Reversible Cerebral Vasoconstriction Syndrome: A Thunderclap Headache–Associated Condition

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Current Neurology and Neuroscience Reports 2009, **9:**108–114
Current Medicine Group LLC ISSN 1528-4042

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by a sudden, severe headache at onset, vascular narrowing involving the circle of Willis and its immediate branches, and angiographic evidence of vasoconstriction reversibility within minutes to weeks of onset. RCVS is underrecognized and often misdiagnosed; it can defy clinical detection because it can mimic common conditions such as migraine and ischemic stroke. A lack of shared nosology has hampered awareness and understanding of the syndrome. Clinicians must consider primary angiitis of the central nervous system because of its high rates of morbidity and mortality if left untreated. RCVS has a number of primary and secondary associations (cerebral hemorrhage, vasoactive substances, the peripartum period, bathing, and physical exertion) but also occurs in isolation. RCVS can present in conjunction with hypertensive encephalopathy, preeclampsia, and reversible posterior leukoencephalopathy. This review provides an up-to-date account of RCVS.

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by sudden, severe headache at onset, reversible vascular narrowing involving the circle of Willis and its immediate branches (Fig. 1), and evidence of near to complete resolution of vasoconstriction within days to weeks of onset. RCVS is an underrecognized, often misdiagnosed condition that was first described akin to its current definition by Call et al. [1]. RCVS has been attributed to a wide range of clinical entities, including Call-Fleming syndrome, benign angiopathy of the central nervous system (CNS), isolated benign cerebral vasculitis, drug-induced vasospasm, postpartum angiopathy, crash migraine, migrainous vasospasm, and migraine angiitis [2–8]. A lack of shared nosology both within and across disciplines has contributed to poor clinical recognition and hindered the pathophysiologic understanding of this syndrome. RCVS often defies clinical detection because it mimics common conditions such as migraine and ischemic stroke. Cerebral angiography is essential for diagnosis; however, until recently, noninvasive MR (MRA) and CT angiography (CTA) were largely unavailable. Recent reports have attempted to develop a unified classification of RCVS and its associated conditions [9••]. In this review article, we describe the clinical and radiologic features of RCVS and differentiate primary RCVS from well-known secondary causes and differential diagnoses.

Clinical Features of RCVS

RCVS occurs predominantly in women (female–male ratio, 6:1) between age 20 and 60 but can occur at any age. More than two-thirds of RCVS cases occur within the postpartum period or following the ingestion of a vasoconstrictive substance, such as ergot derivatives, sympathomimetics, and serotonergic agents. RCVS also has been reported in the context of Valsalva-like maneuvers and within a range of physical activities including exercise, sexual activity (preorgasmic and orgasmic), swimming, deep-water diving, and defecation (Table 1) [10••,11••]. Headache at presentation occurs in 90% of patients with RCVS [10••]. In slightly more than 70% of patients, RCVS is associated with thunderclap headache (TCH) [10••] and may be described as bilateral, explosive, or throbbing. TCH may recur every day or two throughout the disease course, with each attack lasting 30 minutes to 4 hours [11••,12••]. A history of chronic headache, typically migraine or tension-type headache, is common [10••].

Signs and symptoms of RCVS are often variable depending on the neuroanatomic structure or function that is affected. A third of patients experience moderate to severe hypertension [10••,11••]. Focal neurologic deficits are evident in most cases, and seizures occur in one-third. Other common clinical features include nausea/vomiting; visual disturbances such as blurred vision, vision loss, and

