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Reversible Cerebral Vasoconstriction Syndrome: a Comprehensive Update

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Abstract Reversible cerebral vasoconstriction syndrome (RCVS) is a clinico-radiological syndrome characterized by recurrent thunderclap headache, with or without neurologic symptoms, and reversible vasoconstriction of cerebral arteries. RCVS affects patients in various racial and ethnic groups and in all age groups, although most commonly in the fourth decade of life. Many conditions and exposures have been linked to RCVS, including vasoactive drugs and the peripartum period. Disturbance of the cerebral vascular tone is thought to contribute to the disease's pathophysiology. RCVS generally follows a monophasic course. Associated strokes and cerebral hemorrhages are not uncommon. In this review we will attempt to provide a comprehensive overview of RCVS, with emphasis on the controversies in the field and the newest findings in the reported literature.

Keywords Reversible cerebral vasoconstriction syndrome · Call-Fleming syndrome · Primary angiitis of the central nervous system · Thunderclap headache · Subarachnoid hemorrhage · High-resolution magnetic resonance imaging

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Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is a clinico-radiological syndrome (or group of syndromes) characterized by recurrent thunderclap headaches, with or without concomitant neurologic signs and symptoms, in the context of prolonged yet reversible vasoconstriction of the cerebral arteries.

Starting the early 1960s, case reports surfaced in the literature describing RCVS in various clinical settings [1, 2]. By the late 1980s, this phenomenon was described in diverse conditions, including migraine, [2–4], other headache syndromes [5], eclampsia and pre-eclampsia [6, 7], puerperium [8], unruptured cerebral aneurysms [9], various drugs [10–12], as well as a complication of various neurosurgical procedures [13, 14]. The first notable case series was published by a French group in 1983, and described 11 patients with similar clinical, radiologic, and angiographic findings [15]. In the series, Rousseaux et al. described patients presenting with severe headache and seizures, in addition to transient neurologic deficits; all patients shared arteriographic findings of multifocal and asymmetric stenoses of the cerebral arteries. They also shared a benign course, and from this the authors introduced the term "acute benign cerebral angiopathy." In 1988, Call et al. reported 19 patients with similar features [16]. The term "Call-Fleming syndrome" was proposed in reference to this group.

In the following years, many other reports appeared describing this phenomenon in relation to various exposures and different systemic conditions (Table 1). In addition to the aforementioned names, and despite the striking similarity in the reported cases, many different syndromic labels were coined from these observations, depending upon the discipline where it was presented. These included "postpartum angiopathy" [17], "migrainous vasospasm" [3], "migraine angiitis" [18], "drug-induced angiopathy" [11], "benign

Table 1 Conditions associated with reversible cerebral vasoconstriction syndrome

Pregnancy-related conditions	• Late pregnancy • Early puerperium • Pre-eclampsia and eclampsia
Drugs (list includes the most common drugs; others have been implicated)	• Pseudoephedrine • Epinephrine • Ergotamine tartrate • Bromocriptine, • Hydroxycut (weight-loss aid) • Selective serotonin reuptake inhibitors • Serotonin noradrenaline reuptake inhibitors • Sumatriptan and other triptans • Tacrolimus • Cyclophosphamide • Erythropoietin • Interferon alpha • Nicotine patch • Oral contraceptive pills/hormonal agents • Cocaine, Ecstasy, Marijuana • Lysergic acid diethylamide (LSD) • Amphetamine derivatives
Headache disorders	• Migraine • Primary thunderclap headache • Primary cough headache • Benign sexual headache
Medical problems	• Hypercalcemia • Porphyria • Pheochromocytoma • Bronchial carcinoid tumor • Unruptured saccular cerebral aneurysm • Head trauma • Spinal subdural hematoma • Carotid glomus tumor • Post-bone marrow transplant • Thrombotic thrombocytopenic purpura • Systemic lupus erythematosus • Anti-phospholipid antibody syndrome
Surgical procedures	• Carotid endarterectomy • Neurosurgical procedures • Tonsillectomy • Neck surgery
Blood product transfusion	• Red blood cell transfusion • Intravenous immune globulins (IVIg)
Miscellaneous	• High altitude • Swimming • Bathing

