CASE REPORT

The reversible cerebral vasoconstriction syndrome in association with venlafaxine and methenamine

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SUMMARY

The reversible cerebral vasoconstriction syndrome (RCVS) is characterised by thunderclap headache and multifocal vasoconstriction of cerebral arteries on angiography. It is often drug induced, but it can occur postpartum, and as a result of a number of other precipitants. To make the diagnosis, it is necessary to exclude other causes of severe headache (such as aneurysmal subarachnoid haemorrhage, carotid dissection and primary angiitis of the central nervous system). However, it is also important to show that the vasoconstriction has resolved with repeat angiography at the 3-month stage. Here we report two cases of RCVS in association with venlafaxine and the urinary antiseptic, methenamine. Serotonin–norepinephrine reuptake inhibitors have recently been reported as a possible precipitant, but this is the first report to implicate methenamine. Although RCVS is relatively uncommon, it should be considered in the differential of those presenting with thunderclap headache.

BACKGROUND

Patients with the reversible cerebral vasoconstriction syndrome (RCVS) present with thunderclap headache in the absence of aneurysmal subarachnoid haemorrhage (SAH).^{1–3} RCVS is characterised by the multifocal vasoconstriction of cerebral arteries,^{1–6} and although the underlying mechanism remains obscure, it is likely to involve a transient disturbance of vascular tone.³ It is often drug induced^{1–3} but may also occur postpartum⁴ and following a number of other precipitants.³ Different nomenclature has been used to describe the condition including ‘The Call-Fleming syndrome’, ‘drug induced arteritis’ and ‘post partum angiopathy’, but RCVS is now the accepted term.³ The clinical presentation is usually that of severe thunderclap headache, with or without focal neurology.^{4–6} Although primary angiitis of the central nervous system (PACNS) shares a number of similar features, the headache in PACNS is usually more insidious.³ It is therefore usually possible to distinguish between the two conditions, sparing patients with RCVS unnecessary immunosuppression or an invasive brain biopsy.³ The diagnosis depends upon demonstration of segmental cerebral artery vasoconstriction (in the absence of an aneurysmal SAH) on digital subtraction or indirect angiography (MR angiography or CT angiography).¹ In addition, follow-up angiography at 12 weeks should confirm normalisation of the cerebral vasculature.^{1–3} Complications of RCVS include non-aneurysmal SAH (which often affects the convexity),⁷

intracerebral haemorrhage, cerebral ischaemia (usually within a watershed territory) and posterior reversible leukoencephalopathy.^{1–3} Treatment involves withdrawal of the precipitant and calcium channel blockers, although these have yet to be studied in a controlled trial.^{1–2} The prognosis is usually good with most patients recovering well without recurrence over days to weeks.^{1–6}

CASE PRESENTATION

Case 1

A 55-year-old woman presented with sudden onset occipital headache associated with several hours of anterograde amnesia. Two years before, she had been successfully treated for right-sided breast carcinoma with a wide local excision and radiotherapy (but not chemotherapy) followed by tamoxifen. Months before presentation, venlafaxine was initiated to control tamoxifen associated flushing. An initial CT head and cerebrospinal fluid (CSF) examination on admission were normal. There was no xanthochromia. An MRI head performed 2 days later revealed a small amount of subarachnoid blood near the vertex (figure 1). The following day, a CT angiogram revealed a new left frontal intraparenchymal haemorrhage (figure 1) with no evidence for an aneurysm or vascular malformation. An MR venogram was normal. At that stage she deteriorated and became drowsy and disorientated, with word finding difficulties, but no focal signs. All of these symptoms began to improve over the subsequent 48 h but she then had a generalised tonic-clonic seizure and she was treated with intravenous phenytoin. Her conscious level improved but the headaches continued and on day 8, she developed new left-sided numbness, with mild left-sided weakness. A repeat MRI head revealed new posterior white matter abnormality (more on the right) (figure 1) and a cerebral digital subtraction angiogram (DSA) showed evidence for vasoconstriction at multiple sites including branches of both posterior, middle and anterior cerebral arteries (figures 2 and 3). A repeat lumbar puncture was normal. Thereafter, she began to improve, but she continued to report headaches, mild word finding difficulties and mild imbalance. The clinical and radiological picture led to a diagnosis of RCVS, and the venlafaxine was stopped. A follow MRI at 3 months, and at 12 months showed residual posterior white matter changes (these were unchanged on comparing the three MRIs), resolving blood products in the left frontal region, but no new lesions. The patient did not want a repeat DSA. Clinically, at follow-up at 9 and 12 months, she

To cite: Davies G, Wilson H, Wilhelm T, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009701

Figure 1 Case 1—MRI and CT showing convexity subarachnoid haemorrhage (left), frontal intracerebral haemorrhage (middle) and posterior leukoencephalopathy (right).

had only mild, residual, word finding difficulties, and there have been no new neurological events. Although follow-up angiography was not performed, the clinical and radiological picture was sufficient in keeping with RCVS that immunosuppression was not given.

