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Reversible cerebral vasoconstriction syndrome

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ABSTRACT Reversible cerebral vasoconstriction syndrome (RCVS) is an under-diagnosed condition which usually presents as severe headache with or without neurological deficit. We report the case of a 55-year-old woman who presented with headache and multifocal intracerebral haemorrhage. We review the literature regarding the presentation, pathophysiology and management of RCVS and discuss how to differentiate it from cerebral vasculitis.

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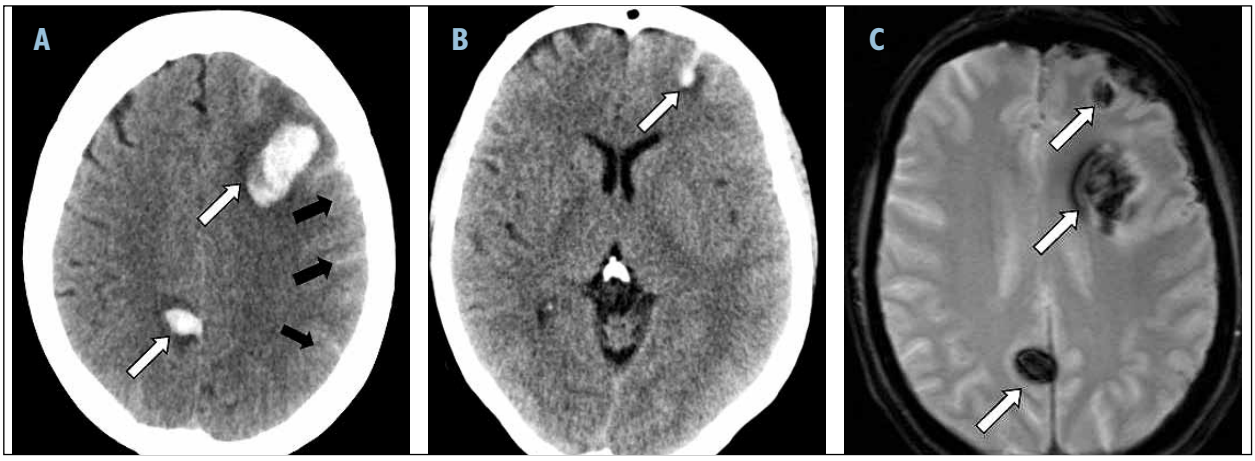
CASE REPORT

A 55-year-old female teacher was admitted to our stroke unit with headache, amnesia, dizziness and aphasia. Her symptoms had begun six days earlier when she experienced a severe, sudden onset occipital headache associated with vomiting, while running for the train. A junior doctor from the department (RL) had been on the train and witnessed the patient suddenly clutching the back of her head and becoming agitated. She was taken to a local hospital where she was diagnosed with migraine. She had two further Emergency Department (ED) attendances over the next few days, each time presenting with episodes of severe headache. In the 24 hours before her final admission she developed amnesia, dizziness and aphasia.

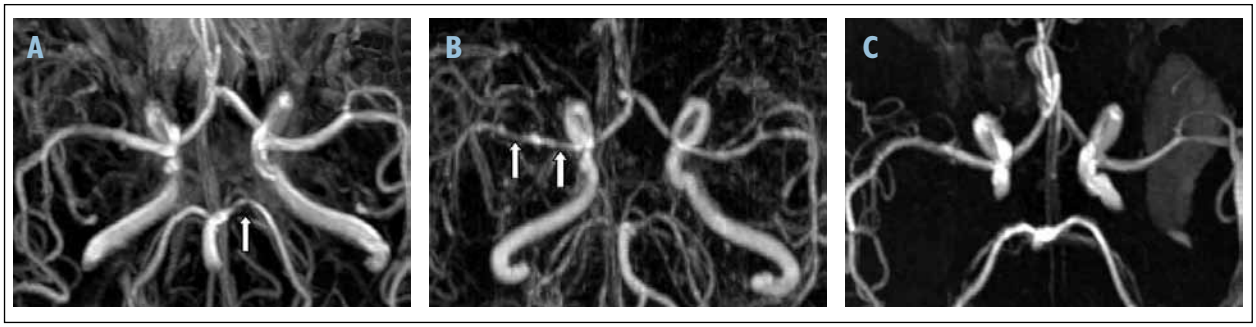
The patient had a longstanding history of migraine with aura but felt that these headaches were different to her normal migraines. In the week before presenting, she had been under a great deal of personal stress.

