized seizure at home after smoking spice. Initial blood pressure was 85/31 mm Hg. EKG was sinus rhythm, 65 bpm. Head CT revealed bifrontal SAH, with left frontal and right parieto-occipital IPH (figure 1A). Digital subtraction angiography (DSA) showed beading of the right middle cerebral, left anterior cerebral, and both posterior inferior cerebellar arteries (figure 1B), with dilation of the left posterior cerebral and both vertebral arteries. Intra-arterial verapamil was given. During follow-up DSA,

Figure 1 Noninvasive imaging and catheter-based cerebral angiography from case 1

(A) Admission noncontrast CT scan shows multiple intraparenchymal hematomas and bilateral frontal subarachnoid hemorrhages. (B) Digital subtraction angiography (DSA), left internal carotid artery injection, lateral view, shows multiple areas of vessel narrowing (vasospasm) within the left anterior cerebral and middle cerebral arteries (arrows). (C) DSA following administration of intra-arterial verapamil. Improved caliber of the left anterior cerebral artery is seen, indicating vasospasm improvement.

Figure 2 Noninvasive imaging and catheter-based cerebral angiography from case 2

(A) Admission CT shows diffuse subarachnoid hemorrhage. (B) Admission MRI demonstrates acute ischemic strokes in bilateral cortical hemispheres and the cerebellum on diffusion-weighted imaging (DWI) maps, with corresponding signal changes on apparent diffusion coefficient (ADC) maps. (C) Admission DSA, left vertebral artery injection, anteroposterior view. Uniformly decreased basilar artery diameter (arrows) indicates vasospasm. (D) Follow-up DSA on hospitalization day 6 shows worse vasospasm in the posterior circulation (arrows).

vasospasm improved (figure 1C). Laboratory studies and urine toxicology were unremarkable. Liquid chromatography tandem mass spectrometry (LC-MS/MS) was negative for AM-2201, JWH-018, JWH-019, JWH-073, and JWH-250. His spice packet was sent to the Drug Enforcement Administration (DEA), where gas chromatography/mass spectrometry confirmed XLR-11 ([1-(5-fluoropentyl)-1H-indol-3-yl] [2,2,3,3-tetramethylcyclo-propyl] methanone), a potent agonist for cannabinoid receptors CB1 and CB2. Examination revealed left homonymous hemianopsia and left leg paralysis, and mentation improved after 10 days.

Case 2. A 25-year-old woman presented with seizure after smoking synthetic and nonsynthetic marijuana at a party. Her medical history included

preeclampsia. Initial blood pressure was 130/77 mm Hg. EKG revealed sinus rhythm, 74 bpm. Examination revealed left leg monoplegia. CT showed SAH in the bilateral sylvian fissures and interpeduncular and prepontine cisterns (figure 2A). MRI demonstrated restricted diffusion in the left temporal lobe, left cerebellum, right frontal lobe, and bilateral parietal and occipital lobes, consistent with multifocal AIS (figure 2B). DSA demonstrated probable vasospasm with narrowed basilar and left vertebral arteries (figure 2C) and nonopacification of the right posterior cerebral artery. Follow-up DSA showed worsening vertebrobasilar vasospasm (figure 2D), improving modestly with intra-arterial verapamil. Urine toxicology was positive for cannabinoids. LC-MS/MS for synthetic cannabinoids was negative. Expanded testing for a wider array of synthetic cannabinoids was inconclusive.

Discussion. Synthetic marijuana analogues have gained popularity over the past decade among recreational drug users seeking an inexpensive legal high and drug-naïve curious experimenters.^{2,3} Packaged in plastic bags of dried leaves resembling potpourri and labeled herbal blends, air fresheners, or incense, spice often cannot be detected by routine drug tests. Specialized reference laboratories can analyze serum, urine, or saliva for many synthetic cannabinoids, and in 2011 the DEA categorized 5 (JWH-018; JWH-073; JWH-200; CP-47,497; and [C8]-CP-47,497) as Schedule I substances under the Controlled Substances Act.²

