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Vasoconstriction Cerebral Reversible Syndrome is an Entity That Does Not Missed in the Emergency Rooms

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Abstract

Background: Call-Fleming syndrome, also called reversible cerebral vasoconstriction syndrome (RCVS), is a clinical-radiological pathology, characterized by sudden-onset headache (thunderclap headache) with or without neurological deficit, in relation to multisegmental cerebral arterial vasoconstriction with spontaneous resolution in the following months, becoming a diagnostic-therapeutic challenge in relation to its nosological counterparts.

Case presentation: We present the case of a woman admitted to the emergency department with thunderclap headache without neurological deficit neither documented precipitating factors, identifying a cortical subarachnoid hemorrhage non-aneurysmal on the left fronto-parietal lobe, with data suggestive of vasoconstriction and increased velocity of the left middle cerebral artery evidenced by transcranial color Doppler, secondary causes of cerebral vasoconstriction were ruled out, with resolution in the control image performed at 3 months, for which it was classified as RCVS.

Conclusions: In this case we demonstrate the importance of carrying out an approach to differential diagnoses.

Keywords: Thunderclap Headache, Cerebral Vasoconstriction, Subarachnoid Hemorrhage, Transcranial Doppler, Neurological Emergencies

Background

Call-Fleming syndrome also called; Reversible cerebral vasoconstriction syndrome (RCVS) is a clinical phenomenon that in 85% of cases presents as thunderclap headache (TH; Headache peaking in seconds), with or without other neurological symptoms (focalization or formation of alertness), secondary to segmental or diffuse constriction of cerebral arteries that resolves spontaneously within 3 months [1, 2]. Precipitating factors are observed in up to 70% of cases; including exertion, exposure, sexual activity, and Valsalva, pregnancy, postpartum, vasoactive drugs, catecholamine, disorders related to head and neck, and various medical conditions such as exposure to immunosuppressive drugs or blood products [2, 3]. Physical examination results are usually normal, except when RCVS is associated with secondary causes (systemic vasculitis, autoimmune diseases) or posterior reversible encephalopathy syndrome in the setting of eclampsia, septic shock, or other serious predisposing conditions [4].

RCVS is clinically indistinguishable from other causes of TH, so the differential diagnosis includes subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH), acute migraine, cerebral sinus venous thrombosis, meningitis, spontaneous intracranial hypotension, pituitary apoplexy, and arterial dissection. Primary and secondary Central nervous system (CNS) vasculitides [5].

The approach should focus first on TH; computed tomography (CT) and computed tomography angiography (CTA) of the brain or magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) should be obtained urgently for further evaluation and identification of parenchymal lesions to support or refute the diagnosis of RCVS. If no vasoconstriction is identified a digital subtraction angiography is suggested. If vasoconstriction is identified, transcranial Doppler can be performed to establish a baseline for further serial follow-up. The classic radiological findings include the appearance of "string of beads" on angiography [6]. In patients with RCVS, cortical SAH is the most frequent finding, acute ischemia was more frequent in CNS vasculitis than in RCVS (76% vs 8%). Some brain lesions were observed only in primary central nervous system vasculitis, such as multiple small diffuse deep infarcts, extensive and deep white matter lesions [7, 8]. Early distinction from CNS vasculitis is important in the initial evaluation of RCVS because glucocorticoids, required to treat vasculitis, may worsen the clinical, imaging, and angiographic abnormalities in RCVS. TH with normal brain images or

cortical-only infarcts or vasogenic edema have a positive predictive value (PPV) of 100% for the diagnosis of RCVS. In patients with an abnormal angiogram and without TH, the combination of deep cerebral infarcts and abnormal CSF analysis has a PPV of 98% for the diagnosis of primary CNS vasculitis [9].