Additional past medical history included type 2 diabetes and postnatal depression requiring electroconvulsive therapy. Her medications included venlafaxine, zolmitiptan and propranolol. There was no history of recreational drug use.

On examination, her blood pressure was 170/80 mmHg, there was no abnormality of the cranial nerves, limbs or gait. Her Glasgow Coma Scale was 14/15, but she was disorientated in time and place and had a moderate severity, predominantly expressive aphasia. Her National Institutes of Health Stroke Scale (NIHSS) score was two. A cranial computerised tomography (CT) scan showed multifocal, intraparenchymal haemorrhages with subarachnoid extension (Figures 1A and B). She had a normal full blood count, coagulation screen, electrolytes, renal and liver function tests and 24-hour urinary metanephrines. Her autoantibodies, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-neutrophil cytoplasmic antibodies (ANCA), immunoglobulin electrophoresis, HIV



FIGURES 1A–B Axial computed tomography (CT) scan of the brain shows multifocal areas of intraparenchymal haemorrhage (white arrows) associated with convexity subarachnoid haemorrhage within the left frontal lobe (black arrows). **C** An axial T2* magnetic resonance imaging (MRI) scan shows similar findings with no evidence of microbleed.



FIGURES 2A A contrast enhanced magnetic resonance angiography (MRA) of the circle of the Willis shows narrowing of the P1 segment of the left posterior communicating artery (arrow). **2B** A repeat MRA a week later shows interval changes of new multifocal stenoses of the right middle cerebral artery (arrow). **2C** Abnormalities resolved at four weeks.

and hepatitis screen were normal/negative. She underwent magnetic resonance imaging and angiography (MRI/MRA) which showed the multiple supratentorial haematoma that had been seen on the CT scan; on the MRA there was narrowing of the P1 and A1 segments of the left posterior communicating artery (Figures 1C and 2A) and left anterior cerebral artery respectively. There were no ischaemic lesions on diffusion weighted imaging (DWI).

She was treated with slow release verapamil 120 mg daily and her headaches resolved. Repeat MRI/MRA a week later showed new multifocal stenoses within the right middle cerebral artery (Figure 2B), but the stenosis noted in the proximal left A1 segment on the earlier MRA was no longer apparent. These had resolved on repeat scanning a month later, which confirmed the diagnosis of RCVS (Figure 2C). The patient has made a full recovery and has not had any further headache or migraine while on verapamil.

DISCUSSION

The history in this case of initial severe headache followed by recurrent headaches was crucial and aided by an eyewitness account. It highlights the importance of imaging in those presenting with sudden onset severe headache. In their prospective study, Linn et al. examined 145 patients who presented with sudden severe headache defined as one that started within one minute or less and lasted for at least one hour.[1] They found that 37/145 (25%) were diagnosed with a subarachnoid headache (SAH).[1] Bø et al. found that 71/433 (16%) consecutive adult patients presenting to ED with thunderclap headache had a SAH,[2] so there is a high probability of diagnosing pathology with this presentation.

Reversible cerebral vasoconstriction is an under-diagnosed condition which typically presents with a thunderclap headache, with or without focal neurological deficits. The term was first coined in 2007 by Calabrese et al. to describe a heterogeneous group of disorders characterised by reversible constriction of the cerebral arteries.[3] The headaches can be singular or multiple, typically acute, severe and peaking in less than one minute.[4] The key radiological diagnostic feature is the demonstration of reversible constriction of the intracerebral arteries which can now be achieved using widely available, high resolution, non-invasive angiography.

This condition affects more women than men. In one case series of 67 patients, 55% were taking vasoactive substances such as serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, as in this case.[5] A review by Satter et al. of 214 reported cases in the literature identified other triggers including exercise, sudden emotion, sudden head movement and hormonal changes, in addition to disorders such as porphyria, posterior reversible encephalopathy syndrome with its associated conditions, and phaeochromocytoma.[4] A prospective study examining headache associated with sexual activity found that 18/30 (60%) of patients had underlying RCVS.[6] Therefore although coital headaches are often diagnosed as idiopathic, on further investigation, RCVS is a common cause.

The pathophysiology of RCVS remains unknown, although the unpredictable and transient failure of regulation of cerebral arterial tone with sympathetic overactivity leading to segmental and multifocal arterial constriction and dilatation has been implicated.[4] Ducros et al. demonstrated in their prospective series that a non-contrast CT brain scan is abnormal in only 12% of cases and cerebral spinal fluid (CSF) can be non-specifically abnormal in less than half of patients.[5] The causes of non-traumatic multiple intracranial haemorrhages on imaging are listed in Table 1. Another difficulty for clinicians is in differentiating between the segmental arterial narrowing in RCVS and cerebral vasculitis, since the latter may require urgent immunosuppressive treatment. Table 2 discusses features and management of the two conditions.