angiopathy of the central nervous system (CNS)" [19], and "CNS pseudovasculitis" [20]. It was not until 2007 when Calabrese et al. published their landmark review [21••] that the name "reversible cerebral vasoconstriction syndrome" was proposed to encompass all the cases reported in the literature with similar clinical, laboratory, and radio-angiographic features. Understanding that individual entities certainly carry unique features, the term RCVS has since been generally accepted as the big umbrella.

Since the inception of the notion of RCVS, many more reports and large case series have been published, spanning various medical fields including primary care, emergency medicine, neurology, neurosurgery, rheumatology, obstetrics, and intensive care.

Epidemiology

The many reported case series of RCVS extend across continents and encompass a range of racial and ethnic groups [22••, 23••, 24, 25]. RCVS has been reported to affect patients aged 19 months to 70 years [22••, 23••, 26, 27], with mean age of onset around 42 years. It rarely affects children. There is a female predilection, with a female-to-male ratio of 2:1 to 4:1 [22••, 23••].

Although the true incidence of the disease remains unknown, based upon our practice and the published data, we believe that it is not uncommon and that it remains largely under-diagnosed. Cheng et al. recently reported that 45.2 % of patients with sudden headache and 45.8 % with thunderclap headache (TCH) were eventually diagnosed with RCVS [28•]. Despite the fact that this is a small study with possible referral bias and underrepresentation of true vascular emergencies (subarachnoid hemorrhage), given the outpatient setting, the study shows that RCVS in general, and the pure cephalalgic subtype in particular, is not a rare entity.

Associated Conditions

Over the years, RCVS has been associated with different exposures. In various series, up to two-thirds of cases (30–60 %) have occurred in the context of an underlying condition or exposure [21••, 22••, 23••], most notable of which are vasoactive medications, pregnancy complications, and the puerperium.

The puerperium [8], along with the pregnancy complications of eclampsia and pre-eclampsia [6, 7], have long been associated with RCVS, and with perhaps the more severe forms of it. Various vasoactive medications have been incriminated as well, including selective serotonin reuptake inhibitors [29], alpha-sympathomimetic decongestants [30], Hydroxycut and other diet pills [31], and acute migraine medications [32]. Most illicit drugs have also been implicated, including cocaine [10] and cannabis [23••]. Table 1 provides a list of the myriad conditions and exposures that have been reported in association with RCVS.

Clinical Manifestations

Recurrent TCH is the hallmark of RCVS, occurring in more than 95 % of patients, and it is the sole symptom in more than

two-thirds of cases [22••, 23••]. Presentation is typically dramatic, with the "worst-ever" headache, which reaches its peak intensity in less than a minute. It is normally severe to excruciating, bilateral, starts posteriorly but generalizes quickly, and lasts anywhere from minutes to days. It is sometimes associated with nausea, vomiting, photophobia, and phonophobia. Moreover, 30–39 % of patients have acute blood pressure elevation, which may be secondary to pain. Although a single attack is possible, attacks typically recur over a period of one to four weeks, with an average of four attacks. About 50 % of patients report a residual mild-intensity headache between the severe exacerbations. Interestingly, patients are usually able to identify a trigger for the exacerbations, such as strenuous exercise, sexual activity, bathing, swimming, coughing, sneezing, defecating, urinating, laughing, or other Valsalva-triggering maneuvers [22••, 23••, 24]. It is prudent to exclude carotid or vertebral artery dissection in the presence of lateral or posterior neck pain specifically in pregnant or post-partum patients [33–35].

Focal neurologic deficits and seizures can be manifestations of RCVS. Neurologic symptoms and seizures range from 8–43 % and 1–17 % of cases, respectively [22••, 36•]. This difference is secondary to the recruitment strategy of those studies.