Clinical Case

A 46-year-old woman, presented to the emergency department with a new-onset headache. The patient described a pulsatile headache with nausea and vomiting on the left side and a visual analog scale of 10/10 in the first minute. The patient had a history of episodic migraine with aura, and she also commented that her headache episodes occurred tree times by year. The rest of her medical record without pathological findings in the past.

On admission, the patients' vital signs were as follows: BP 146/68 mmHg, heart rate 77 bpm, respiratory rate 14 rpm, temperature 35.5ºC, saturation 95%.

The initial neurological examination showed both dilated pupils (6 mm) and strength reflex exalted. The neurology team decided to measure the optic nerve sheath by POCUS protocol from her, which was 40 mm, with and CT brain scan was performed.

Contrast-enhanced CT of the skull showed subarachnoid hemorrhage in the pre-central and post-central sulcus on the left side. The cerebral vessels presented an aspect of stenosis and dilatation ("in rosary") in insular segments of the middle cerebral artery. Angiography segments do not show dilated aneurysms. Initially, the transcranial Doppler (TD) does not show findings that suggest ischemia and vasospasm in the patient. Initial labs showed Hb 15.2 g/dl, Leu 8.8 X 10^3/µL, platelets 536 X 10^3/µL, Na 139 mEq/L, K 4.9 mEq/L, Cl 101 mEq/L, Cr 0.69 mg/dl, Glu 94 mg/dl, BUN 10 mg/dl, Ca 10.1 mg/dl, P 4.9 mg/dl, Mg 2.2 mg/dl. Negative pregnancy test.

The diagnostic possibilities in this case, that was temporally conclude as a non-aneurysmal, non-traumatic subarachnoid hemorrhage had been focused on disorders of cerebral vascular dysregulation, these patterns could be seen in patients with reversible posterior encephalopathy syndrome or reversible cerebral vasoconstriction syndrome.

The patient was brought to the intensive care unit for intracranial pressure monitoring and headache management. A new measurement of the optic nerve sheath increased to 54 mm (<50 mm) in less than 24 hours. Physical examination of the patient did not show pain on palpation of her temporal arteries, or she doesn't in her skin show evidence of systemic vasculitis.

An MRI brain scan was performed three days after the initial symptoms showed subarachnoid blood in both hemispheres' frontoparietal and occipital regions, predominantly on the left, with parenchymatous hemorrhage and perilesional edema surrounding. The angiography found areas of segmental stenosis in the insular branches of the left insular branch from the middle cerebral artery. Due to the high suspicion of vasculitis, we request made vessel – wall weighted (black blood approach), without abnormal findings. A second TD performed 48 hours after admission showed increased middle cerebral artery velocities with a increase Lindegaard index suggestive of moderate vasospasm.

Other diagnosis to consider was a central nervous system vasculitis in the patient. Furthermore, an approach included a HIV test, hepatitis B and C panel, acute inflammatory reactants (sedimentation rate velocity and ultrasensitive C-reactive protein), markers of antiphospholipid syndrome (lupus anticoagulant, anti-beta 2-glycoprotein IgG/IgM antibodies, anticardiolipin IgG/IgM antibodies), systemic vasculitis (ANCA 1: 20, anti-MPO, anti-PR3), generalized lupus erythematosus (anti-nuclear antibodies), Sjogren's syndrome (anti-SSA and Anti-SSB antibodies), rheumatoid arthritis (anti-cyclic citrullinated peptide), which were unremarkable.

A lumbar puncture was made that showed red blood cells: 60 x 10^3 /mL; white blood cells: 18/mL (80% neutrophils, 16% lymphocytes, 4% monocytes); protein: 60 mg/dL; and glucose: 45 mg/dL (CSF/serum glucose ratio: 0.6). The infectious panel (cryptococcus antigen, polymerase chain reaction herpes simplex type 1 and 2, varicella zoster, cytomegalovirus and Epstein Barr, Gram stain, CSF acid fast bacilli, smear and India ink) was negative. Rheumatological panel in CSF included ANCAs, anti-PR3, Anti-MPO, ANAs, rheumatoid factor and citrullinated peptide antibody, that were negatives.

