

Brief Communication

Catastrophic Reversible Cerebral Vasoconstriction Syndrome Associated With Serotonin Syndrome

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Objectives.—To report fulminant cases of reversible cerebral vasoconstriction syndrome (RCVS) in the setting of serotonin syndrome.

Background.—RCVS is characterized by acute onset of severe headaches, with or without neurologic deficit, with evidence of reversible cerebral vasoconstriction. It is often benign, and prognosis is generally considered favorable. In the largest prospective study on RCVS, only 4% of patients were disabled from strokes and there were no fatalities.

Methods.—We report a case series.

Results.—We report 2 women with history of depression on selective serotonin re-uptake inhibitors who presented with thunderclap headache and dizziness, respectively. Through the course of hospitalization, both patients developed rigidity, diaphoresis, fever, tachycardia with labile blood pressures and clonus on examination. Since there was a recent addition/increase in a known serotonergic agent, they met criteria for serotonin syndrome. Cerebrovascular imaging in both patients revealed severe multi-focal vessel narrowing. The first patient developed large bi-hemispheric ischemic infarcts and increased intracranial pressure that was refractory to management, and she eventually expired. The second patient developed bilateral parieto-occipital strokes and decerebrate posturing. Her course slowly stabilized, and she was eventually discharged with residual left-sided hemiparesis. Repeat cerebrovascular imaging 1 month later showed normal vessels. In both patients, intra-arterial nicardipine infusion improved angiographic appearance of stenoses, consistent with RCVS.

Conclusions.—Both cases satisfied the Sternbach criteria for serotonin syndrome. Fatality in case 1 prevents demonstration of reversal of cerebral vasoconstriction, but improvement of arterial diameters with intra-arterial calcium channel blockers in both cases suggests that both had RCVS. Serotonergic agents are known triggers of RCVS, but the concurrent presence of serotonin syndrome likely precipitated the malignant course in our patients. Severe clinical and angiographic manifestations should be considered as part of the spectrum of RCVS.

Key words: reversible cerebral vasoconstriction syndrome, serotonin syndrome, thunderclap headache, stroke

Abbreviations: CSF cerebrospinal fluid, CT computed tomographic, IA intra-arterial, INR international normalized ratio, MRA magnetic resonance angiography, MRI magnetic resonance imaging, RCVS reversible cerebral vasoconstriction syndrome

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Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by acute onset of severe headaches, with or without neurologic deficit, with evidence of reversible cerebral vasoconstriction. The course of RCVS is often benign, and prognosis is

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generally considered favorable. In the largest prospective study on RCVS patients, only 4% were disabled from strokes and there were no fatalities.¹ We report 2 patients who developed a fulminant course of RCVS in the setting of serotonin syndrome. Although serotonergic drugs are commonly implicated as putative agents for triggering RCVS,² there have been no reports of RCVS with concomitant serotonin syndrome. We hypothesize that concurrent presence of serotonin syndrome likely precipitated the malignant course in our patients.

CASE 1

A 45-year-old female with depression on escitalopram 10 mg daily presented to a local hospital with thunderclap headache and confusion. Three weeks prior, she had sustained accidental head trauma, which was treated with hydrocodone. Past medical history included migraine, and mechanical aortic and mitral valve replacements secondary to remote infectious endocarditis, for which she was maintained on anticoagulation.

She was hospitalized and treated with intravenous dihydroergotamine and multiple doses of hydromorphone. Her initial neurological examination was normal without focal neurological deficits. International normalized ratio (INR) was >9 on admission. Initial brain magnetic resonance imaging (MRI) showed T2 hyperintensities in the cerebellum, resembling posterior reversible encephalopathy syndrome, but did not demonstrate acute ischemia or hemorrhage (Fig. 1A,B). Repeat MRI brain 2 days after symptom onset showed focal T2 hyperintensity in the bilateral parietal subarachnoid space consistent with a bleed (Fig. 1C). Magnetic resonance venogram was normal, and magnetic resonance angiography (MRA) demonstrated narrowing in the proximal anterior and middle cerebral arteries. The patient was started on verapamil and corticosteroids for presumptive RCVS 2 days after onset of thunderclap headache. During the hospital course, she also had intermittent fevers, for which empiric meningitis coverage antibiotics were initiated. Cerebrospinal fluid (CSF) was obtained and showed 1 red blood cell/ μ L, 1 white blood cell/ μ L, protein of 37 mg%, and negative cultures. Urine toxicology demonstrated pres-

ence of tetrahydrocannabinol. Antibiotics were discontinued after CSF results were obtained. A transthoracic echocardiogram was done, which showed no evidence of valvular vegetation, thrombus, or other source of cardiac embolism.

