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Cerebrovascular Disease and Stroke (D Greer, Section Editor)

Reversible Cerebral Vasoconstriction Syndromes: What the Cardiologist Should Know

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Opinion statement

Over the past decade, the reversible cerebral vasoconstriction syndromes (RCVS) have emerged as a group of conditions with easily recognizable clinical-angiographic features and a usually benign prognosis. The RCVS affect young individuals, mostly women, and the majority present with recurrent, severe, 'thunderclap' headaches. Vascular imaging studies show dynamic and reversible narrowing and dilatation of multiple intracerebral arteries. Brain imaging usually shows no parenchymal lesions, however, approximately one-third of patients develop ischemic or hemorrhagic strokes or reversible brain edema. The etiopathogenesis of this syndrome remains unclear. It has been associated with diverse conditions such as pregnancy, vasoconstrictive drug use, and neurovascular procedures. Recent studies characterizing RCVS have made it relatively easy to exclude mimics such as aneurysmal subarachnoid hemorrhage and primary angiitis of the central nervous system. There is no proven treatment, although calcium channel blockers may help to reduce the intensity of headaches. Empiric glucocorticoid treatment should be avoided. Since most patients do well with simple observation alone, invasive strategies such as pharmacologically-induced hypertension, balloon angioplasty, and direct intra-arterial vasodilator infusion should be reserved for patients showing clear clinical progression.

Introduction

Cerebral angiographic abnormalities commonly result from pathological conditions such as atherosclerosis, inflammatory vasculitis, infectious arteritis, and fibromuscular dysplasia. Historically, *reversible* cerebral

arterial vasoconstriction ("vasospasm") has been associated mainly with aneurysmal subarachnoid hemorrhage (SAH) and exceptional cases of migraine. However, a review of the literature shows that over the last 6 decades over 400 case reports have documented of reversible multifocal cerebral vasoconstriction in the absence of aneurysmal subarachnoid hemorrhage, and without evidence for underlying infection or inflammation [1–3]. Reversible cerebral vasoconstriction has been associated with diverse conditions including pregnancy and the puerperium, the use of vasoconstrictive drugs, thunderclap headache, and hypertensive encephalopathy, among others (Table 1). The number of RCVS case reports has increased over the 6–7 years, with cases being reported from virtually every continent, indicating that RCVS is fairly common and is being recognized more frequently. RCVS appears to be an important cause for ischemic and hemorrhagic stroke in young individuals, particularly young women.

A major reason why RCVS remained under-recognized until recently is that it was reported using varying nosology, each term reflecting the reporter's bias towards the presumed precipitating factor or associated underlying condition: migrainous vasospasm [4], migraine angiitis [5], postpartum angiopathy [3, 6], pseudovasculitis, and drug-induced vasculitis [7]. An important case series of 16 patients [8] published in 1988 brought attention to the phenomenon of reversible cerebral segmental vasoconstriction among stroke neurologists. Only over the past decade have we recognized that despite the varied nosology and the wide range of associated conditions, these patients have virtually identical clinical-imaging features, justifying their inclusion under the umbrella term 'Reversible Cerebral Vasoconstriction Syndromes' (RCVS)[9, 10, 11••, 12, 13, 14••, 15••, 16••]. While several conditions are now included under RCVS, it is conceivable that individual entities may have unique features.

Clinical features

RCVS predominantly affects individuals between age 20–50 years [9, 11••, 12, 16••, 17]. Children can be affected [18, 19]. Women are predominantly affected, with a male:female ratio of 2:1 to 4:1 in published studies. The syndrome appears to occur spontaneously (without a clear precipitant) in approximately one-third of patients. In the rest, factors such as migraine, pregnancy, or exposure to vasoactive drugs such as cocaine, the ergot derivatives, or diet pills, have been implicated (Table 1).

