Rare disease

A reversible cerebral vasoconstriction syndrome

Fang Ba, Fabrizio Giuliani, Richard Camicioli, Maher Saqqur

Division of Neurology, University of Alberta, Edmonton, Canada

Correspondence to Maher Saqqur, maher.saqqur@ualberta.ca**Summary**

Reversible cerebral vasoconstriction syndrome (RCVS) is typically presented with severe headaches where, vascular imaging demonstrates multiple intracranial arterial narrowing. Variable triggers are related to RCVS, such as serotonin agents and bromocriptine. Thus, a detailed medication history is important. Subarachnoid haemorrhage (SAH) is not uncommon in RCVS. Repeat vascular imaging at 2–3 months with complete reversal of the narrowed vessels confirms the diagnosis of RCVS.

The authors present a case where use of triptan along with multiple psychotropic medications, was associated with RCVS. Neuroimaging demonstrated focal SAH and diffuse beaded appearance involving the intracranial vasculature. The patient improved clinically with oral nimodipine treatment. Repeat angiography and a follow-up transcranial Doppler showed complete resolution of vasoconstriction.

In the setting of acute severe headache, with any 'red flags', it is important to evaluate the medication use and other precipitating risks for RCVS. Vascular imaging is the key for diagnosis.

BACKGROUND

Reversible cerebral vasoconstriction syndrome (RCVS) is considered a rare phenomenon that was first reported by Call and Fleming in 1980's. The diagnosis remains difficult. Angiography can document segmental cerebral artery vasoconstriction with no evidence for subarachnoid haemorrhage (SAH). Other clinical features include normal or near-normal cerebrospinal fluid (CSF) analysis, and acute headache with or without additional neurologic signs or symptoms. The diagnosis cannot be confirmed until the angiographic abnormality is reversed within 12 weeks after onset. Multiple medications can precipitate RCVS. Because it is rare, it is still underdiagnosed commonly.

CASE PRESENTATION

A 39-year-old female presented with acute onset of severe-bifrontal-throbbing headache, associated with nausea, vomiting, photophobia and phonophobia. She had a long history of migraine without aura. She had taken naratriptan, with relief of the headache after 4 h. However, the headache recurred the next day, and persisted for the next 6 days despite daily naratriptan. The patient did not report fixed language deficit, motor or sensory changes or seizures. She had intermittent agitation and confusion, manifesting as disorientation and incoherent speech, lasting up to 2 h, which were different than her usual migraine. She was brought to the hospital, and subsequently admitted to neurosurgery, because of a small right frontal cortical SAH. The patient had a history of hypertension, dyslipidemia, migraine without aura and fibromyalgia. She was taking atorvastatin, triamterene/hydrochlorothiazide, topiramate, methadone, quetiapine, venlafaxine (serotonin norepinephrine reuptake inhibitor (SNRI)), sertraline (selective serotonin reuptake inhibitor (SSRI)) and baclofen daily for over 2 years.

On assessment, blood pressure was 125/72 mm Hg. Neurological examination did not reveal focal signs. During

the first 2 days of hospitalisation, she was agitated and had fluctuating level of consciousness.

INVESTIGATIONS

CT scan revealed the small acute haemorrhage within a single sulcus of the left frontal lobe (figure 1a). A cerebral angiogram showed a diffuse beaded appearance of the intracranial vasculature (figure 1c). Brain MRI did not demonstrate additional findings (figure 1b). Investigations including a vasculitic investigation were negative (normal white count, coagulation panels including lupus anticoagulant and antiphospholipid antibody, renal function, liver panels, C reactive protein, erythrocyte sedimentation rate, antinuclear antibodies/extractable nuclear antigens, rheumatoid factor, cryoglobulin, thyroid stimulating hormone, antineutrophil cytoplasmic antibodies, viral hepatitis serology, HIV serology and syphilis serology and urine cytodiagnosics).

CSF analysis showed no white blood cells, and normal chemistry. Microbiology studies were negative and no oligoclonal bands were present. Electroencephalograph did not show any epileptic discharges.

DIFFERENTIAL DIAGNOSIS

Vasospasm versus vasculitis or primary arteritis of the central nervous system was initially considered in the differential diagnosis. After negative vasculitic investigation, a presumed diagnosis of RCVS was considered.

TREATMENT

She was treated with nimodipine 60 mg po every 4 h. Naratriptan was stopped on admission. She was put on a methadone withdrawal program. SSRI dose was reduced to half, (aiming for discontinuation), SNRI was tapered as well and topamax was left unchanged.

Figure 1 (a) CT scan showed a small subarachnoid haemorrhage within a single sulcus of the left frontal lobe. MRI brain did not reveal additional findings (b). A cerebral angiogram showed a diffuse beaded appearance of the intracranial vasculature (c). Repeat angiogram 12 weeks after showed complete resolution of the narrowing of the vessels (d).

