Reversible cerebral vasoconstriction syndrome

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Recurrent thunderclap headaches, seizures, strokes, and non-aneurysmal subarachnoid haemorrhage can all reveal reversible cerebral vasoconstriction syndrome. This increasingly recognised syndrome is characterised by severe headaches, with or without other symptoms, and segmental constriction of cerebral arteries that resolves within 3 months. Reversible cerebral vasoconstriction syndrome is supposedly due to a transient disturbance in the control of cerebrovascular tone. More than half the cases occur post partum or after exposure to adrenergic or serotonergic drugs. Manifestations have a uniphasic course, and vary from pure cephalalgic forms to rare catastrophic forms associated with several haemorrhagic and ischaemic strokes, brain oedema, and death. Diagnosis can be hampered by the dynamic nature of clinicoradiological features. Stroke can occur a few days after initial normal imaging, and cerebral vasoconstriction is at a maximum on angiograms 2–3 weeks after clinical onset. The calcium channel blocker nimodipine seems to reduce thunderclap headaches within 48 h of administration, but has no proven effect on haemorrhagic and ischaemic complications.

Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) is characterised by severe headaches, with or without other acute neurological symptoms, and diffuse segmental constriction of cerebral arteries that resolves spontaneously within 3 months.[1,2] Manifestations are attributed to a transient disturbance of the regulation of cerebral arterial tone. Thunderclap headache—severe pain peaking in seconds—is usually the first symptom and typically recurs for 1–2 weeks.[3–5] Ischaemic and haemorrhagic stroke are the major complications of the syndrome.[5–9] In 2007, Calabrese and colleagues[2] proposed the name RCVS and a set of diagnostic criteria to regroup all similar cases that had been reported since the 1970s under several other names (panel 1).[10,11,13–23] Since then, large case series of the syndrome have been published.[5,7–9,24] In this Review, I focus on the clinical and radiological features of RCVS. I describe the clinical heterogeneity of the syndrome, appropriate investigations, and approaches to diagnosis (including possible differential diagnoses) and management. I aim to show that, although the pathological process is unknown and no specific diagnostic test or proven treatment is available, diagnosis is easy and an important step in the care of patients with RCVS.

Panel 1: **Previous names for reversible cerebral vasoconstriction syndrome**

- Isolated benign cerebral vasculitis[10,11]
- Acute benign cerebral angiopathy[12]
- Reversible cerebral segmental vasoconstriction[13,14]
- Call or Call-Fleming syndrome[14]
- CNS pseudovasculitis[15]
- Benign angiopathy of the CNS[16,17]
- Post-partum angiopathy[18]
- Migraine angiitis[19]
- Migrainous vasospasm[11]
- Primary thunderclap headache[20]
- Cerebral vasculopathy[21,22]
- Vasospasm in fatal migrainous infarction[23]

Epidemiology

RCVS has been reported in people aged from 10 to 76 years,[7,25,26] but occurrence peaks at around 42 years and the syndrome is more common in women than in men.[5,7,9] Incidence is unknown, but the syndrome does not seem to be especially rare—the first large series[5] included 67 patients who presented to the same institution during 3 years. Cases have been reported on every continent, and three large series from Asia, Europe, and North America have shown the broad range of presentations, from common benign to rare lethal forms (table).[7–9] Many characteristics of both RCVS and the patients studied differ between these large series, but whether these differences are due to ethnic factors or recruitment biases is unknown.

Clinical features

Clinical manifestations typically follow an acute and self-limiting course without new symptoms after 1 month.[5] Headache is the main symptom and often remains the only manifestation of RCVS (table).[5] Onset is acute with thunderclap headache—extreme head pain peaking in less than 1 min, mimicking that of a ruptured aneurysm.[12,13] Screaming, crying, agitation, confusion, and collapse are common because of the excruciating pain. Typical headache is bilateral (although it can be unilateral), with posterior onset followed by diffuse pain. Nausea, vomiting, photophobia, and phonophobia frequently occur.

By contrast with the headaches associated with ruptured aneurysms, the severe pain of RCVS is short lived (usually lasting 1–3 h). Thunderclap headaches can be as short as a few minutes but cases lasting several days have been reported. A single attack is possible, but usually patients have a mean of four attacks, during 1–4 weeks.[4,5,24] Moderate headache frequently persists between exacerbations. Patients typically report at least one trigger—eg, sexual activity (usually just before or at orgasm), straining during defecation, stressful or emotional situations, physical exertion, coughing, sneezing, urination, bathing or

showering, swimming, laughing, and sudden bending down.[2,4,5,7,8,25,27–30] The final thunderclap headache occurs a mean of 7–8 days after onset of thunderclap headache, and all noteworthy headaches are generally gone 3 weeks after onset.[5,7,24]

In some cases, headache is more progressive or less severe than it is in typical cases, but the absence of headache at onset of other symptoms is exceptional. Associated neck pain should prompt investigations for cervical artery dissection.[5,31] Focal deficits, which can be transient or persistent, and seizures have been reported in 8–43% and 1–17%, respectively, of the cases in the three large series (table).[7–9] Seizures can be inaugural, and recurrence is rare.[12,13,18,28,32] Transient focal deficits are present in slightly more than 10% of patients, last from 1 min to 4 h, and are most frequently visual, but sensory, dysphasic, or motor deficits can also occur. Most focal deficits have a sudden onset and are typical of those noted in transient ischaemic attacks, but they can mimic a migraine aura with positive symptoms progressing over a few minutes.[5] Persistent deficits, including hemiplegia, aphasia, hemianopia, or cortical blindness, suggest a stroke.[8,9,13,17,30]

The results of physical examinations are usually normal, except when RCVS is associated with posterior reversible encephalopathy syndrome in the setting of eclampsia, septic shock, or other severe predisposing disorders. A third of patients have surges in blood pressure during acute headaches[5,7,13] because of the pain, the syndrome itself, or an associated disorder.