Visual disturbances are the most frequent neurologic symptoms encountered, and include scotomas, blurring, hemianopia, and cortical blindness. Other symptoms such as hemiplegia, dysarthria, aphasia, numbness, and ataxia can also occur. Most deficits are usually transient and resolve within minutes to a few hours. Persistent deficits would suggest a stroke (ischemic or hemorrhagic) [19, 22••, 23••]. Posterior reversible encephalopathy syndrome (PRES) shares many clinical features with RCVS, including headache, seizure, and visual disturbance, and has been reported to occur in 10–38 % of RCVS cases [17, 22••, 23••, 37].

It is worth noting that despite the reversible nature of the cerebral vasoconstriction, given the prolonged nature of the process, permanent damage occurs in around 10 % of patients [22••]. Moreover, progressive vasoconstriction occurs in less than 5 % of patients, resulting in major ischemic and hemorrhagic stroke, progressive brain edema, and even death [38–40].

Cerebrovascular and Brain Imaging Findings

In the various reported series, 20–80 % of initial brain computed tomography (CT) or magnetic resonance imaging (MRI) scans are normal, despite extensive vasoconstriction on concomitant angiography [22••, 23••, 37]. Lesions reported are in the form of stroke (convexity subarachnoid hemorrhage [cSAH], intracerebral hemorrhage, or ischemic cerebral infarction) or reversible brain edema. Different lesions can coexist in the same patient.

Ischemic infarctions were the most common lesions found in the cohort analysis by Singhal et al. [22••], occurring in 39 % of cases. Only 6 % and 8 % of patients demonstrated those lesions in the French and Taiwanese cohorts, respectively [37, 41]. Infarctions could be multiple, bilateral, and symmetric, and tended to occur in arterial watershed areas [22••, 37]. cSAH occurred in one-third of cases [22••, 37], and was limited to a few sulci near the convexity unilaterally or bilaterally. These were manifested as hyperintense lesions on fluid-attenuated inversion-recovery MRI and hypointense lesions on T2-weighted images [42••]. Intracerebral hemorrhages occurred in 12–20 % of patients, and they were mostly single, lobar, and tended to occur concomitantly with other lesions [22••, 37, 42••]. Reversible brain edema in a pattern similar to that of PRES appeared to be a common feature, occurring in 8–38 % of cases [22••, 36•, 43].

As the diagnosis of RCVS rests upon the demonstration of diffuse reversible cerebral vasoconstriction, cerebral vascular evaluation is warranted. While the gold standard remains catheter angiography, the sensitivity of indirect angiographic imaging (MR or CT angiography) is about 70 % [44, 45•]. These modalities demonstrate the characteristic diffuse "string of beads" appearance of the cerebral arteries indicating segmental narrowing and dilatation [21••, 46]. Affected vessels are typically bilateral, diffuse, and include the anterior and posterior circulation [16, 47]. It is very important to understand the dynamic nature of the disease process, as the vasoconstriction is not fixed, and a repeat angiography a few days later would show resolution at some vessels, with potentially new constrictions [29, 42••, 48]. Indeed, the patient's first angiogram will be normal in up to 30 % of cases, if done early in the disease process (within one week) [42••]; a repeat angiographic evaluation several days later would normally be diagnostic.

It should be emphasized that while these radiologic findings are suggestive of RCVS, they are in no way specific. They are also seen in atherosclerosis, infectious arteritis, inflammatory vasculitis, and fibromuscular dysplasia. The most specific evidence for RCVS is the demonstration of resolution of vasoconstriction within a 12-week period [21••].

