#### LETTER TO THE EDITOR



# Cyproheptadine in the treatment of reversible cerebral vasoconstriction syndrome

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### Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a transient vasculopathy of the cerebral blood vessels often characterized by thunderclap headache and transient cerebral vasoconstriction with ischemic and/or hemorrhagic stroke [1]. Various risk factors have been described to predispose or trigger RCVS including usage of serotonergic antidepressants, migraine medications, and nasal decongestants [1, 2]. Apart from removing the precipitating agents, medical management is limited to supportive care, calcium channel blockers, and blood pressure optimization to prevent worsening of vasoconstriction and ischemic complications [3].

Serotonin plays a major role in vascular tone as both a vasoconstrictor and vasodilator [2, 4]. These vasoactive effects of serotonergic medications can worsen or trigger vasospasm in patients with RCVS [2, 3]. A few cases have described reversal of vasoconstriction in coronary arteries with the use of the serotonin receptor antagonist

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<sup>2</sup> Epilepsy Center, Neurological Institute, Cleveland Clinic Foundation, Cleveland, OH, USA cyproheptadine, but the effect of cyproheptadine on serotonin-induced cerebral artery vasoconstriction is largely unknown [4, 5]. We report a case of a patient with sumatriptan-induced cerebral vasoconstriction successfully treated with cyproheptadine.

#### Method/case presentation

A 44-year-old female with a past medical history of marijuana use, opioid dependence on methadone, hypertension, and attention deficit hyperactivity disorder on dexamphetamine presented to the emergency department (ED) with a 2-week history of intermittent severe headaches with associated nausea/vomiting and photophobia. The patient was noted to be a poor historian and had difficulty characterizing the onset of her headaches. Computerized tomography of the head (CT) and angiography (CTA) were normal. She was diagnosed with migraine and prescribed sumatriptan which provided some headache relief. She presented to ED two more times (day 3 and day 8 after initial ED visit) with a similar headache and both times was noted to be extremely agitated and difficult to interview. Both times she was discharged from the ED without further imaging.

She presented to the ED for a fourth time 16 days after her initial visit, now with constant severe headache and inability to lift her right arm. Repeat CT brain showed a hypodensity in the left parietal lobe and she was admitted to the hospital. Magnetic resonance imaging (MRI) of the brain on day 17 showed bilateral parieto-occipital edema and signal abnormality consistent with posterior reversible encephalopathy syndrome (PRES). On day 18 she developed bilateral vision loss and inability to move her right upper and lower extremity. She also developed severe agitation requiring sedation and intubation, and was admitted to the neurocritical care unit.

CTA head on day 19 revealed diffuse multifocal areas of moderate to high-grade stenosis throughout the intracranial circulation. Transcranial Doppler (TCD) was obtained on day 20 which showed elevated mean flow velocities (MFV) in the bilateral MCA, R ACA, and basilar arteries. Digital subtraction angiography (DSA) was performed immediately after TCD, and confirmed multifocal, moderate to severe vasoconstriction (Fig. 1). She received 10 mg intra-arterial verapamil in each ICA and in the left vertebral artery during the DSA. Following verapamil infusion, angiography demonstrated mild improvement in the left M1, A1, and vertebral artery with mild-moderate residual stenosis, and no improvement in the right ACA or MCA. MRI brain was repeated after angiography, which demonstrated multifocal areas of infarction involving the left perirolandic and bilateral parietal-occipital lobes as well as subarachnoid blood in the areas of infarction. She received one dose of oral

verapamil 40 mg, but was unable to tolerate further doses due to hypotension.

