Reversible cerebral vasoconstriction syndrome: a clinical and therapeutic challenge

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Abstract

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by thunderclap headache and intracranial segmental vasoconstriction with or without signs of neurological deficit with a variable course that requires extensive study to prevent complications. The evidence shows RCVS is characterized by being multi-etiological; both the cause and the specific symptoms must be treated to reduce the chance of complications and recurrence. The timely identification of the RCVS and its etiology is the cornerstone of success in managing the disease. New data must be generated to have more efficient resources for the approach to this disease.

Keywords

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is an uncommon disease with a broad form of presentation. The diagnosis is clinical and radiological, and the condition usually resolves within three months [1, 2]. The main symptom of RCVS is thunderclap headache associated with symptoms of focal neurological deficit. On intracranial vascular imaging, the most frequent finding is a "string of beads" of cerebral vessels which can be associated with nonaneurysmal subarachnoid hemorrhage (SAH) [1]. Given its variable clinical course, it is difficult to diagnose; therefore, there is no clear data on prevalence and incidence worldwide [3, 4].

The approach for RCVS is based on the etiological identification of vasospasm since its prompt detection and treatment have been shown to reduce the probability of recurrences and serious outcomes such as stroke and even death [2, 5–9]. Among the most important etiologies are the use of vasoactive

substances, drugs, and neuroendocrine tumors, or tumors with compressive effects on structures that influence vascular tone [4]. Therefore, early identification of the etiology is crucial for the management of RCVS and its associated complications [3, 4]

This article aims to examine recent literature on general aspects of RCVS, to provide tools for a comprehensive approach to the syndrome, and to strengthen research on this topic, which is little known and with a correct approach leads to much more favorable clinical outcomes for patients.

History

Described for the first time in 1988 by Call and Fleming in their series of four patients, in whom they found a common finding the segmental and reversible cerebral arterial vasoconstriction associated with thunderclap headache with or without neurological deficit [6], however, this disease is described as a group of clinical entities since 1960 associated to other conditions such as postpartum and migraine [9].

Historically, RCVS has had different names, such as Call-Fleming syndrome or postpartum angiopathy. In 2007, Calabrese et al. [5] proposed the diagnostic criteria for RCVS, which are still valid today, as follows: 1) presence of multifocal and segmental cerebral arterial vasoconstriction by digital subtraction angiography or indirectly by angiotomography/resonance angiography, 2) no evidence of aneurysmal SAH, 3) normal or near normal cerebrospinal fluid (CSF; protein < 80 mg/dL, leukocytes < 10 mm^3, normal glucose), 4) acute, severe headache with or without neurological symptoms or signs, 5) angiographic reversibility of cerebral vasoconstriction 3 months after onset [2]. In the last decade, there have been attempts to advance the study of physiopathology; however, they remain unknown [9].

Epidemiology

Is considered a rare disease. However, this may be related to underdiagnosis [4]. RCVS usually affects patients between 20 and 50 years old [10]. It is more common in women than men and does not seem limited to any ethnic or racial group [4, 10, 11].

It may occur spontaneously or be secondary to a specific trigger (approximately 25% to 60% of the times) [12, 13]. The use of vasoactive substances and postpartum are the most reported etiologies [1]. In cases where medications act as exogenous triggers, patients may take the drug regularly or infrequently, either in recommended doses or in excess [4] and the most common medications reported associated with RCVS are antidepressants [1].

Vasoactive drug use and the postpartum state account for more than 50% of cases in most published series [13]. Drugs with vasoactive effects have been associated with SAH and ischemic stroke, which retrospectively may reflect the sequelae of drug-induced RCVS [14, 15].

It is also related to having a history of migraine (20% to 40% of cases), possibly associated with the use of triptans [6, 11, 16]. Finally, some published series have noted a significant association between RCVS and the use of cannabis or other psychoactive substances [17].

Etiology

Although little is known regarding the etiopathogenesis of RCVS, it is believed that there is an alteration in the regulation of cerebral vascular tone [18]. This is assumed to be secondary to spontaneous or evoked central vascular discharge of vasoactive agents. It may also be precipitated by various endogenous or exogenous factors that have been associated with RCVS [3]; these include catecholamines, endothelin-1 (E1), serotonin, prostaglandins, and nitric oxide [19, 20].