Laboratory investigations

The results of blood counts, measurements of ESR and concentrations of serum electrolytes, and liver and renal function tests are usually normal in patients with RCVS. A few patients have a transient inflammatory response, which might be due to the clinical situation preceding the clinical onset of RCVS (eg, cold treated with nasal decongestants[6] or skin rash treated with steroids[13]). Tests for angiitis, including measurements of rheumatoid factor, antinuclear and antineutrophil cytoplasmic antibodies, and tests for Lyme disease are generally negative. Urinary concentrations of vanillylmandelic acid and 5-hydroxyindoleacetic acid should be measured to exclude a diagnosis of phaeochromocytoma.[15,33] Serum and urine toxicology screens should be done to check for drug use.[34]

Slight abnormalities of CSF are reported in 0–60% of patients—eg, an excess of white blood cells (5–35 per µL), red blood cells with or without visible subarachnoid blood on an MRI scan,[5,8] and increased protein concentrations of as much as 100 mg/dL.[2,5,9,13] If the white blood cell count exceeds 10 cells per µL or the protein concentration exceeds 80 mg/dL, or if both measures are exceeded, analysis of CSF should be repeated after a few weeks to ensure that concentrations have returned to normal.

Neuroimaging

Brain scans of many patients with RCVS look healthy despite the presence of diffuse vasoconstriction on concomitant cerebral angiograms. Lesions are noted in 12–81% of patients, dependent on patterns of study recruitment (table, figure).[5,7–9] Lesions include three types of stroke—convexity subarachnoid haemorrhage, intracerebral haemorrhage, and cerebral infarction—and reversible brain oedema.[2,7,8,33,35] Chen and co-workers[7,24] used haemorrhage as an exclusion criterion in their prospective study of RCVS, which precluded a description of this manifestation. In the French series,[8] 65 of the 89 patients had headache as their only symptom (eg, the purely cephalalgic form of RCVS), and MRI scans showed a localised convexity bleeding in 16 of 65 (25%) and posterior reversible encephalopathy syndrome in 5 of 65 (8%). Signs of stroke were visible

	Chen et al[7] (n=77)	Ducros et al[8] (n=89)	Singhal et al[9] (n=139)
Recruitment	Prospective, from a headache clinic	Prospective, from a single institution with an emergency headache centre and a stroke unit	Retrospective, from an internal medicine department and a stroke unit
Duration	2002–09	2004–08	1993–2009
Mean age (range)	47·7 years (10–76)	43·2 years (19–70)	42·5 years (13–69)
Sex distribution (men:women)	1:8·6	1:2·2	1:4·3
History of migraine	17%	27%	..*
History of hypertension	25%	11%	..
Any precipitant for syndrome	8%	62%	..
Post partum†	1%	13%	11%
Vasoactive substances	3%	52%	42%
Headaches at onset	100%	100%	95%
Recurrent thunderclap	100%	91%	78%
Any trigger for headaches	80%	75%	..
Focal neurological deficit	8%	25%	43%
Seizures	1%	4%	17%
Blood pressure surge	46%	34%	Some‡
Initial CT or MRI normal	..	80%	55%
Any abnormal CT or MRI	12%	37%	81%
Subarachnoid haemorrhage	0%§	30%	34%
Intracerebral haemorrhage	0%§	12%	20%
Cerebral infarction	8%	6%	39%
Posterior reversible encephalopathy syndrome	9%	8%	38%
CSF analysis available	18%	88%	82%
Protein concentration >60 mg/dL	0%	12%	16%
5–10 white blood cells per µL	..	17%	12%
>10 white blood cells per µL	0%	8%	3%
Death	0%	0%	2%
Persistent focal neurological deficit from stroke at follow-up	3%	6%	20%

*40% of patients had a history of headaches. †Percentages refer to female patients only. ‡No specific data were reported. §Haemorrhage was an exclusion criterion in this series.

