Pearls & Oy-sters: A Journey Through Reversible Cerebral Vasoconstriction Syndrome

Sex, Drugs, and Headaches

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Pearls

- Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by thunderclap headache and reversible constriction of intracranial arteries; it may present with immediate or delayed neurologic deficits related to brain edema, ischemic or hemorrhagic stroke, or seizure.
- Classic conditions and triggers associated with RCVS include recent/ongoing pregnancy, migraine, physical exertion, sexual activity, and most notably, substances like ergot derivatives, sumatriptan, serotonin-specific reuptake inhibitors, cocaine, amphetamines, and marijuana.
- Although RCVS is a self-limiting condition with a mostly good prognosis, thunderclap headache should always be evaluated as a medical emergency. Ergot derivatives and triptans, which are commonly used to treat acute migraine, are contraindicated in RCVS.

Oy-sters

- RCVS complications can appear delayed (such as stroke or edema): while initial imaging may appear normal in up to 55% of cases, 81% of patients eventually develop brain lesions. These patients require close observation, and a consideration of admission.
- A normal noncontrast CT or MRI scan does not rule out RCVS. Although less frequent than subarachnoid hemorrhage (SAH) (38%), intraparenchymal hemorrhage (IPH) is still common in patients with RCVS (20%).
- Headache, vessel changes, and IPH require a broad differential, which includes RCVS, sinus venous thrombosis, hemorrhagic stroke, and SAH.

A 32-year-old woman presented to the emergency department (ED) with a sudden-onset right-sided, postcoital throbbing headache reaching maximal intensity within seconds. It was associated with photophobia, phonophobia, nausea, vomiting, and subjective left leg numbness. She denied any visual disturbances and examination was recorded as normal. She had a remote history of migraine and heavy use of marijuana. Her only medication was occasional ranitidine. She was given a prescription and a dose of sumatriptan before being discharged home. No neuroimaging was ordered and neurology was not consulted. She returned 3 days later with worsened, intractable headache. Blood pressure was 142/77 mm Hg and examination was significant for left superior quadrantanopia. She was admitted to the hospital for workup and management.

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Investigations

On admission, noncontrast CT of the head showed an intracerebral hemorrhage (ICH) in the right temporal lobe with extension into the right lateral ventricle and perifocal edema suggesting that the bleeding occurred more than a day prior.

MRI and magnetic resonance angiogram (MRA), done 6 days after symptom onset, showed right posterior temporal and parietal ICH with adjacent subarachnoid blood (figure, A). There was multifocal segmental vascular narrowing and irregularity in the anterior and posterior circulation bilaterally, in the basilar artery, both posterior cerebral arteries, particularly the P2 and P3 segments, right M2 branches, left sided M2 and M3 branches, and bilateral distal V4 segments (figure, B). There was no aneurysm or vascular malformation. Normal flow-related signal loss (i.e., flow void) was present in the right transverse and sigmoid sinuses (not shown). Digital subtraction angiography (DSA) showed multifocal segmental narrowing involving all cerebral arteries bilaterally, as well as posteroinferior segmental arteries bilaterally (figure, C). Internal carotid, intracranial, vertebral, and basal artery were widely patent.

Lumbar puncture (LP) revealed 193 nucleated cells and no oligoclonal bands. Protein was 193 mg/L (<100 mg/dL). Pregnancy test was negative. The patient had normal levels of urine vanillylmandelic acid, homovanillic acid, 5-hydroxindoleacetic acid, and serum total immunoglobulin G. C-reactive protein was 5.6. She tested negative for C3 and C4 complement deficiency, anti-nucleic acid antibodies, rheumatoid factor, anti-double-stranded DNA antibody, anti-neutrophil cytoplasmic antibodies, HIV, syphilis, Lyme disease, CSF cultures, herpes simplex virus, and varicella zoster virus.

