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LICORICE-ASSOCIATED REVERSIBLE CEREBRAL VASOCONSTRICTION WITH PRES



The reversible cerebral vasoconstriction syndromes (RCVS) are a group of conditions characterized by reversible segmental constriction and dilatation of cerebral arteries, typically associated with recurrent thunderclap headaches, and often complicated by ischemic or hemorrhagic strokes.^{1,2} The posterior reversible encephalopathy syndrome (PRES) is another clinical–radiologic syndrome characterized by reversible, posterior-predominant brain edema, usually associated with headache, altered mental status, seizures, and visual symptoms.³ These entities may share pathophysiologic elements.¹⁻³ We report a patient with RCVS-PRES overlap syndrome associated with excessive licorice consumption. Knowledge of the pharmacologic effects of licorice may offer insights into the pathophysiology of RCVS and PRES.

Case report. A 49-year-old woman developed a severe headache reaching peak intensity within seconds. Similar thunderclap headaches recurred twice over the next 2 days and were associated with intermittent loss of central vision. On day 4 after symptom onset, she developed a generalized seizure. She was hypertensive (230/130 mm Hg), and her neurologic examination showed hyperreflexia. Urinalysis and toxicology screen were unremarkable. Brain MRI showed vasogenic edema in the bilateral parieto-occipital regions (figure, A), with underlying regions of brain hemorrhage detected on gradient echo sequences (not shown). Head CT angiogram (CTA) showed smooth, segmental narrowing of multiple intracranial arteries (figure, B), which was confirmed on gold standard transfemoral cerebral angiography (figure, C). Oral nimodipine was initiated. On day 5, her headache recurred. Repeat CTA revealed worsening cerebral vasoconstriction.

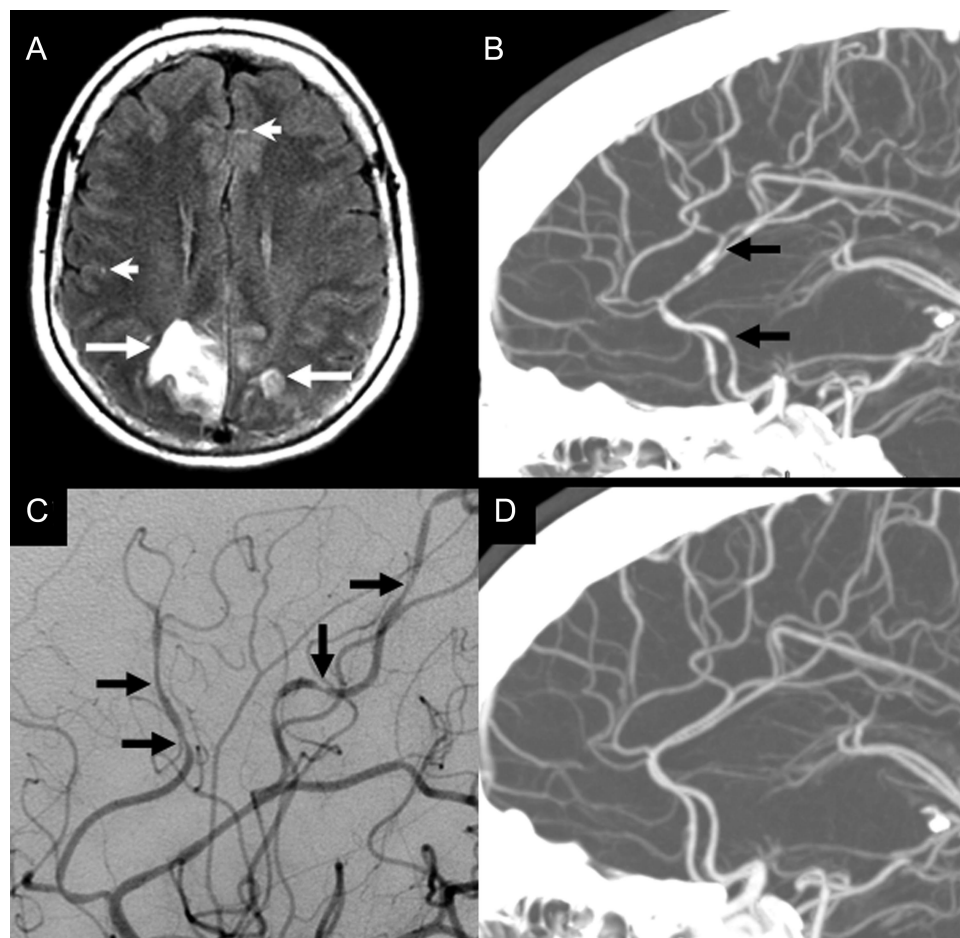
A diagnostic evaluation for etiologies of secondary hypertension showed elevated morning serum cortisol (12.3 $\mu\text{g/dL}$, normal $<10 \mu\text{g/dL}$), elevated urine free cortisol (260.4 mcg per 24 hours, normal 17–47 mcg per 24 hours), serum renin below the reference range ($<0.6 \text{ ng/mL}$), and serum aldosterone below the reference range ($<21 \text{ ng/dL}$). Urinary metanephrines were

normal. She was not taking any medications known to perturb the renal-angiotensin-aldosterone system. She denied taking any vasoconstrictive medications, illicit drugs, or over-the-counter agents. However, the medical team discovered a package of licorice at her bedside. Further inquiry revealed that she had been eating 1 pound per day for 4 months. She was instructed to discontinue licorice consumption.