Table: **Large case series of reversible cerebral vasoconstriction syndrome**

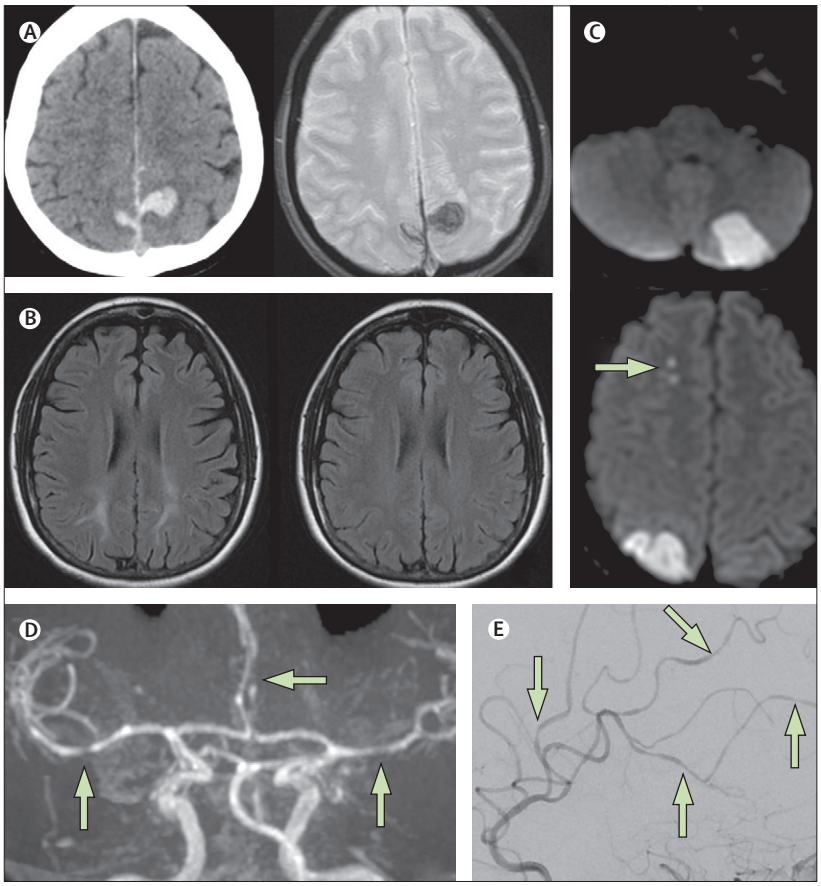

Figure: **Lesions in patients with reversible cerebral vasoconstriction syndrome**
(A) CT (left) and T2*-weighted MRI (right) scans showing a bilateral occipital haematoma with interhemispheric subarachnoid haemorrhage in a 57-year-old-woman who also had a left capsulothalamic haematoma (not shown). (B) MRI (left) showing bilateral cortical–subcortical areas of high signal on fluid-attenuated inversion recovery sequences consistent with posterior reversible encephalopathy syndrome in a 36-year-old woman post partum. Follow-up MRI (right) at 6 weeks was normal. (C) Diffusion-weighted MRI showing a left cerebellar infarction (top), a right occipital infarction (bottom), and patchy small areas of restricted diffusion at the border zone between the right anterior and middle cerebral arteries (arrow) in a 33-year-old female cannabis smoker. (D) Magnetic resonance angiogram showing segmental narrowings (arrows) of the middle and anterior cerebral arteries in the patient shown in (A). (E) Transfemoral angiogram showing segmental narrowings of the branches of the anterior cerebral artery (arrows) in a 58-year-old woman with a left frontal haematoma and subarachnoid haemorrhage in several sulci. A follow-up angiogram at 2 months was normal.

on MRI scans of all 10 patients with persistent focal deficits for longer than 24 h.[8] A combination of lesions can be present, and different types of lesion can develop successively. In Singhal and colleagues' US investigation,[9] 55% of patients had a normal initial CT or MRI scan, but 81% had visible lesions when imaging was repeated.

Convexity subarachnoid haemorrhage

Convexity subarachnoid haemorrhages are non-aneurysmal, usually mild, unilateral or bilateral, and manifest as a hyperintense signal on fluid-attenuated inversion recovery (FLAIR) MRI and a hypointense signal on T2*-weighted MRI in a few sulcal spaces near the convexity (figure).[8,12,17,18,28,35–41] Only roughly 52% of these bleedings were detectable by CT in the French series.[8] Very rarely, a more diffuse haemorrhage occurs that includes the perimesencephalic cisterns.[8] Convexity subarachnoid haemorrhage is usually diagnosed within the first week of headache onset, sometimes after an initial normal MRI.[8] About 50% of cases are associated with another type of stroke, either at onset or later in the course of the disorder. Subdural haemorrhage is sometimes noted.[8,30,42,43] FLAIR sequences might also show dot or linear hyperintensities in sulcal spaces, which are distinct from subarachnoid haemorrhage and show slow blood flow in dilated small surface vessels.[9,44,45]

Focal intracerebral haemorrhage

Parenchymal haemorrhages are of variable volume, more frequently single than multiple and lobar than deep, and more often associated with another type of stroke (convexity haemorrhage or infarction, or both) than isolated.[8,9,12,21,30,42,46–49] They occur early in the course of RCVS and are revealed mostly by a persisting focal deficit concomitant with thunderclap headache. However, parenchymal haemorrhages can also occur in purely cephalalgic cases, and can occur several days after initial normal imaging.[8,30] Haemorrhagic forms of RCVS seem to be more common in women than in men and in people with migraine than in those without.[8]

Cerebral infarction

Infarctions occur mainly in arterial watershed regions of the cerebral hemispheres, often between the posterior circulation and the carotid territories.[7–9,50–52] Cerebellar infarcts can also occur.[53] Although most patients with infarctions present with a focal deficit (transient or persistent), some are asymptomatic. Ischaemic strokes usually occur later than do haemorrhagic strokes in the course of RCVS.[5,30,54] In the French study,[8] they were diagnosed a mean of 9 days after the first thunderclap headache (range 2–15 days), compared with a mean of 10·8 days (2–17) in the Taiwanese study.[7] Areas of hypoperfusion might show up on perfusion-weighted scans.[55]

Reversible brain oedema

Oedema is an early manifestation of RCVS and is usually diagnosed within a few days of clinical onset. It is more frequently associated with at least one variety of stroke than isolated.[8] Oedema is better seen on MRI than on CT scans, with symmetrical FLAIR hyperintensities showing a distribution similar to that of posterior reversible encephalopathy syndrome.[7–9,18,56] Oedema usually totally reverses within 1 month of clinical onset, much earlier than does vasoconstriction.