Postpartum

Postpartum RCVS is one of the most common etiologies, usually occurring after an uncomplicated pregnancy and normal deliveries [21], although it has been reported up to six weeks postpartum [17]. It is believed that the association between RCVS and postpartum is due to an increase in the levels of antiangiogenic factors [5] and that both female reproductive hormones and physiological changes of

pregnancy may contribute to alterations in cerebral arterial tone [22], so, for this reason, RCVS should be a differential etiological diagnosis of headaches in the postpartum period [23].

Tumors

RCVS has been described in patients with neuroendocrine tumors [24]. Paragangliomas are slow-growing vascular tumors that originate in non-chromaffin cells; less than 5% are catecholamine-secreting and are usually associated with RCVS [25, 26].

Psychoactive substances

Psychoactive substance use is the most common trigger of RCVS, accounting for 60% of cases [27], and the three most common vasoactive factors are cannabis, cocaine, and heroin [28]. Cannabis was the most frequently reported substance triggering RCVS in a prospective series published by Ducros et al. [8], documented in 30% (20/67) of patients, whereas cocaine was the trigger in 4.8% of cases.

Medications

Among the most frequently reported drugs with vasoactive effects associated with RCVS are some antidepressants [1], ergot derivatives [2], sympathomimetics, nasal decongestants, serotoninergic drugs [2, 14], triptans, and some chemotherapeutic agents such as tacrolimus and cyclophosphamide [2]. However, in recent years, there has been an increase in the report of new drugs associated with RCVS such as aromatase inhibitors (anastrozole), among others [2, 28].

A significant number of published cases associated with RCVS have a variable period between exposure and the onset of vascular events, from an immediate onset to prolonged periods (months or years); therefore, many of these drugs do not always have a direct causal relationship [11, 28–30].

Pathophysiology

It has been proposed that there is a reversible dysregulation of the tone of cerebral vessels, an effect that may be related to overactivity of the autonomic system, endothelial dysfunction, and oxidative stress through markers such as urinary 8-iso prostaglandin F2 alpha that has been associated with to the severity of increased vascular tone [31].

Different hypotheses have been proposed to associate RCVS and specific conditions such as paraganglioma [30]. Some of these hypotheses suggest that the foci of stenosis are secondary to undetectable adrenergic production with essential effects on the tone of the cerebral arteries, while another theory proposes that, depending on the location of the tumor, it can generate a mechanical compressive effect on the carotid baroreceptors inducing vasospasm [26].

Diagnosis

Clinical approach

RCVS has a sudden, variable, and multi-etiologic presentation. Its broad clinical presentation depends on the location and size of the affected vessels. The most frequent symptoms are thunderclap headache, focal neurological deficit, nausea, emesis, photophobia, blurred vision, and arterial hypertension [2, 27].

Anamnesis

Within the interrogation, it is essential to define the presence of a headache and inquire about its characteristics. The localization, onset, intensity, and recurrency are the most important topics to search in RCVS headache. However, the disease can occur with other types of headaches or even in the absence of it [32]. RCVS is frequently associated with seizures or other persistent or transient neurological symptoms [9].

If there is a previous history of headaches or seizures, the usual pattern of presentation and its frequency should be investigated. Clinicians should ask about medical history, specially try to determine if there is a history of vascular risk factors such as hypertension or diabetes. The adequate control or not of these

diseases and therapeutic adherence should be clarified as well [9]. Regarding mental health, current or recent psychosocial problems should be inquired and finally, the use of non-conventional drugs should be ruled out [3].

A history of cancer, dyslipidemia, arterial hypertension, and diabetes mellitus are important risk factors for presenting different types of cerebral vascular events [9], as well as psychiatric pathologies such as psychosis, depression, and anxiety that require medications whose systemic effects may be related to changes in the vascular caliber of intracranial arteries. It is relevant to inquire about the type, dose, and number of medications consumed. Likewise, in the surgical history, it should be determined if there is a history of head and neck procedures (both open and endovascular) [31].

Neurological examination

It can be variable, from normal to even severe neurological deficits such as altered mental status, motor, sensitive or coordination deficit, or a wide range of clinical signs depending on the vessels affected. So a complete neurological examination provides a closer approach to the topographic diagnosis [2, 9, 31].