Case 2

A 59-year-old woman presented with acute onset headache. She had a long history of recurrent urinary tract infections. Urological investigations had revealed bladder diverticula and a sacral nerve bladder stimulator had been implanted (to promote bladder emptying). However, despite this, she continued to have urinary tract infections and she was started on long-term prophylactic antibiotics. She had previously taken ciprofloxacin and nitrofurantoin, but 3 days prior to her neurological symptoms, she had started methenamine. On the day that she presented, she developed lower abdominal pain, quickly followed by a rapidly worsening generalised headache with vomiting. A CT head showed a right-sided SAH, with blood in the Sylvian fissure (figure 4). A cerebral digital subtraction angiogram (DSA) revealed irregularity of several cerebral arteries (a posterior branch of the right middle cerebral artery and both superior cerebellar arteries) (figure 4) but no aneurysm or arteriovenous malformation. A lumbar puncture confirmed subarachnoid

blood and blood tests for causes of systemic vasculitis were negative. A diagnosis of RCVS was made and methenamine was stopped. Her headache slowly improved over the next few days and she was discharged. A follow-up DSA at 3 months was within normal limits and on follow-up, 8 months after presentation, she has had no further neurological events.

DISCUSSION

RCVS is increasingly recognised as a cause of thunderclap headache. The diagnosis depends on the presence of the characteristic symptoms with normal or near normal CSF, the exclusion of other causes of severe headache (including PACNS, aneurysmal SAH and carotid dissection) and a characteristic pattern of vasoconstriction on direct or indirect angiography. In addition, the diagnosis depends upon the demonstration of reversibility of vasoconstriction with repeat angiography at 12 weeks. It is normally possible to distinguish RCVS from PACNS on clinical grounds and after initial investigation, without the need for a brain biopsy.^{1–3}

Our first case appears to be typical of those described in the literature, and although a repeat DSA was not performed, she remained well on prolonged follow-up, without immunosuppression. Our second case presented with a large non-aneurysmal SAH, with blood in the Sylvian fissure. Convexity SAH, thought to arise from minor leaks from surface vessels, has been described in about a third of patients with RCVS,¹ but the SAH in case 2 is atypical for this. Nonetheless, there was clear evidence on DSA for early (within 48 h) multifocal vasoconstriction at sites anatomically distinct from the site of the bleed and which could not be explained by secondary vasospasm. Reversibility of the vasoconstriction was demonstrated at 3 months.

A number of drugs are known to precipitate RCVS. These include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors (as in our first case), nasal decongestants, sumatriptan, ergotamine, bromocriptine, ecstasy, cocaine, amphetamines, marijuana, tacrolimus, cyclophosphamide, erythropoietin, intravenous immunoglobulin and red cell transfusions.^{1–3} A number of non-drug precipitants have also been described including the postpartum state, head injury, neurosurgery, vascular manipulation, carotid endarterectomy and metabolic disturbances, such as hypercalcaemia, porphyria and those associated with catecholamine secreting tumours.^{1–3}

Here we report two cases of RCVS. The serotonin-norepinephrine reuptake inhibitors have recently been identified as a

Figure 2 Case 1—Digital subtraction angiography showing cerebral vasoconstriction (arrowed).

Figure 3 Case 1—Digital subtraction angiography showing cerebral vasoconstriction (arrowed).

precipitant,¹ but this report is the first to implicate the urinary antiseptic methenamine. Methenamine is converted to formaldehyde by the acidic environment of the bladder but it is generally well tolerated and there have been no reports of headache or other vascular side effects in several trials.⁸

Methenamine (hexamethylenetetramine) is related chemically to both memantine and amantadine, as all three have a similar cage-like molecular structure. Memantine and amantadine are derivatives of the cycloalkane, adamantane (which

makes up the 10 carbon cage-like backbone in both compounds). Methenamine is an adamantane analogue, and in this, the cage-like backbone includes seven carbons and three nitrogens.⁹ In healthy subjects, amantadine results in an increase in circulating norepinephrine, and a decrease in epinephrine, dopamine and serotonin.¹⁰ It is not known whether methenamine has an effect on catecholamine metabolism, but this could be a possible mechanism for the induction of RCVS in this case.

Figure 4 Case 2—CT showing subarachnoid haemorrhage and digital subtraction angiography, showing areas of vasoconstriction (middle and bottom) and resolution of vasoconstriction on follow-up at 3 months (right).

Learning points

- ▶ The reversible cerebral vasoconstriction syndrome is a rare but important cause of thunderclap headache.
- ▶ It is often drug induced.
- ▶ The angiographic appearances can be confused with primary angiitis of the central nervous system, and so a prompt diagnosis of reversible cerebral vasoconstriction syndrome would spare patients an unnecessary brain biopsy and/or immunosuppression.

Contributors JB was involved in the care of both patients and he helped considerably in drafting the manuscript. HW has continued the outpatient care of one of the patients and she also provided valuable advice when drafting the manuscript. GD looked after both patients during their admission and he wrote the manuscript. TW reported some of the imaging at the time, and helped select images for the manuscript. He also helped draft the manuscript.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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