Cerebral angiography

To diagnose RCVS, direct (transfemoral) or indirect (CT or magnetic resonance) cerebral angiography is needed to show segmental narrowing and dilatation (string of beads)

of one or more arteries (figure).[2,57] Calibre irregularities can affect the anterior and the posterior circulation, and are mostly bilateral and diffuse. The basilar artery, carotid siphon,[3,13] or external carotid artery can be affected.[58] Narrowing of arteries is not fixed; a repeat angiogram after a few days might show resolution of some vessels,[59] with eventual new constrictions often affecting more proximal vessels.[13] No blinded studies of the sensitivity and specificity of angiography in the diagnosis of RCVS have been done. However, the sensitivity of indirect methods of angiography is about 70% that of catheter angiography.[5,30] Furthermore, the patient's first angiogram, irrespective of type, might be normal if it is done early—ie, within a week of clinical onset—even in the presence of haemorrhage or brain oedema. In such cases, a second angiogram several days later might be diagnostic.[8,32,59,60] Maximum vasoconstriction of the branches of the middle cerebral arteries (shown by magnetic resonance angiography) is reached a mean of 16 days after clinical onset.[7]

Angiograms can show unruptured aneurysms.[8] Cervical angiography and MRI fat saturation sequences are useful to identify associated cervical artery dissection.[5,7,8,18,40,50,61–63]

Ultrasonography

Cervical ultrasonography is normal except in cases of RCVS associated with cervical arterial dissection.[5] Transcranial doppler ultrasonography can be useful in monitoring cerebral vasoconstriction.[24,64] Maximum mean flow velocities in the middle cerebral arteries might be normal during the first few days after onset of symptoms but then increase and peak (<2 m/s) about 3 weeks after headache onset.[5,24]

Pathological investigations

Biopsy of the brain or temporal artery is not recommended for diagnosis of RCVS, and should be done only in cases in which cerebral angiitis is strongly suspected.[13] In RCVS, arterial histology has been normal and active inflammation, vasculitis, and micro-thrombosis absent in brain biopsies and autopsies.[6,11,13,49,60] However, in some cases interpretation of pathological samples can be difficult because prolonged, severe vasoconstriction can induce secondary inflammation.[65]

Diagnosis

Recurrent thunderclap headache for a few days immediately suggests RCVS, as does convexity subarachnoid haemorrhage. The disorder should also be suspected in patients with cryptogenic stroke, especially when the patient also has headache.[2,8,33,37,66] RCVS with stroke but minimum or even absent headache probably can occur.[34] The diagnostic criteria in panel 2 were proposed by experts[1,2] and modified on the basis of the results of the three large case series.[7–9]

Transcranial doppler and indirect angiography should be done to assess multifocal cerebral stenosis; clinicians should bear in mind that the results of early investigations can be normal.[5,8,54,60] In the French study, catheter angiography triggered a transient ischaemic attack in 9% of patients.[5] In patients with recurrent but isolated thunderclap headaches (eg, recurrent sexual headaches) and normal brain imaging, CSF, and indirect angiography results, catheter angiography is not warranted. These patients should be viewed as having probable or possible RCVS. Depending on the patient's clinical state, magnetic resonance or CT angiography can be repeated after a few days or the patient can simply have a follow-up clinical assessment. In the latter case, a definite diagnosis is not possible.[67] The dynamic nature of RCVS should always be kept in mind. Whereas thunderclap headaches, seizures, intracranial haemorrhage, and posterior reversible encephalopathy syndrome are early manifestations that lead to a suspicion of RCVS, transient ischaemic attack and cerebral infarction can occur as late as 2 weeks after clinical onset, sometimes when the headache has improved or resolved or after the patient has been discharged.[4,5,7,8,24]

A diagnosis of RCVS can only be confirmed when the reversibility of the vasoconstriction is assessed; 12 weeks from onset of symptoms has been proposed as a cutoff by which reversal should be complete or at least substantial, but complete resolution can be slower in some patients.[2] Most clinicians prefer a control indirect angiogram to establish the resolution of vasospasms. Ultrasonography and angiography findings are not always correlated; about 20% of patients still have high intracranial velocities 3 months after symptom onset, while results of magnetic resonance angiography have returned to normal.[24]

Panel 2: Diagnostic criteria for reversible cerebral vasoconstriction syndrome

- Acute and severe headache (often thunderclap) with or without focal deficits or seizures
- Uniphasic course without new symptoms more than 1 month after clinical onset
- Segmental vasoconstriction of cerebral arteries shown by indirect (eg, magnetic resonance or CT) or direct catheter angiography
- No evidence of aneurysmal subarachnoid haemorrhage
- Normal or near-normal CSF (protein concentrations <100 mg/dL, <15 white blood cells per μL)
- Complete or substantial normalisation of arteries shown by follow-up indirect or direct angiography within 12 weeks of clinical onset

Adapted from the International Headache Society criteria[1] for acute reversible cerebral angiopathy and the criteria proposed in 2007 by Calabrese and coworkers.[2]

Thunderclap headache caused by intracranial haemorrhage

All cases of thunderclap headache necessitate emergency investigations. An underlying cause is discovered in

Panel 3: **Causes of thunderclap headache**

Usually detected by non-contrast CT
- Subarachnoid haemorrhage (most cases detected by non-contrast CT done within 24 h of symptom onset)
- Intracerebral haematoma
- Intraventricular haemorrhage
- Acute subdural haematoma
- Cerebral infarcts (after 3 h)
- Tumours (eg, third ventricle colloid cyst)
- Acute sinusitis

Usually detected by analysis of CSF after normal CT
- Subarachnoid haemorrhage
- Meningitis

