Reversible cerebral vasoconstriction syndrome: an under-recognized clinical emergency

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***Abstract*:** Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by recurrent thunderclap headaches and reversible cerebral vasoconstrictions. RCVS is more common than previously thought and should be differentiated from aneurismal subarachnoid hemorrhage. RCVS can be spontaneous or evoked by pregnancy or exposure to vasoactive substances. Patients tend to be middle-aged women but pediatric patients have been seen. Up to 80% of sufferers have identifiable triggers. Thunderclap headaches tend to recur daily and last for a period of around 2 weeks, while the vasoconstrictions may last for months. About one-third of patients have blood pressure surges accompanying headache attacks. The potential complications of RCVS include posterior reversible encephalopathy syndrome, ischemic strokes over watershed zones, cortical subarachnoid hemorrhage and intracerebral hemorrhage. Magnetic resonance images including angiography and venography and lumbar punctures are the studies of choice, whereas catheter angiography should not be implemented routinely. Patients with a mean flow velocity of the middle cerebral artery greater than 120 cm/s shown by transcranial color-coded sonography have a greater risk of ischemic complications than those without. The pathophysiology of RCVS remains unknown; sympathetic hyperactivity may play a role. Open-label trials showed calcium channel blockers, such as nimodipine may be an effective treatment in prevention of thunderclap headache attacks. In severe cases, intra-arterial therapy may be considered. Most patients with RCVS recover without sequelae; however, relapse has been reported in a small proportion of patients.

***Keywords*:** reversible cerebral vasoconstriction syndrome, thunderclap headache, posterior reversible encephalopathy syndrome

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Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) encompasses a constellation of disorders, which are characterized by multiple acute-onset severe headaches and reversible cerebral vasoconstriction (Figure 1), with or without neurological deficits or seizure [Calabrese *et al.* 2007]. A variety of eponymic names, including the Call–Fleming syndrome [Call *et al.* 1988], thunderclap headache with reversible vasospasm [Chen *et al.* 2006b; Dodick *et al.* 1999], benign angiopathy of the central nervous system [Calabrese *et al.* 1993], postpartum angiopathy [Singhal and Bernstein, 2005; Bogousslavsky *et al.* 1989], migrainous vasospasm or migraine angiitis [Jackson *et al.* 1993], and drug-induced cerebral arteritis or angiopathy [Singhal *et al.* 2002; Kaye and Fainstat, 1987; Margolis and Newton, 1971], etc., have been proposed to describe the same clinical-radiological syndromes. To avoid confusion, RCVS was proposed as a unifying term in 2007 by a panel of experts [Calabrese *et al.* 2007].

Etiology and associated condition

With the advance of knowledge, RCVS has been increasingly recognized in recent years although it is still an under-diagnosed disease entity. RCVS can be either spontaneous [Chen *et al.* 2006a; 2008] or evoked by various factors [Ducros *et al.* 2007]. The possible etiologies and associated conditions of RCVS that have been reported in the literature are summarized in Table 1 [Calabrese *et al.* 2007; Ducros *et al.* 2007;

