Reversible Cerebral Vasoconstriction Syndrome Secondary To Drugs: Case Report

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Introduction: *Reversible cerebral vasoconstriction syndrome is a clinical-radiologic syndrome characterized by recurrent thunderclap headache, with or without other acute neurological symptoms, and diffuse segmental constriction of cerebral arteries that resolves spontaneously within 3 months.* ***Methods:*** *The clinic case of a woman who was diagnosed with reversible cerebral vasoconstriction syndrome is described. A literature search and an update of the latest information regarding this disease were performed.* ***Conclusion:*** *At least half of the cases of this syndrome are secondary, especially postpartum and/or exposure to vasoactive substances such as illicit drugs, sympathomimetics and serotonergic drugs. It is crucial to identify this disorder in order to remove possible causative agents, or avoid potential complications.*

Keywords: *headache; headache disorders, secondary; vasoconstriction; cerebrovascular disorders; vascular headaches*

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a clinical and radiological syndrome characterized by recurrent thunderclap headaches and multifocal segmental vasoconstriction of the cerebral arteries, sometimes accompanied by other neurological deficits, which resolves spontaneously within one to three months1. This syndrome has been described in literature under several names, such as the Call-Fleming syndrome, angiopathy or postpartum cerebral angiitis, migraine vasospasm, drug-induced cerebral arteritis or arteriopathy, pseudovasculitis of the central nervous system (CNS), thunderclap headache with reversible vasospasm, primary thunderclap headache, etc.2. The term RCVS was proposed to encompass all these cases featured in reported literature with similar clinical, laboratory, and radio-angiographic characteristics, facilitating the recognition and management of this pathologhy3. In around 50% of the cases, a secondary cause is identified and there are a wide range of factors that have been reported as triggering. (Table 1)4-7. The growing use of vasoactive drugs, including antidepressants, nasal decongestants, and triptans, as well as the use of illicit drugs, such as amphetamines, cocaine, ecstasy, and cannabis, increases the number of people who could develop this condition4,8.

The physiopathogenic mechanism has not yet been completely clarified. Several processes have been suggested, including predisposing

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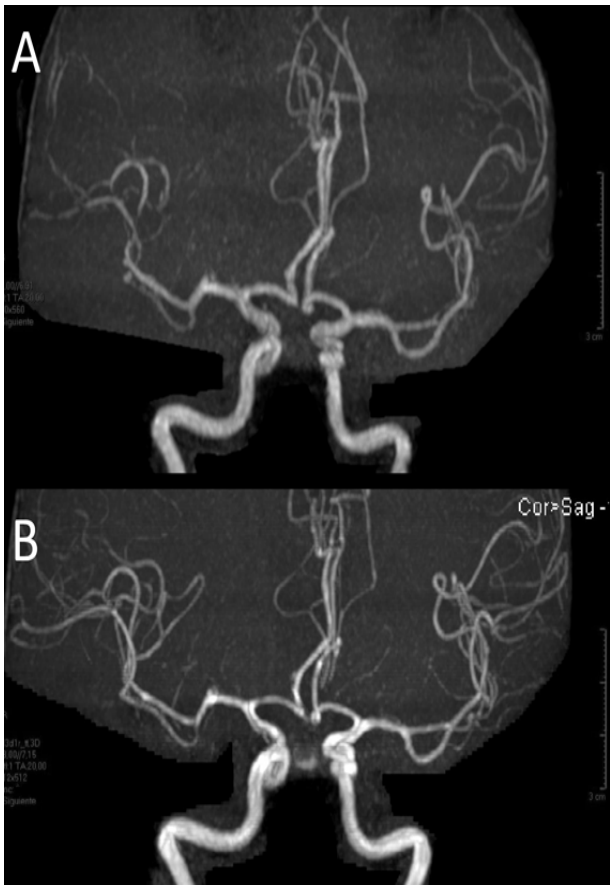
genetic factors, increase of oxidative stress, endothelial dysfunction, an unpredictable and transitory failure of the regulation of the cerebral arterial tone against a sympathetic hyperactivity, etc.4,9.

The evaluation of the RCVS patient involves clinical, laboratory and radiological findings. The objective of this study is to present a clinical case and review diagnostic aspects, imaging features, prognosis and current treatment of this little-known syndrome.