Diagnosis

Diagnostic Approach

Given the acute and dramatic presentations of RCVS patients, initial evaluation should be focused on excluding other diagnoses such as aneurysmal subarachnoid hemorrhage (aSAH), sentinel bleed, parenchymal hemorrhage, ischemic stroke, pituitary apoplexy, cerebral artery dissection, cerebral venous

sinus thrombosis, meningitis, spontaneous intracranial hypotension, and cerebral vasculitis [49]. An unenhanced brain CT is uniformly the first-line imaging modality to exclude a subarachnoid or parenchymal hemorrhage. Cerebrospinal fluid (CSF) analysis is helpful for excluding inflammation as is typical in vasculitis or in an infectious process. Normal CSF analysis is expected in RCVS [21••], with minor abnormalities occurring in the context of cSAH [22••]. If the CSF analysis is benign, further brain and cerebrovascular imaging should include MRI, MR angiography, and MR venography to further exclude alternate etiologies.

Laboratory investigations in RCVS serve merely a "rule-out" function. Blood counts, electrolytes, and renal and hepatic function testing are all within normal limits, as are the inflammatory markers [22••, 37]. Rheumatologic workup (rheumatoid factor, antinuclear, and antinuclear cytoplasmic antibody testing) helps exclude an underlying connective tissue disorder. Vasoactive tumors such as pheochromocytoma and carcinoid tumors are excluded by measuring urine vanillylmandelic acid and 5-hydroxyindoleacetic acid levels.

Pathologic brain evaluation has no role in the evaluation of RCVS, with the exception of the highly challenging cases where primary CNS vasculitis cannot be entirely ruled out.

Diagnostic Criteria

Calabrese at al. proposed the first diagnostic criteria for RCVS [21••], emphasizing five conditions that must be met for a definite diagnosis of RCVS :

1. Acute severe headache, often thunderclap, with or without neurologic signs and symptoms;
2. Demonstration of multifocal segmental cerebral artery vasoconstriction via direct (catheter) or indirect angiography;
3. Absence of aneurysmal subarachnoid hemorrhage;
4. Normal, or near normal, CSF analysis;
5. Demonstration of reversibility of angiographic findings within 12 weeks of disease onset.

In clinical practice, repeat angiographic evaluation may not always be obtained, especially in the setting of a benign course and complete resolution of symptoms, or in rare cases where death occurs. In these cases, a definite diagnosis cannot be made, and thus they are considered probable RCVS.

Natural History

RCVS is a self-limited disease. The headaches generally resolve in three weeks [23••]. As for the neurologic processes, Ducros et al. [23••, 37] reported that hemorrhagic strokes and brain edema tended to happen within one week of disease onset, as opposed to the ischemic complications that occur later in the second and third weeks.

Katz et al. recently reported on 59 RCVS patients and assessed them for "clinical worsening" [25]. As 34 % of their cohort experienced clinical worsening, the authors argued that the disease may not be strictly monophasic. While one-third of the reported cohort did suffer new clinical symptoms, the median time for clinical worsening was 2.5 days, which is well within the one-month time period of expected new symptomatology. No patients in their cohort had clinical worsening beyond one month, underscoring the monophasic nature of the disease. It is important here to emphasize the importance of not confusing the initial disease progression that characterizes RCVS within one month of onset with its monophasic pattern defined as the absence of new symptoms after this first month [21••, 45•, 50].

In most patients, all symptoms, along with the angiographic findings, resolved completely within days to weeks [19, 22••, 43]. Residual deficits were reported in less than 10 % of cases in both the French [37] and Taiwanese [36•] cohorts. In the American cohorts, the percentage was 20 %, of which 11 % were characterized as severe in one cohort [22••] and 13.6 % in another [25]. Progressive vasoconstriction yielding major morbidity and possibly death remained a rare occurrence [13, 38–40].

John et al. evaluated the long-term outcomes of 20 patients with RCVS through multiple surveys [51]. Median follow-up time was 91.5 months (range 10–254 months). While half of the patients continued to have headaches, most (91 %) were of different character and severity than seen in RCVS. Moreover, although three-quarters of patients in this cohort suffered an initial ischemic stroke or hemorrhage, almost all (94 %) were independent, with little disability. The majority of the patients had no problems with mobility, self-care, or leisure, although pain and anxiety adversely affected their quality of life.