The onset of RCVS is usually catastrophic with sudden-onset, severe thunderclap headaches that tend to recur over a span of days to weeks, usually after minor physical activity or while straining during micturition or during a bowel movement. A retrospective analysis of 139 cases showed that 85 % present with sudden severe headache [16••]. Thunderclap headache was the only symptom in 76 % of patients studied prospectively in France [12]. In these reports multiple thunderclap headaches occurred in 82 %–94 % of patients, and the average number of recurrent headaches was 4.5 (range, 2–18). In most patients, the intensity and frequency of headache diminishes over time, with no interval complications. Many patients develop nausea, photophobia, and a mild encephalopathy during the first few days. An especially common symptom is ill-defined visual 'blurring'. However, these symptoms typically resolve with the resolution of headaches.

Approximately one-third develop focal neurologic deficits or generalized seizures [8, 9, 11••, 12, 16••, 17, 20, 21]. In such patients, visual scotomas and blindness are common symptoms, and the neurological examination often reveals cortical blindness or elements of the Balint syndrome[16••, 22]. The visual

Table 1. Conditions associated with RCVS

A. Pregnancy and puerperium
Early puerperium, late pregnancy, eclampsia, pre-eclampsia, delayed postpartum eclampsia
B. Exposure to drugs and blood products
Phenylpropanolamine, pseudoephedrine, epinephrine, ergotamine tartrate, methergine, bromocryptine, hydroxycut, lisuride, selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs), sumatriptan and other triptans, isometheptine, cocaine, ecstasy, amphetamine derivatives, marijuana, lysergic acid diethylamide (LSD), tacrolimus (FK-506), cyclophosphamide, erythropoietin, intravenous immune globulin (IVIg), interferon alpha, nicotine patch, red blood cell transfusions, licorice, oral contraceptive pills, hormonal agents
C. Miscellaneous
Hypercalcemia, porphyria, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma, postcarotid endarterectomy, neurosurgical procedures, carotid glomus tumor, tonsillectomy, neck surgery, high altitude, swimming, bathing, severe exertion
D. Headache Disorders
Migraine, primary thunderclap headache, benign exertional headache, benign sexual headache, primary cough headache

deficits correlate well with the location of ischemic lesions in the posterior watershed regions of the brain. Seizures tend not to recur after the first 3–4 days. While a preceding history of hypertension is uncommon, the blood pressure can be elevated in the initial stages, either due to underlying pain, eclampsia, or recent exposure to drugs such as cocaine, or as a result of the systemic response to cerebral vasoconstriction. Hemiplegia, dysarthria, aphasia, numbness, and ataxia can ensue in patients with progressive cerebral vasoconstriction and stroke. Hyper-reflexia is very common, similar to the observation in patients with eclampsia, but the basis for hyper-reflexia is not clear since it occurs regardless of the presence of brain lesions.

As stated, in most patients the symptoms usually resolve spontaneously over a period of 2 to 6 weeks, and the outcome is usually benign. However, in 3 %–10 % of reported cases, clinical and angiographic progression can occur in the first few days and result in massive strokes, brain edema, and even death [2, 16••, 23, 24, 25••]. For this reason, it is reasonable to admit patients for observation for the first few days after symptom onset.

Vascular and brain imaging findings

The diagnosis of RCVS rests on the documentation of dynamic, reversible, segmental angiographic narrowing and dilatation affecting multiple cerebral arteries (Fig. 1). Interestingly, the arterial narrowing usually begins shortly after the dural penetration of the affected cerebral arteries. The circle of Willis arteries (anterior, middle, and posterior cerebral arteries) and their branches, the basilar artery, and the superior cerebellar artery are the most commonly involved arteries. The hyperintense MCA "dot sign", a marker of slow flow within dilated cortical surface arteries, is frequently observed on fluid-attenuated inversion recovery (FLAIR) MRI sequences and correlates with the angiographic abnormalities [26]. Extra-cranial cerebral artery vasoconstriction is rare, but has been observed in the vertebral arteries and occasionally in the carotid arteries.