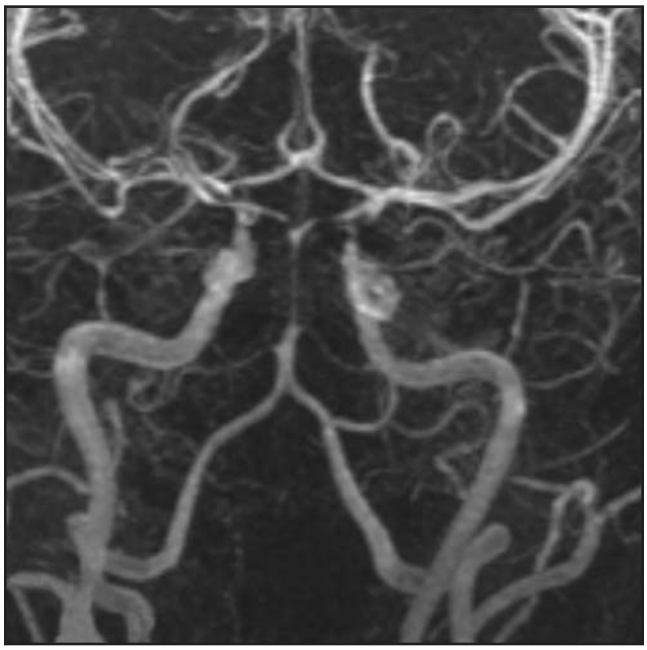

Figure 1. MR angiography showing segmental vasoconstriction of the basilar artery, the P1 segments of the posterior cerebral arteries, and the supraclinoid segment of distal internal carotid arteries.

visual field deficits; aphasia; paresis; sensory changes, such as dysesthesias, paresthesias, and hypesthesias; and alterations in cognitive status, ranging from confusion to coma. Mortality directly attributed to RCVS is rare [10••,13•].

Blood work is generally nondiagnostic, but the erythrocyte sedimentation rate may be elevated. Cerebrospinal fluid (CSF) red and white blood cell counts tend to be within normal limits. The CSF red blood cell count may be mildly elevated due to a traumatic tap or sequelae associated with cerebral ischemia or intracerebral hemorrhage. An elevated CSF white blood cell count, when present, is usually less than 20/μL. CSF protein levels above 45 mg/dL occur in about one-third of patients but rarely exceed 100 mg/dL. [9••,10••].

CT or MRI abnormalities such as cerebral infarction or posterior leukoencephalopathy are present in more than two-thirds of patients over the entire disease course [10••]. In most cases, cerebral angiography reveals segmental cerebral vasoconstriction affecting the circle of Willis or its immediate branches, including the distal segments of the internal carotid arteries (Fig. 1). Headaches may precede angiographic evidence of vasoconstriction, and vasoconstriction often persists beyond the cessation of headaches [11••,12••]. Near to complete resolution of the segmental vasoconstriction may be observed within hours to days [14–16], and angiographic resolution is demonstrated in 86% of subjects within 12 weeks of the initial study [10••]. Although clinical recovery occurs in most RCVS cases, up to one-quarter have significant residual neurologic deficits, suggesting that RCVS cannot be accurately described as a "benign" cerebral angiopathy [10••].

RCVS demonstrates high comorbidity with a number of other syndromes, including hypertensive encephalopathy, preeclampsia, and reversible posterior leukoencephalopathy syndrome (RPLS) [15]. Aberrant central regulation of sympathetic vascular tone may explain the clinical and radiologic features of these syndromes [17]. Hypertensive encephalopathy is well known to occur in association with RPLS and preeclampsia [18], and RPLS occurs both in the presence and absence of severe hypertension [19–21]. RPLS is characterized by nausea, vomiting, visual changes, altered mental status, seizures, and radiologic evidence of vasogenic edema within the posterior circulation [22]. Vasoconstriction resulting in posterior ischemic changes is one posited link between RCVS and RPLS [12••,22–24]. Call's first case description of RCVS meets the present-day criteria for RPLS [1]. The patient experienced visual disturbances and a focal seizure; CT head imaging revealed bilateral low-density white matter lesions in the occipital and parietal lobes. A recent review of "postpartum cerebral angiopathy" by Williams et al. [13•] discussed the highly significant association between postpartum eclampsia and postpartum angiopathy both in the presence and absence of vasoactive substances.