Several reports attempted to investigate prognostic factors in RCVS patients. Occurrence of stroke appeared to be the major prognostic determinant. This was more severe in the hemorrhagic forms in the French cohort [37] and in the ischemic forms in the American cohorts [22••]. In the cohort from the Mayo Clinic [25], the only factor that correlated significantly with clinical worsening was acute ischemia. Despite the fact that reported literature seems to point toward worse prognosis in peripartum RCVS [38, 40, 52], this was never replicated in larger series, perhaps indicating reporting and publication bias.

Etiology and Pathophysiology

While little is known at this time with regard to the etiopathogenesis of RCVS, it is widely accepted that a

disturbance in the cerebral vascular tone is at the heart of the disease's pathophysiology [21••]. This is hypothesized to be secondary to abnormal vascular receptor activity or sensitivity resulting from either a spontaneous or evoked central vascular discharge [21••, 45•]. It may also be precipitated by the various endogenous or exogenous factors that have been associated with RCVS.

It has been speculated that, at the molecular level, the numerous immunologic factors that are involved in the subarachnoid hemorrhage-related vasospasm may also be involved in RCVS [21••]. These include catecholamines, endothelin-1 (E1), serotonin, prostaglandins, and nitric oxide. Our group recently reported a study comparing plasma E1 levels in seven RCVS patients during the ictal phase to those of healthy controls [53•]. Significantly higher E1 levels were noted in RCVS patients. Moreover, E1 levels in RCVS patients showed a significant decline between the ictal and the resolution phase, approaching those of healthy controls. As speculated, these results suggest a role for E1 in the pathogenesis of the disease.

Additionally, Chen at al. [54•] recently reported elevated urinary levels of an oxidation marker, 8-iso-prostaglandin F2α. in RCVS patients compared to patients with other forms of acute headache as well as healthy controls, suggesting a possible role for oxidative stress in the disease process. The same group also published a study investigating autonomic functions as assessed by heart rate variability in 39 RCVS patients and 39 controls [55•]. Although no detailed characteristics were provided on the RCVS cohort, the investigators found markedly attenuated parasympathetic activity and heightened sympathetic activity in RCVS patients, particularly during the ictal period. These parameters improved in the resolution phase, but not to control values.

Ducros at al. [23••] noted the frequent occurrence of PRES concomitantly with RCVS [22••, 23••]. Endothelial dysfunction is postulated to be at the core of the pathophysiology of PRES, causing disruption in small vessels and blood-brain barrier. This results in transient edema and convexity hemorrhage similar to what is seen in certain RCVS cases. The authors thus hypothesized that the pathologic process of RCVS may, at least in part, resemble PRES, and suggested that the pathologic process of RCVS first involves distal arteries and then progresses toward the Circle of Willis [23••].

On another note, the cerebral vessels are densely innervated with sensory afferents from the first branch of the trigeminal nerve and dorsal root of C2. This may provide an anatomic basis as to how the vascular phenomenon is coupled with headache [21••]. It should be noted that the alteration of the vessel tone is very dynamic, and it is challenging to correlate that with the timing of the headaches. As such, it remains questionable whether the headache is caused by the vasoconstriction of the cerebral vessels. Moreover, maximal vasoconstriction occurs nearly 20 days after the headache onset and can persist for months, at which time the headache will have resolved. An alternate explanation may be that the headache results from stretching of the vessel wall due to segmental vasodilatation [37].

Differential Diagnosis

The differential for TCH, which is the hallmark of RCVS, is quite wide. On one end of the spectrum there are the potentially life-threatening conditions that include aSAH, sentinel bleed, parenchymal hemorrhage, ischemic stroke, pituitary apoplexy, cerebral artery dissection, cerebral venous sinus thrombosis, meningitis, spontaneous intracranial hypotension, and cerebral vasculitis [49, 56]. As noted in the diagnosis section above, most of those conditions can be ruled out via brain and vascular imaging in addition to CSF analysis.

