

Narrative Review: Reversible Cerebral Vasoconstriction Syndromes

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Reversible cerebral vasoconstriction syndromes (RCVS) comprise a group of diverse conditions, all characterized by reversible multifocal narrowing of the cerebral arteries heralded by sudden (thunderclap), severe headaches with or without associated neurologic deficits. Reversible cerebral vasoconstriction syndromes are clinically important because they affect young persons and can be complicated by ischemic or hemorrhagic strokes. The differential diagnosis of RCVS includes conditions associated with thunderclap headache and conditions that cause irreversible or progressive cerebral artery narrowing, such as intracranial atherosclerosis and cerebral vasculitis. Misdiagnosis as primary cerebral vasculitis and

aneurysmal subarachnoid hemorrhage is common because of overlapping clinical and angiographic features. However, unlike these more ominous conditions, RCVS is usually self-limited: Resolution of headaches and vasoconstriction occurs over a period of days to weeks. In this review, we describe our current understanding of RCVS; summarize its key clinical, laboratory, and imaging features; and discuss strategies for diagnostic evaluation and treatment.

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Reversible cerebral vasoconstriction syndromes (RCVS) comprise a group of disorders characterized by prolonged but reversible vasoconstriction of the cerebral arteries, usually associated with acute-onset, severe, recurrent headaches, with or without additional neurologic signs and symptoms. These syndromes are diverse (Table 1) (1) and have been given various eponymic or syndromic labels, including the Call syndrome (or the Call–Fleming syndrome) (2, 3), benign angiopathy of the central nervous system (4), postpartum angiopathy (5), thunderclap headache with reversible vasospasm (6–8), migrainous vasospasm or migraine angiitis (9–12), and drug-induced cerebral arteritis or angiopathy (13–15). In general, these disorders have been poorly characterized and continue to be frequently confused with cerebral vasculitis because the latter condition has overlapping angiographic features, and to a certain degree, clinical features.

An understanding of RCVS has been limited by the lack of a clear underlying pathologic basis and consensus definition. Furthermore, patients with RCVS have historically presented to different specialists, including stroke neurologists, headache specialists, obstetricians, and rheumatologists, and all in turn impart their own biases on nomenclature, theories of pathogenesis, and clinical approach. Some authors (1, 16–18) only recently started defining the unifying features of these conditions and proposing that they be collectively called RCVS.

It is likely that primary care providers, internists, emergency department physicians, neurologists, neurosurgeons, intensivists, rheumatologists, obstetricians, and other clinicians will detect RCVS in more patients because of the wider availability of newer, relatively noninvasive technologies to assess cerebral vasculature and blood flow velocity (computed tomography angiography [CTA], magnetic resonance angiography [MRA], and transcranial Doppler ultrasonography). In addition, use of vasoactive drugs, especially diet pills; exercise stimulants; certain antidepressants; nasal decongestants; and drugs of abuse, such as amphetamines, cocaine, and ecstasy, is increasing. This narrative review, by specialists in the field of rheumatology,

headache, and stroke, will outline the cause and pathophysiology, symptoms and signs, diagnosis, treatment, and prognosis of RCVS and areas of uncertainty.

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CAUSE AND PATHOPHYSIOLOGY

Reversible cerebral vasoconstriction syndromes have been reported to occur in various clinical settings (Table 1), and although the pathophysiology is not clearly understood, a disturbance in the control of cerebral vascular tone seems to be a critical element. This alteration in vascular tone may be spontaneous or evoked by various exogenous or endogenous factors. Sympathomimetic and serotonergic drugs and tumors (3, 13–15, 19–22), endocrine factors, direct or neurosurgical trauma (18, 23–28), and uncontrolled hypertension (29, 30) have all been implicated. The molecular pathophysiology of RCVS is unknown. It is conceivable that the numerous immunologic and biochemical factors known to be involved in subarachnoid hemorrhage–related vasospasm (catecholamines, endothelin-1, serotonin, nitric oxide, and prostaglandins) (31, 32) play a similar role in the pathophysiology of vasoconstriction in RCVS. Ultimately, because vascular tone and caliber is dependent on vascular receptor activity and sensitivity, a spontaneous or evoked central vascular discharge may underlie the alteration and reversible nature of RCVS and contribute to the severe and acute headache seen with these

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Reversible cerebral vasoconstriction syndromes (RCVS) are characterized by multifocal areas of constriction involving the cerebral arteries that resolve within days to weeks.

Patients with RCVS often present with acute onset of severe headache (“thunderclap headache”) with or without neurologic symptoms and signs.

RCVS can occur without identifiable cause, during pregnancy or the puerperium period, as an idiosyncratic response to certain medications or illicit drugs, and in the setting of catecholamine-secreting tumors.

Diagnosis is made by characteristic symptoms and signs in the setting of normal results on cerebrospinal fluid analysis, exclusion of other causes of sudden severe headache, segmental cerebral arterial vasoconstriction demonstrated by direct or indirect angiography, and reversibility of the vasoconstriction within 12 weeks.

RCVS must be differentiated from primary angiitis of the central nervous system, a condition with similar angiographic abnormalities but a substantially different diagnostic and therapeutic approach.