To our knowledge, spice-associated ICH has not been reported. Although our patients denied severe headaches, DSA showing early, transient vasospasm soon after ingestion suggests a reversible cerebral vasoconstriction syndrome-like mechanism, one of many proposed pathophysiologies for AIS associated with both cannabis⁴ and spice.⁵ Cannabinoids can rapidly alter neurotransmitter release from nerve terminals, potentially activating vascular smooth muscle cells while disrupting endothelial cell function, potentially resulting in both ischemia and hemorrhage.⁶ Transient vasospasm may also be a mechanism for the recently reported spice-associated acute renal failure,⁷ or arrhythmias and myocardial infarctions seen in healthy adolescents.² Alternatively, spice may cause ICH via direct sympathomimetic effects, a mechanism supported clinically by reports of concurrent tachyarrhythmias, palpitations, xerostomia, diaphoresis, and mydriasis.² The timing of spice use and hyperacuity of our patients' vasospasm (simultaneously with SAH, IPH, and AIS) suggests a possible causation—distinct from delayed, reactive vasospasm days after primary SAH.

XLR-11, identified in case 1, is a synthetic cannabinoid classified in 2012 as Schedule I in Florida,⁸ not included on routine toxicology screens. XLR-11

recently has been associated with acute kidney injury and AIS.^{5,7} New analogues are entering the market² and evading detection. Spice's association with seizures, heart attacks, renal failure, and now both ischemic and hemorrhagic stroke makes a thoughtful, thorough history critical.⁹

Although another etiology of ICH may exist (e.g., labile hypertension, occult connective tissue disease, noninflammatory vasculitis, amyloid angiopathy), our patients had an otherwise unrevealing workup (erythrocyte sedimentation rate, hs-C-reactive protein, platelets, coagulation, transthoracic/transesophageal echocardiograms, hypercoagulability panel). Nonetheless, spice may contain other, unknown components. Moreover, spice smokers may be polysubstance abusers. Methamphetamine use and an irregular, dilated radiculomedullary artery confounded one report of spice-associated spinal SAH.¹⁰ Our patients had no

further illicit drug use found on history or screening, vascular malformations, or other apparent risk factors.

Physicians, nurses, emergency medical technicians, hospitals, public health officials, educators, and law enforcement see dangers of inhaled synthetic compounds firsthand. Collectively, we should address this growing public health threat aggressively.

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Author contributions: David Z. Rose: drafting/revising the manuscript for content. Waldo R. Guerrero: drafting/revising the manuscript for content. Maxim V. Mokin: drafting/revising the manuscript for content. Clifton L. Gooch: drafting/revising the manuscript for content. Andrea C. Bozeman, ARNP: drafting/revising the manuscript for content. Julia M. Pearson: drafting/revising the manuscript for content. W. Scott Burgin: drafting/revising the manuscript for content.

Study funding: No targeted funding reported.

Disclosure: The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received February 9, 2015. Accepted in final form May 11, 2015.

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Comment: Spice, reversible cerebral vasoconstriction, and intracranial hemorrhage

There is a view prevalent in society that cannabis and its synthetic analogues are safe. However, there are increasing reports of ischemic stroke coming on during or soon after the use of cannabis and its synthetic analogues.^{1,2} Patients tend to be younger and without traditional vascular risk factors. A number of mechanisms have been proposed, including cardiac embolism, reversible vasoconstriction, and cerebral arteriopathy.

Two young patients with subarachnoid hemorrhage, one with intraparenchymal hemorrhage and the other with multifocal ischemic stroke, are presented in this issue of *Neurology*.³ Both patients had used the synthetic marijuana "spice" and one had also used nonsynthetic marijuana. Changes seen on digital subtraction angiography consistent with cerebral vasoconstriction improved with intra-arterial verapamil. In reporting subarachnoid and intraparenchymal hemorrhage, the authors have expanded the spectrum of adverse effects following the use of synthetic cannabinoids, and have confirmed that reversible cerebral vasoconstriction is a likely cause of stroke in at least some patients.

Reports such as this one emphasize the need for clinicians to ask about the use of, and screen patients for, cannabis and its synthetic analogues, particularly where there are no other stroke risk factors. Vascular imaging with CT or magnetic resonance angiography and even digital subtraction angiography should be considered where no other cause of stroke has been identified. Those patients with history of recent use of, or positive screens for, these agents should be counseled against further use as recurrent stroke has been reported with repeated exposure.

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Study funding: No targeted funding reported.
Disclosure: The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Neurology 2015;85;1177-1179 Published Online before print August 28, 2015

DOI 10.1212/WNL.0000000000001973

This information is current as of August 28, 2015

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2015 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

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