On the other end of the spectrum are the benign etiologies of TCH. In addition to RCVS, these include primary thunderclap headache, cough-related headache, and headache associated with sexual activity. These entities do not generally exhibit the reversible cerebral vasoconstrictive properties unless within the context of RCVS itself.

The Controversy of cSAH and Vasoconstriction: Which Came First?

RCVS is associated with cSAH in around 30 % of patients [22••, 36•, 37]. While RCVS is an important cause of cSAH, other etiologies include PRES, cerebral amyloid angiopathy, distal mycotic aneurysms, coagulopathy, and dural arteriovenous malformations [57]. This has led several authors to question the cause of the hemorrhage in RCVS and its relationship to the vasoconstriction [58–60].

From a symptomatology standpoint, short of RCVS, TCH is not typical of any of the aforementioned causes of cSAH. Furthermore, recurrent attacks as seen in more than 80 % of RCVS patients would be exceedingly unusual [61]. As for the angiographic findings, it is highly improbable that the minor cSAH as seen in RCVS would explain the diffuse, dynamic, and prolonged vasoconstriction observed. Had the analogy with aSAH been valid, one would expect that the site and severity of the vasospastic reaction would correlate with the site of the hemorrhage. As a matter of fact, vasoconstriction in RCVS appears to affect arteries that are remote from the bleeding site [42••, 45•, 61]. Given this reasoning, we strongly believe that cSAH represents a genuine manifestation of RCVS.

An interesting article was recently published that explored predictors of RCVS in a large retrospective cohort of SAH patients [62•]. As compared to patients with aSAH and cryptogenic SAH, RCVS patients with SAH were younger and had a history of chronic headache, depression, and chronic

obstructive pulmonary disease. They had lower Hunt-Hess grade and Fisher SAH group and had a higher number of arteries affected, along with bilateral arterial narrowing. The clinical impact of these findings has yet to be determined.

RCVS vs. Primary Angiitis of the CNS (PACNS), an Ongoing Dilemma!

Perhaps the major differential – and in certain scenarios, the hardest to exclude when evaluating a patient with possible RCVS – is PACNS. This is particularly important as treatment strategy and prognosis vary drastically between the two groups. From a historical standpoint, many RCVS patients were misinterpreted as having PACNS [63, 64]. The confusion undoubtedly stems from the overlapping clinical, laboratory, and radioangiographic features of both diseases. Headache and seizures, along with neurologic symptoms, can occur in both diseases. Normal metabolic, inflammatory, and rheumatologic profile is the norm in both, and the angiographic appearances, as emphasized earlier, can be quite similar [65, 66••].

While the overlap can certainly be remarkable, the characteristic TCH that is the hallmark of RCVS is rare in PACNS patients, who usually present with a progressive chronic-type headache. The clinical course in RCVS is monophasic, as opposed to chronic relapsing with PACNS. CSF analysis can prove quite helpful in this scenario, as the normal analysis of RCVS would be highly unusual in PACNS, where an inflammatory CSF is expected. Moreover, brain imaging in RCVS can be normal or show watershed infarcts and lobar hemorrhages, as opposed to the uniformly abnormal images of PACNS showing deep infarcts and T2-hyperintense lesions [66••, 65]. Quick stabilization and reversibility of the angiographic pattern in RCVS remains the most important differentiating feature. In the right clinical setting, therefore, a watch-and-wait strategy may not be unreasonable. Table 2 summarizes the major differentiating features of the two disease entities.