Possibly presenting with normal CT results and normal or near-normal results of analysis of CSF
- Intracranial venous thrombosis
- Dissection of cervical arteries (extra or intracranial, carotid or vertebral)
- Pituitary apoplexy
- Reversible cerebral vasoconstriction syndrome with or without posterior reversible encephalopathy syndrome
- Symptomatic aneurysm without evidence of subarachnoid haemorrhage (painful third nerve paralysis)
- Intracranial hypotension (CSF pressure low)
- Cardiac cephalalgia due to myocardial ischaemia (very rare)

about 50% of patients (panel 3).[68,69] Subarachnoid haemorrhage should be the first cause searched for by non-contrast CT followed by analysis of CSF for xantochromia if the scan is normal. First-line MRI can be done if readily available. Aneurysmal rupture is the most frequent cause of non-traumatic subarachnoid haemorrhage (85%); other causes include RCVS itself.[5,37,38,66] Diagnosis of RCVS can be difficult in patients presenting with thunderclap headache and subarachnoid haemorrhage because vasoconstriction, which is often noted after this type of haemorrhage, could be attributed to vasospasm secondary to the haemorrhage. This diagnosis is controversial, and some researchers are reluctant to accept that RCVS can cause intracranial haemorrhages.[70] However, subarachnoid haemorrhage due to RCVS is usually easy to distinguish from aneurysmal subarachnoid haemorrhage, which is not associated with small convexity bleeding and causes a localised vasospasm near the ruptured malformation. By contrast, patients with RCVS have a diffuse segmental vasoconstriction, implicating arteries remote from the site of bleeding, and no evidence of a ruptured aneurysm. Besides RCVS, small convexity bleedings can occur in amyloid angiopathy, but patients do not present with recurrent thunderclap headache. The results of a retrospective study[66] suggested that RCVS was the most frequent cause of convexity subarachnoid haemorrhage in patients aged 60 years or younger, whereas amyloid angiopathy was the leading cause in those older than 60 years. Another cause is cortical vein thrombosis, which can also present as headache in post-partum women and should be ruled out on T2* MRI.

The question of cause and effect also arises for intracranial haemorrhage and RCVS, but again a focal haematoma does not explain widespread vasoconstriction.

Other causes of thunderclap headache

Many disorders can present as isolated thunderclap headaches (panel 3).[68,69,71–79] In addition to RCVS, several of these disorders, notably cerebral venous thrombosis and cervical artery dissection, do not show up on CT or through analysis of CSF. Thus, MRI to examine the parenchyma, and cervical and cerebral angiography to visualise arteries and veins, are necessary. No other method exists to diagnose the underlying vascular disorder, and delays can have catastrophic consequences.

Primary angiitis of the CNS

RCVS and primary angiitis of the CNS were only recognised as distinct disorders in the 1990s, and many clinicians are wary of missing a diagnosis of angiitis and delaying treatment.[2,16,80–83] By contrast with RCVS, primary angiitis of the CNS usually has an insidious onset. Headaches are frequent but not of the thunderclap type, and are followed by a stepwise deterioration with transient deficits, several infarcts, or cognitive decline. MRI scans are abnormal in most cases and show several small deep or superficial infarcts of different ages, with or without associated white matter abnormalities.[82,83] Analysis of CSF shows an inflammatory reaction.[82,83] Angiography is frequently normal in primary angiitis of the CNS, whereas by definition it is always abnormal in RCVS (except when done early). Some clinical features suggest primary angiitis—namely, irregular, eccentric, and asymmetrical narrowings or several occlusions on angiograms[82] and contrast enhancement of the vessel wall in MRI scans.[84] In rare cases when clinicians remain unsure of diagnosis, waiting for a few days might be best; RCVS should stabilise and improve quickly (and vasoconstriction will reverse) whereas arterial irregularities in primary angiitis of the CNS do not improve so rapidly.[9] Response to intra-arterial nimodipine has been proposed as a differential diagnosis test that remains to be validated; the drug immediately normalised arterial abnormalities in a few cases of RCVS,[85] but is not expected to change the lesions in primary angiitis of the CNS.[86]

Migraine

People with proven RCVS frequently have a history of migraine. Acute headaches due to RCVS are sometimes mistaken for bad migraine attacks.[11,19,64,87,88] Headaches in RCVS are secondary (ie, symptomatic), whereas migraine is a primary headache.[1] Patients with migraine who had had RCVS recognised the thunderclap headaches as

totally different from migraine attacks.[5] However, they often complained at admission of a worst ever migraine attack, and reported only after careful questioning that the pain had peaked within seconds. Migraine seems to be a risk factor for haemorrhage during RCVS.[8] Acute migraine treatments (triptans and ergots) can precipitate RCVS or aggravate the vasoconstriction when given to alleviate a thunderclap headache mistaken for a migraine attack.[6,30,52] Patients with migraine who have RCVS should be advised to give up vasoactive migraine drugs during follow-up.

Other primary headaches

Recognition that patients could present with recurrent thunderclap headaches and a segmental reversible vasoconstriction without other abnormalities led to the inclusion of primary thunderclap headaches in the International Classification of Headache Disorders in 2004.[1] The rules of headache classification specify that a diagnosis of primary headache can be accepted only after exclusion of all causes of secondary headaches.[1] Since results of initial angiography can be normal, diagnosis of RCVS can be missed. In one study,[4] results of magnetic resonance angiography showed no visible vasoconstriction in two-thirds of patients with thunderclap headaches, although their clinical features and rate of eventual cerebral ischaemia were similar to those of patients with visible vasoconstriction. These patients without visible vasoconstriction should be thought to have a probable purely cephalalgic form of RCVS, and not so-called primary thunderclap headaches. Furthermore, in a 2010 prospective series,[89] 18 of 30 patients investigated for isolated sexual headaches had RCVS. Therefore, clinicians should suspect RCVS before diagnosis of primary headache in patients with recurrent headaches triggered by sex or exertion.