OUTCOME AND FOLLOW-UP

Transcranial doppler 4 weeks postdischarge did not record any haemodynamic changes at bilateral internal carotid artery, middle cerebral artery or arterial cerebral artery. She was clinically stable. A repeat cerebral angiogram 3 months postevent showed complete resolution of the segmental narrowing, which is consistent with diagnosis of RCVS.

DISCUSSION

Our case likely demonstrated RCVS associated SAH in the setting of polypharmacy, including the use of naratriptan. RCVS predominantly affects young individuals between the ages of 20 to 50 years, with a preference for the female sex (64% female).^{1 2} Multiple case series and case reports have shown that this condition is associated with migraine and other primary headaches, traumatic head injuries, transient hypertensive emergencies and the postpartum period.^{2 3} Thunderclap headaches with photophobia and phonophobia are the hallmark of its clinical presentation, raising the concern of SAH.¹ Focal neurologic deficits including seizures are common.⁴ In most cases, the course of the disease is relatively benign, with symptoms resolving spontaneously within 2 to 6 weeks. Medical complications including haemorrhagic and ischaemic strokes with neurological deficit do occur.^{1 5}

The aetiology of RCVS is unknown though, based on CSF studies, there is no evidence to suggest an inflammatory process. In rare cases, prolonged and severe vasoconstriction might result in secondary inflammatory changes.⁶

The use of multiple medications has been shown to precipitate RCVS.^{1 4} Triptans, a category of potent vasoconstrictors, can precipitate RCVS.⁷⁻⁹ Here, we present a unique case where the frequent use of naratriptan was associated with RCVS in the setting of using multiple other medications, including serotonergic medications, antipsychotics and opioids.

RCVS is rare, and its onset and triggers are unpredictable. Patients with RCVS face major diagnostic challenges and alternate diagnoses should be considered in patients with server headaches representing a change from a typical headache pattern as reported here. The angiographic picture can resemble vasculopathies (ie, fibromuscular dysplasia) and possible vasculitis. A thorough investigation with negative CSF analysis and normal immunological tests would be against a diagnosis of vasculitis. For a confirmed diagnosis of RCVS, spontaneous reversal of the vasoconstriction is a required criteria, and it usually occurs within 6 to 12 weeks after the initial presentation.³ In the largest available case series study, Ducros *et al* reported that a significant portion of RCVS patients (22%) developed cortical non-aneurysmal SAH¹ as seen in our case, which is presumably caused by the rupture of a pial vessel. However, the diffuse arterial constriction in areas far from the subarachnoid bleed, argued against the diagnosis of SAH-related vasospasm.

Cerebral vasoconstriction in patients with a history of migraine has been reported, and has been termed as 'migraine angiitis', and 'migrainous vasospasm'.⁴ Many

patients with RVCS had a history of primary headache disorder. Multiple headaches are an uncommon presentation in RCVS in the literature. Because of the headache history the diagnosis of RCVS can be delayed. In addition, attention should be drawn to the treatment strategies for patients with migrainous headaches. Serotonergic agents, especially triptans, are commonly used in migraine attack but repeated and daily use of triptans is not recommended. In the setting of severe headache presenting with or without focal neurological deficit, it is vital to carefully assess the headache history with a detailed medication profile. Different pharmacologic agents that need to be considered as potential precipitants include ergotamine, pseudoephedrine cocaine, amphetamines, ecstasy, cannabis, bromocriptine and over-the-counter decongestants (table 1). Immunological investigation, CSF examination and vascular imaging are the key components for a diagnosis of RCVS.

In the majority of cases, RCVS has a good prognosis and is usually a self-limiting condition characterised by reversible vasoconstriction. However, some patients may have fluctuating focal neurologic deficit including seizures. Both ischaemic and haemorrhagic strokes have been reported,^{1 5} with cortical SAH being the most common presentation.^{1 4 10} In a large case series, of the 22% of patients with cortical SAH, all were female.¹ However, ischaemic strokes tend to occur later. Chen *et al* in their large post-RCVS MR angiography series showed that the extent and degree of arterial constriction reached their maximum during the first month even when the headaches resolved.¹¹ It is critical to follow patients closely in the first month even their symptoms resolved. The rate of permanent neurologic deficit due to RCVS is low compared with other stroke syndromes.^{1 12} The possibility of recurrence of RCVS is exceedingly low though it is prudent to avoid medications such as triptans or ergotamine to treat these patients.

