Reversible Cerebral Vasoconstriction Syndrome Associated with the Use of Sibutramine. Report of two cases and literature review

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ABSTRACT

The reversible cerebral vasoconstriction syndrome, also known as Call-Fleming syndrome, was initially described in 1988, and is characterized by a clinical syndrome of headaches episodes, generally the “thunderclap” pattern, due to a deregulation of the vascular tonus, leading to segmentary cerebral vasoconstriction and secondary neurological deficits, including those by ischemic or hemorrhagic stroke. In this paper, we present two illustrative cases of this syndrome due to the use of sibutramine. To our knowledge, this situation hasn’t been described as related drug before.

Keywords: Reversible cerebral vasoconstriction; Sibutramine

RESUMO

A síndrome da vasoconstrição cerebral reversível, também chamada de síndrome de Call-Fleming, foi inicialmente descrita em 1988 e corresponde a uma síndrome clínica caracterizada por episódios de cefaleia, geralmente de padrão thunderclap após um quadro de desregulação do tônus vascular. Ocorre uma vasoconstrição cerebral segmentar que pode cursar com déficits neurológicos focais secundários a acidentes vasculares cerebrais isquêmicos ou mesmo hemorrágicos. Apresentamos dois casos ilustrativos dessa síndrome em decorrência do uso de sibutramina. Segundo nosso conhecimento, até o presente momento não há outros relatos na literatura dessa associação.

Palavras-chave: Vasoconstrição cerebral reversível; Sibutramina

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The reversible cerebral vasoconstriction syndrome (RCVS), also known as Call-Fleming syndrome, was originally described in 1988 by Gregory Call and Marie Fleming, and is characterized by sudden, recurrent headaches that can be followed by focal neurological deficits, which is believed to be due to a vascular tonus deregulation.

The disease generally presents with vasospasm in cerebral arteries leading to the episodes of severe headaches, often in a “thunderclap” fashion, with or without associated neurological deficits. It is more common in middle aged women and usually self-limited, with complete recovery in a few months. However, more serious complications such as ischemic or hemorrhagic stroke or subarachnoid hemorrhages may appear (7 and 22% of all cases, respectively).

Though its etiology has not been entirely clarified to this moment, it is believed that the exposition to sympathomimetic drugs, such as selective serotonin recapture inhibitors and amines, like cocaine, can be precipitating factors.

This condition has been previously described as benign isolated cerebral vasculitis, reversible segmental cerebral vasoconstriction, acute benign cerebral angiopathy, pseudovasculitis, post-partum angiopathy, and migratory vasoconstriction. Even though rare, an incidence increase has been observed, likely due to the increasing use of vasoactive drugs, such as the aforementioned antidepressants, nasal decongestants, and illicit drugs – such as cocaine, ecstasy, and cannabis – as well as appetite inhibitors, like amphetamines.

This paper aims to describe two cases of RCVS associated to the use of sibutramine.

**Case 1**

Female, 35 years-old, admitted to the emergency room with mental confusion, aphasia and right side hemiplegia, with a National Institutes of Health Stroke Scale (NIHSS) of 10 points. The symptoms had begun 90 minutes before arrival. She was in irregular use of anti-hypertensive medication and sibutramine, with no medical indication, for weight loss. Her magnetic resonance imaging (MRI) showed an acute ischemic stroke in territory of the left middle cerebral artery (Figure 1). The patient underwent intravenous thrombolysis with alteplase and improved from the motor deficits, though the aphasia remained. A resonance angiography two days later showed anterior irregularities and flow reduction, more evident on the left middle cerebral artery and in the vertebro-basilar system, with a pattern of vasospasm (Figure 2). The patient was discharged after eight days with a NIHSS of 7, with right central facial paresis, expression aphasia, and in use of platelet inhibitors. A new resonance angiography after four months showed resolution of the vasospasm (Figure 3).

**Case 2**

Male, 33 years-old, admitted with “thunderclap” headache with nausea and emesis associated with a hypertensive peak (160×90 mmHg). The patient was tetraplegic due to a car accident 14 years before, and was in use of oxibutinine, baclofen, and had begun using sibutramine 15 days before, also for weight loss. He underwent a brain computerized tomography that showed an extensive subarachnoid hemorrhage. A digital subtraction angiography two days later showed no aneurysms of vascular malformations, but revealed diffuse areas of vasoconstriction. A transcranial Doppler, a day later, confirmed diffusely increased velocities, more evident in the anterior circulation. The patient had a complete recovery and was discharged with no new deficits after seven days.
Case Report
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**Figure 1.** Diffusion-weighted magnetic resonance imaging (DWI) showed an acute ischemic stroke in territory of the left middle cerebral artery.

**Figure 2.** Resonance angiography: anterior irregularities and flow reduction, more evident on the left middle cerebral artery and in the vertebro-basilar system, with a pattern of vasospasm.