Fourteen days after symptom onset, she acutely worsened with deteriorating mental status, fevers, tachycardia, rigidity, and hyperreflexia. A repeat MRI on that day showed patchy bilateral acute infarcts predominantly in the parieto-occipital region (Fig. 1D,E). She was intubated and transferred to our institution 2 days later. Although we are not certain, the escitalopram was presumably stopped after the development of the above symptoms, and was off the medication list when transferred to our institution. Admission INR was 5. She was comatose on examination with decerebrate posturing but maintained preserved brainstem reflexes. She was also extremely rigid and had clonus, in addition to significant blood pressure and heart rate lability. A computed tomographic (CT) head scan showed large bi-hemispheric ischemic infarcts with mass effect and sulcal effacement. A cerebral angiogram on day 16 after symptom onset showed severe segmental vessel narrowing in all vascular distributions. Infusion of intra-arterial (IA) nicardipine into the right and left internal carotid artery and the right vertebral artery resulted in moderate angiographic improvement. Aggressive medical and surgical management of raised intracranial pressure was unsuccessful. Repeat MRI brain revealed large bi-hemispheric infarcts, with significant edema and midline shift (Fig. 1F). Worsening examination and imaging prompted family to withdraw care, and the patient passed away few hours after extubation.

CASE 2

A 57-year-old female with chronic opiate dependence on buprenorphine 8 mg t.i.d., and depression on bupropion 200 mg b.i.d. and mirtazapine 15 mg daily, with recent increase in citalopram dose (from 40 mg daily to 60 mg daily), presented to a local hospital with dizziness of 4 days duration. A day after admission, she developed acute confusion, followed by a seizure and unresponsiveness. On examination, she was diaphoretic, febrile, tachycardic with mark-