Clinical manifestations

Thunderclap headache

It was described in 1986 by Day and Raskin [33]. It is defined as a sudden-onset headache that reaches its maximum intensity in less than one minute [34]. It is the most frequent symptom of RCVS, occurs in 94–100% of cases, and disappears three weeks after the onset of symptoms [4, 35, 36]. It is characterized by global headache; however, 19% of the times it is hemicranial [33], with a variable duration between 1 h and 5 h [8, 10]. Up to 76% of the cases, it is the only referred symptom and has a recurrence in the first weeks in 82–94% of the patients [35, 36]. Additionally, it can be associated with photophobia, phonophobia, nausea, and emesis [4, 31].

A prospective series published by Ducros et al. [8] observed that in 63/67 patients, there was a recurrence of thunderclap headache in a period of 7.4 days (range of 1 to 26). The average pain intensity was 9.5/10, generating disability for activities of daily living. The duration was variable, with a range between 5 min and 36 h, and appeared secondary to a trigger such as Valsalva maneuvers (32%), sexual activity (29%), and bathing (10%) or even in the absence of any trigger in 21% of patients.

The diagnostic criteria for headaches attributable and probably attributable to RCVS proposed by the International Classification of Headache Disorders (ICHD-3) are listed below [37]:

(A) Any new headache fulfilling criterion C.

(B) RCVS has been diagnosed.

(C) Evidence of causation demonstrated by at least one of the following:

    a. Headache, with or without focal deficit and/or seizures, has led to the performance of angiography (with "strings and beads" appearance) and diagnosis of RCVS.

    b. Headache has either or both of the following characteristics: 1) Recurrent during less than one month and with thunderclap onset; 2) triggered by Valsalva, sexual activity, emotion, bathing, and/or showering; 3) no new significant headache at one month after onset.

(D) One of the following:

    a. Headache resolution within three months.

    b. Persistent headache for more than three months since the first episode.

(E) Not better accounted for by another diagnosis.

Thunderclap headache is a neurological emergency and requires prompt neuroimaging studies. Lumbar puncture and CSF analysis allow for measuring the opening pressure and identifying the presence or not of SAH or an inflammatory/infectious differential diagnosis, findings to be considered within the differential diagnoses [33, 38].

Other neurological symptoms

RCVS courses have variable neurological symptoms because many vascular territories are affected secondary to intracranial stenosis. The frequency of occurrence of neurological deficits varies according to case series, but they are present in 15–81% of cases [35, 36, 38, 39].

Symptoms of focal deficit may be secondary to the disease per se or to complications such as ischemic or hemorrhagic stroke. Additionally, some symptoms are usually transient, but permanent sequelae have been reported in up to 7% of cases [8]. The most frequent neurological findings are hemiparesis, aphasia, and ataxia, representing approximately 35% of cases, and visual defects in 29% [10, 11].

As for seizures, they can be generalized or focal onset with bilateral irradiation, with variable semiology. They usually appear within the first week of the disease, generally after episodes of headache [4, 31], and have been reported in 3–17% of patients [40].

Diagnostic studies

Among non-conventional studies to consider during the approach of RCVR are plasma metanephrine and urine toxins that can suggest drug consumption. In cases of suspected tumor pathology, the corresponding radiological studies should be requested according to the diagnostic suspicion [8, 22, 36].

For the differential diagnosis of RCVS, CSF analysis is required, mainly to rule out other infectious, inflammatory, or vascular diagnoses such as primary central nervous system (CNS) vasculitis [11]. However, in most cases, leukocytes and proteins in CSF should be normal to suspect RCVS. When the results of CSF are atypical, it can generate confusion and lead to erroneous diagnoses such as CNS vasculitis, which will result in inappropriate treatments, so the clinical and paraclinical findings must be correlated [41].

Imaging features

In the initial evaluation of thunderclap headache with or without signs of focal neurological deficit, neuroimaging, either computerized tomography (CT) or brain magnetic resonance imaging (MRI), is performed [2, 42]. The most common finding is the non-aneurysmal SAH of the cerebral convexities. MRI has a better sensitivity to detect cortical SAH, cerebral edema, and ischemia [42].

The gold standard for diagnosis is conventional cerebral angiography with digital subtraction (DSA) [42], and in-hospital follow-up to evaluate vasospasm should be done with transcranial Doppler [43].