The Reversible Cerebral Vasoconstriction Syndrome (RVSC) score was 7 points, making this diagnosis the most probable in the patient. We decided to start the patient on lercanidipine 20 mg daily for five days. She presented improvement in the headache three days after her admission to the intensive care unit. After five days of treatment with the calcium antagonist drug, the headache had remission.

The patient was treated with lercarnidipine 20 mg every 24 hours for 35 days. The headache presented gradual improvement with complete remission 7 days after admission, she was discharged from the hospital with lercarnidipine. We decided to request a follow-up brain MRI three month after it began to show areas of frontoparietal bleeding, which were reduced in size compared to the previous images. On the other hand, the arterial vessels showed decreased areas of stenosis and persistence of focal thinning at the level of the insular branch of the left middle cerebral artery. Currently asymptomatic and continues primary prevention for migraine.

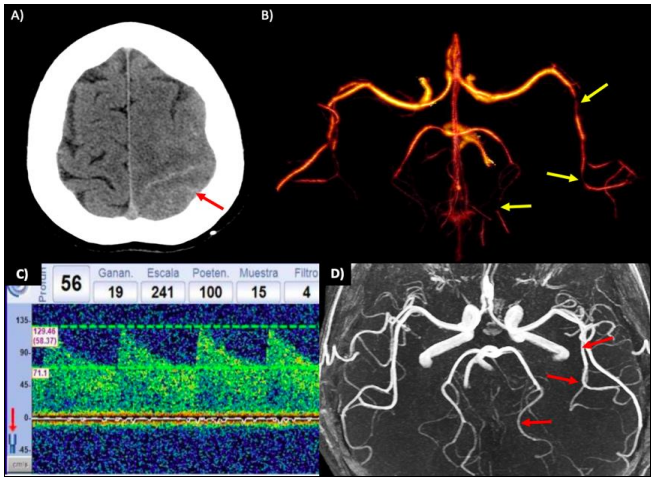

Fig: A) Subarachnoid hemorrhage in the left precentral sulcus. B) Segmental stenosis in insular areas of the LMCA and LPCA. C) TCD on LMCA with SV 129 cm/s, and DV 71.1 cm/s. MV 90.5 cm/s, PI 0.6, Lindegaard index 3.1 D) Vascular permeability of previously affected LMCA and LPCA at 3-month follow-up LMCA; Left middle cerebral artery, LPCA; Left posterior cerebral artery, SV; systolic velocity, DV; diastolic velocity, IP; pulsatility index

Discussion

This case illustrates the complexity of the approach to primary headache patients presenting to the emergency department with new-onset headaches, which may be mistaken for an acute exacerbation of primary headache. Therefore, secondary causes of headaches would be forgotten. The SNNOOP-10 mnemonic may not apply to all patients. The patient had no medical history of illness. She was younger than 50 years old; the neurological examination did not reveal focal neurological involvement or data suggestive of acute intracranial hypertension [10].

In the second interview, she does not describe other headaches in the last weeks suggestive of sentinel headache. This type of headache is typical of an aneurysmal subarachnoid hemorrhage [11]. On the other hand, she did not refer to intermittent decrease of visual acuity to Valsalva maneuver, diplopia, or alterations in the state of consciousness. The headache in the patient, which we classified as thunderclap according to the criteria of the international headache society, obliges us to rule out vascular pathology and initially directs the investigation of these patients [12].

The finding of subarachnoid hemorrhage in a young patient without risk factors for aneurysms requires a more comprehensive approach and getting along with other differential diagnoses. Reversible cerebral vasoconstriction syndrome (RVCS) is clinically indistinguishable from other causes of thunderclap headache; differential diagnoses include, SAH, ICH, acute migraine, cerebral sinus venous thrombosis, meningitis, spontaneous intracranial hypotension, pituitary apoplexy, and arterial dissection, primary and secondary CNS vasculitis [7, 13].