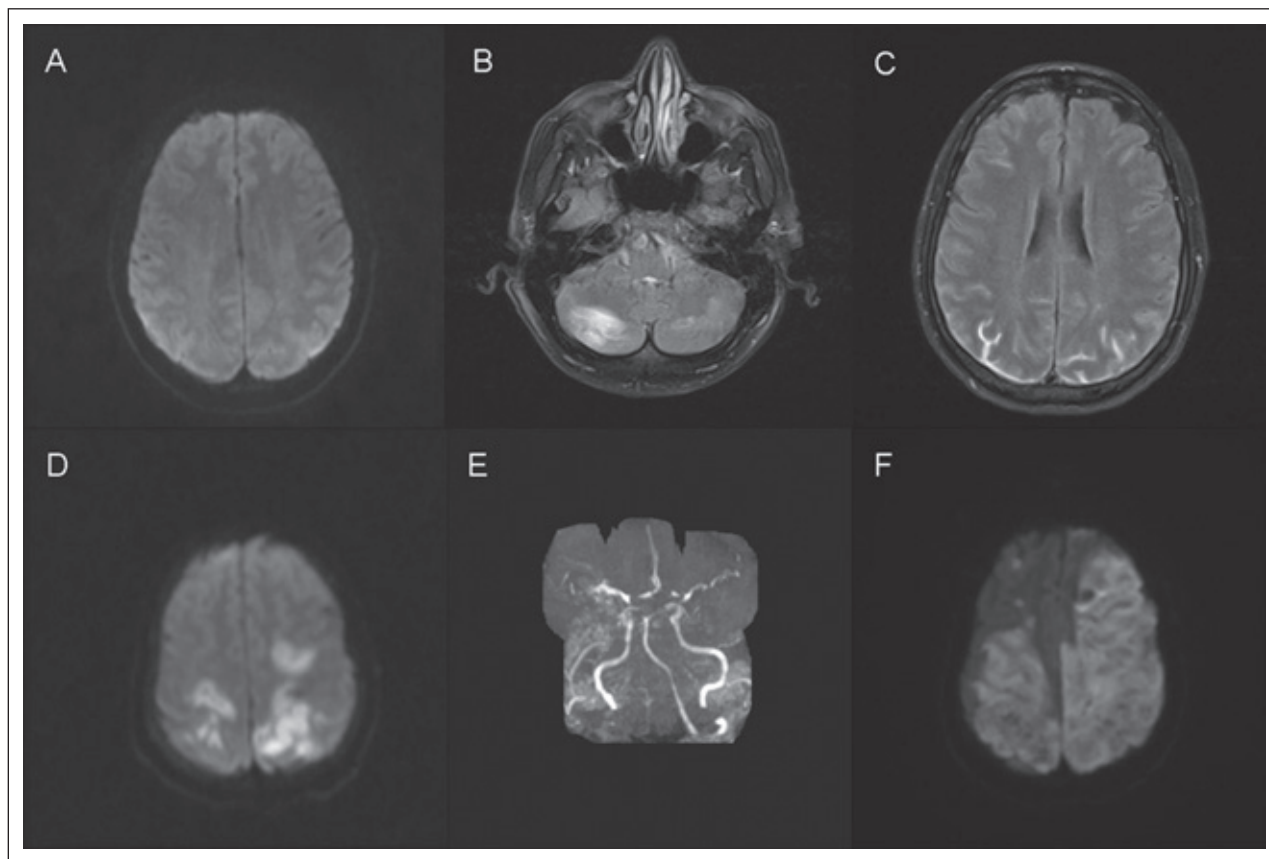


Fig 1.—Axial magnetic resonance imaging images of case 1. Diffusion weighted imaging (DWI) upon presentation demonstrated absence of restricted diffusion (A). Fluid attenuated inversion recovery on admission (B) and 2 days after symptom onset (C) showed hyperintensities in the cerebellum and then sulcal hyperintensities in addition, respectively. Repeat imaging 14 days after symptom onset demonstrated acute infarcts on DWI (D) in the bilateral fronto-parietal lobes, and there was narrowing of the bilateral middle and anterior cerebral arteries on intracranial magnetic resonance angiography (E). Large bi-hemispheric acute infarcts seen on DWI, 19 days after symptoms onset (F).

edly labile blood pressures, rigidity, and hyperreflexia. A CT head showed bilateral parieto-occipital hypodensities, and an MRI confirmed bilateral parietal infarcts. She was intubated and transferred to our hospital where initial exam was similar but also revealed decerebrate posturing and clonus, although she continued to remain awake and intermittently follow commands. A CT head was repeated on day 8 after symptom onset, which showed new areas of hypoattenuation in the posterior frontal lobes. A CT angiogram demonstrated diffuse vessel narrowing. A cerebral angiogram confirmed severe vessel narrowing worse in the posterior circulation. In the absence of structural lesions, the decerebrate posturing was hypothesized to be from brainstem hypoperfusion, and IA nicardipine was administered into the right

and left internal carotid artery and the right vertebral artery, which improved the narrowing slightly. The antidepressants were stopped, and cyproheptadine was started for presumed serotonin syndrome. She was also started on verapamil. Twelve days after symptom onset, due to a period of worsening decerebrate posturing, another cerebral angiogram was performed and revealed improvement in narrowing in all vascular territories. IA verapamil was injected into the basilar artery, with marked improvement in its caliber. Although her initial course was characterized by hemodynamic instability and worsening rigidity, she started to improve a day after the second angiogram. At the time of discharge, she had residual left-sided hemiparesis. An MRA repeated 26 days after symptom onset was normal (Fig. 2). Three

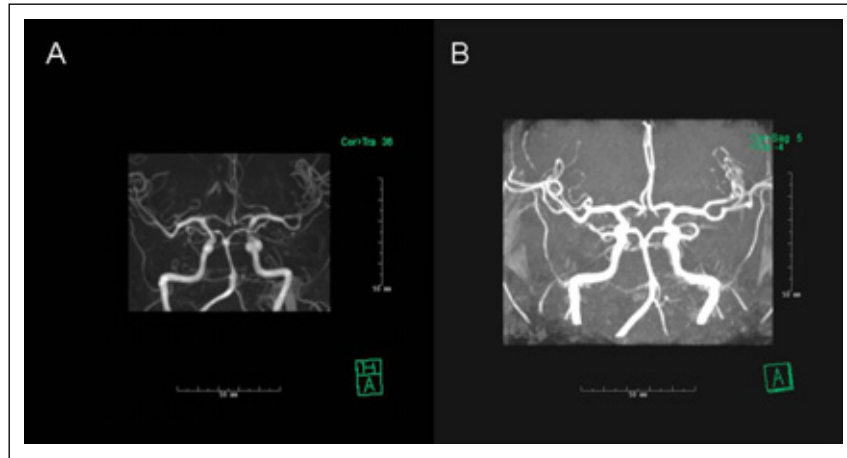


Fig 2.—Intracranial magnetic resonance angiography (MRA) images of case 2. MRA done 10 days after symptom onset (A) showed diffuse distal vessel irregularity in the anterior cerebral and posterior cerebral arteries, and moderate degree of basilar artery stenosis. MRA repeated 26 days after symptom onset (B) was normal.

months after hospital discharge, the patient did not have any further episodes of thunderclap headache or new neurological deficits, and the hemiparesis had significantly improved.

An extensive evaluation for other causes of ischemic stroke was unrevealing in both patients. Serum did not reveal markers of systemic autoimmune disease, and CSF revealed was normal, including nucleated cell count and protein (case 2 CSF: 29 red blood cells/ μ L, 1 white blood cell/ μ L, protein of 22 mg%, normal immunoglobulin G synthesis, and negative cultures). A transthoracic and transesophageal echocardiogram was done in case 2, which did not show any evidence of valvular vegetations or thrombus.