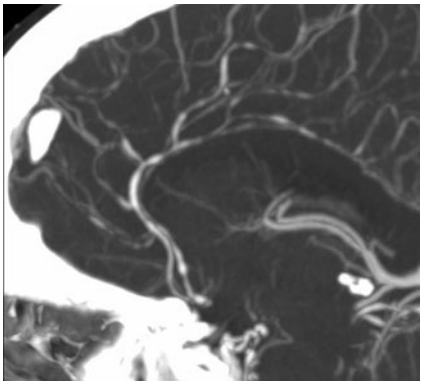

Figure 1. Typical findings on cerebral angiography: head computerized tomography angiogram image (*sagittal view*) shows the classic 'sausage on a string' appearance of the medium-sized intracerebral arteries in a patient with RCVS.

Vertebral and carotid artery dissection is frequent, and may be either an epiphenomenon due to surges in blood pressure or indicative of a vessel wall abnormality that predisposes to both vasoconstriction and dissection [27•, 28, 29]. Retinal arteries are usually spared, as are systemic arteries. The cerebral vasoconstriction typically lasts weeks to 3 months, outlasting the period of recurrent thunderclap headaches.

In lieu of angiography, some authors have used transcranial Doppler ultrasound (TCD) to diagnose RCVS. However, it can be difficult to distinguish vasoconstriction from hyperemia on TCD, and some patients exhibit normal blood flow velocities even in the setting of severe angiographic vasoconstriction. When abnormal, TCDs usually show diffusely elevated blood flow velocities that typically normalize over a period of days to weeks [6, 13, 21].

The majority of patients show no lesions within the brain on initial imaging despite relatively severe arterial narrowing. Approximately one-third to half develop ischemic or hemorrhagic strokes, or develop reversible brain edema in a pattern identical to what is described in hypertensive encephalopathy, eclampsia, and other conditions associated with the 'posterior reversible encephalopathy syndrome' (PRES). The overlap with PRES suggests suggesting a shared pathophysiology between these syndromes [25••, 30]. Ischemic strokes (Fig. 2) are usually located in borderzone arterial territories, suggesting severe proximal vasoconstriction with "low-flow" ischemia or distal thromboembolism as the mechanism. Brain hemorrhages are believed to result from acute, severe hypertension, however, they are often multiple, lobar, and co-exist with ischemic strokes, suggesting that they result from postischemic reperfusion injury. Hemorrhages tend to occur in the first week, and ischemic strokes in the second week after symptom onset [14••]. Hemorrhages appear to be more common in women, and in patients with prior migraine and medication exposure [14••, 16••]. Small, nonaneurysmal subarachnoid hemorrhages along the cortical surface are observed in up to one-third of patients with RCVS, presumably resulting from rupture of pial vessels in the face of impaired autoregulation [31••]. Perfusion-MRI studies can show areas of hypoperfusion in deep watershed regions as would be expected from the angiographic vasoconstriction [32].

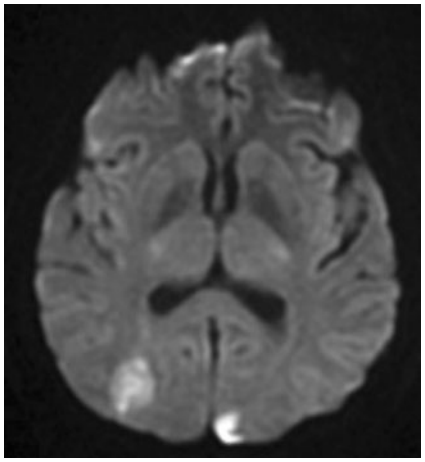

Figure 2. Brain lesions in reversible cerebral vasoconstriction syndrome: while most patients with RCVS show no acute lesions on brain imaging, approximately one-third develop ischemic or hemorrhagic strokes, or reversible brain edema. This image shows bilateral ischemic lesions in the occipital and parietal lobes on axial diffusion-weighted brain magnetic resonance imaging in a patient with RCVS.