Given clinical and radiological worsening, and recent exposure to serotonergic medication, oral cyproheptadine 12 mg loading dose was administered followed by 4 mg every 8 h as maintenance dose (day 21). TCD was utilized to monitor vasoconstriction (Fig. 2). She was extubated day 23 and TCD showed decreased MFV in bilateral MCA, left ACA, bilateral PCA, and left basilar arteries. Repeat CTA showed significant improvement in vasoconstriction in all the intracranial vessels. On day 25, MFV was normalized in all intracerebral arteries, she regained minimal movement in her right arm, and her vision improved to the point of being able to track objects. Cyproheptadine was discontinued after 7 days of treatment (day 28). The patient was discharged to an acute rehabilitation facility on day 29. On discharge she continued to have minimal movement of her right arm, and had a residual left hemianopia but was able to read and name objects. At a 6-month follow-up, her vision and speech

Fig. 1 Digital subtraction angiography. a, b Right internal carotid artery anteroposterior, and lateral views showing segmental vasoconstriction in the supraclinoid region, anterior and middle cerebral artery territories. c Left vertebral artery injection showing segmental vasoconstriction in V4 segment of the vertebral artery, basilar artery, and bilateral posterior cerebral arteries. d Left internal carotid artery injection showing supraclinoid, anterior, and middle cerebral artery multifocal vasoconstriction



Fig. 2 Serial transcranial Doppler monitoring showing mean flow velocities of intracranial arteries. The loading dose of cyproheptadine was given on day 21 and discontinued on day 28. Bilateral PCAs were not evaluated on day 22 and bilateral vertebral arteries were not evaluated on day 23 due to patient agitation. Values on these days are entered as 0. RMCA right middle cerebral artery, LMCA left middle cerebral artery, RACA right anterior cerebral artery, LACA left anterior cerebral artery, RPCA right posterior cerebral artery, LPCA left posterior cerebral artery, BA basilar artery, RVA right vertebral artery, LVA left vertebral artery

#### TRANSCRANIAL DOPPLER MONITORING SHOWING MEAN FLOW VELOCITIES DURING CYPROHEPTADINE TREATMENT



returned to baseline with only mild residual right-sided weakness and spasticity remaining.

#### Discussion

RCVS can be a challenging diagnosis as headache may be the sole initial presenting symptom [3]. This is an important consideration when prescribing triptans as patients with RCVS may initially be diagnosed with migraine or may develop RCVS following treatment for migraine. Serotonin can cause vasoconstriction via direct activation of vascular smooth muscle cells or through amplification of other vascular mediators such as norepinephrine [2, 3]. Serotonin agonists such as sumatriptan are believed to trigger RCVS through this mechanism [1, 2]. Our patient endorsed multiple migrainous features to her headache including nausea, vomiting, photophobia, and a throbbing sensation. We suspect she developed RCVS following her use of triptans prescribed for migraine, as her initial brain imaging was negative and she developed focal neurologic deficits following treatment with Imitrex. Her RCVS diagnosis may have been delayed due to severe agitation and lack of cooperation. The RCVS2 score can help aid in the diagnosis of RCVS [6]. Our patient's RCVS2 score was 8 (recurrent thunderclap headache, vasoconstrictive trigger, female sex, subarachnoid hemorrhage), which corresponds with a 99% specificity and 90% sensitivity for RCVS [6]. Her repeat CTA and MFV on days 23 and 25 showed normalization of vasospasm, also supporting the diagnosis of RCVS.

The mainstay of treatment for RCVS is calcium channel blockers such as verapamil, which may be given orally, intravenously, or intra-arterially (IA) in refractory cases [6–8]. There have been several cases reported of intra-arterial calcium channel blockers used to treat refractory vasospasm in RCVS, though no randomized trials have been done to determine their efficacy [8, 9]. The duration of IA verapamil is thought to be in the range of 2–6 h, and multiple treatments may be needed [9, 12, 13]. Our patient was unable to tolerate oral calcium channel blockers due to hypotension, and while she did improve with intra-arterial verapamil, it was only a mild improvement with significant residual vessel stenosis.