TCH and RCVS

There is a strong association between RCVS and the clinical syndrome of TCH [9••,10••,25]. TCH is traditionally associated with subarachnoid hemorrhage (SAH) and is now linked to an expanding list of secondary causes (Table 2). TCH occurs in most patients with RCVS [10••]. Despite their close association, the two phenomena may occur independently. In a recent prospective study of recurrent TCH and RCVS, there was a marked discordance between the timing of headache occurrence and cerebral vasoconstriction, leading the investigators to conclude that headaches could not be directly attributable to vasoconstriction [11••]. Cerebral vasoconstriction could persist days to months after resolution of headache.

The second edition of the International Classification of Headache Disorders (ICHD-2) defines headaches associated with reversible angiopathy of the CNS along the same lines as RCVS but with some clinically important exceptions [26]. According to criteria D, the "headache (and neurologic deficits, if present) resolves spontaneously within 2 months." This excludes cases with spontaneous angiographic resolution that continue to have residual morbidity from cerebral vasoconstrictive-induced ischemic events [1,5,27,28]. Recent accounts of RCVS [9••–11••,29••] provide more detailed, inclusive characteristics of the syndrome (Table 3).

Primary TCH and RCVS

In the absence of an identifiable organic cause, including RCVS, primary TCH is a diagnosis of exclusion [9••]. According to ICHD-2 criteria for primary TCH, the head pain must not be attributable to any other disorder, and CSF analysis and brain imaging must be normal [17]. Other forms of primary headaches, including primary

Table 1. Classification of RCVS

Primary RCVS	Secondary RCVS
No precipitant or associated context	CNS blood and blood product exposure
Headache-associated conditions	Subarachnoid hemorrhage
Primary thunderclap headache	Intracerebral hemorrhage
Primary exertional headache	Spinal subdural hematoma
Primary headache associated with sexual activity	Erythropoietin
Primary cough headache	Red blood cell transfusions
Bathing headache	Intravenous immunoglobulin
	Surgical procedures and trauma
	Neurosurgery
	Postcarotid endarterectomy
	Head trauma
	Pregnancy and the postpartum period
	Preeclampsia
	Postpartum angiopathy
	Vasoactive drugs
	Ergot and ergoline derivatives (ergotamine, methergine, lisuride, bromocriptine)
	Sympathomimetic amines and decongestants (isometheptene, pseudoephedrine, phenylpropanolamine)
	Serotonergic agents (SSRIs, sumatriptan)
	Immune suppressants (tacrolimus, cyclophosphamide)
	Recreational drugs (cocaine, ecstasy, marijuana)
	Others
	Unruptured cerebral aneurysm
	Pheochromocytoma
	Hypercalcemia
	Porphyria
	Carcinoid tumor

CNS—central nervous system; RCVS—reversible cerebral vasoconstriction syndrome; SSRI—selective serotonin reuptake inhibitors. (*Data from* Calabrese [29••] and Singhal and Bernstein [50].)

cough headache, primary exertional headache, and primary headache associated with sexual activity, can occur in conjunction with RCVS [23,26,27,30–32]. Bathing-triggered TCH is also identified in the presence and absence of RCVS [32,33], arguing for its inclusion as a variant of primary TCH. Because the pathophysiology of RCVS is poorly understood, it remains uncertain whether vasoconstriction is an underlying mechanism of these primary headache conditions or simply a process that occurs in association with them. It is becoming increasingly evident that headaches and reversible vasoconstriction may occur independently of each other or in combination [11••].

Primary Versus Secondary RCVS

Despite the common angiographic phenotype of cerebral vascular narrowing, RCVS appears to have a number of distinct primary and secondary causes (Table 1). For example, blood degradation products or vessel wall damage is presumed to trigger vasospasm in SAH, hormonal alterations may be related to peripartum RCVS, and drug-induced RCVS may be associated with exogenous vasoactive substances.