Treatment is empirical and includes observation, calcium-channel blockers (nimodipine or verapamil), and possibly high-dose corticosteroids.

Prognosis is uncertain, but most patients do well. Permanent neurologic deficits and deaths have been reported.

disorders. The anatomical basis for this may be that cerebral blood vessels are also densely innervated with sensory afferents from the first division of the trigeminal nerve and dorsal root of C2.

SYMPTOMS AND SIGNS

The typical patient with RCVS is a woman between the ages of 20 and 50 years presenting with a hyperacute severe headache, often called a “thunderclap headache.” Historically, this refers to a severe headache that reaches its peak intensity within seconds, like a “clap of thunder” (6, 33). Thunderclap headache is most characteristic of subarachnoid hemorrhage, but it has also been described as a spontaneous and idiopathic condition and a manifestation of other intracranial or extracranial disorders, such as arterial dissection and cerebral venous sinus thrombosis (33, 34). Primary thunderclap headache is by definition not associated with cerebral vasoconstriction (34). Patients with RCVS commonly have recurrent thunderclap headache associated with cerebral vasoconstriction. As with pri-

mary thunderclap headache, the RCVS headache may be occipital or diffuse; severe and throbbing; and associated with nausea, emesis, and photosensitivity. It can recur spontaneously while the patient is at rest or can be precipitated by exertion or the Valsalva maneuver. Severe neurologic symptoms and signs, including transient or permanent visual defects, hemiplegia, dysarthria, aphasia, numbness, or ataxia, can occur secondary to ischemia in brain regions that are perfused by a severely constricted artery. Transient hypertension, which at times can be marked, is not uncommon. Generalized seizures may occur during the acute period, but epilepsy does not ensue. Major ischemic or hemorrhagic stroke, progressive brain edema, and even stroke-related death from progressive or severe, sustained cerebral vasoconstriction have been described (35–41).

DIAGNOSIS

Although there are no validated criteria for the diagnosis of RCVS, it is not difficult to recognize or diagnose. For the diagnosis of RCVS, the patient ideally should have all of the features that are outlined in Table 2. Although these criteria have not been prospectively validated, we believe that they have considerable sensitivity and specificity in the appropriate clinical setting and are a summary of published and personal experience to date.

Clinically, RCVS should be considered in patients who present with a hyperacute severe headache, with or without neurologic symptoms or signs, and without evidence of aneurysmal subarachnoid hemorrhage. Reversible cerebral vasoconstriction syndrome should also be considered in patients with cryptogenic stroke, particularly in those with severe-onset headache or thunderclap headache and symmetrical brain infarctions or edema. The initial

Table 1. Conditions Associated with Reversible Cerebral Vasoconstriction Syndromes*

Pregnancy and puerperium

Early puerperium, late pregnancy, eclampsia, preeclampsia, and delayed postpartum eclampsia

Exposure to drugs and blood products

Phenylpropanolamine, pseudoephedrine, ergotamine tartrate, methergine, bromocryptine, lisuride, selective serotonin reuptake inhibitors, sumatriptan, isometheptine, cocaine, ecstasy, amphetamine derivatives, marijuana, lysergic acid diethylamide, tacrolimus (FK-506), cyclophosphamide, erythropoietin, intravenous immune globulin, and red blood cell transfusions

Miscellaneous

Hypercalcemia, porphyria, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma, postcarotid endarterectomy, and neurosurgical procedures

Idiopathic

No identifiable precipitating factor

Associated with headache disorders, such as migraine, primary thunderclap headache, benign exertional headache, benign sexual headache, and primary cough headache

*Adapted from reference 1: Singhal AB, Bernstein RA. Postpartum angiopathy and other cerebral vasoconstriction syndromes. *Neurocrit Care*. 2005;3:91-7.

Table 2. Summary of Critical Elements for the Diagnosis of Reversible Cerebral Vasoconstriction Syndromes*

| |
|--|
| Transfemoral angiography or indirect CTA or MRA documenting multifocal segmental cerebral artery vasoconstriction |
| No evidence for aneurysmal subarachnoid hemorrhage |
| Normal or near-normal cerebrospinal fluid analysis (protein level < 80 mg%, leukocytes < 10 mm ³ , normal glucose level) |
| Severe, acute headaches, with or without additional neurologic signs or symptoms |
| Reversibility of angiographic abnormalities within 12 weeks after onset. If death occurs before the follow-up studies are completed, autopsy rules out such conditions as vasculitis, intracranial atherosclerosis, and aneurysmal subarachnoid hemorrhage, which can also manifest with headache and stroke |

*CTA = computed tomography angiography; MRA = magnetic resonance angiography.

evaluation should uniformly include unenhanced brain computed tomography (CT) to exclude subarachnoid or parenchymal brain hemorrhage. If the results of the CT scan are negative for hemorrhage, lumbar puncture should be performed to exclude “CT-negative” subarachnoid hemorrhage and inflammatory conditions, such as infection and cerebral vasculitis. If the results of the cerebrospinal fluid examination are benign, additional brain and neurovascular imaging to assess for other causes of severe headache, including cerebral venous sinus thrombosis, arterial dissection, unruptured saccular aneurysms, and RCVS, should be pursued. Magnetic resonance imaging (MRI), MRA, and CTA of the brain and cerebral blood vessels are appropriate first-line imaging techniques to evaluate for RCVS; however, conventional catheter-based angiography is still the gold standard.