The major diagnostic challenge occurs in the rare RCVS cases with severe progressive vasoconstriction that could incite secondary inflammation, thus rendering the radioangiographic and CSF findings closer to those of PACNS [67, 61]. These are the patients who are usually started on immunosuppressive therapy until the diagnosis of PACNS is excluded, generally via a brain biopsy. Some authors have proposed a less invasive approach utilizing an intra-arterial nimodipine application to make the distinction in these challenging cases. [68] Nimodipine is hypothesized to reverse the angiographic findings of RCVS and not PACNS. This has yet to be validated. We advocate against these interventions given the risk of reperfusion injury [69]. More recently, however, attention has turned to non-invasive diagnostic tools, namely high-resolution contract-enhanced MRI (HR-MRI) to evaluate for vessel wall enhancement as a surrogate for vessel inflammation [70]. Our group recently reported a study utilizing HR-MRI to compare intracranial vessel wall characteristics between 13 RCVS and 13 CNS vasculitis patients [71••]. Marked vessel wall enhancement was seen in 12 of the vasculitis patients versus none of the RCVS patients (Fig. 1). Pending larger trials, these data suggest that vessel wall enhancement as seen on HR-MRI may be of diagnostic value in distinguishing between RCVS and PACNS during initial presentation.

Management

There have been no randomized clinical trials investigating treatment strategies in RCVS. Observational data and expert opinions guide management of the disease at the current time. Nonetheless, several agents have been utilized in treating RCVS patients, most of which have shown a favorable response. This may stem from the fact that the disease is largely self-limited, with spontaneous resolution of signs and symptoms. Calcium channel blockers such as verapamil and nimodipine have been utilized extensively in aSAH patients, perhaps due to their anti-vasospastic properties [22••, 24, 37, 72–75]. These agents may reduce the frequency and intensity of the headaches, but they have not been shown to alter the course of the cerebral vasoconstriction and the possible neurologic sequelae [24, 37]. Magnesium sulfate [17] and ryanodine [76] have also been utilized. Short courses of glucocorticosteroids have been tried, and do not appear to prevent clinical deterioration; indeed, a trend toward worse outcomes was observed [22••]. While this could be a reflection of selection bias, an actual effect cannot be excluded. With the exception of the rare case of rapidly worsening clinical course, we recommend against the routine empiric use of steroids in patients in whom the diagnosis of RCVS versus PACNS is entertained. Clearly, steroids should be stopped as soon as a diagnosis of RCVS is confirmed.

It is our belief that given the benign self-limited nature of the disease, the primary focus of treatment in the vast majority of cases should be symptom management. Identification and elimination of aggravating or precipitating conditions is of paramount importance. This includes rest, with avoidance of strenuous activity, sexual intercourse, and activities that are Valsalva-stimulating (stool softeners are recommended). Vasoactive medications should be strictly avoided.

From a medication standpoint, analgesics should be used liberally for pain, antiepileptic drugs for seizures, and blood pressure medications to treat extreme hypertension (systolic above 180 mm Hg), understanding that hypotension in the context of cerebral vasoconstriction is potentially more detrimental than hypertension.

Table 2 Differentiating PACNS and RCVS

	PACNS	RCVS
Gender and mean age of onset	Male, 50 years	Female, 42 years
Clinical presentation	Insidious with subacute onset of headache with focal and non-focal deficit	Acute onset of thunderclap headache with or without neurological deficit
Clinical course	Chronic, relapsing	Remission within one month, monophasic
CSF findings	Lymphocytic pleocytosis and elevated protein levels	Normal
Common neuroimaging findings	-Ischemic, high intensity T2/FLAIR lesions -Abnormal MRI images in 100 % of cases	-Ischemic, edema, cSAH, ICH -Normal MRI images in 20 % of cases
Vascular findings	Normal in one-third of cases	Abnormal in all cases
Histologic findings	Vasculitic changes	Normal
Immunosuppressive therapy	Essential	Not indicated
Prognosis	Improved with immunosuppressive therapy	Excellent

Abbreviations: *PACNS:* primary angiitis of the central nervous system, *RCVS:* reversible cerebral vasoconstriction syndrome, *CSF:* cerebrospinal fluid, *cSAH*: convexity subarachnoid hemorrhage, *FLAIR*: fluid-attenuated inversion recovery, *ICH:* intracranial hemorrhage

Adopted with permission from Hammad et al. [66••]

In severe cases with progressive clinical worsening, endovascular procedures with balloon angioplasty [77, 78] and intra-arterial administration of a vasodilating agent (milrinone [79], nimodipine [74, 68, 80], epoprostenol [81]) have been utilized, with mixed results. These interventions carry a high risk of reperfusion injury, and therefore should be entertained only in highly selected cases [69].