An unresolved issue is the attribution of hemorrhagic events to cerebral vasoconstriction. Recent studies of RCVS attributed cerebral hemorrhage to vasoconstriction based on the temporal course of events or the location of the SAH [34•,35]. These conclusions were made without antecedent angiography demonstrating vasoconstriction in the absence of cerebral hemorrhage. In a recent prospective analysis of patients with TCH and RCVS, follow-up MRI and MRA did not reveal evidence of SAH or aneurysm [11••]. Further study of the relationship between hemorrhage and RCVS is required to resolve the issue.

Table 2. Causes of thunderclap headache

Subarachnoid hemorrhage
Cerebral venous sinus thrombosis
Carotid artery dissection
Pituitary apoplexy
Spontaneous intracranial hypotension (secondary to cerebrospinal fluid leak)
Acute hypertensive crisis
Spontaneous retroclival hematoma
Sentinel headache
Ischemic stroke
Third ventricle colloid cyst
Intracranial infection
Reversible cerebral vasoconstriction syndrome
Primary thunderclap headache (without reversible vasoconstriction)
Primary cough, sexual, and exertional headache

(*Data from* Schwedt et al. [9••] and Dodick [25].)

Pathophysiology

The pathophysiology of RCVS remains elusive. The characteristic feature of transient segmental vasoconstriction is suspected to represent an alteration in vascular tone that may be provoked by intrinsic (eg, SAH, hypertension) or extrinsic (eg, sympathomimetic drugs) factors in a number of clinical contexts (eg, postpartum, bathing). Cerebral vasoconstriction most commonly occurs after cerebral hemorrhage, typically due to a ruptured cerebral aneurysm or arteriovenous malformation. Cerebral bleeding provides a model to understand the transient vascular narrowing inherent to RCVS, presuming a shared pathophysiologic pathway among many etiologies. This model is limited by the fact that the precise mechanism of hemorrhage-induced vasospasm also remains unknown.

Aberrant central regulation of a spontaneous or evoked sympathetic surge may underlie the reversible vascular alterations of RCVS [17,29••]. This theory is derived from the association of RCVS with exertion, sympathomimetic agents, pheochromocytoma, and hypertensive crises. Calabrese et al. [29••] suggested that this may occur as a result of cerebral vascular receptor activity from sensory afferent stimulation from the first division of the trigeminal nerve and dorsal root of C2. This preliminary hypothesis may explain the bizarre cases of RCVS that occur in conjunction with noxious external sensory stimulation, such as cold water [33,36].

The final common pathway of vascular smooth muscle constriction perhaps is a rise in intracellular calcium from either influx or the release of intracellular stores. A complementary possibility of calcium-independent vasoconstriction is smooth muscle contraction due to myosin light-chain phosphorylation induced by the activation of rho-associated kinase and protein kinase C [37].

Distinguishing RCVS from PACNS

Primary angiitis of the CNS (PACNS) is an uncommon form of vasculitis that exclusively involves the CNS vasculature, with an incidence of 2.4 cases per 1 million person-years [38•]. The clinical manifestations of PACNS are varied and include headache, visual changes, and hemiparesis, which are largely indistinguishable from those associated with RCVS. Early recognition and treatment of PACNS are vital to a favorable clinical outcome [39].

PACNS has been described as "granulomatous angiitis of the brain," "granulomatous angiitis of the nervous system," "isolated angiitis of the CNS" [40], and more recently as "primary CNS vasculitis" [38•]. RCVS can be mistaken for PACNS due to the similar angiographic appearance of segmental narrowing of cerebral arteries. Biopsies of the leptomeninges, cerebral lesion, and cortex are considered the diagnostic gold standard. Cerebral biopsy is limited by the possibility of sampling error and its invasiveness despite the low complication rate (< 2%) [41,42]. The diagnostic yield of cerebral biopsy may be higher when performed in conjunction with abnormal MRI and CT findings. Angiography is often preferred despite its poor sensitivity and specificity for PACNS. Conventional angiography is more sensitive than MRA, especially when lesions are limited to small vessels [38•].