In our patient, oral nimodipine may have provided benefit in symptom management. In addition, triptans were discontinued, and SNRI/SSRI and opiates were adjusted to lower dose. Two prospective case series in evaluating the efficacy of nimodipine did not confirm their benefits in improving vasoconstriction in RCVS.^{1 13} However, previous case reports indicated a variable success, particularly by intravenous nimodipine in severe case.¹⁴ Intravenous magnesium, steroids and dantrolene have been used in RVCS, however, no standard treatment strategy has been established.¹⁴

Table 1 Precipitating medications associated with RCVS

Precipitating medications and substrates
Illicit drugs and toxins
Binge drinking alcohol; Cocaine, amphetamine derivatives, cannabis, ecstasy, lysergic acid diethylamine
Dopamine or serotonin agents
Ergot derivatives, triptans, selective serotonin reuptake inhibitors, methergine, bromocriptine, lisuride, isometheptine
Over-the-counter preparations
Nasal decongestants, pseudoephedrine, phenylpropanolamine, ephedrine
Chemotherapy agents
Tacrolimus, cyclophosphamide
Blood related products
Intravenous immune globulins, red blood cell transfusion, interferon α , erythropoietin

Adapted from^{1-2 11}.

CONCLUSION

The difficulties associated with the diagnosis and management of RCVS are related to the rarity of the condition, the wide range of clinical presentations, the variety of possible precipitating factors and the lack of a standard treatment strategy. Patients presenting with acute onset of severe headache, particularly with 'red flags' should be evaluated thoroughly, and RCVS should be considered in the differential diagnosis. A detailed medication history is exceedingly important in cases of RCVS since multiple serotonergic agents can lead to RCVS. Vascular imaging is vital to establish a diagnosis.

Learning points

- ▶ RCVS is typically presented with severe headaches where, vascular imaging demonstrates multiple intracranial arterial narrowing.
- ▶ Variable triggers are related to RCVS. A detailed medication history is important.
- ▶ SAH is not uncommon in RCVS.
- ▶ Repeat vascular imaging at 2–3 months with complete reversal of the narrowed vessels confirms the diagnosis of RCVS.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. Ducros A, Boukobza M, Porcher R, *et al*. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. *Brain* 2007;**130**(Pt 12):3091–101.
2. Singhal AB, Hajji-Ali RA, Topcuoglu MA, *et al*. Reversible cerebral vasoconstriction syndromes: analysis of 139 cases. *Arch Neurol* 2011;**68**:1005–12.
3. Calabrese LH, Dodick DW, Schwedt TJ, *et al*. Narrative review: reversible cerebral vasoconstriction syndromes. *Ann Intern Med* 2007;**146**:34–44.
4. Singhal AB, Caviness VS, Begleiter AF, *et al*. Cerebral vasoconstriction and stroke after use of serotonergic drugs. *Neurology* 2002;**58**:130–3.
5. Santos E, Zhang Y, Wilkins A, *et al*. Reversible cerebral vasoconstriction syndrome presenting with haemorrhage. *J Neurol Sci* 2009;**276**:189–92.
6. Calado S, Viana-Baptista M. Benign cerebral angiopathy: postpartum cerebral angiopathy: characteristics and treatment. *Curr Treat Options Cardiovasc Med* 2006;**8**:201–12.
7. Dash S, Bogdanova O, Xavier A, *et al*. Cerebral vasospasm from sumatriptan. *Neurology* 2004;**63**:2128.
8. Varghese A, Hong Z, Weir EK. Serotonin-induced inhibition of KV current: a supporting role in pulmonary vasoconstriction? *Circ Res* 2006;**98**:860–2.
9. Edvinsson L, Uddman E, Wackenfors A, *et al*. Triptan-induced contractile (5-HT_{1B} receptor) responses in human cerebral and coronary arteries: relationship to clinical effect. *Clin Sci* 2005;**109**:335–42.
10. Call GK, Fleming MC, Sealfon S, *et al*. Reversible cerebral segmental vasoconstriction. *Stroke* 1988;**19**:1159–70.
11. Chen SP, Fuh JL, Wang SJ, *et al*. Magnetic resonance angiography in reversible cerebral vasoconstriction syndromes. *Ann Neurol* 2010;**67**:648–56.
12. Chen SP, Fuh JL, Lirng JF, *et al*. Recurrent primary thunderclap headache and benign CNS angiopathy: spectra of the same disorder? *Neurology* 2006;**67**:2164–9.
13. Chen SP, Fuh JL, Chang FC, *et al*. Transcranial color doppler study for reversible cerebral vasoconstriction syndromes. *Ann Neurol* 2008;**63**:751–7.
14. Nowak DA, Rodiek SO, Henneken S, *et al*. Reversible segmental cerebral vasoconstriction (Call-Fleming syndrome): are calcium channel inhibitors a potential treatment option? *Cephalalgia* 2003;**23**:218–22.

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