Management

Management is guided by observational data and expert opinion. No randomised clinical trials of treatment for RCVS have been done, but early recognition of the syndrome is important so that symptoms can be managed effectively. Patients with consistent clinical and brain imaging features, no evidence for another cause of symptoms, and normal initial cerebral angiograms should be viewed as having possible or probable RCVS, and should receive the same symptomatic treatment as patients with visible vasoconstriction.

All patients need symptomatic management, which is primarily based on the identification and elimination of any precipitating or aggravating factors. Patients should be told to rest (even if they have the purely cephalalgic forms) and advised to avoid sexual activity, physical exertion, Valsalva manoeuvres, and other headache triggers for a few days to a few weeks, depending on initial severity. Any vasoactive drugs should be stopped and avoided even after disease resolution. Treatment should include analgesics, antiepileptic drugs for seizures, monitoring of blood pressure, and admission to intensive-care units in severe cases. Clinicians should treat hypertension according to the guidelines for patients with acute stroke, but should keep in mind that hypotension in the setting of cerebral vasoconstriction is potentially more dangerous. At my institution, we give benzodiazepines to relieve anxiety, which is common and could be an aggravating factor.

Drugs targeted at vasospasm can be considered when cerebral vasoconstriction has been assessed. Nimodipine,[4,5,7,9,20,90] verapamil,[14] and magnesium sulphate[18] have been used to relieve arterial narrowing. Nimodipine was given intravenously or orally at the dose used for the prevention of vasospasm in aneurysmal subarachnoid haemorrhage. Duration of treatment ranged from 4 to 12 weeks. Although nimodipine seemed to reduce the number and intensity of headaches, prospective and retrospective large studies suggest that it does not affect the timecourse of cerebral vasoconstriction.[4,5,8,9] New haemorrhages, transient ischaemic attacks, and infarction have been reported in some patients treated for several days.[5,20,30] Since RCVS is usually self limiting, observation and symptomatic management might be reasonable in patients who show no signs of clinical progression and no brain lesion.

Short courses of glucocorticoids do not seem to prevent clinical deterioration,[9] and have been postulated to worsen the clinical course.[91] Thus, they should be avoided.

In severe cases, intra-arterial administration of milrinone, nimodipine, and epoprostenol and balloon angioplasty have been used with variable and debatable success.[51,60,85,86,92,93] These interventions have a risk of reperfusion injury and use should be restricted to patients showing clear signs of clinical progression.[49] Fatal cases were refractory to any intra-arterial treatments.[49,60]

Prognosis

In most patients, headaches and angiographic abnormalities resolve within days or weeks. Long-term prognosis of RCVS is determined by the occurrence of stroke.[8,9] Most patients who have strokes gradually improve for several weeks, and few have residual deficits.[2,5,7] Less than 5% develop life-threatening forms with several strokes and uncontrolled massive brain oedema.[9,23,49,60,94–97] The combined case fatality in the three largest studies[7–9] was less than 1%. Intractable vasoconstriction could be more frequent in post-partum RCVS; in a 2012 retrospective study[50] of 18 post-partum women, 4 died and 5 had residual deficits. RCVS is so called because of the dynamic nature of vasoconstriction; residual deficits from stroke might persist, and rarely the vasoconstriction (particularly if severe and prolonged) might not fully reverse in some patients.[9] Recurrence of the syndrome is possible.[17,36] The rate is unknown, but is probably low because such cases would probably have been reported.

Panel 4: **Precipitants of reversible cerebral vasoconstriction syndrome**

Post partum[2,18,50,97]
- With or without vasoactive substances, with or without eclampsia or pre-eclampsia

Vasoactive drugs[2,5,9]
- Illicit drugs—eg, cannabis,[5,34] cocaine,[105] methylenedioxymethamfetamine,[29] amphetamines, lysergic acid diethylamide
- Antidepressants—eg, selective serotonin reuptake inhibitors,[6,59] serotonin–noradrenaline reuptake inhibitors[9,59]
- α-sympathomimetics—eg, nasal decongestants (phenylpropanolamine, pseudoephedrine, ephedrine),[98,99] norepinephrine[100]
- Triptans[9,41,52,101,102]
- Ergot alkaloid derivatives[50]—eg, methergine, bromocriptine,[103] lisuride[48]
- Nicotine patches[5]
- Ginseng and other herbal medicines[22,53,104]
- Binge drinking[5]

Catecholamine-secreting tumours[15,108]
- Phaeochromocytoma, bronchial carcinoid tumour, glomus tumours

Immunosuppressants or blood products
- Intravenous immunoglobulin,[46] red-blood-cell transfusion,[109] interferon alfa[5]

Miscellaneous
- Hypercalcaemia, porphyria, head trauma,[110–112] neurosurgery,[95,113] subdural spinal haematoma, carotid endarterectomy,[55,114] cerebral venous thrombosis,[115] CSF hypotension,[116] autonomic dysreflexia,[117] phenytoin intoxication[118]

Putative precipitants and associated disorders

Although RCVS can occur spontaneously, especially in middle-aged women,[7,24] at least half the cases occur after exposure to vasoactive drugs or post partum.[2,5,6,9,12,17,18,22,28–30,33,34,41,48,50,52,53,59,86,97–107] Women are more susceptible to RCVS than are men, in whom exposure to several vasoactive drugs, and sometimes binging on cannabis and alcohol, is often required for the disorder to develop.[5,34] Panel 4 lists the putative precipitants of the syndrome.[15,46,55,95,108–118]