The results of brain MRI are frequently normal in RCVS but can reveal evidence of infarction, particularly in arterial “watershed” and “borderzone” regions, as well as parenchymal hemorrhages and small nonaneurysmal subarachnoid hemorrhages overlying the cortical surface (37, 42). Brain infarction presumably results from severe hypoperfusion distal to severe vasoconstriction, and hemorrhage presumably results from reperfusion injury. Changes consistent with the posterior reversible leukoencephalopathy syndrome have also been reported (16, 43, 44).

Figure 1 shows the neuroimaging findings of a typical case of RCVS. The patient presented with a postcoital thunderclap headache and developed bilateral occipital lobe infarctions. The characteristic angiographic findings in RCVS are alternating areas of arterial constriction and dilatation, often called “beading,” in multiple vascular beds. Alternating areas of constriction and normal vascular caliber, rather than areas of dilatation, can also be seen. These findings may be seen in the large and medium cerebral arteries that constitute the anterior circulation (internal carotid and middle and anterior cerebral arteries) and the posterior circulation (vertebral, basilar, posterior cerebral, superior cerebellar, anterior inferior cerebellar, and posterior inferior cerebellar arteries) (36–39). It cannot be

overemphasized that these findings, although highly characteristic, are not specific for RCVS and cannot be differentiated from the angiographic abnormalities seen with cerebral vasculitis (45). Therefore, diagnosis of RCVS is heavily influenced by the pretest probability derived from the clinical findings; presence of cofactors (Table 1); and adjunctive studies, such as cerebrospinal fluid examination.

The most specific evidence for RCVS is the timely demonstration of complete or near-complete reversibility of vasoconstriction, invariably within 3 months. Although serial direct or indirect MRA or CTA is the method of choice for documenting reversibility of vasoconstriction, transcranial Doppler ultrasonography can be used to monitor the progression or resolution of vasoconstriction on the basis of the measurement of flow velocities. Transcranial Doppler ultrasonography has been used successfully to follow the clinical course of RCVS where improvement in blood flow velocities has been observed within days to weeks (3, 5, 46, 47). The suggestion of 12 weeks as the interval for angiographic and/or flow velocity improvement is somewhat arbitrary, but is based on the chronology of angiographic resolution in most cases reported thus far and studied at random periods of follow-up. Figure 2 shows the resolution of angiographic changes.

Analysis of cerebrospinal fluid is also critical not only to rule out subarachnoid hemorrhage, but also to help differentiate RCVS from cerebral vasculitis. In RCVS, the cerebrospinal fluid is generally normal or near normal. In Singhal’s systematic review (37) of 152 patients reported as having reversible cerebral vasoconstriction without aneurysmal subarachnoid hemorrhage, 95% of patients had cerebrospinal fluid cell counts less than 10 per mm³ and protein levels below 80 mg%, whereas 80% of patients had normal results. Finally, some patients with suspected RCVS may not have the classic thunderclap headache and the cerebrospinal fluid might show minor abnormalities of cells and protein, such that a diagnosis of cerebral vasculitis should still be seriously considered. In this circumstance, particularly if there are neurologic deficits and/or diffuse parenchymal abnormalities or multifocal strokes on MRI, a brain biopsy to exclude cerebral vasculitis may be indicated early, rather than waiting to evaluate for angiographic reversibility.

DIFFERENTIAL DIAGNOSIS

Various disorders that share the core clinical and imaging features of RCVS have been described as isolated and distinct clinical syndromes, often on the basis of the clinical circumstances or evaluating specialty, and we believe they should be included in this broad diagnostic category. In contrast, various disorders that are not RCVS have overlapping clinical and imaging features. Thus, establishing a differential diagnosis for RCVS involves consideration of clinical syndromes with evidence of reversible vasoconstriction that have been previously given different names and distinguishing RCVS from other disorders that have simi-

lar symptoms and signs but that differ in clinically significant ways.

