Brief Report

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Reversible cerebral vasoconstriction syndrome induced by adrenaline

Jose-Alberto Palma, Ariadna Fontes-Villalba, Pablo Irimia, Reyes Garcia-Eulate and Eduardo Martinez-Vila

Abstract

Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by acute severe thunderclap headaches and evidence of multifocal, segmental, reversible vasoconstrictions of the cerebral arteries. Several precipitating factors have been identified and reported, including the use of recreational substances or sympathomimetic drugs and the postpartum state.

Case description: Here we present the case of a woman who developed RCVS after the administration of adrenaline (epinephrine) in the setting of an anaphylactic reaction during antibiotic allergy testing.

Discussion: To our knowledge, this is the first reported case of RCVS following the administration of exogenous adrenaline. This case contributes to the understanding of the physiopathological mechanisms underlying reversible cerebral vasoconstriction.

Keywords

RCVS, adrenaline, anaphylaxis, vasoconstriction, thunderclap headache

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Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by the association of acute severe headaches and multifocal, segmental, reversible vasoconstrictions, demonstrable by neurosonography or neuroimaging, with or without additional neurologic signs or symptoms, and is most common in middle-aged women (1). Although there are controversies regarding the classification of this entity owing to overlapping features with other syndromes, and there are no validated criteria for its diagnosis (1,2), RCVS has a characteristic clinical and radiological course, usually initiated by an unanticipated, sudden onset, 'worst-ever' headache, consistent with a thunderclap headache (TCH), that recurs over days to weeks (3,4). Headache is, in most cases, the only symptom, although other features include focal deficits and seizures. Although it is most frequently benign, RCVS may lead to subarachnoid haemorrhages and ischemic or haemorrhagic strokes (5). Symptom onset can be spontaneous but has also been associated with the exposure to a wide spectrum of drugs, including, but not limited to, recreational substances (ecstasy, cocaine, cannabis, amphetamines), serotoninergic drugs (selective serotonin reuptake inhibitors), triptans and sympathomimetic drugs (phenylephrine, pseudoephedrine) (1,3). We report a patient with antibiotic allergy who developed RCVS related to the administration of intramuscular adrenaline after developing anaphylaxis during metronidazole desensitization. Although cases of RCVS related to catecholamine-secreting tumours potentially producing adrenaline (such as pheochromocytoma) have been described (6–9), there have been no previous reports of RCVS related to exposure to exogenous adrenaline. Understanding of the effects of adrenaline in cerebral vessels may offer insights into the physiopathology of RCVS.

University Clinic of Navarra, Pamplona, Spain

Corresponding author:
Dr E Martinez-Vila, Department of Neurology and Neurosurgery, University Clinic of Navarra, Pamplona, Spain
Email: emartinezv@unav.es

Case report

The patient is a 60-year-old woman (weight 55.5 kg, height 161 cm, BMI 17.2 kg/m2) with a medical history of multiple allergies to metronidazole, penicilines and quinolones. Vascular risk factors included dyslipidaemia and a history of smoking (45 packs per year). She was taking simvastatin 10 mg/day as the only regular medication. There was no history of episodic headache disorder and her usual blood pressure was in the range 110–120/60–70 mmHg.

During a diagnostic procedure of oral tolerance to several antibiotics, she developed anaphylaxis symptoms (pruritus, rash and dyspnoea) 15 minutes after taking metronidazole 125 mg (116/61 mmHg; oxygen saturation of 94%). She was immediately administered adrenaline 0.5 mg intramuscularly and symptoms resolved, but she then developed tachycardia and a severe TCH, without other associated symptoms. Her blood pressure was then 156/96 mmHg. Neurologic examination was unremarkable and she was treated with intravenous paracetamol and steroids, and the pain resolved in 45 minutes.

Four days later (day 5) she developed a second episode of TCH with no other neurologic symptoms. Blood pressure was 157/67 mmHg. The patient was admitted to the emergency room where she received intravenous treatment with paracetamol and dexketoprofen. Her symptoms improved although she complained of a mild background headache at the time of discharge.

The next day (day 6), she woke up with a sudden TCH and was admitted to the neurology department. A CT scan did not show any signs of aneurysmal subarachnoid haemorrhage; cerebrospinal fluid analysis (CSF) was within normal limits (proteins 23.6 mg/dl, glucose 73 mg/dl and 4 leukocytes/μl). A brain magnetic resonance imaging (MRI) and angiography (MRA) did not show aneurysms or other abnormalities; electrocardiography was also normal. During this hospitalization she experienced 13 additional episodes of TCH, managed with intravenous diazepam, diclofenac and opiates. During one of these TCH episodes, she developed blurred vision and bilateral inferior hemianopsia that lasted for 10 minutes. She was discharged 14 days later (day 20), with the diagnosis of 'primary TCH', and was prescribed amitriptyline 25 mg/day for headache prevention.