Vascular disorders can be highly suspect in a patient with a thunderclap headache. If the neuroimaging shows vasoconstriction in at least two arteries and resolves at three months, a diagnosis of RVCS will have made. Classically, patients are female with a history of migraine and usually have a trigger, such as vasoactive substance use or postpartum status [4, 13].

Another critical point in the neuroimaging findings is diffuse and multifocal vasoconstriction of vessels and blood in subarachnoid space focused on a possible Primary vasculitis of the central nervous system (PVCNS) diagnosis. Cortical strokes and subarachnoid bleeding are more common in patients with RCVS, while deep brain lesions are more common in vasculitis [5, 13, 14].

It is necessary to repeat the angiographic study to differentiate an RCVS vs. PVCNS. In the first, there is improvement or reversal of vasospasm. The second will show persistence, worsening, or progression. On the other hand, the early distinction of RVCS from PVCNS is crucial because steroid treatment can worsen the clinical, imaging, and angiographic abnormalities in RVCS [9].

In addition, the use of scores in the appropriate context can be a tool to lean towards the most likely diagnosis, the RCVS2 score, whose ranges from −2 to +10, a score >5 has a specificity of 99% and a sensitivity of 90%. For the diagnosis, the patient presented 7 points [14].

Treatment of patients with SAH with nimodipine has been shown in several studies to be effective in reducing the incidence of poor outcomes and severe neurological deficits. Although the underlying neuroprotective mechanism of nimodipine is not yet fully understood, a positive effect on functional outcome in patients with SAH has been confirmed. In our patient, due to the shortage of nimodipine in the country, lercarnidipine (third-generation calcium antagonist) was used, which, in addition to blocking activity of calcium channels, has antioxidant, anti-inflammatory and antiapoptotic properties, finding an improvement in the speeds evidenced by TD and vasospasm in MRI, this only as an anecdotal case, further studies are needed [15, 16].

Conclusion

RCVS is a complex entity that is not harmless and should be considered in the case of primary headache, but the importance of identifying this entity in the fact that the characteristic cerebral vasoconstriction can be associated with life-threatening neurological complications. In view of the differences in prognosis and treatment, appropriate imaging tests should be performed for each patient with thunderclap headache, in the case of RCVS Diagnosis requires the demonstration of the "string and beads" aspect of cerebral arteries by a cerebral angiogram (MRA, CTA) and the demonstration of the complete or marked normalization of arteries by a repeat angiogram performed within 12 weeks of onset. Treatment is based on nimodipine that seems to reduce thunderclap headaches within 48h.

Table 1: Abbreviations

RCVS	Reversible Cerebral Vasoconstriction Syndrome
TH	Thunderclap Headache
SAH	Subarachnoid Hemorrhage
ICH	Intracerebral Hemorrhage
CNS	Central Nervous System
PPV	Positive Predictive Value
CT	Computed Tomography
CTA	Computed Tomography Angiography
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography (MRA)
TD	Transcranial Doppler
CSF	Cerebrospinal Fluid
ANCA	Antineutrophil Cytoplasmic Antibody
SSA	Anti-Sjogren's Syndrome A
SSB	Anti-Sjögren's Syndrome Type B
PR3	Proteinase-3
MPO	Myeloperoxidase
ANA	Antinuclear Antibodies
IGG	Immunoglobulin G
IGM	Immunoglobulin M
PVCNS	Primary Vasculitis of the Central Nervous System

Declarations

Ethics Approval: National Institute of Medical Sciences and Nutrition "Salvador Zubiran" does not require ethical approval for reporting individual cases or case series.

Informed Consent: Written informed consent was obtained from the patient for their anonymous information to be published in this article.

Availability of data and materials: Data will be provided by contacting David Prestegui

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