DISCUSSION

We report 2 cases of RCVS with severe diffuse vasospasm causing large ischemic strokes and death in 1, and severe functional ischemia in the other. Death in case 1 prevents demonstration of reversal of cerebral vasoconstriction, but improvement of arterial diameters with IA calcium channel blockers in both cases suggests that both had RCVS.³ Tetrahydrocannabinol is associated with and is a known precipitant of RCVS, and could have precipitated the attack in case 1. Headache was conspicuously absent in case 2, and this is exceptional in RCVS. Both cases satisfied the Sternbach criteria of serotonin syndrome, which

require the recent addition of or increase in a known serotonergic agent (escitalopram and dihydroergotamine in the first case, increased citalopram in the second, with opiates contributing to both). The criteria also require the absence of other possible etiologies (infection, substance abuse, withdrawal, etc), *plus* no recent addition or increase of a neuroleptic agent, *and* at least 3 of the following symptoms: mental status changes (confusion, hypomania), agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, or fever.⁴ Both cases also had clonus, which is the cardinal feature for the diagnosis of serotonin syndrome by the Hunter's criteria.⁵

Posterior reversible encephalopathy syndrome (PRES) is found in a significant proportion of patients with RCVS,⁶⁻¹⁰ and patients with PRES also demonstrate diffuse or focal vasculopathy and vessel pruning in up to 87% of cases.¹¹ Both conditions can also have similar clinical presentations, including acute onset headache, visual changes, and seizures. In addition, both conditions can also have similar precipitating factors, like immunosuppressive and cytotoxic medications.¹² As such, there is a significant overlap between these syndromes, and they may represent a continuum of the same disease with a common pathophysiology. Impaired vascular autoregulation is hypothesized to cause PRES. Vascular permeability contributes to vasogenic edema, and progressive increase in vascular resistance causes

vasoconstriction, which when severe produces irreversible ischemic infarction.^{11,12} Usually, ischemia is contained within the area of vasogenic edema. In case 1, patient had large bi-hemispheric infarcts that clearly extended beyond the area of posterior predominant vasogenic edema. In case 2, imaging revealed cytotoxic edema from the acute ischemic infarcts without any vasogenic edema. These factors support the diagnosis of RCVS, with concurrent presence of PRES in case 1.

The long-term prognosis of RCVS is usually benign and is generally considered favorable. Prognosis is dependent on the development of strokes, but most patients recover gradually with minimal deficits. In the 3 largest cohorts of RCVS patients, the combined fatality was less than 1%.⁸⁻¹⁰ However, the course can be extremely variable, and some patients can develop severe vasospasm with subsequent large strokes and massive cerebral edema. Most fatal cases of RCVS have been associated with post-partum vasoconstriction.¹³⁻¹⁶ It is unclear why this is the case, but there is female preponderance in RCVS, and both of our cases are women.

Serotonergic agents, including selective serotonin re-uptake inhibitors,² serotonin and noradrenaline re-uptake inhibitors,¹⁷ ergotamine derivatives,¹⁸ triptans,^{10,19} and 3,4-methylenedioxymethamphetamine ("ecstasy"),²⁰ are commonly associated with RCVS. It is unknown whether these drugs are present coincidentally or causative, or whether they trigger vasoconstriction in a susceptible individual. Serotonin-induced vasoconstriction is mediated by its action on the 5-HT_{1B} and/or 5-HT_{2A} receptors, which are found on the smooth muscle cells in peripheral and cerebral vessels.²¹ Upregulation of the 5-HT_{1B} receptors in cerebral blood vessels has been shown to occur in subarachnoid hemorrhage²² and ischemia.²³ As such, the magnitude of the vascular response can vary according to pathophysiological state.

Although a number of reports have described the occurrence of RCVS with serotonergic agents, there have been no reports of RCVS along with concomitant serotonin syndrome. The presence of the serotonin syndrome might have caused these patients to take a malignant course. Continued inadvertent administration of serotonergic agents in the presence

of ischemia and subarachnoid hemorrhage could have further worsened vasoconstriction and extended the infarcts.

Severe clinical and angiographic manifestations should be considered as part of the spectrum of RCVS. Careful attention should be paid to patient medication lists and recent drug exposures. We hypothesize that excess serotonergic activity can potentially cause severe vasospasm and precipitate a fulminant course. Recognition of this syndrome and the impact of serotonergic agents are important for treating clinicians. The diagnosis of RCVS in the acute setting is challenging, but this syndrome should be considered especially with presentations of thunderclap headache. Recurrent thunderclap headache after an initial negative evaluation with non-contrasted head CT and CSF should also raise the suspicion for possible RCVS.

STATEMENT OF AUTHORSHIP

Category 1

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Category 2

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