Clinical Syndromes with Evidence of Reversible Cerebral Vasoconstriction

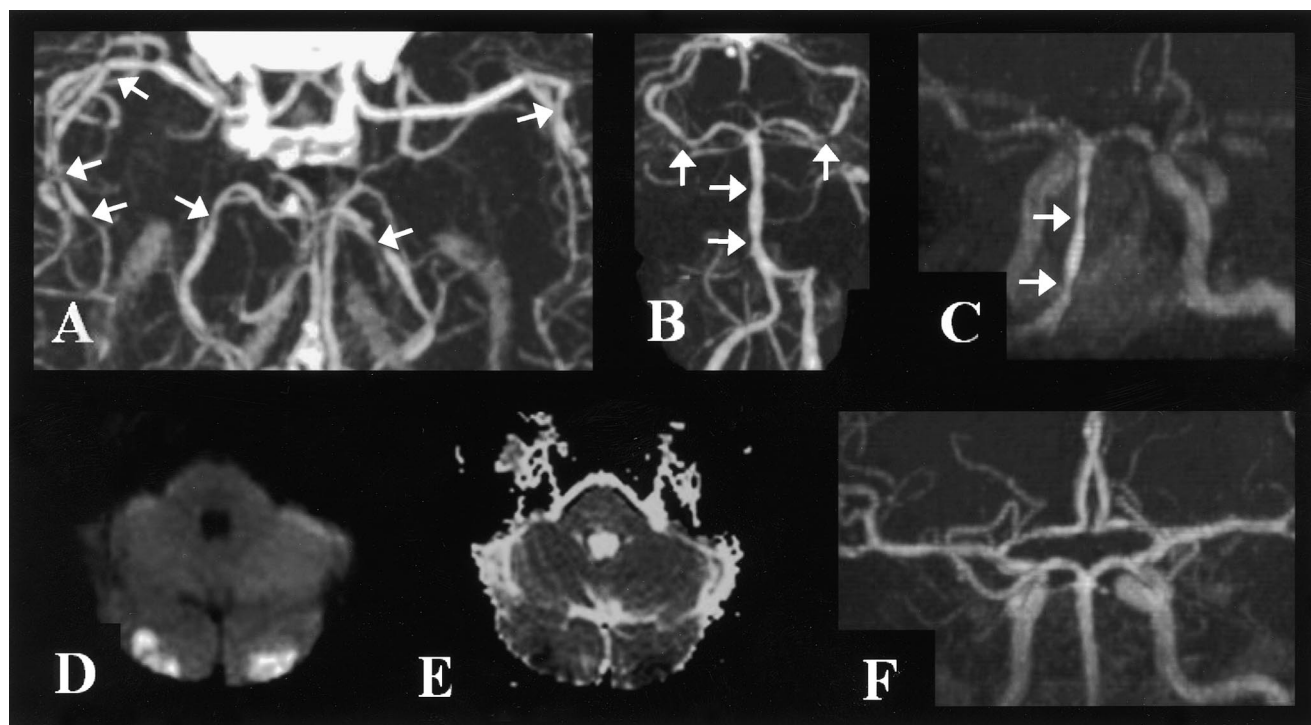
The Call Syndrome (or the Call–Fleming Syndrome)

In 1988, Call and colleagues (2) reported a series of 19 patients as having “reversible cerebral arterial segmental vasoconstriction.” These patients presented with acute headache, with or without focal neurologic deficits and seizures. The headaches occurred either spontaneously or in association with various cofactors, such as vasoactive drug exposure, pregnancy, and arterial manipulation or mechanical trauma. Results on cerebrospinal fluid analysis were usually normal. Although the pathophysiologic basis was unknown, “migrainous vasospasm” was considered likely. The eponyms, Call syndrome and Call–Fleming syndrome, have endured and are still used largely in the neurology literature (3, 20, 48–50) for patients with RCVS.

Migrainous Vasospasm

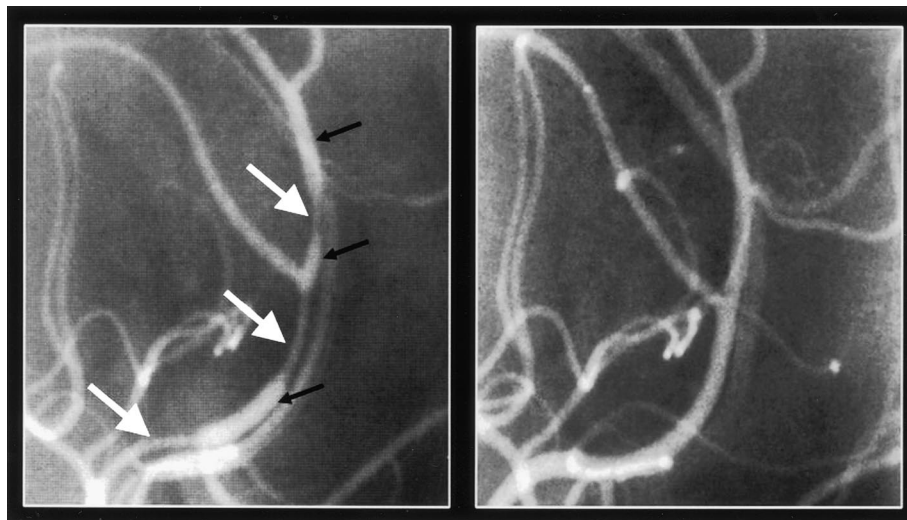
Reversible cerebral segmental vasoconstriction has been documented in patients with a history of migraine and reported as migrainous vasospasm or “crash migraine” (9–11, 51–58). With a prevalence of 12% in the population, a history of migraine may be present in some patients with reversible vasoconstriction. However, the presenting headache in RCVS is invariably hyperacute, is not preceded by the premonitory or aura symptoms often seen with migraine, and does not resemble the patient’s previous attacks of migraine. Similar to the other conditions included under RCVS, patients reported as having migrainous vasospasm have had floridly abnormal results on cerebral angiography demonstrating reversibility in hours to days, benign results on cerebrospinal fluid examinations, and a history of precipitation by exercise or the Valsalva maneuver. Thus, patients with virtually identical clinical syndromes, each sharing the features of headache and reversible cerebral segmental vasoconstriction, may be given

Figure 1. Neuroimaging findings in a 46-year-old man with reversible cerebral vasoconstriction syndrome.