Five days later (day 25) she came to our department complaining of moderate background headache and brief episodes of blurred vision. Neurologic examination, including visual fields, was unremarkable. A brain MRI revealed an acute ischemic stroke within the right posterior cerebral artery territory. Diffusion-weighted images also showed bilateral occipital hyperintensities, predominantly in the right side (Figure 1, A and B). MRA disclosed irregularities of the vessel diameters, predominantly in the posterior circulation, with multisegmental stenoses bilaterally (Figure 2A). Selective arterial angiography was not performed to avoid iodinated contrast, owing to the patient's history of multiple allergies. On transcranial Doppler ultrasound (TDU), peak systolic velocities in the middle cerebral artery (MCA) were slightly increased bilaterally, predominantly on the right side (158 cm/s left, 166 cm/s right).

The history of several episodes of TCH, as well as the clinical and imaging findings, were overall highly suggestive of RCVS. She was prescribed nimodipine 60 mg, three times daily. At 3-month follow-up visit she was asymptomatic. Blood pressure and neurologic examination were normal. TDU showed that MCA peak systolic velocities had normalized (120 cm/s bilaterally). MRI revealed an improvement in posterior hyperintensities, except for the small right occipital stroke (Figure 1, C and D), and MRA showed no evidence of abnormalities of the intracranial arterial vessels (Figure 2B).

Discussion

Our patient illustrates the cardinal features of RCVS, including recurring episodes of thunderclap headache, the lack of aneurysmal subarachnoid haemorrhage, a normal CSF analysis, and multifocal segmental cerebral arterial vasoconstrictions documented by MRA and TDU, which were reversible within 12 weeks. In this case, between the thunderclap attacks, the patient described a mild background headache, which can be present in around half of patients with RCVS (3,5). Our patient also had documented episodes of hypertension during headache exacerbations, which are usual in more than a third of patients with RCVS (3). Moreover, this case exemplifies how ischemic stroke can be a complication of RCVS. Diagnosis of RCVS can be challenging in some patients (10), in part owing to its overlapping features with other hyperadrenergic states (11,12).

The main therapeutic measure is the identification and discontinuation of the potential trigger and the initiation of calcium-channel blockers (13). RCVS has been related to pregnancy, postpartum state, some tumours, neurosurgical procedures, hydroelectrolytic disturbances and serotoninergic drugs (1). Although several sympathomimetic drugs (14) and catecholamine-secreting tumours (6–9) have been associated with RCVS (14), exogenous adrenaline (epinephrine) has not been previously implicated. The physiopathology of RCVS is poorly understood. Transient alterations in vascular tone modulated by the sympathetic