Table 3 describes the key features that distinguish RCVS from PACNS. Unlike RCVS, PACNS is rarely accompanied by TCH and generally follows a slow, insidious course. An elevated erythrocyte sedimentation rate, which occurs in 40% of histologically proven cases, may help to distinguish PACNS from RCVS. CSF analysis often reveals pleocytosis and/or elevated protein but is of limited value because an absence of abnormalities does not exclude a diagnosis of PACNS. MRI reveals abnormal findings in nearly all subjects over the disease course but is not sensitive enough to exclude a diagnosis of PACNS if clinical suspicion is high [10••]. Diseases other than RCVS that may mimic PACNS angiographically include malignant lymphoma [42], sarcoidosis [40], moyamoya disease [43], cerebral amyloid angiopathy [44], and other vasculitides [45].

Angiographic differentiation of RCVS and PACNS is very difficult. There are no published reports that examine the value of vessel wall enhancement as a distinguishing characteristic. Histologically proven cases of PACNS often fail to show the classic angiographic pattern of beading and ectasia. Vascular segmental narrowing is present in 25% to 43% of cases in which cerebral angiography is performed [10••,43], and it affects the circle of Willis or its immediate branches in 50% to 66% of these instances [10••,38•], making these cases indistinguishable from RCVS angiographically. In a more recent retrospective review of 101 cases of PACNS from a large multispecialty clinic, Salvarani et al. [38•] concluded that angiography and cerebral biopsies provide complementary diagnostic information. Consistent with prior comparisons of patients evaluated by cerebral biopsy and angiogram [10••,43], several cases diagnosed

Table 3. Typical features distinguishing RCVS and PACNS

RCVS	PACNS
Sudden onset	Slow, insidious progression
TCH at presentation	Typically no TCH, but headaches often present
ESR normal	± ESR elevation
Normal or near-normal CSF analysis	CSF pleocytosis (lymphocytes) and protein elevation
± abnormal MRI	Abnormal MRI
No MRI leptomeningeal enhancement	± MRI leptomeningeal enhancement
Segmental cerebral vasoconstriction involving the circle of Willis and/or its immediate branches	Segmental cerebral vasoconstriction not resolved within 2 months of initial angiography
Early angiographic or TCD/TCCD ultrasound evidence of near to complete resolution of cerebral vasospasm	Diagnostic biopsy
± clinical resolution of neurologic deficits	

CSF—cerebrospinal fluid; ESR—erythrocyte sedimentation rate; PACNS—primary angiitis of the central nervous system; RCVS—reversible cerebral vasoconstriction syndrome; TCCD—transcranial color Doppler; TCD—transcranial Doppler; TCH—thunderclap headache; ±—with or without. (*Adapted from* Gerretsen and Kern [10••].)

by positive histology did not show findings on angiography (25%), and 56% of cases diagnosed by angiography had nondiagnostic biopsies. The primary means of differentiating RCVS from PACNS is the demonstration of reversible cerebral vasoconstriction within 1 to 4 weeks. In cases of PACNS verified pathologically, near to complete normalization on follow-up angiography has not been shown to occur less than 2 months from the initial study [10••].

Diagnosis

RCVS typically presents with TCH, focal neurologic deficits, or seizures. In the presence of TCH and inconclusive CT head imaging and CSF analysis to rule out SAH, recent reviews of TCH and RCVS uniformly recommend MRI, followed by MRA or CTA as soon as possible to identify potentially reversible secondary causes of TCH [9••,10••,29]. A firm diagnosis of RCVS cannot be made until follow-up angiography demonstrates some degree of resolution of vascular narrowing. Reversibility has been shown to occur within minutes [14], with most cases resolved within 12 weeks. This variability of time to resolution does not appear entirely related to the disease process but rather to the time at which follow-up vascular imaging was instigated. Evidence of angiographic reversibility should be sought within 1 to 4 weeks of clinical presentation. Cerebral vascular narrowing may not be entirely resolved, but there may be significant correction in the initially affected vessels [11••,15,46]. Early reversibility may help distinguish RCVS from PACNS (Table 3) because angiographic resolution in histologically confirmed cases of PACNS has not been demonstrated to occur earlier than 2 months after clinical presentation [10••].