The patient, who had a history of migraine without aura, hypertension, hyperlipidemia, and cannabis abuse, developed a severe postcoital “thunderclap” headache. Severe headaches recurred, and on day 3, he developed cortical blindness and mild left hemiparesis. Computed tomography angiography obtained at admission showed multifocal segmental stenosis (“beading”) of the bilateral middle cerebral arteries (A) and the basilar, posterior cerebral, and superior cerebellar arteries (B). These abnormalities were also present on brain magnetic resonance angiography (C). Diffusion-weighted magnetic resonance imaging (D) and apparent diffusion coefficient maps (E) showed symmetrical lesions in the bilateral occipital lobes consistent with ischemic stroke. In addition, brain magnetic resonance imaging showed small infarctions in the bilateral cerebellar hemispheres and in the right frontal lobe (not shown). Serologic tests and the results of 2 cerebrospinal fluid examinations showed no evidence for vasculitis or subarachnoid hemorrhage. The patient was treated with analgesics and verapamil. His deficits resolved completely over a period of 3 weeks, and follow-up magnetic angiography (F) showed resolution of the cerebral arterial vasoconstriction.

Figure 2. Cerebral angiography of a patient with reversible cerebral vasoconstriction syndrome at diagnosis (left) and after 1 month of calcium-channel blocker therapy (right).



Note the multiple areas of stenosis (*white arrows*) and dilatation in multiple vessels (*black arrows*) and their resolution after treatment. Reprinted with permission from reference 36: Hajj-Ali RA, Furlan A, Abou-Chebel A, Calabrese LH. Benign angiopathy of the central nervous system: cohort of 16 patients with clinical course and long-term followup. *Arthritis Rheum.* 2002;47:662-9.

different labels on the basis of an elicited history of migraine.

Benign Angiopathy of the Central Nervous System

In isolated reports in the rheumatology literature, patients fulfilling the clinical description of RCVS were initially thought to have a benign form of primary angiitis of the central nervous system (PACNS) (9, 59, 60). In 1993, Calabrese and colleagues (4) reviewed these cases and proposed the term “benign angiopathy of the central nervous system” to characterize the subset of patients with isolated cerebral arteritis defined on the basis of their female predominance, acute presentation, reversible angiographic abnormalities, normal results on spinal fluid examination, and monophasic course. In a series of 16 patients, dramatic resolution of angiographic abnormalities was demonstrated within 4 to 12 weeks without intensive immunosuppressive therapy (36). Several of these patients received either calcium-channel blockers alone or were merely observed. In 2 patients brain biopsies were obtained, which revealed no evidence of inflammation. On the basis of these data, it became increasingly apparent that for most patients presenting with what was recognized as benign angiopathy, the underlying pathophysiologic disorder was reversible vasoconstriction rather than vasculitis.

Postpartum Angiopathy

Cerebral arterial vasoconstriction can also be seen in the postpartum setting. The obstetric neurologic literature has similarly described an entity, given various labels, in-

cluding postpartum angiopathy (5, 15, 18, 46, 47, 61–64), postpartum angitis (65), and puerperal vasospasm (35), characterized by acute onset of headache, variable neurologic deficits, and reversible cerebral segmental vasoconstriction. Although a similar syndrome can be seen with preeclampsia or eclampsia (16, 66), most patients with RCVS have a history of uncomplicated pregnancy and normal labor and delivery, followed within days to a few weeks by acute onset of headache with or without various neurologic signs and symptoms similar to those described previously.

Drug-Induced Arteritis

Similar confusion has surrounded the concept of drug-induced cerebral “arteritis,” most often ascribed to such vasoactive agents as cocaine, amphetamines, ephedrine, pseudoephedrine, and phenylpropanolamine (67–69). Diagnosis of drug-induced arteritis has almost exclusively been based on angiographic evidence alone (70, 71), although evidence for vascular inflammation more consistent with nonspecific injury or vascular necrosis rather than arteritis has been described (72). In a recent systematic review of amphetamine-associated intracranial hemorrhages, Buxton and McConachie (71) concluded that the angiographic abnormalities were representative of “vasculitic beading,” although no evidence of vasculitis was demonstrated histologically (71). Alternatively, 2 reviews of biopsy data from cases of cocaine-associated intracranial hemorrhage, including 1 prospective autopsy series (73, 74), found no evidence of vascular inflammation. From

these reports it was concluded that the clinical and angiographic abnormalities observed in these patients were probably due to the pharmacodynamic effects of the drug and not an underlying arteritis; thus, this disorder should be considered a variant of RCVS. Similar cases have also been described with various other drugs, including ecstasy; bromocriptine; nasal decongestants; diet pills; serotonergic drugs, such as sumatriptan and the selective serotonin reuptake inhibitors (3, 13–15, 19, 20).

Miscellaneous

Cerebral vasoconstriction syndrome has been described in various settings (Table 1), such as with catecholamine-secreting tumors (21, 22); after head trauma, vascular manipulation, carotid endarterectomy, or neurosurgical procedures (18, 23–28); in the presence of hypercalcemia (where activation of vascular smooth muscle has been documented) (75–78), acute porphyria (79), and unruptured aneurysms (6, 41, 80, 81); and after intravenous immunoglobulin therapy (44, 82, 83). In several of these associations, the pathophysiologic basis of prolonged but reversible cerebral vasoconstriction remains unclear. Finally, it should be appreciated that patients occasionally present in the absence of a recognized secondary cofactor or condition. These patients may be considered to have primary or idiopathic forms of RCVS (18, 36).