Arterial imaging confirming segmental vasoconstriction which reverses within 12 weeks is required to diagnose RCVS.[5] In our case the diagnosis was supported by early reversible changes on sequential MRA as well as the

TABLE 1 Differential diagnosis of non-traumatic multiple haemorrhages in the brain

Malignant hypertension
Eclampsia/pre-eclampsia
Venous sinus thrombosis
Brain metastases, especially melanoma and bronchial carcinoma
Vasculitis
Reversible cerebral vasoconstriction
Cerebral amyloid angiopathy
Cocaine vasculopathy
Moyamoya disease

absence of diffusion-weighted imaging (DWI) positive lesions that would be anticipated if there was an active cerebral vasculitis. The sensitivity of MRA or CT angiogram is about 70% of the gold standard catheter angiography.[5] There is no study comparing the sensitivity of time-of-flight and contrast-enhanced intracranial MRA in the detection of cerebral vasoconstriction in RCVS. A recent study has raised the possibility that a high-resolution contrast-enhanced MRI of the vessel wall can be used to differentiate between non-enhancing RCVS and enhancing vasculitis.[7]

Management of patients with RCVS is symptomatic, involving analgesia, stopping problematic drugs and advising against strenuous physical activity in the short term. No randomised clinical trials have been conducted. However, the literature indicates that nimodipine, verapamil and magnesium sulphate have been used.[4] We elected to use verapamil in our case based on its anti-migrainous activity and class effect.

The prognosis for patients with RCVS is generally good, with 71% of patients showing no evidence of disability in the long term.[4] It depends on the presence of brain parenchymal injury (stroke occurs in 6–9% of cases).[8] In a retrospective analysis of 139 cases by Singha et al. the fatality rate was 2%.[8] Only one out of 214 patients in the Satter et al. series relapsed.[4]

CONCLUSION

This case highlights the challenges clinicians face in making a diagnosis of RCVS and in particular how to distinguish RCVS from benign thunderclap headache, other causes of multifocal haemorrhage and cerebral vasculitis. It stresses the need for doctors to differentiate between a patient's normal migraine and new types of headache. If patients present with this, arterial imaging should be considered.

TABLE 2 Features of reversible cerebral vasoconstriction syndrome (RCVS) and cerebral vasculitis

Feature	Reversible cerebral vasoconstriction syndrome	Cerebral vasculitis
Symptoms and signs at presentation	Sudden onset severe headache which may be the only symptom. Focal neurology, seizures and cognitive deficit. Can have blood pressure surges and facial flush during thunderclap headache.[4,5]	Headache (63%), altered cognition (50%), focal neurology (40%), seizures (16%). Often fluctuating symptoms. May be encephalopathy or psychosis with diffuse presentation. Pyrexia, night sweats, oligoarthropathy, livido reticularis.[7,9]
Radiological features	Computed tomography (CT) scan of the brain often normal. A magnetic resonance imaging (MRI) scan commonly shows small convexity subarachnoid headache (SAH) (22%) and rarely haematoma (4%) and infarction (2%).[5] Magnetic resonance angiography/computed tomography (MRA/CT) demonstrates segmental narrowing and dilatation. Can be normal if done within five days of symptoms.	CT may show infarct/haemorrhage but can be normal. MRI shows multiple infarcts (53%) gadolinium enhancing mass lesion (33%), haemorrhages (8%). MRA/CT angiography shows segmental narrowing/beading.[7]
Blood tests	Auto-antibodies negative. Usually normal although may be a transient rise in inflammatory markers.[5]	Anti-neutrophil cytoplasmic antibody may be positive, but often negative. Raised erythrocyte sedimentation rate (ESR) and C-reactive protein.[9]
CSF results	Mild abnormalities including leukocytosis, erythrocytosis and increased protein up to 1 g/l.[5]	Leukocytosis and raised protein. Opening pressure high in 50% of cases.[9]
Underlying pathology	Transient disturbance in arterial wall tone leading to segmental constriction and dilatation.[5]	Direct antibody attack and immune complex mediated vascular injury results in inflammation of vessel walls.[9]
Management	Calcium channel antagonists.[5]	Steroids and immunosuppressants.[9]

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