Clinical Case

A 52 year-old female patient, referred from an external neurology clinic due to high-intensity, recurrent thunderclap headache episodes, related to nauseas and phonophotophobia, in the past ten days. These headaches lasted hours, and the patient stated that they worsened with any type of effort (she mentioned the need to stop physical activity and not being able to go shopping to the supermarket). Several times she sought care in emergency units, where she was diagnosed with acute migraines, despite of the recurrence of the condition. She was treated with non-steroidal and cortical anti-inflammatories, with partial response and average pain recurrence of 12 hours. She had chronic migraines, and also presented overuse of symptomatic medication for at least 3 years (she took between 4-5 pills per week of the ergotamine-caffeine-dipyrone association). She mentioned having started treatment with 100 mg/day of sertraline, prescribed a month before for a mood disorder condition. Her neurological and vital signs exams were normal, as well as the fundoscopy. A computed axial tomography (CAT) performed in an emergency unit five days before was reviewed, revealing a focal subarachnoid hemorrhage (ASH) in the right parietal convexity. The exploration was extended with a magnetic-resonance angiography (Angio-MRA), which revealed an irregular and beaded aspect in the calibre of the arteries that form the bilateral sylvian fissure (Figure 1A). Based on the clinical profile and the findings from the images, a presumptive diagnosis of RCVS is determined. As a therapeutic approach, it was decided to suspend vasoactive drugs (sertraline and ergotamine), and rest from her activities, oral nimodipine and rescue analgesia was indicated. The patient showed good clinical evolution. A new NMR-Angio was performed eight weeks after the start, where the caliber of the bilateral Silvian vasculature was restored (Figure 1B). The symptomatic evolution was very favorable; she was pain-free at three weeks.

Figure 1. Angio-MRA, where a superior reduction of the arteries that make-up the Silvian valley bilaterally associated with an irregular and corroded appearance in the caliber of the remaining arteries is observed in the superior image (A). In the bottom image (B), ad integrum restoration of the bilateral Sylvian vasculature is objectified



Observations

Various differential diagnoses may be proposed before a patient who presents to the consultation with thunderclap headaches, such as primary headaches, vascular lesions, headache due to cerebrospinal fluid (CSF), tumor, infectious, primary CNS angeitis9. RCVS is considered the most frequent cause of thunderclap headaches that recurs for a few days or months8,10. A

Table 1. Predisposing factors for the reversible cerebral vasoconstriction syndrome

Puerperium.
Vasoactive drugs: -Illicit drug: cannabis, cocaine, amphetamines, ecstasy, etc. -Antidepressants: serotonin receptor inhibitors, norepinephrine-serotonin receptor inhibitors. -Ergotamine. -Bromocriptine. -Triptans. -Alpha-sympathomimetics: nasal decongestants (phenylpropanolamine, pseudoephedrine, ephe drine), norepinephrine -Nicotine. -Indomethacin. -Erythropoietin. -Gingsen.
Catecholamine-secreting tumors: pheochromocytoma, bronchial carcinoid tumor, glomus tumor.
Immunosuppressors: intravenous immunoglobulins, interferon alpha, cyclophosphamide, tacrolimus.
Blood transfusions.
Surgical procedures: carotid endarterectomy, tonsillectomy, neurosurgery
Traumatic brain injury.
Rheumatologic: systemic lupus erythematosus, Antiphospholipid syndrome
Others: hypercalcemia, porphyria, thrombotic thrombocytopenic purpura, eclampsia, uninjured cerebral saccular aneurysm, hypercalcemia

series of diagnostic criteria have been proposed by experts and modified based on observational studies of case series (Table 2)9,11-12.

Headaches are usually triggered by sexual activity, physical exercise, Valsalva manoeuvres and/or excitement, and can be the only symptom of RCVS10. They can be accompanied by nausea, vomit, photophobia, and phonophobia, and they partially respond to non-steroidal anti-inflammatory drugs or paracetamol12. The International Headache Society attributes a headache to RCVS when it meets the diagnosis criteria mentioned below (Table 3)10. Patients whose angiography shows no pathological findings but reveals other RCVS criteria should be classified as headache probably attributable to RCVS10.

Just as in the case described, the physical exam is usually normal. Around 25-30% of the patients present arterial hypertension during headaches, either due to the pain, the illness itself or a related infection (e.g. eclampsia), and some of them also experience facial flushing1.

The abnormal or excessive adrenergic response to several vasoactive substances, such as sympathomimetic drugs, would play an important role in the development of RCVS13. The association of drugs whose vasoactive

Table 2. Diagnosis criteria for the reversible cerebral vasoconstriction syndrome. Adapted from the criteria of the International Headache Society for acute reversible cerebral angiopathy and the criteria proposed by Calabrese et al. en 2007 and Ducros in 20129,11,12.

Acute and severe headaches (usually bursting), sometimes accompanied by focal deficits or convulsions.
Monophasic course without new symptoms after the first month of the condition.
Segmental vasoconstriction of the cerebral arteries evidenced either indirectly (angio-NMR, angio-CT) or directly (angiography by catheterization).
No evidence of aneurysmatic subarachnoid haemorrhage.
Normal CSF or in normal level (Spinal fluid protein concentration<100mg/dL, white blood cells<15/uL).
Complete or substantial normalization of the arteries, demonstrated by indirect or direct angiographic monitoring, within 12 weeks of onset.