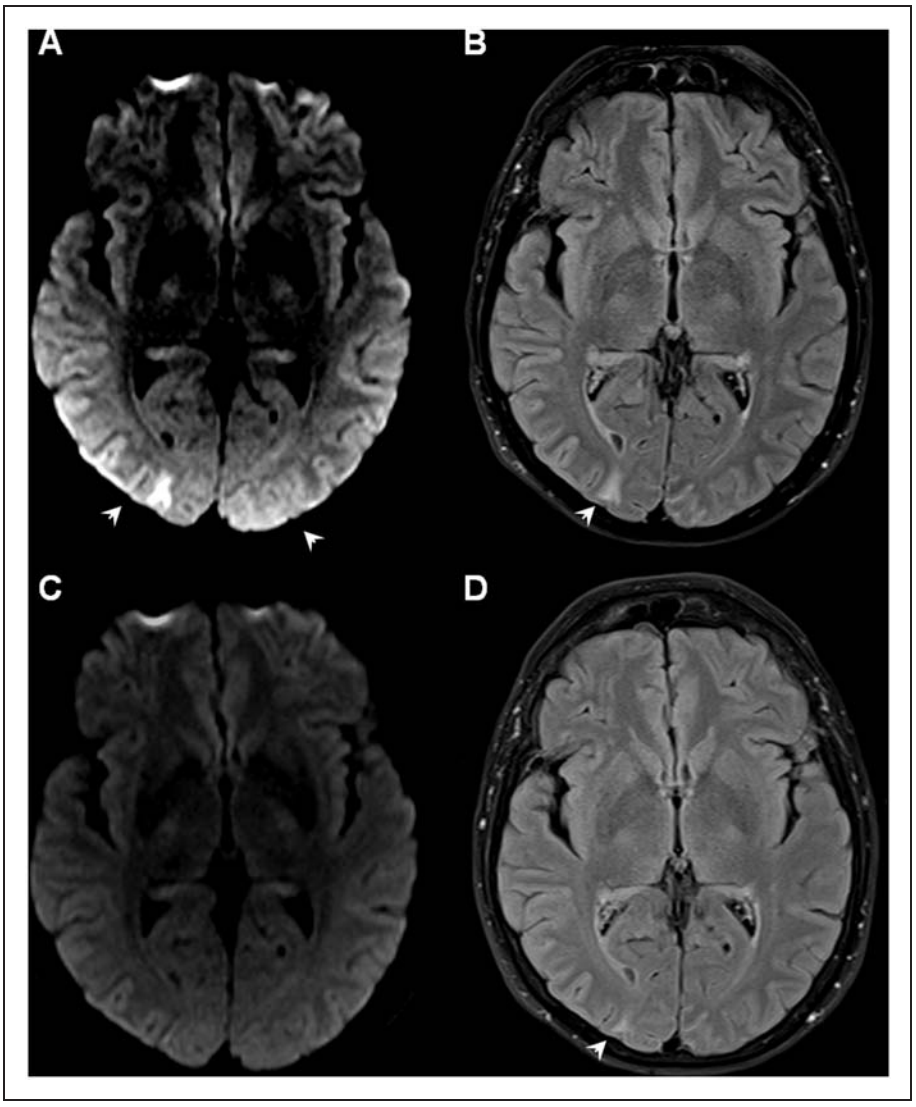

Figure 1. Diffusion-weighted (DWI) MRI (A) and fluid attenuated inversion recovery (FLAIR) (B), revealing hyperintensities in both occipital lobes, with a right occipital lesion consistent with ischemic stroke (arrows). MRI performed 3 months later showing no abnormalities in DWI (C) and a marked improvement in the hyperintense right occipital lesion in FLAIR (arrow, D).

nervous system are suspected to have a central role (15) and many of the accepted triggers for RCVS are vasoactive. The vasospastic event may start in small distal arteries and then progress to medium-sized and large arteries.

Adrenaline is the drug of choice for treating anaphylaxis. Hence, allergic patients undergoing drug tolerance tests and developing symptoms of anaphylaxis frequently receive adrenaline. Known adverse effects of adrenaline include cardiac arrhythmia, headache and arterial hypertension. Investigations into the effects of adrenaline on the cerebral circulation have yield conflicting results, some showing dilatation, some vasoconstriction and others no effect (16,17); thus, the exact mechanism of RCVS induced by adrenaline is unclear. Moreover, adrenaline is used in the treatment of shock and cardiac arrest; in this situation a cerebral vasoconstrictor effect would be highly deleterious. However, classic investigations clearly show that local application of adrenaline constricts the basal and pial cerebral arteries (17), leading to the hypothesis that moderate, single doses of intravenous adrenaline diminish cerebral blood flow, whereas there is little effect with bigger doses (16–18).

In our case, the low dose of adrenaline used for the treatment of anaphylaxis (0.3 mg intramuscularly) was the only identified precipitating factor that could have triggered the hypertension, and it may have reached the cerebral arterial circulation, producing vasoconstriction. Additionally, the previous administration of metronidazole may have triggered an immunoglobulin-E (IgE)-mediated immune reaction, with the

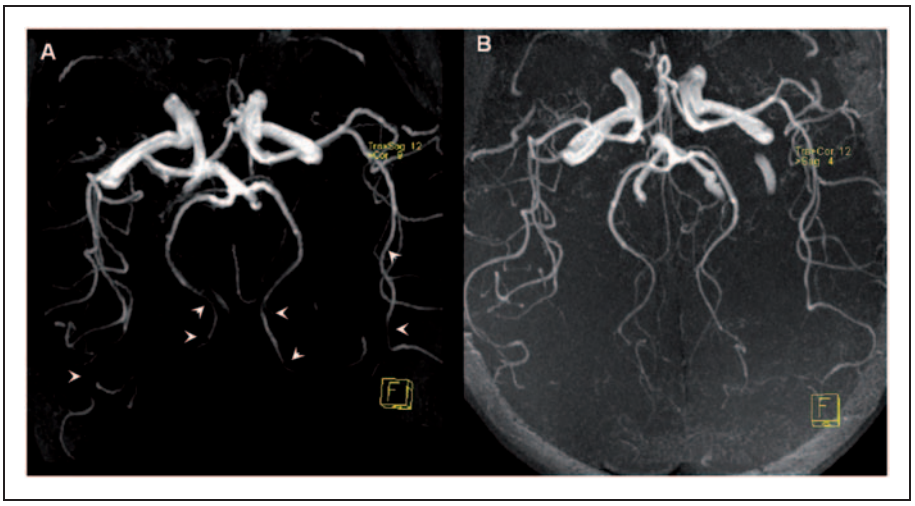

Figure 2. (A) MRA showing multifocal segmental vasoconstrictions predominantly in the posterior circulation (arrows). (B) Follow-up MRA 3 months later revealing resolution of the vasoconstrictions.

induction of blood-brain barrier and endothelial cell toxicity, which, together with the vasoactive effect of adrenaline, may have contributed to the cerebral vasoconstriction (19,20). The selective involvement of parts of the brain perfused by the posterior circulation may indicate a loss of autoregulation of the vertebrobasilar system, probably because of its relatively sparse sympathetic innervation.

In conclusion, RCVS is an uncommon and underrecognized entity. Thus, clinical suspicion is important to its detection, and early treatment is crucial, especially in patients with recurrent TCH, even if early neuroimaging shows no multifocal spasm. In this case, the administration of adrenaline and RCVS were temporally related. Hence, we hypothesize that, in this patient, vasoreactivity associated with adrenaline concurrently with a previous IgE-mediated reaction induced by metronidazole precipitated RCVS. Although infrequent, physicians must be aware of this potential complication in patients developing TCH following the administration of adrenaline.

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Competing interests

The authors declare that they have no conflict of interests.

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