Diagnosis

Repeat DSA at 3 months showed complete resolution of multiple focal segmental narrowing (figure, D). What appeared to be a filling defect in the right transverse sinus (figure, B) was an artifact related to positioning and flow-related phenomenon of the noncontrast MRA, making venous thrombosis less likely. It is also possible that ICH precipitated thunderclap headache (TCH). The more likely cause of TCH was RCVS with a secondary ICH, which resulted in the development of visual disturbance. RCVS was likely triggered by an episode of coitus and previous heavy consumption of cannabis, and was likely worsened by sumatriptan.

Treatment

The patient was treated with nimodipine 60 mg q4 hours for a total of 35 days. Her headache was controlled with acetaminophen. She experienced great improvement of her symptoms. She was discharged home with the left superior quadrantanopia still present. At 3 months, her visual deficits and headache have nearly resolved. Despite recommendations, she continues to smoke marijuana.

Discussion

RCVS is characterized by acute, severe, or TCH and constriction of intracranial arteries, which reverses within 3 months. TCH is best defined as sudden, excruciating headache that reaches its peak intensity in seconds to less than a minute.[1] It is often described by patients as the "worst headache of my life." RCVS is one of the more common causes of TCH evaluated in the ED and may be as common as SAH.[1] It must be stressed that a normal neurologic examination does not rule out a serious cause of TCH.

In about 85% of cases, RCVS presents as TCH.[2] In more than half of cases, RCVS has numerous triggers and conditions, including recent/ongoing pregnancy, history of migraine, physical exertion, sexual activity, and most notably, sympathomimetic substances like ergot derivatives, antidepressants (including serotonin-specific reuptake inhibitors), over-the-counter medications (for cold, flu, and diet), cocaine and amphetamines, as well as sumatriptan and marijuana.[1–3] Females are at a higher risk of RCVS.[3] In up to 43% of cases, TCH is accompanied by focal neurologic findings.[2] Even if TCH is the only presenting symptom, urgent brain imaging is needed to rule out cerebral edema, bleed, or infarction.[3]

RCVS is often clinically indistinguishable from other causes of TCH, and RCVS may account for up to 46% of all TCH.[4] Differential diagnosis of RCVS includes SAH and ICH of other causes, acute migraine, cerebral sinus venous thrombosis, meningitis, spontaneous intracranial hypotension, pituitary apoplexy, and arterial dissection.[5] Causes of multifocal segmental narrowing of intracranial arteries, notably primary angiitis of the CNS (PACNS), must also be differentiated.[1]

The pathophysiology of RCVS is not well understood. The prevalent hypothesis implicates a transient dysregulation of cerebral arterial tone.[3] This abnormality of cerebrovascular tone could, in turn, be triggered by (either endogenous or exogenous) sympathetic overactivity, endothelial dysfunction, and oxidative stress.[1]