We believe that all of the conditions described previously share an underlying mechanism of reversible cerebral vasoconstriction, although they may vary with respect to the frequency and severity of neurologic signs and symptoms, imaging abnormalities, neurologic sequelae, and circumstances at onset (for example, precipitated by exercise, sexual intercourse, pregnancy, or drugs). It seems logical to consider all such patients as having an RCVS. Identifying the precipitating secondary cofactors or disease is important because these associated factors may guide treatment (for example, discontinuation of vasoactive drugs) and may eventually lead toward a better understanding of the pathogenesis.

Disorders with Clinical Features Similar to Reversible Cerebral Vasoconstriction Syndromes

The differential diagnoses primarily include disorders that may present with thunderclap headache. A comprehensive discussion of the differential diagnoses is beyond the scope of this paper, but such diagnoses include aneurysmal subarachnoid hemorrhage, parenchymal brain hemorrhage, cerebral venous sinus thrombosis, pituitary apoplexy, intracranial infection, carotid or vertebral artery dissection, posterior cerebral artery embolic stroke, spontaneous intracranial hypotension, retroclival hematoma, third ventricle colloid cyst, and cerebral vasculitis. Schwedt and colleagues (84) have recently reviewed the differential diagnosis of thunderclap headache. Once brain hemorrhage is excluded through normal results on brain CT and

cerebrospinal fluid examination, the remaining disorders that may present in this fashion can be reliably excluded on the basis of a thorough history and physical examination and appropriate imaging of the brain parenchyma, cerebral venous sinuses, and intracranial and extracranial arteries. Table 3 shows the conditions that may be most problematic to differentiate from RCVS because they share abnormalities on neurovascular imaging.

Reversible cerebral vasoconstriction syndromes represent the most common and most important clinical mimic of true cerebral vasculitis, particularly the variant limited to the central nervous system called isolated or primary angitis of the central nervous system (PACNS) (45). Differentiating between RCVS and true cerebral vasculitis is of vital clinical importance because therapy for inflammatory arteritis differs greatly from therapy for RCVS. Patients with RCVS can be spared the risks for brain biopsy and intense and prolonged immunosuppression, which is the treatment for PACNS. The differentiation of these disorders generally is straightforward but can occasionally be complex. Although the angiogram can be identical in vasoconstriction and arteritis, the diagnosis is secured within the clinical context, including presentation, analysis of cerebrospinal fluid, and the presence of clinical cofactors (Table 3). Patients with RCVS generally present acutely and have a background of excellent health, although a history of migraine is not uncommon. As described previously, the most common presentation in RCVS is a sudden and severe headache that often peaks within seconds, with or without other neurologic signs and symptoms. Headache also is the most common symptom in patients with PACNS, but it is not of the thunderclap variety; rather, the history is typically that of a generally constant, indolent, and progressive headache accompanied by transient episodes of neurologic dysfunction and ultimately cortical and subcortical infarctions (85). The results of cerebrospinal fluid analysis are virtually always normal or near-normal in patients with RCVS, although these results are frequently abnormal in those with cerebral arteritis (45, 85). Furthermore, patients with RCVS often have a history of associated cofactors, such as a temporal relationship with childbirth, or incriminate drug exposure, which provide clues to the diagnosis (Table 1).

Results of brain MRI are abnormal in the vast majority of patients with PACNS, whereas they are frequently normal in those with RCVS. There is no specific MRI finding indicative of PACNS, although multifocal infarctions widely distributed in the gray and white matter, with or without diffuse white matter hyperintensities, are most common (42).

An important clinical pitfall in the diagnosis of PACNS is the failure to appreciate the low level of test specificity of cerebral angiography, and in turn, CTA or MRA. Sensitivity of angiography for the diagnosis of cerebral arteritis varies but may be as low as 10% to 20% when there is small-vessel involvement with granulomatous his-

Table 3. Differential Diagnosis of Disorders That May Mimic Reversible Cerebral Vasoconstriction Syndromes*