By hospital day 8, the headaches had resolved, repeat morning cortisol level was normal at 5 $\mu\text{g/dL}$, and 24-hour urine free cortisol level had decreased to 61 mcg per 24 hours. Nimodipine was transitioned to long-acting oral verapamil before discharge. At 1- and 2-month follow-up visits, she was noted to be asymptomatic; blood pressure and neurologic examination were normal. Repeat tests showed normal serum and 24-hour urine free cortisol levels. CT/CTA performed after 3 months showed resolution of the lobar hemorrhages, edema, and vasoconstriction (figure, D).

Discussion. The onset of symptoms with recurrent thunderclap headaches, bilateral lobar hemorrhages, and reversible cerebral angiographic abnormalities are consistent with RCVS. However, the patient also had severe transient hypertension and reversible brain edema, consistent with PRES. This case exemplifies an increasingly recognized overlap between these 2 syndromes, and supports the hypothesis that they share pathophysiologic elements.¹⁻³

Excessive licorice consumption was the only identified precipitating factor. Licorice is derived from the root of the herb *Glycyrrhiza glabra*. The biologically active component, glycyrrhizic acid, inhibits 11β -hydroxysteroid dehydrogenase (11β -HSD). Excessive ingestion leads to a glucocorticoid and functional mineralocorticoid excess in the setting of low serum renin and aldosterone. This syndrome of apparent mineralocorticoid excess is characterized by metabolic alkalosis, hypokalemia, volume expansion, and hypertension.⁴ Inhibition of 11β -HSD via licorice in rat models is associated with hypertension, potentiation of vasoconstrictor activation, impaired vasorelaxation, and endothelial damage.⁵ These actions might explain the occurrence of PRES in our patient. Licorice derivatives, including glycyrrhetic acid and carbenoxolone, have



(A) Brain MRI, axial fluid-attenuated inversion recovery image showing bilateral parieto-occipital vasogenic edema (arrows). These lesions did not show restricted diffusion and are consistent with the posterior reversible encephalopathy syndrome. The hyperintense dots in the sulcal spaces (arrowheads) suggest the presence of dilated cortical surface arteries and have been reported in patients with the reversible cerebral vasoconstriction syndrome. (B) Head CT angiogram, sagittal maximum intensity projection images, and (C) transfemoral cerebral angiogram show smooth, segmental narrowing and dilatation of multiple cerebral arteries (arrows). (D) Follow-up head CT angiogram performed after 3 months shows reversal of the cerebral vascular abnormalities.

been shown to directly and indirectly enhance vasoconstriction within vascular smooth muscle.⁶ Furthermore, in vitro evidence of serotonin reuptake inhibition by licorice suggests a potential serotonin-mediated cerebral vasoconstrictive effect.⁷ RCVS has been previously associated with serotonin-enhancing drugs.^{1,2}

Despite the relatively long (4 months) interval between the start of excessive licorice consumption and onset of symptoms, the effects of licorice intake described above support a mechanistic relationship between licorice consumption and RCVS/PRES. Similarly, other drugs (e.g., sumatriptan, chemotherapeutic agents) are implicated in RCVS/PRES based on their mechanism of action and do not always have a close temporal relationship. These drugs may lower the threshold for developing RCVS/PRES or act in concert with other factors that ultimately precipitate these cerebrovascular syndromes.

This case suggests that RCVS and PRES represent syndromes along a spectrum of vascular dysregulation and endothelial dysfunction. Hormonal and serotonergic mechanisms appear to be important. In addition to prescription and illicit drugs, overexposure to common dietary products such as licorice may be a risk factor and should be explicitly reviewed in the medical history.

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ces; his wife receives royalties from publishing *Obstetric Anesthesia* (Cambridge Pocket Clinicians, 2007); serves/has served as a consultant to CryoCath® Technologies Inc., Research Triangle Inc., Massachusetts Department of Public Health, and the Canadian Stroke Network; and receives research support from Lundbeck Inc., the NIH (NINDS P50 NS051343-01 [Coinvestigator], NINDSU01 NS052220 IMS-3 [Site PI], NCRR 1 UL 1 RR025758-01 [CRC Staff]), and the Department of Health and Human Services (CDC 5U13 DP001176-02 [PI]); and has provided expert medical opinions in malpractice lawsuits [re: stroke treatment and prevention]. Dr. Singhal has received research support from the NIH/NINDS (R01NS051412 [PI], P50 NS051343 [PI, Project 1], P01 NS035611 [Coinvestigator], R01NS059775 [Coinvestigator], R01NS38477 [Coinvestigator], and R21NS061119 [Coinvestigator]); has provided expert medical opinions in malpractice lawsuits; and his wife is an employee of, and owns stock and stock options in, Vertex Pharmaceuticals.

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