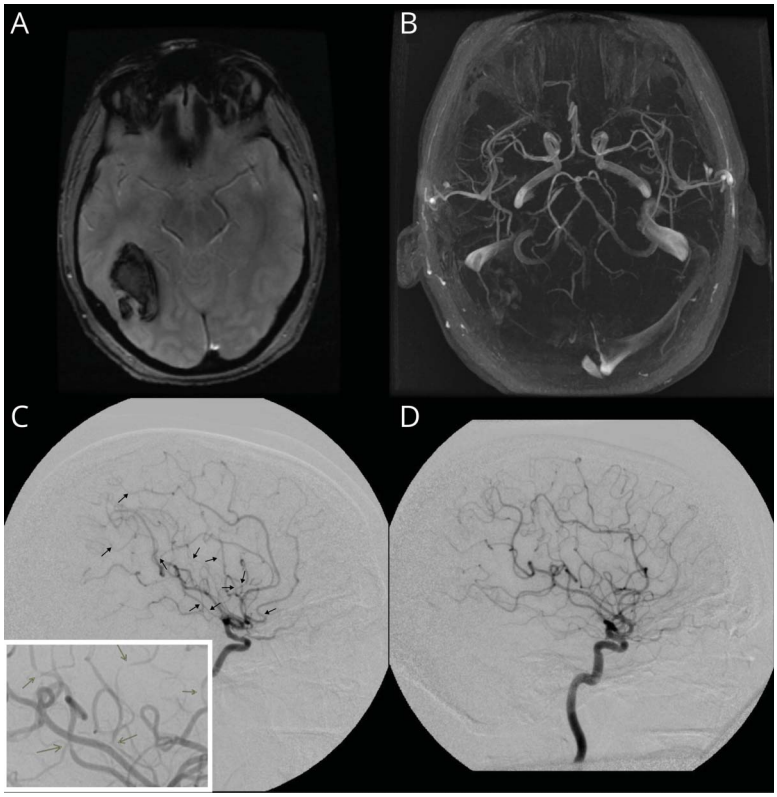
Investigations of TCH include urgent imaging of the brain and cerebral vessels with CT/CT angiogram (CTA) or MRI/MRA. If the initial imaging is unremarkable, the next step is usually LP. Routine CSF investigations include measurement of opening pressure, protein, and cell counts. Although the CSF is usually normal or near normal in RCVS, up to 3% of patients with RCVS may have elevated white cell counts,[2] as was seen in our case; this may be explained by aseptic inflammation in response to intraventricular extension of the ICH. In SAH, CSF will typically have persistently high erythrocyte count in tubes 1 and 4 or evidence of xanthochromia; in meningitis, CSF will contain high cell counts, protein, and, if it is a bacterial infection, low glucose.

CSF samples may also be stored for more comprehensive testing. Repeat imaging is frequently needed during hospital stay. Although in up to 55% of cases initial CT or MRI may be reported as normal, 81% of patients eventually develop brain lesions: ischemic stroke (39%), brain edema (38%), or convexity SAH (34%); less frequent than SAH, lobar ICH is still common in patients with RCVS (20%).[2] In cases of SAH, baseline vessel imaging (such as CTA or MRA) can be helpful in distinguishing RCVS from other causes of SAH.[6] For example, narrowing of ≥2 arteries and bilateral vessel narrowing suggests SAH due to RCVS, rather than to aneurysm or cryptogenic SAH.[6] Not only does baseline CTA help identify aneurysms or vascular malformations, diffuse and multifocal vasoconstriction that is unrelated to the presence or location of subarachnoid blood (as in our case) favors RCVS.[6] In addition to the benefits of CTA, time-of-flight MRI does not require contrast and can identify flow void—loss of signal in both arteries and venous sinuses when patent. The angiographic findings seen in RCVS are classically described as segmental narrowing and dilatation, commonly known as "string of beads" or "sausage string" appearance.[7] Of note, up to 45.8% of patients who presented with acute severe headaches and were subsequently diagnosed with RCVS had radiographic evidence of arterial wall inflammation; this suggests that RCVS is more than simply sustained vasospasm.[8] Repeat vessel imaging is useful to differentiate RCVS from PACNS: whereas subsequent imaging of RCVS will demonstrate improvement/reversal of vasospasm (figure, D), PACNS will show persistence or worsening/progression. $RCVS_2$ is a recently described tool that assists with the diagnosis of RCVS without repeat vascular imaging.[9] In that study, a score of 5 or greater had 99% specificity and 90% sensitivity for the diagnosis of RCVS; in contrast, a score of 2 and less had 100% specificity and 85% sensitivity for excluding RCVS. In our case, the $RCVS_2$ score was 10 (5 points for TCH, 3 for vasoactive trigger, 1 for sex, 1 for SAH).