| Variable | RCVS | PACNS | SAH | Arterial Dissection |
|----------------------------|---|--|--|---|
| Sex | Female predominant, ratio 2–3 to 1 | No sex predilection | Female predominant, ratio 1.6 to 1 | No sex predilection |
| Onset | Acute (seconds to minutes) | Typically subacute to chronic | Acute (seconds) | Acute or subacute |
| Headache | Acute and severe, throbbing, often thunderclap | Insidious and progressive, dull aching | Thunderclap | Thunderclap in about 13% |
| CSF examination | Normal or near-normal | Abnormal in >95% of PACNS; variably abnormal in non-PACNS variants | Abnormal (elevated erythrocyte count, xanthochromia) | Normal |
| CT/MRI of brain parenchyma | Normal in the majority of patients; or shows symmetric arterial “watershed” infarctions or parenchymal brain hemorrhage. In addition, small SAH overlying the cortical surface or reversible brain edema may occur. | Abnormal in 90% of cases of PACNS No characteristic findings but small infarctions in gray or white matter, varying ages, affects multiple vascular territories with or without diffuse white matter lesions | SAH, which usually correlates with the site and severity of arterial vasospasm. Ischemic stroke and brain edema can develop distal to the site of vasospasm. Rare patients can have “CT-negative” SAH. | Results of brain CT and MRI are normal in the absence of ischemic stroke. Axial MRI or CTA may show crescentic intramural hematoma involving the vertebral or internal carotid artery. |
| Neurovascular imaging | By definition, shows diffuse areas of multiple stenoses and dilatation involving intracranial cerebral arteries. These abnormalities are present in the acute stage and are reversible within days to weeks. | Variable sensitivity. Frequently normal in PACNS; otherwise, findings range from single or multiple arterial cut-off areas, to luminal irregularities in single or multiple arteries, to diffuse abnormalities that are occasionally indistinguishable from RCVS. These abnormalities are frequently irreversible. | Usually shows saccular aneurysm or alternate cause of the bleeding (e.g., arteriovenous malformation). Vasospasm typically is not multifocal, affects 1–2 medium arteries, and peaks between days 4 and 11. Acute vasospasm on the day of onset is extremely rare. | Long-segment stenosis, double-lumen, intimal flaps, and arterial pseudoaneurysms are characteristic angiographic signs. Stenosis resolves in 90% within 3 months. Unlike RCVS, stenosis is smooth, involves extracranial carotid extracranial and intracranial vertebral arteries, and involves a single vessel (except in rare cases of multivessel dissection). |

*CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging; PACNS = primary angiitis of the central nervous system; RCVS = reversible cerebral vasoconstriction syndrome; SAH = subarachnoid hemorrhage

topathologic features (86). In terms of specificity, several investigators have shown that even when angiographic abnormalities are limited to those considered most specific for arteritis (that is, alternating areas of vascular constriction and ectasia or beading in multiple vascular beds), the ability of this test to distinguish vasculitis from other disorders is only 24% to 60% (87–89). Therefore, angiography is most useful when the pretest probability for vasculitis is high. Findings occasionally present in PACNS that are uncharacteristic of RCVS include isolated areas of irregularly irregular or nonsymmetrical vascular luminal abnormalities or extensive vascular cut-offs or drop-out. Finally, it should be noted that although the sensitivity of cerebral angiography in RCVS is very high, it lacks specificity for this diagnosis and thus must be interpreted in the appropriate clinical context. The most specific finding for RCVS is the resolution of the vascular abnormalities within days or weeks documented by vascular imaging (Figure 2). There are few studies of serial angiography in PACNS, but limited investigations have suggested that although improvement can be seen, stabilization and failure of medium-caliber vessels to return to normal from pre-

sumed scarring are characteristic (90). The demonstration of prompt resolution of vasoconstriction decreases the likelihood of confusing RCVS with atherosclerosis or other forms of noninflammatory vascular disease, such as atherosclerosis and fibromuscular dysplasia, which do not improve on serial angiography but can also present with acute headache and stroke.

TREATMENT

Treatment for RCVS is guided by observational data because, to our knowledge, no clinical trials of any treatment for this disorder have been conducted. A therapeutic view of RCVS must be balanced by 2 opposing groups of observations. On the one hand, successful outcomes, including alleviation of symptoms and rapid reversibility of vascular abnormalities, have been reported with various methods of treatment, including calcium-channel blockers (38, 91); brief courses of glucocorticoids (36); magnesium sulfate (16); and most important, simple observation (1, 3, 36, 92). On the other hand, the clinical course may also be pernicious, and it is not uncommon for symptoms to clear

initially only to return repeatedly within days, culminating in stroke (36, 38, 39). Stroke as an outcome has been reported in as many as 54% of patients in 1 review (37). However, there are no clear clinical or imaging features that reliably predict outcome.

Empirical therapy is not justified for patients presenting with thunderclap headache who have not had vascular imaging. However, once cerebral vasoconstriction has been documented, treatment can be considered. In the absence of any proven therapy, simple observation may be justified. However, because of the moderate risk for ischemic stroke and poor outcome, it seems prudent to initiate therapy with agents that have a favorable tolerability profile in patients who present with RCVS, especially if the headache recurs, vasospasm is severe, or transient neurologic symptoms occur. Nimodipine or verapamil has been used successfully and should be considered as first-line therapy (36, 38, 91). Calcium-channel blockers should be administered with caution because of the risk for watershed infarction in cerebral regions that may be tenuously perfused by a severely constricted cerebral artery. Alternatively, short-term high-dose glucocorticoids have been reported to be effective (36). The rationale for this approach is based on the efficacy of high-dose glucocorticoids to reverse experimentally induced vasoconstriction (93).

Because of the lack of validated diagnostic criteria and the need for a delay to establish reversibility to secure the diagnosis of RCVS, should all patients be initially treated for PACNS as well? We strongly believe that in most patients with RCVS presenting with classic symptoms of thunderclap headache, no evidence of subarachnoid aneurysmal hemorrhage, normal results on cerebrospinal fluid and on MRI, and typical abnormalities on vascular imaging, the high probability of a diagnosis justifies treatment for RCVS alone in light of the risks for immunosuppression required to treat PACNS. However, in some cases of ambiguous pretest probability (that is, borderline cerebrospinal fluid analysis, progressive continuous headaches, or subacute onset), empirical therapy covering both possibilities may be warranted. Definitive answers to such important clinical questions await the development of validated diagnostic criteria and appropriate therapeutic trials.