Brain computerized axial tomography

It is usually the first neuroimaging in the suspicion of an acute vascular event. In the case of RCVS, it may initially be abnormal in only 12% of cases, evidencing early complications (in the first week) such as cortical SAH and/or in the cerebral convexities or intraparenchymal hemorrhages, while in the second week, ischemic changes associated with areas of vasospasm may be seen [2, 44].

In RCVS, CT angiography is helpful in identifying the presence and distribution of vasoconstriction foci in proximal vessels and ruling out differential diagnoses such as aneurysms, arteriovenous malformations, or intra- or extra-cranial arterial dissections [6].

MRI of the brain

It is useful in screening RCVS-associated complications. The fluid attenuated inversion recovery (FLAIR) sequence is very sensitive to identifying SAH; however, not all hyperintensities in the subarachnoid space in FLAIR correspond to bleeding since some vessels may present a high signal within the sulci, a phenomenon known as the "dot sign", which is present in 22% of cases. The magnetic susceptibility weighted imaging (SWI) sequence also allows observing intraparenchymal, and subarachnoid bleeding; Magnetic diffusion allows for establishing the co-existence of acute ischemic events or other conditions that generate diffusion restriction within the encephalic tissue [6].

In the first week, brain MRI may be normal in up to 20% of cases, or findings such as SAH of convexity of non-aneurysmal origin may appear, and in the second week, as in CT, secondary infarct areas may

appear [2, 27, 45]. Acute ischemic stroke secondary to RCVS affects 39% of patients with the disease. They are usually bilateral and symmetrical and increase the chance of worse clinical outcomes [3].Cerebral magnetic resonance (MR) angiography is considered a sensitive and specific tool to evaluate changes in vascular tone and can evidence areas of intracranial segmental vasoconstriction and vascular lesions such as vertebral or carotid dissections [46].

Cerebral angiography

It is the gold standard in the diagnosis of RCVS. Irregularities in the vascular caliber can generate compromise of both anterior and posterior circulation, in both hemispheres and in vessels of any caliber [36].

It is beneficial in cases of distal vasoconstriction. When the cerebral parenchymogram is performed in the arterial phase, filling defect and tissue hypoperfusion are usually seen; however, these changes are temporary, and after a few days or weeks, in the control angiographies, partial or complete resolution of the previously mentioned findings is observed, or there may be the presence of the same changes, but in different vascular territories [4].

The maximum peak of arterial vasoconstriction is around day 16 from the onset of symptoms, which is why, during the first days, there may not be significant angiographic findings [4, 47]. Another characteristic of RCVS is the complete restitution of normal vascular tone and blood flow after intra-arterial administration of nimodipine, a feature that differentiates this disease from other conditions, such as primary CNS vasculitis, among others, in which improvement is usually null or partial [4, 47].

Transcranial Doppler

Very useful in monitoring the evolution of cerebral vasoconstriction. It is essential to detect dynamic changes in vascular tone daily and identify small changes with much better performance than cerebral MR angiography. The average velocities in the middle cerebral arteries may be normal within the first few days of the course of the disease; subsequently, it starts to increase until it reaches its peak (< 200 cm/s) at the end of the third week of evolution [47].

Differential diagnosis

It is relevant to know the main differences with other entities that may simulate RCVS, such as primary CNS vasculitis [18], which are described in Table 1.

Table 1. Differential diagnosis of RCVS

Pathology	Difference with RCVS
Cluster headache	Episodic
SAH aneurysmal	Findings of ruptured aneurysm
Primary angiitis of the CNS	No thunderclap headache
	Ischemic infarctions
	Abnormal CSF

Therapeutic approach

The initial therapeutic approach should provide basic general support, including neurological observation, analgesia, rest, and avoidance of Valsalva maneuvers or other triggers [36].

The evidence regarding the most appropriate therapeutic alternative for these patients remains uncertain, given the lack of randomized studies and the fact that knowledge in this regard has been based mainly on reports, case series, observational studies, and some systematic reviews.

The cornerstone of RCVS treatment is first to identify the etiology and try to cease or avoid exposure to the trigger causing the vascular changes. Although there are no randomized clinical trials, calcium channel blockers have been described, the most commonly used being nimodipine by intravenous or oral administration, followed by verapamil and nifedipine, even in cases where no apparent cause is found [27].