Etiology

The etiology of the abrupt-onset headache, and the prolonged but reversible vasoconstriction, is not known. Angiographic 'sausaging' of large and medium-sized cerebral arteries is the pathognomonic feature (Fig. 1) and suggests an abnormality in the control of cerebrovascular tone. It remains unclear whether the angiographic abnormalities trigger the headaches, or result from severe headache, but there certainly is a close relationship [33]. Conceivably, the anatomic basis to explain vasoconstriction as well as the associated headaches may be the innervation of cerebral blood vessels with sensory afferents from the first division of the trigeminal nerve and dorsal root of C2. But what triggers this acute syndrome remains a mystery. Authors have loosely implicated migraine, pregnancy, head trauma, neurosurgical procedures, norepinephrine, serotonin, hypercalcemia, hormonal imbalances, and other factors due to their known vasoconstrictive effects or temporal relationship with the onset of this syndrome. Widely prescribed drugs such as sumatriptan, diet pills, cough and cold decongestants, and the serotonergic antidepressants have similarly been implicated [21]. Some authors have speculated that the vasoconstriction is related to transient vasculitis, however, there is no evidence to support a role for inflammation. CSF examination and extensive serological tests are normal, and pathological studies of the brain and temporal arteries have shown no abnormality.

Approach to diagnosis

Patients with RCVS pose major diagnostic and therapeutic challenges. A similar (but not identical) clinical and angiographic picture can result from a

wide range of potentially ominous conditions that have ill-defined treatment options and a considerably worse prognosis. Recent studies characterizing RCVS have made it relatively easy to diagnose RCVS based on the history of recurrent thunderclap headaches combined with 'sausaging' on cerebral vascular imaging studies. Table 2 lists the typical clinical, laboratory, and imaging features of this syndrome [11••]. A stepwise diagnostic approach with consideration of the clinical setting, the tempo of the disease, the nature of the headache and vascular imaging findings, normal CSF results, and a negative rheumatologic work-up, helps to exclude mimics like aneurysmal brain hemorrhage, cerebral vasculitis, and infectious arteritis [34].

The differential diagnosis of a *sudden*, *severe headache* includes aneurysmal subarachnoid hemorrhage, intracerebral hemorrhage, pituitary apoplexy, cerebral artery dissection, cerebral venous sinus thrombosis, meningitis, and spontaneous intracranial hypotension [35]. Most of these conditions can be easily excluded with urgent brain and vascular imaging studies eg, CT-angiography or MR-angiography of the head and neck. In my experience, *recurrent* thunderclap headaches are rarely seen in conditions other than RCVS and should alert the clinician towards the possibility of RCVS, especially if the initial brain scan shows none of the above conditions associated with thunderclap headache.

The next challenge is to definitively exclude 'minor' or 'impending' aneurysmal bleeds, where the CT scan may also be normal. Further complicating the initial evaluation of RCVS is the fact that approximately one-third of RCVS patients develop *convexal subarachnoid hemorrhage*, which can also result from the rupture of distal mycotic aneurysms, dural arteriovenous malformations, coagulopathies, and cerebral amyloid angiopathy. Again, the presence of recurrent thunderclap headache, and the presence of early angiographic 'sausaging' affecting multiple cerebral arteries, helps to exclude these mimics. Small convexal hemorrhages are not usually associated with vasospasm. A recent large retrospective study identified the following predictors of RCVS in patients with evidence for subarachnoid blood on head imaging: younger age, history of chronic headaches, depression and chronic obstructive pulmonary disease, lower Hunt-Hess grade, lower Fisher SAH group, higher number of affected arteries, and the presence of bilateral arterial narrowing [31••].

Table 2. Summary of critical elements for the diagnosis of RCVS

1. Transfemoral angiography or indirect (CT or MR) angiography documenting segmental cerebral artery vasoconstriction.
2. No evidence for aneurysmal subarachnoid hemorrhage.
3. Normal or near-normal cerebrospinal fluid analysis (proteins <80 mg%, white blood cells < 10 per mm3, normal glucose).
4. Severe, acute headache, with or without additional neurologic signs or symptoms.
5. The diagnosis cannot be confirmed until reversibility of the angiographic abnormalities is documented within 12 weeks after onset, or if death occurs before the follow-up studies are completed, autopsy rules out conditions such as vasculitis, intracranial atherosclerosis, and aneurysmal subarachnoid hemorrhage, which can also manifest with headache and stroke.