PROGNOSIS

The natural history of RCVS is not well-known because, to our knowledge, there have been no prospective series using validated diagnostic or classification criteria, and our current understanding is based on observational reports and retrospective series. However, because reversibility is necessary for the diagnosis, many patients fully recover with few if any sequelae. There may also be a lag in the resolution of the clinical or angiographic features after either has resolved. In a retrospective study of 16 patients, half were asymptomatic and half had only minor symptoms, such as residual headache at the first follow-up visit.

In the long term, 71% had no evidence of disability, and 29% had only minor disability; 61% reported no evidence of cognitive impairment, and 31% reported only minor problems. One patient had a relapse. It seemed that the presence of stroke was the major determinant of short-term and long-term morbidity (36). Stroke has been documented to occur in as many as 54% of patients: 14% experience hemorrhagic stroke (37). Although ultimately reversible, severe vasoconstriction can lead to large hypoperfusion and hemorrhagic infarctions, which can be disabling or fatal (35, 40, 41).

AREAS OF UNCERTAINTY

We reemphasize that RCVS is a descriptive term, bringing together various conditions with similar clinical and radiologic features. It is possible that these conditions each have a unique pathophysiologic basis, or differ from one another in some respects.

One issue likely to generate concern is the rationale and meaning of the term “reversible” in the name of the syndrome. We clarify that reversibility applies to the angiographic vasoconstriction in this setting. Although clinically most patients with RCVS experience complete resolution of headache and neurologic symptoms within days to weeks, others may be left with permanent neurologic deficits secondary to ischemic or hemorrhagic stroke. Although rare exceptions exist (62, 69, 94), the reversibility of vasoconstriction over days to weeks is the feature that best distinguishes this disorder from central nervous system vasculitis. Vascular remodeling may be possible in cases of prolonged and irreversible vasoconstriction. In the setting of subarachnoid hemorrhage-associated vasoconstriction, inflammation with vascular cell proliferation leading to perivascular thrombosis and vascular wall thickening has been documented (95). If similar remodeling occurs at times in RCVS, then neither rapid nor complete reversal of vasoconstriction may always be possible.

Because migraine headache has been associated with cerebral angiographic abnormalities in rare cases (10), some authors have questioned whether RCVS is simply a severe migraine attack with the fortuitous documentation of angiographic vasoconstriction (96). Although the headache (severity, throbbing quality, and aggravation with activity) and associated features (photophobia, phonophobia, and nausea) of migraine have high sensitivity, specificity is poor. Many neurologic disorders that present with headache, especially those associated with thunderclap headache, share many of these same features and can easily be mistaken for migraine. In addition, a serotonergic basis is implicated in migraine and RCVS (3), and there are similarities in the topography of migraine-associated stroke and RCVS-associated stroke in that both favor a “posterior” location, although most migrainous infarctions remain in the distribution of a single vascular territory (posterior cerebral artery) compared with the watershed distribution of

most infarctions associated with RCVS (3, 37, 42). However, there are also important differences between migraine and RCVS. Cerebral angiography in migraine is invariably normal, migraine has a neuronal pathophysiologic basis, and these headaches are stereotyped and recur for years (unlike the thunderclap headaches in RCVS that start abruptly, recur for days to weeks, and then subside). Further, only 25% of patients with RCVS have a history of migraine, and these patients report that their current headaches differ unequivocally from previous migraine headaches, especially with regard to the apoplectic onset of the headache associated with RCVS.

The relationship between RCVS and hypertensive encephalopathy and posterior reversible leukoencephalopathy is also unclear. Posterior reversible leukoencephalopathy is characterized by reversible gray matter and white matter lesions on MRI that often occur in the setting of hypertensive encephalopathy but also have been described in patients with presentations typical of RCVS (16, 43). It is possible therefore that RCVS may occur as a cause of posterior reversible leukoencephalopathy, due to ischemia or cerebral edema, and as a consequence of hypertension in posterior reversible leukoencephalopathy when cerebral autoregulation is overwhelmed by massive increases in arterial and cerebral perfusion pressure. The coexistence of posterior reversible leukoencephalopathy and RCVS suggests that a disturbance in cerebral arterial tone is the pathophysiologic basis of both syndromes.

This narrative review has some limitations. It is based on a collective personal experience of approximately 120 cases, and knowledge gained from published case reports and case series. The lack of a concentrated population of patients and consensus definition renders the clinical phenotype incomplete and a pathologic basis unavailable. Furthermore, the lack of systematic and randomized clinical trials and long-term outcome data on substantial numbers of patients makes therapeutic recommendations difficult and preliminary. However, the synthesis of literature on a disorder whose nomenclature has been incomprehensible and the proposal of a syndrome with a unifying set of diagnostic and clinical features will allow refinements in diagnosis; determination of an underlying pathogenesis; systematic long-term studies of outcome; and the development of controlled, randomized clinical trials for this important group of disorders.

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