Regarding the use of nimodipine, multiple administration regimens have been described. One of the most commonly used is oral administration at doses of 30 mg to 60 mg every 4 h for 4 to 8 weeks [27]. The use of verapamil and nimodipine intra-arterially during cerebral angiography is an intervention documented in case reports and small case series, with good results and in which restitution of cerebral blood flow and vascular caliber in stenotic areas can be evidenced [2].

In some cases, the use of corticosteroids in severe clinical presentations has been reported, but it has been demonstrated that these patients have poor evolution, so their use is not recommended [27, 48]. The evidence in this regard is based on some cohorts, such as that of Singhal and Topcuoglu [49] of 162 patients with RCVS, to whom corticosteroids were administered to 28%, with clinical deterioration in 37% of cases *versus* 5% worsening in the group that did not receive corticosteroids.

The use of i.v. magnesium sulfate has been described in patients with postpartum RCVS, with favorable results, at doses reported to be between 1 g and 2 g i.v. in association with calcium channel blockers. However, this intervention doesn't have enough studies that evaluate its efficacy and safety [48, 50, 51].

Regarding RCVS secondary to medications, the decision to restart the drug causing the condition should be based on how indispensable its use is and evaluating the risk-benefit ratio of the intervention, making it clear that the risk of recurrence after the resolution of RCVS, even by restarting the drug, is low [36]. It is important to note that in some cases, RCVS can be associated with SAH, which can lead to post bleed seizures. Some authors consider it reasonable to incorporate antiepileptic drugs into the treatment depending on the patient's risk for seizure recurrences. Some of the factors that should be taken into account assessing that risk are: if the patient is young, the severity of SAH, those with cortical irritation, or patients who are undergoing a craniotomy [52, 53].

Also, in cases with residual SAH, persistent headaches can be a main concern for clinicians, however, little data exists on the efficacy of the different therapeutic options [54]. There are no current guidelines for the management of this condition. Still, the most commonly used medications in the literature are a combination of opioids and common analgesics such as acetaminophen or caffeine [54]. Other options have shown some level of headache improvement in these patients. These include pregabalin, gabapentin, and magnesium [54].

The loss of cerebral blood flow autoregulation derivated from the vascular event, can lead to delayed cerebral ischemia, especially in cases of RCVS with SAH [55]. Delayed cerebral ischemia is caused by vasoconstriction-mediated perfusion mismatch, as well as inflammatory responses in the brain [55]. There have been reports of animal models on the role of endogenous calcitonin gene-related peptide in the acute and subacute phase due to its vasodilatation properties which may have direct and indirect effects aimed at reducing secondary brain injury (such as ischemia and apoptosis) but this is still under investigation [55]. It has been suggested a potential therapeutic efficacy in this clinical setting but due to its short half-life and narrow therapeutic index, it has failed to reach clinical trials [55].

Prognosis

RCVS usually has a benign course, with complete recovery and a low recurrence rate of 5%, even 71% of cases do not present disability and 29% present with mild functional sequelae [27, 36], however, they can present with severe complications such as ischemic stroke [27, 56], which is a complication that can lead to permanent residual deficits [1]. Death as an outcome has been documented in the literature in up to 2% of cases [36].

Limitations

This study has multiple limitations. First, we performed a non-systematic review, and important knowledge of the disease comes from case reports and case series, there are not an important number of prospective cohorts or clinical trials, which increases the likelihood of publication, reporting, and selection bias at the time of choosing the studies included in this article.

Conclusions

RCVS is a diagnostic and therapeutic challenge. Identifying and correcting the underlying cause of the disease as well as the use of calcium antagonists have shown to be the keystones of treatment. Measures should be taken to avoid recurrences or complications, considering that a small percentage of patients may present fatal outcomes. The prognosis of RCVS depends on the occurrence of stroke or prolonged cerebral hypoxia which can eventually lead to permanent deficits. Besides the management of the disease, it is important to determine and treat the symptoms after the acute episodes, many derivated from SAH, such as persistent headaches and seizures. More research needs to be done regarding the best therapeutic strategies to prevent recurrences, and the identification of new etiologies should be reported in the literature.

Abbreviations

CNS: central nervous system

CSF: cerebrospinal fluid

CT: computerized tomography

MRI: magnetic resonance imaging

RCVS: reversible cerebral vasoconstriction syndrome

SAH: subarachnoid hemorrhage

Declarations

Author contributions

ARF: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. LRS: Investigation, Writing—original draft, Writing—review & editing. NMG: Validation, Writing—review & editing.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

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