Treatment of RCVS is supportive. In case of ICH, routine care includes blood pressure control, seizure treatment, avoidance of triggers, and treatment of vasospasm with calcium channel blockers such as nimodipine.[3] There is no established role for corticosteroids in RCVS.[2,3] Although some patients with RCVS have a history of migraine, triptans or ergot derivatives are contraindicated, as they may worsen RCVS.[3]

RCVS is an important cause of TCH and is characterized by reversible vasoconstriction of cerebral arteries. Classic triggers of RCVS must be elucidated by obtaining a careful and specific history. Because a normal neurologic examination does not rule out a life-threatening case of TCH, it must be investigated as an emergency. Delineation of the presenting TCH and early recognition of RCVS, especially in patients with a longstanding headache history, is essential. Misdiagnosis of RCVS may lead to adverse events and inappropriate, potentially harmful use of triptans or ergot derivatives.

Figure Imaging Findings of Reversible Cerebral Vasoconstriction and Intraparenchymal Hemorrhage



(A) Axial gradient echo MRI scan. There is a parietal lobar hemorrhage with surrounding edema and local mass effect. (B) Noncontrast time-of-flight magnetic resonance angiogram shows multifocal segmental narrowing and irregularity of the basilar artery and both posterior cerebral arteries, particularly the P2 and P3 segments. There is also narrowing of several right M2 branches and several left-sided M2 and M3 branches of middle cerebral arteries. There is flow void in the right transverse and sigmoid sinuses (not shown). (C) Lateral view of baseline cerebral angiogram of the right internal carotid artery (ICA) shows multifocal cerebral arterial narrowing (magnified in an inset). (D) 3-month cerebral angiogram of the right ICA shows resolution of multifocal narrowing.

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Appendix Authors

Name	Location	Contribution
Maksim Son, MD	Department of Clinical Neurologic Sciences, Western University, London, Canada	Gathered data, wrote the manuscript
David Dongkyung Kim, MD	Department of Clinical Neurologic Sciences, Western University, London, Canada	Gathered data, reviewed the manuscript
Ruba Kiwan, MD	Division of Neuroradiology, Department of Radiology, Western University, London, Canada	Gathered data, reviewed the imaging and figure legends
Michael Mayich, MD	Division of Neuroradiology, Department of Radiology, Western University, London, Canada	Reviewed the imaging and the manuscript

Appendix *(continued)*

Name	Location	Contribution
Alexander V. Khaw, MD	Department of Clinical Neurologic Sciences, Western University, London, Canada	Conceived the study, reviewed the imaging and the manuscript

References

1. Ducros A, Wolff V. The typical thunderclap headache of reversible cerebral vasoconstriction syndrome and its various triggers. Headache 2016;56:657–673.
2. Singhal AB, Hajj-Ali RA, Topcuoglu MA, et al. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. Arch Neurol 2011;68:1005–1012.
3. Velez A, McKinney JS. Reversible cerebral vasoconstriction syndrome: a review of recent research. Curr Neurol Neurosci Rep 2013;13:319.
4. Cheng YC, Kuo KH, Lai TH. A common cause of sudden and thunderclap headaches: reversible cerebral vasoconstriction syndrome. J Headache Pain 2014;15:13.
5. Long D, Koyfman A, Long B. The thunderclap headache: approach and management in the emergency department. J Emerg Med 2019;56:633–641.
6. Muehlschlegel S, Kursun O, Topcuoglu MA, Fok J, Singhal AB. Differentiating reversible cerebral vasoconstriction syndrome with subarachnoid hemorrhage from other causes of subarachnoid hemorrhage. JAMA Neurol 2013;70:1254–1260.
7. Papathanasiou A, Zouvelou V, Breen DP, et al. Reversible cerebral vasoconstriction syndrome as a cause of thunderclap headache: a retrospective case series study. Am J Emerg Med 2015;33:859.e3–6.
8. Chen CY, Chen SP, Fuh JL, et al. Vascular wall imaging in reversible cerebral vasoconstriction syndrome: a 3-T contrast-enhanced MRI study. J Headache Pain 2018;19:74.
9. Rocha EA, Topcuoglu MA, Silva GS, et al. RCVS(2) score and diagnostic approach for reversible cerebral vasoconstriction syndrome. Neurology 2019;92:e639–e647.