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,
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] methane), 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 preopticine 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-naive 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; 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 vasocostriction 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, potently 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.
recently has been associated with acute kidney injury and AIS.\textsuperscript{5,7} New analogues are entering the market\textsuperscript{1} and evading detection. Spice’s association with seizures, heart attacks, renal failure, and now both ischaemic and hemorrhagic stroke makes a thoughtful, thorough history critical.\textsuperscript{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.\textsuperscript{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.

From Morsani College of Medicine (D.Z.R., W.R.G., M.V.M., C.L. G., A.C.B., W.S.B.), University of South Florida; and Hillsborough County Medical Examiner’s Office (J.M.P.), Tampa, FL.

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Correspondence to Dr. Rose: drose1@health.usf.edu

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