From: Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative review: reversible cerebral vasoconstriction syndromes. Ann Intern Med. 2007;146 (1):34–44. [11••].

Similar *angiographic abnormalities* can result from intracranial atherosclerosis, infectious arteritis, inflammatory vasculitis, and fibromuscular dysplasia. While the latter conditions are usually chronic and progressive, RCVS is a disorder that begins abruptly. In this author's experience, a carefully documented history combined with a review of the type and distribution of lesions on brain imaging, is invaluable in distinguishing between RCVS and these other conditions. Historically, many patients with RCVS have been misinterpreted as having *primary angiitis of the central nervous system* (*PACNS*) due to overlapping clinical-imaging features such as headache, stroke, and angiographic abnormalities [36–38]. While there is overlap, the nature of the headaches and imaging abnormalities are quite different. Patients with PACNS usually have an insidious progressive clinical course with chronic headaches. Brain imaging in RCVS can be normal or show watershed infarcts or lobar hemorrhages, whereas PACNS is usually associated with accumulating T2-hyperintense brain lesions, leptomeningeal enhancement, and scattered deep infarcts. In rare cases, severe and prolonged vasoconstriction can induce secondary inflammation and render the angiographic changes irreversible, making the distinction between vasculitis and vasoconstriction extremely difficult in some cases [39]. In challenging cases, high-resolution contrast MRI may help since anecdotal reports suggest a lack of contrast enhancement of the cerebral arteries in RCVS, but not inflammatory cerebral vasculitis [40].

Diagnostic work-up

Based on the above approach to diagnosis, the following tests should be considered. In patients presenting with thunderclap headache, which is the usual presenting symptom of RCVS, the initial focus should be to rule out other, more common conditions that have similar clinical or angiographic features [35]. Urgent neuroimaging with head CT or brain MRI, and CSF studies, are warranted to exclude subarachnoid or parenchymal hemorrhage, arterial dissection, meningitis, intracranial hypotension, and cerebral vasculitis. Blood counts, erythrocyte sedimentation rate, serum electrolytes, and liver and renal function tests are usually normal. Rheumatoid factor, antinuclear, and antinuclear cytoplasmic antibody tests, lyme titer, and urine vanillylmandelic acid and 5-hydroxyindoleacetic acid levels, are useful to rule out vasculitis and vasoactive tumors (pheochromocytoma and carcinoid). There is no role for brain biopsy or temporal artery biopsy other than to rule out vasculitis in truly challenging cases. Serum and urine toxicology screens, and a careful medication history, are important to uncover exposure to vasoactive drugs like cocaine, ecstasy, ephedra, ma huang, and antimigraine agents.

Management

There is no proven or established treatment strategy. The literature is replete with various treatment approaches invariably showing good outcome, likely reflecting strong publication biases. It is critical to acknowledge that in most cases, clinical and angiographic resolution occurs spontaneously; a patient, observational approach is hence, essential.

Calcium channel blockers such as oral nimodipine are offered based upon their known vasodilator effects and the efficacy of nimodipine in improving clinical outcome after aneurysmal SAH. However, the data from prospective and retrospective case series show that these agents do not alter the course of cerebral vasoconstriction in RCVS [12, 13, 16••]. Dantrolene, a ryanodine receptor antagonist that inhibits intracellular calcium release from the sarco-endoplasmic reticulum, has been used with success in a patient with RCVS [41]. Patients with RCVS often have wide swings in their blood pressure. Theoretically, hypoperfusion carries the risk of cerebral hypoperfusion and ischemic strokes, and severe hypertension can result in brain hemorrhage or even worsening of the cerebral vasoconstriction. A reasonable approach is to control the blood pressure only if it crosses extreme values, eg, 100–180 mm Hg. Seizure prophylaxis is prudent in the acute stage. In the absence of lobar hemorrhage, long-term anticonvulsants are probably unnecessary. It is important to avoid further use of marijuana, cocaine, diet pills, exercise stimulants, herbal remedies like ma huang, and any other vasoactive agents. Despite the severe migraine-like headaches that accompany this syndrome, it is prudent to avoid antimigraine drugs like sumatriptan and ergotamine since they have vasoconstrictive effects that can precipitate further vasoconstriction, culminating in stroke. Since the recurrent headaches are often exacerbated with the Valsalva maneuver, patients should avoid physical exertion and use stool softeners for a period of 4 to 6 weeks. The usual stroke prevention agents like antiplatelets and warfarin are probably not indicated given the risk for cerebral hemorrhage. Finally, the intensity of head pain is often extreme, so the liberal use of medications including opioids is justified.