Conclusions and Future Perspectives

Since the inception of the concept of RCVS in 2007, significant attention has been turned toward this disease entity. We have come to realize that the disease is not uncommon and should be considered in any patient presenting with recurrent TCH in the absence of other etiologies. RCVS affects all age groups, with a female predilection. Disordered cerebral vascular tone is hypothesized to be the major pathologic anomaly leading to reversible cerebral vasoconstriction. Up to two-thirds of cases can be secondary to a specific exposure, medical, or surgical condition, the most common of which are vasoactive drugs and the peripartum period. The hallmark of RCVS is recurrent TCH with or without focal neurologic deficits, which are generally transient. The disease follows a monophasic course, with complete resolution of all signs and symptoms in the vast majority patients. A small percentage of patients are left with permanent deficits, and very rarely do major complications or death ensue. In the right clinical setting, diagnosis rests upon ruling out other potential etiologies and demonstrating reversible cerebral vasoconstriction via repeated cerebrovascular studies . Watchful waiting is a reasonable management plan, given the self-limiting nature of the disease, with focus on symptom control and precipitant avoidance.

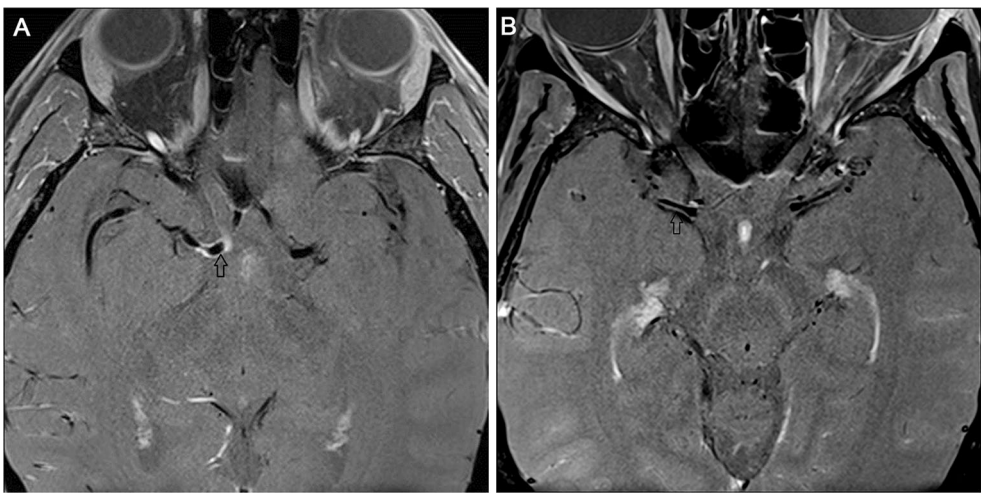

Fig. 1 HR-MRI brain axial section post gadolinium contrast: Vasculitis patient (**a**) shows vessel wall enhancement and thickening (arrow) while RCVS patient (**b**) shows minimal wall enhancement (arrow)

Many questions linger within the world of RCVS. Given the wide clinical manifestations and imaging findings and the varied frequencies reported in different series, it remains unclear whether RCVS is, in fact, a single disease or a common presentation of various disease entities. Another question arises from the rare cases where progressive rather than reversible vasospasm occurs. Whether those are actually manifestations of the same disease spectrum or a totally different disease process with a different etiopathogenic basis is not clear. As more insight is gained into the etiopathogenesis of RCVS, we will undoubtedly achieve a better understanding of the disease on the clinical level as well.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Ali Mehdi declares no potential conflicts of interest.

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- •• O major importance

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