Cyproheptadine is a non-selective serotonin and histamine H1 receptor antagonist [5]. Cyproheptadine has also been shown to reverse vasospasm in patients with Prinzmetal angina and post-catheterization vasospasm [10, 11]. Our patient showed clinical and radiographic improvement after administration of cyproheptadine. It is unlikely that her continued improvement was a delayed response from the IA verapamil given its effects are generally seen immediately on DSA, and its duration of effect is believed to be around 2–6 h [9, 12, 13]. While the patient's decreasing MFV may be partially explained by the natural decline in vasospasm over the course of RCVS, her rapid clinical and radiographic improvement following administration of cyproheptadine suggests it may have played a role in shortening the course of vasospasm. Unfortunately, MFV was not measured prior to day 20 and we cannot establish the trend of her MFV before that time.

The use of noninvasive tools such as TCD has been suggested as a useful tool in diagnosing RCVS [7]. Daily

transcranial Doppler monitoring was used to monitor our patient's treatment response. After initiating cyproheptadine, our patient's mean flow velocities in all the vessels improved within 48–72 h with normalization of all vessels after 4 days. We did not observe any significant side effects of cyproheptadine. This case suggests that cyproheptadine may have a role in reversal of cerebral vasospasm secondary to serotonin modulating medications. Further prospective studies will need to be done to determine the efficacy of cyproheptadine in the treatment of serotonin-induced RCVS.

#### **Compliance with ethical standards**

**Conflict of interest** The authors have no conflicts of interest to declare relevent to this article.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent is required.

## References

- Headache attributed to reversible cerebral vasoconstriction syndrome (2018) The International Classification of Headache Disorders. Cephalalgia 38(1):86–88
- Singhal AB, Caviness VS, Begleiter AF, Mark EJ, Rordorf G, Koroshetz WJ (2002) Cerebral vasoconstriction and stroke after use of serotonergic drugs. Neurology 58(1):130–133
- Miller TR, Shivashankar R, Mossa-Basha M, Gandhi D (2015) Reversible cerebral vasoconstriction syndrome, part 1: epidemiology, pathogenesis, and clinical course. AJNR Am J Neuroradiol 36(8):1392–1399

- Van Nueten JM, Janssens WJ, Vanhoutte PM (1985) Serotonin and vascular reactivity. Pharmacol Res Commun 17(7):585–608
- Bush LR (1987) Effects of the serotonin antagonists, cyproheptadine, ketanserin and mianserin, on cyclic flow reductions in stenosed canine coronary arteries. J Pharmacol Exp Ther 240(2):674–682
- Rocha EA, Akif Topcuoglu M, Silva GS, Singhal AB (2019) RCVS<sub>2</sub> score and diagnostic approach for reversible cerebral vasoconstriction syndrome. Neurology 92(7):639–647
- Miller TR, Shivashankar R, Mossa-Basha M, Gandhi D (2015) Reversible cerebral vasoconstriction syndrome, part 2: diagnostic work-up, imaging evaluation, and differential diagnosis. AJNR Am J Neuroradiol 36(9):1580–1588
- Al-Mufti F et al (2018) Chemical angioplasty for medically refractory reversible cerebral vasoconstriction syndrome. Br J Neurosurg 32(4):431–435
- Sehy JV et al (2010) Improvement in angiographic cerebral vasospasm after intra-arterial verapamil administration. Am J Neuroradiol 31(10):1923–1928
- El-Bialy ASM, Caraang C (2006) Refractory coronary vasospasm following drug-eluting stent placement treated with cyproheptadine. J Invasive Cardiol 18(2):E95–E98
- Schecter AD, Chesebro JH, Fuster V (1994) Refractory prinzmetal angina treated with cyproheptadine. Ann Intern Med 121(2):113–114
- 12. Mussa S, Prior T, Alp N et al (2004) Duration of action of antispasmodic agents: novel use of a mouse model as an in vivo pharmacological assay. Eur J Cardiothorac Surg 26(5):988–994
- 13. Morgan Stuart R et al (2011) High-dose intra-arterial verapamil for the treatment of cerebral vasospasm after subarachnoid hemorrhage: prolonged effects on hemodynamic parameters and brain metabolism. Neurosurgery 68(2):337–345

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