Many patients who ultimately prove to have RCVS are treated with a short course of glucocorticoids in the acute setting. The rationale for this empiric treatment strategy is to address the possible alternate diagnosis of PACNS, a condition that (as stated above) shares certain features with RCVS, and which is believed to be progressive and potentially fatal without prompt immunosuppressive therapy. Unfortunately, diagnosing PACNS is challenging and time-consuming, and many patients remain on glucocorticoids for prolonged durations and incur the risk of serious steroid-related adverse effects. In my opinion, empiric glucocorticoid therapy should be avoided for several reasons. First, several recent studies have crystallized the clinic and imaging features of RCVS and PACNS, making it easier to distinguish these conditions in the acute setting (see the section on "approach to diagnosis" above). Second, there is little evidence that a therapeutic delay of a few days would significantly impact long-term outcome in PACNS, and the eventual diagnosis in challenging cases usually becomes apparent after a week or 2 of observation. Finally, a large retrospective analysis suggests that glucocorticoids may be associated with worse outcome, either due to selection (treatment) bias or due to a paradoxical effect of therapy [16••]. It is hence, paramount to focus on distinguishing RCVS from PACNS on the basis of the initial clinical and imaging features, and reserve empiric glucocorticoid therapy for the rare patient with a rapidly worsening clinical course while the diagnosis remains uncertain.

An increasing number of case reports claim therapeutic success with balloon angioplasty or direct intra-arterial infusion of vasodilator therapy [42–44]. Indeed, intra-arterial vasodilator therapy in a single constricted artery (eg, the right middle cerebral artery) can promptly reverse vasoconstricton in multiple brain arteries, including those in the contralateral hemisphere. Some physicians have used intra-arterial vasodilation as a 'diagnostic test' to distinguish RCVS from mimics such as PACNS and intracranial atherosclerosis, where the arteries show little or no reversal of vasoconstriction [44]. Unfortunately, intra-arterial approaches often require repeated attempts [45, 46] and carry the risk of significant reperfusion injury resulting in brain edema and hemorrhages [25••, 47]. Since more than 90 %–95 % of RCVS patients have a benign, self-limited syndrome despite the presence of severe angiographic vasoconstriction and ischemic or hemorrhagic brain lesions, invasive diagnostic or therapeutic approaches should be reserved for patients in whom there is clear evidence for clinical progression [48].

Outcome and prognosis

The onset of RCVS is unpredictable, and there is a long list of unproven associated risk factors. Thus, there is no opportunity for prevention. While some patients can show acute, usually minor, neurological worsening, the long-term prognosis is usually excellent. Over 90 %–95 % of patients recover completely or near-completely within days to weeks. Fulminant vasoconstriction resulting in progressive symptoms or death can occur in a minority of cases [2, 16••, 23, 25••]. Among the various syndromes included under RCVS, postpartum angiopathy may carry a worse prognosis [49•, 50]. Long-lasting visual deficits and mild hemiparesis may develop in patients who develop stroke. Thunderclap headaches can recur for weeks, but with diminishing frequency and intensity. Triptans are contraindicated in patients who develop stroke. Avoiding further exposure to the offending agent, for example vasoconstrictive drugs, appears reasonable to prevent acute progression. Whether re-exposure to such agents carries a risk for recurrence is not known, but is logical to avoid re-exposure and use alternate nonvasoconstrictive medications if clinically warranted. Recurrence of this syndrome is exceedingly rare [51].

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Aneesh Singhal has given expert testimonial for Mediolegal Firms and received honoraria from American Academy of Neurology

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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