**Figure 3.** Resonance angiography: resolution of the vasospasm.

**Figure 4.** Brain CT scan: extensive subarachnoid hemorrhage.

**DISCUSSION**
The reversible cerebral vasoconstriction syndrome is a segmentary constriction of cerebral arteries that can lead to ischemia and hemorrhagic events. It is generally followed by a sudden, intense headache, and non-
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The reversible cerebral vasoconstriction syndrome is a segmentary constriction of cerebral arteries that can lead to ischemia and hemorrhagic events. It is generally followed by a sudden, intense headache, and non-aneurysmatic segmentary vasoconstriction on vascular imaging, such as MRI or angiography.

It generally affects middle aged patients, with a few studies reporting a larger pool of susceptible patients, with ages ranging from 19 months to 70 years (average of 42 years). It has a predilection for female patients, with a female-to-male ratio ranging from 4:1 to 10:1.67.

It is believed that a transitory failure in the control of arterial tonus with sympathetic hyperactivity is the main mechanism involved in RCVS. In cases of hemorrhage, the endothelial lesion seems to be the main factor, besides the possibility of reperfusion hemorrhage7.

Many risk factors have been identified for RCVS, including medication, pregnancy and post-partum periods, pheochromocytoma, intracranial hemorrhages, and blood transfusions. Vasoactive drugs such as triptans, ergotamines, selective serotonin recapture inhibitors, nasal decongestants, and drugs such as cannabis, cocaine, ecstasy, lysergic acid, alcohol, and amphetamines have also been implicated.

Sibutramine is an inhibitor of recapture of both noradrenaline and 5-hidroxitriptamine (5-HT), or serotonin, which promotes weight loss due to effects on appetite and metabolic rates. Sibutramine and its active metabolites cause no release of monoaminergic neurotransmitters and has no affinity to its receptors. In the review for this present study we found no articles linking directly sibutramine and RCVS.

However, in cases reported by Singhal et al., the sole etiology to vasoconstriction would be the recent exposition to serotonergic drugs (sertraline, paroxetine, trazodone, sumatriptan, mirtazapine, in various combinations) in all patients, as well as pseudoephedrine, a sympathomimetic, in one single case. Similar cases were described by Noskin et al., who suggested that venlafaxine and paroxetine, with their serotonergic or noradrenergic effects, could precipitate reversible vasoconstriction in susceptible individuals. This corroborates our hypotheses for the cases we described, considering that the patients had used sibutramine, a serotonergic drug.

Also according to Noskin et al., RCVS can be caused by interaction of serotonergic drugs and other risk factor, such as oral contraceptives, pregnancy, carotid lesions, viral infections (such as those by the Epstein-Barr virus), or by induction of serotonergic syndrome, in the concomitant use of various serotonergic drugs.

Specifically, the vasospastic effect of SAID drugs is due to the constriction caused by serotonin in the large intracranial arteries; this vasospastic effect also seems to be enhanced in association with previous atherosclerotic disease.

Regarding to clinical features of RCVS, headache may be the only symptom, generally sudden and explosive. What emerges as an alert regarding the symptomatology is the possible...
differentiation between this headache and the one due to subarachnoid hemorrhage after the rupture of an intracranial aneurysm. The patients typically report a trigger, such as sexual activity, emotional strain, physical exertion, coughing, among others. The headache mechanism hasn't been completely elucidated. However, it is believed that it is related to the innervation of the brain vessel, originated from the trigeminal nerve and the dorsal roots of the second cervical nerve. The ensuing neurological deficits are transient and occur in 10% of all cases, and may include visual deficits.

In radiological investigation, around 12-81% of all patients have abnormalities on the initial exam, the most common being ischemic stroke, subarachnoid hemorrhage, intraparenchymatous bleeding, and in some cases even brain edema. According to Singhal, 55% of all patients had a radiological abnormality in the first exam. However, his results rose to over 80% in the second exam.

A great variety of differential diagnoses must be investigated simultaneously, as infectious arteritis, and inflammatory brain vasculitis, such as giant cell arteritis and polyarteritis nodosa.

Regarding the management, some authors suggest that RCVS justifies both vasospasm monitorization with transcranial Doppler and calcium/magnesium channel blockers.

In situ administration of milrinone and/or calcium channel blockers (such as nimodipine and nicardipine) has been occasionally used as treatment for RCVS but can also be thought of as a diagnostic test, in which vasodilation, after intra-arterial infusion of milrinone or a calcium channel blocker, points to RCVS more than to other causes of intracranial stenosis. It is important to note that RCVS is, as the name suggests, a transient disease, with spontaneous remission usually within three months.

We conclude that RCVS is a pathological entity that, though still with a somewhat nebulous etiology, is an important differential diagnosis within the cerebral vasoconstriction diseases, being often linked to the use of serotoninergic drugs, to which we may include sibutramine. The use of such drugs, as well as the clinical presentations, identification of other risk factors, and imaging features, have great relevance to the accurate diagnosis and proper treatment of the disease.

REFERENCES


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