Vasoactive drugs

Serotonergic and adrenergic drugs are commonly implicated (panel 4).[5,9,105–107] The syndrome might be precipitated at first ever exposure or after long-term use of one or several drugs at normal or excessive doses. Cannabis was the most common precipitant in the French series; a third of patients admitted use in the 2 weeks before onset.[5] In another French prospective study[34] of 48 patients younger than 45 years who were admitted for ischaemic stroke, 13 were cannabis users, of whom ten had multifocal arterial cerebral stenosis, which was reversible at 3 months in six cases (12%)—ie, they had RCVS. In the US series of 139 cases, 42% (exact number not given) were exposed to a wide range of vasoactive drugs,[9] compared with only two of the 77 patients in the Taiwanese study.[7]

Post partum

In two-thirds of cases, post-partum RCVS (or post-partum angiopathy) starts during the first week after delivery, after a normal pregnancy[12,18,60,97,119] or one complicated by proteinuria or HELLP (haemolysis, increased concentrations of liver enzymes, low platelet count) syndrome.[60] At least a third of patients overall have been exposed to vasoconstrictors used for epidural anaesthesia, post-partum haemorrhage, inhibition of lactation, or depression.[60,97,100] That other patients do not have a history of such drug use suggests that hormonal fluctuations alone might trigger the syndrome. Sudden falls in concentrations of oestrogens and progesterones due to causes other than recent childbirth have been implicated in a few cases.[54,120,121]

Cervical and cerebral large-artery lesions

RCVS can be associated with unruptured cerebral aneurysms.[5,8] Although possibly fortuitous (because it leads to discovery of the aneurysm), this association has clinical consequences. An understandable fear is that an aneurysmal subarachnoid haemorrhage with secondary vasospasm could be overlooked.[122] Patients with aneurysms who were ultimately diagnosed with RCVS had normal CSF, no extravasation of contrast media on catheter angiography,[5,123] and no intraoperative evidence of aneurysmal wall rupture.[39,123–125] RCVS has also been reported in some patients with arterial dysplasia.[5]

RCVS can occur with a cervical—carotid or vertebral—artery dissection. The first case associated with a carotid artery dissection was judged to be incidental.[17] However, the proportion of patients with both vascular disorders in the French series (8%) suggests a non-incidental association,[8] and cases seem to be increasingly recognised.[7,31,40,50,61–63] One hypothesis is that cervical artery dissection could precipitate RCVS, as reported after carotid endarterectomy.[55,126] Alternatively, the dissections could be caused by an abnormal process affecting the small vessels irrigating the cervical artery wall.

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome and RCVS share many clinicoradiographic features, suggesting overlapping or similar pathophysiological mechanisms. The clinical manifestations of posterior reversible encephalopathy syndrome are acute, self limited, and

similar to those of severe RCVS—eg, acute headache, confusion, seizures, visual symptoms.[127–129] By definition, all patients with posterior reversible encephalopathy syndrome have a characteristic MRI pattern with bilateral hemispheric boundary zones of hyperintensities on T2 and FLAIR imaging, with increased apparent diffusion coefficient values, affecting the cortex and subcortical and deep white matter to varying degrees.[130,131] This vasogenic oedema usually reverses completely in a few days, but cerebral infarction, cytotoxic oedema, or haemorrhage can occur.[56,129,131] RCVS and posterior reversible encephalopathy syndrome are frequently associated. Reversible brain oedema occurs in 8–38% of all cases of RCVS.[5,8,9,18,50,56,132] Moreover, a multifocal cerebral vasoconstriction has been noted in more than 85% of patients with posterior reversible encephalopathy syndrome whenever investigations included angiography;[133–136] this vasoconstriction was shown to be reversible on follow-up magnetic resonance angiography.[135,136]

Posterior reversible encephalopathy syndrome can complicate toxaemia of pregnancy, immunosuppressive treatment after transplantation, cancer chemotherapy, autoimmune diseases, hypertension, and septic shock, all of which are associated with endothelial damage or activation (panel 5).[128,129,134,136,138] It was thought to be caused by severe hypertension, leading to altered cerebral autoregulation with hyperperfusion and vasogenic oedema.[129,130] However, a quarter of patients with posterior reversible encephalopathy syndrome are normotensive; these patients have more extensive oedema than do hypertensive patients, suggesting that hypertension could sometimes be a protective reaction.[130] A more recent view is that endothelial dysfunction of any cause can affect the regulation of cerebral arterial tone and trigger vasoconstriction with subsequent hypoperfusion, breakdown of the blood–brain barrier, and vasogenic oedema.[129]

Postulated pathological mechanisms

Unpredictable and transient failure of regulation of cerebral arterial tone with sympathetic overactivity seems to have a role in the development of RCVS.[2,3] In susceptible people—eg, middle-aged women, who frequently present with RCVS without any known precipitant or trigger[5]—deregulation of vascular tone could result from spontaneous neuronal or vascular-driven discharge.[3]

A proposed anatomical explanation for both the vasoconstriction and the headache of RCVS is that cerebral arteries are innervated with sensory afferents from the first division of the trigeminal nerve and dorsal root of the second cervical nerve.[2] However, headache peaks during the first week, and usually disappears before the peak of vasoconstriction of large and medium-sized vessels.[7,24] Furthermore, vasoconstriction can persist for weeks after resolution of headache.[7,24] Therefore, thunderclap headaches are probably not caused by these changes to large and medium-sized arteries.