Noninvasive MRA or CTA is preferred to conventional catheter-based angiography. RCVS tends to affect the circle of Willis or its immediate branches, which are adequately visualized with MRA or CTA. In recent prospective studies of recurrent TCH and RCVS, MCA was involved in all cases [11••,12••]. Alternatively, serial transcranial Doppler/transcranial color Doppler (TCD/TCCD) ultrasound carried out over the first 2 months after presentation may prove to have high specificity and sensitivity for RCVS and cerebral vasculitis, respectively [47,48]. A prospective study of RCVS with serial TCCD found that when subjects' maximum middle cerebral artery velocity (V_{MCA}) met "mild vasospasm criteria for SAH" ($V_{MCA} \geq 120$ cm/sec and a Lindegaard index [V_{MCA}/V_{ICA}, a ratio of middle cerebral to internal carotid artery velocity] score ≥ 3) patients had a greater risk of RPLS and ischemic strokes [12••]. Further prospective analysis regarding the timing and the diagnostic performance of noninvasive vascular imaging and conventional angiography is required.

Treatment

Although there is little evidence of any effective treatment for RCVS, patients typically have a good outcome. Some case reports suggest the possible benefit of calcium channel blockers, such as nimodipine [2,49]. A recent systematic review found no significant difference in outcome between cases treated with calcium channel blockers versus those that were not [10••]. This only suggests that this class of drugs was used in the more severely affected patients. Some evidence exists for the treatment of RCVS-associated headaches with nimodipine [11••], but nimodipine had no effect on V_{MCA} or Lindegaard index, ultrasonographic markers of vasoconstriction [12••]. Studies implementing an experimental design are required to determine the efficacy of calcium channel blockers for the treatment of TCH and RCVS.

Corticosteroids may be withheld for 1 week to look for early signs of angiographic reversibility to rule out PACNS. PACNS has a high fatality rate—up to one-fifth of treated and possibly all untreated cases. Most patients

respond favorably to corticosteroids alone or in combination with cyclophosphamide [38•]. Younger [39] argues that cyclophosphamide should be reserved for patients with histologically confirmed PACNS who progress or fail to improve with corticosteroids.

Conclusions

RCVS predominantly occurs in women and is characterized by sudden, severe headache at onset, no abnormalities on CSF analysis, reversible vasoconstriction involving the Circle of Willis and its immediate branches (Fig. 1), and angiographic or TCD/TCCD ultrasound evidence of near to complete resolution of vasoconstriction within 12 weeks. It is associated with an evolving list of primary and secondary associations, including cerebral hemorrhage, vasoconstrictive drug use, the peripartum period, bathing, and various forms of strenuous physical exertion (Table 1). The pathophysiologic mechanisms of RCVS remain unclear but appear to have many etiologies. Cerebral vasoconstriction may help to explain the phenomena of primary TCH. RCVS is also associated with hypertensive encephalopathy, preeclampsia, and RPLS warranting consideration of cerebral angiography in the presence of these conditions to investigate the possibility of cerebral vasoconstriction.

When angiographic evidence of segmental cerebral vasoconstriction exists, the clinician must rule out a diagnosis of PACNS due to its high rates of morbidity and mortality if left untreated. Table 3 lists the key features that distinguish RCVS from PACNS. It is unclear if calcium channel blockers (eg, nimodipine) have a significant impact on RCVS or associated clinical consequences.

Toward the goal of nosologic clarity and improved clinical recognition, it is essential that a diagnosis of RCVS incorporate its primary or secondary etiologies and associations and that alternative designations for RCVS be discontinued.

Disclosure

No potential conflicts of interest relevant to this article were reported.

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