Table 3. Diagnosis criteria for headaches attributed to reversible cerebral vasoconstriction syndrome.

A.	Any new headache that meets criterion C.
B.	Reversible cerebral vasoconstriction syndrome (RCVS) has been diagnosed.
C.	Causality is demonstrated through at least one of the following:
	1.Headache, with or without focal deficits and/or epileptic crisis, has led to a angiography
	(with beaded image) and to the diagnosis of RCVS.
	2.Headache presents one or two of the following characteristics:
	3.No significant headache is suffered after a month of onset.
D.	No better explanation for another diagnosis of ICHD-III and aneurysmal subarachnoid
	hemorrhage has been ruled out by pertinent complementary studies.

effects are well-known, such as ergotamine, caffeine, and sertraline, could have been triggering factors in the case presented.

This syndrome has traditionally been considered as having a benign and monophasic clinical course. Still, a substantial number of patients with RCVS experience shattering complications, such as ischemic cerebrovascular accident (CVA), SAH, posterior reversible encephalopathy syndrome (PRES), among others14. SHA has been the most frequently reported complication. This usually consists of small localized haemorrhages surface of the brain that would not explain diffused vasoconstriction, which mainly involve arteries that do not have direct contact with subarachnoid blood. Therefore, it would be different from the aneurysmal vasospasm, which generally correlates with the location and the quantity of bleeding, and is not multifocal8.

The case described, from the epidemiological point of view, corresponds to the evidence found in the bibliography that mentions that in women RCVS occurs at an age close to

50 years, it is more frequently secondary to exposure to a single drug (mainly serotonin receptor inhibitors or nasal decongestants) and has a higher frequency of ASH8. On the contrary, in men, RCVS is characterized by an earlier age of manifestation, in their early 30s, by the preponderance of exposure to multiple substances, mainly cannabis, and by a low incidence of ASH and cerebrovascular accidents8. At the same time, RCVS-induced intracranial haemorrhage is more prevalent in patients with a history of migraines15.

In general, a brain CAT scan is the first test performed according to the reported cases. In the literature, close to 30% of the patients showed anomalies in the first CAT, including ASH over the cerebral convexity, ischemic cerebrovascular accidents, and intracerebral haematoma6. The diagnosis can only be considered after the presence of cerebral vasoconstriction is demonstrated through angiographic methods. These show the segmental narrowing and dilation (bead chain) of one or more cerebral arteries. Calibre irregularities can affect anterior and posterior circulation, and are mainly bilateral and diffused1. Non-invasive vascular images, including the transcranial doppler echography, the computed axial tomography angiography and the MRA play a growing fundamental role, even though the digital subtraction angiography is sill the gold standard for the evaluation of vasoconstriction of the brain arteries4.

The final diagnosis can only be confirmed when the reversibility of the arterial abnormalities can be demonstrated. This should happen 12 weeks after the beginning of the condition, but the full resolution could take longer for some patients1.

To this date, no randomized trials have been performed to determine the best treatment. For this reason, there are no specific guidelines for or consensus about it. The first step recommended is to eliminate the triggering agent, if it has been identified. It is also recommended that patients avoid possible triggering factors in the weeks following the beginning of the condition, including vasoactive drugs, illicit drugs and Valsalva manouvers9. Calcium blockers, such as nimodipine, nicardipine and verapamil have been used in patients who showed ASH, for its usefulness in preventing vasospasm. These, in turn, could reduce the frequency and intensity of the headaches, even though their ability to alter the clinical course of the disease or reduce the possible neurological sequels, has not been proven11. In cases with progressive clinical worsening,

intravascular procedures have been used, such as balloon angiography and the administration of vasodilating agents (milrinone, nimodipine, epoprostenol), with mixed results11. Glucocorticoids have been reported as an independent predictor of worse outcome, and should be avoided4.

RCVS recurrence is possible, but the rate is unknown, as there no long-term monitoring studies. Sexual activity as a trigger of RCSV is a possible predictor of recurrence of the condition. The physician should advise patients to avoid further exposure to vasoactive substances after RCVS has been diagnosed14

Conclusion

RCVS is a rare disorder, but it is becoming better known and probably is more frequent than it was thought. It is characterized by recurrent thunderclap headaches and evidence of arterial cerebral vasoconstriction with subsequent resolution. At least half of RCVS cases are secondary, specially those postpartum and/or those related to exposition to vasoactive substances, such as illicit drugs, sympathomimetics and serotoninergics. Disturbances in cerebralvascular tone are believed to be the main underlying physiopatogenic mechanism. Neuroimaging plays a fundamental role in confirming the presence of cerebral vasoconstriction, monitoring the possible complications, and suggesting differential diagnosis. Physicians must have a high degree of suspicion of this clinical condition in order to increase the detection rate in patients with thunderclap headache when there is no evidence of aneurysmatic SAH.

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