***Panel 5:* Potential causes of reversible cerebral vasoconstriction syndrome associated with posterior reversible encephalopathy syndrome**

- Hypertension (hypertensive encephalopathy)[127,129]
- Eclampsia or pre-eclampsia[127,129,136]
- Immunosuppressants—eg, ciclosporin, tacrolimus[127,129]
- Treatment with cytotoxic drugs[129]
- Autoimmune diseases[137]
- Infection or sepsis[134]
- Miscellaneous[129]—eg, hypomagnesaemia, hypercalcaemia, hypercholesterolaemia, intravenous immunoglobulin, linezolid, Guillain-Barré syndrome, ephedra overdose, so-called triple H therapy (hypertension, hypervolaemia, and haemodilution), tumour lysis syndrome, hydrogen peroxide, dimethyl sulfoxide, stem cells, exposure to contrast media, corticosteroids, lysergic acid diethylamide, scorpion poison, ingestion of *Averrhoa carambola* (star fruit)

My coworkers and I previously suggested that the pathological process first includes distal arteries and then progresses towards the branches of the circle of Willis.[5] Early angiograms can be normal in patients who eventually have substantial arterial beading. Stroke can occur in patients who present with recurrent thunderclap headaches and have normal brain imaging and early angiography results, suggesting that the pathological process has started, but is not evidenced by routine imaging techniques.[8]

Convexity haemorrhage frequently occurs with concomitant posterior reversible encephalopathy syndrome, a transient oedema indicating disrupted small vessel and blood–brain barrier functions. Convexity bleedings could result from rupture or reperfusion injuries affecting small arteries of the leptomeninges. Thunderclap headache could be caused by stimulation of the trigeminal afferents located in the leptomeninges. Vasoconstriction of second and first segments of large cerebral arteries might be a reaction to the distal blood-flow abnormalities, and increases over the ensuing 1 or 2 weeks. Ischaemic lesions could by caused either by transformation of vasogenic oedema into cytotoxic oedema in patients with posterior reversible encephalopathy syndrome, or later in the course of RCVS by severe vasospasms of medium-sized and large arteries. Furthermore, because of the frequent association of posterior reversible encephalopathy syndrome with RCVS,[5,8,9,18,50] it is possible that endothelial dysfunction has a role in both disorders. This hypothesis is strengthened by a 2011 study[139] showing an association between RCVS and a functional polymorphism in the gene encoding BDNF, which has previously been implicated in both sympathetic overactivity and endothelial dysfunction.

Conclusions and future directions

RCVS affects patients of all ages and has a female preponderance. The syndrome should be suspected in any

Search strategy and selection criteria

I searched PubMed with the terms "reversible cerebral vasoconstriction", "thunderclap headache", "postpartum angiopathy", "posterior reversible encephalopathy syndrome", and "benign angiopathy of the central nervous system" for papers published between Jan 1, 1980, and April 30, 2012. Older relevant reports were also included. I also searched the reference lists of identified reports and my own files. Only papers published in English or French or with an English abstract were reviewed. I chose the final reference list on the basis of originality and relevance to the broad scope of this Review.

patient who presents with recurrent thunderclap headaches or cryptogenic stroke, especially post partum or after the use of vasoactive drugs. Diagnosis is easy and an important step in the care of patients with RCVS. Despite the absence of a proven treatment, important steps should be taken during the acute phase—ie, removal of precipitants such as vasoactive substances, putting the patient to rest, lowering of blood pressure when highly increased, control of seizures, and resisting the urge to expose the patient to the risks of brain biopsy and the adverse effects of steroids and immunosuppressive treatment, despite fears of angiitis. During the past 5 years, major progress has been made in the recognition of RCVS. The syndrome is now deemed to be the main cause of isolated recurrent thunderclap headaches—such cases were previously regarded as primary headaches. RCVS is becoming widely accepted as a cause of both ischaemic and haemorrhagic stroke. Since cerebral infarcts were shown to be caused mainly by artery-to-artery embolism, lipohyalinosis, and cardioembolism in the 1950s, vasospasm has not been thought to have a role in ischaemic stroke, except in the setting of aneurysmal rupture. Studies of RCVS have contributed to the re-emergence of vasospasm as a cause of cerebral ischaemia. Furthermore, acute deregulation of cerebral arterial tone should be included in the causes of haemorrhagic stroke. RCVS is now thought to be the most frequent differential diagnosis of primary angiitis of the CNS.

Prospective studies are needed to establish the exact frequency of RCVS as a cause of non-traumatic, non-aneurysmal subarachnoid haemorrhage (including isolated perimesencephalic haemorrhage), intracerebral haemorrhage in patients without vascular malformation, and ischaemic stroke not associated with any of the main causes previously listed. These prospective studies should include all consecutive patients with stroke irrespective of clinical presentation.

The underlying mechanisms of RCVS are unknown. Case-control studies could help to better understand the role of vasoactive drugs. Are these drugs causative? Do they trigger the disorder in some susceptible patients, or are they confounding factors? In-vivo measures of cerebral vascular reactivity during the acute phase of RCVS and after reversibility could help to explain the pathological vascular process. Endothelial function should also be assessed. Furthermore, biomarkers of the disorder in the blood or the CSF should be identified by techniques such as proteomics, which could provide insight into the molecular mechanisms of the syndrome.

Finally, the findings from three large series[7–9] of RCVS have raised questions about the use of nimodipine. A randomised controlled trial is needed. Since the disorder presents mainly as thunderclap headache, causes stroke in only a few cases, and usually has a good spontaneous outcome, a possible compound primary endpoint would be the absence of any new manifestations—including thunderclap headache, focal deficit (transient or persistent), and any new brain lesions—from 48 h to 5 weeks after the initiation of treatment.

Conflicts of interest

I have received payment for board membership from Novartis, lecture fees from Almirall, AstraZeneca, GlaxoSmithKline, Merck, and Pfizer, and travel or accommodation and meeting expenses from Almirall and Pfizer.

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