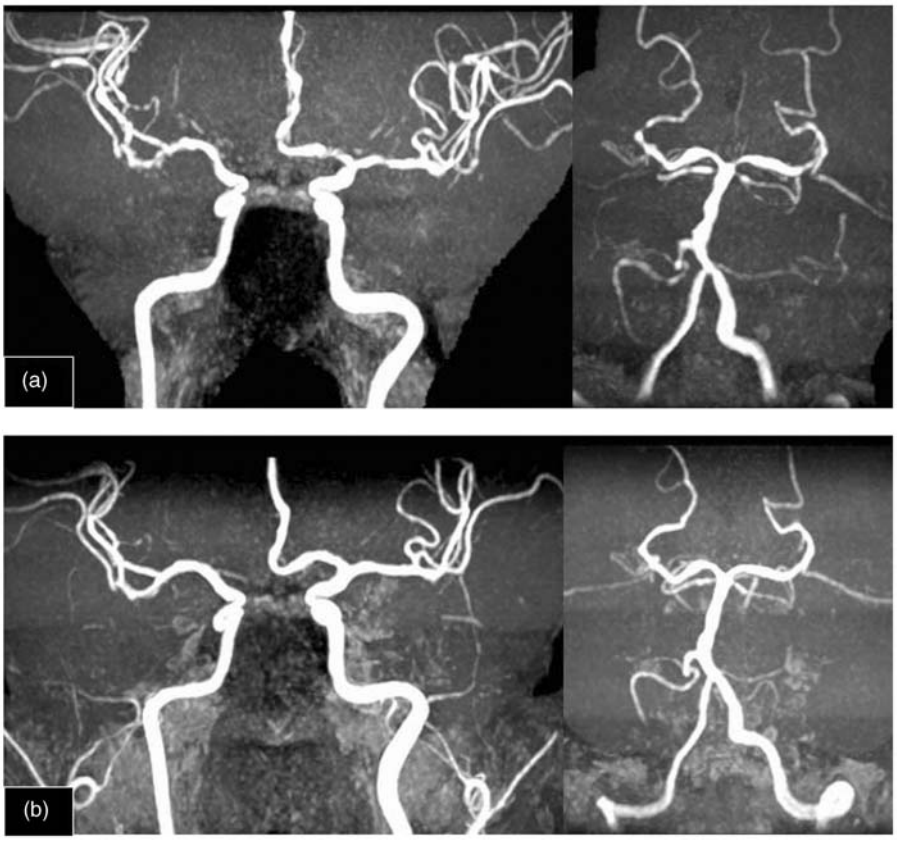

Figure 1. Cerebral vasoconstrictions (a) and their resolution (b) on magnetic resonance angiography in patients with reversible cerebral vasoconstriction syndrome.

Table 1. Potential etiologies and associated conditions of reversible cerebral vasoconstriction syndrome.

Primary (idiopathic, spontaneous)	Primary thunderclap headache
	Headache associated with sexual activity
	Bath-related thunderclap headache
Pregnancy and the postpartum period	Postpartum angiopathy (± use of vasoactive drugs)
	Eclampsia/pre-eclampsia
Exposure to vasoactive substances	Recreational substance: cannabis, cocaine, ecstasy, amphetamines, LSD, binge drinking
	Ergot and ergoline derivatives: ergotamine tartrate, methergine, lisuride, bromocriptine
	Sympathomimetics and nasal decongestants: ephedrine, isometheptene, pseudoephedrine, phenylpropanolamine
	Serotonergic drugs: selective serotonin reuptake inhibitors, triptans
	Immunosuppressants: tacrolimus (FK-506), cyclophosphamide, interferon-α
	Nicotine patches
	Ginseng
Catecholamine secreting tumors	Phaeochromocytoma, bronchial carcinoid tumor, glomus tumors
Extra or intracranial large artery disorders or procedures	Cervical dissection, unruptured intracranial aneurism, dysplasia, postcarotid endarterectomy
Exposure to blood products	Erythropoietin, intravenous immunoglobulin, red blood cell transfusion
Intracranial disorders or surgery	Cerebrospinal fluid hypotension
	Subarachnoid hemorrhage
	Intracerebral hemorrhage
	Spinal subdural hematoma
	Neurosurgery
	Head trauma
Others	Hypercalcemia, porphyria

Chen *et al.* 2006a; Singhal and Bernstein, 2005]. Despite etiological heterogeneity, the clinical presentations are rather similar. The differential lists of secondary RCVS are sizable, but except for puerperium or exposure of vasoactive substances, the other inciting causes are only mentioned in case reports.

In a French cohort, use of vasoactive drugs accounted for more than half (55%) of patients with RCVS [Ducros *et al.* 2007]. Hence, it was recommended that a history of drug exposure should be sought in detail. The vasoactive drugs tended to be sympathomimetics or serotonergic drugs, with the three most common being cannabis (30%), selective serotonin-reuptake inhibitors (SSRIs) (19%), and over-the-counter nasal decongestants (12%) [Ducros *et al.* 2007]. It was also identified that the use of cannabis or multiple vasoactive drugs was significantly more common in men, whereas the use of SSRIs was more common in women. Immunosuppressants or cytotoxic agents were occasionally incriminated, and the diagnosis of RCVS should be kept in mind in patients with autoimmune diseases or undergoing chemotherapy who experience a sudden severe headache.

On the other hand, patients with idiopathic or spontaneous RCVS appeared to be more common than previously thought. The proportion of spontaneous RCVS ranged widely from 37% in a French cohort [Ducros *et al.* 2007] to 96% in our study conducted in Taiwan [Chen *et al.* 2006a]. The proportional differences could be attributed to the variance of patient populations between institutions or ethnic predisposition. It was recently noticed that primary headaches associated with sexual activity have characteristics resembling thunderclap headaches and could exhibit reversible cerebral vasoconstrictions [Ducros *et al.* 2007; Chen *et al.* 2006a; Schlegel and Cucchiara, 2004]. These headache disorders can form a spectrum of spontaneous RCVS.

Demographics

The actual prevalence of RCVS is unknown. In a hospital-based headache clinic in Taiwan, 83 out of 4200 headache patients (2%) had multiple thunderclap headaches [Chen *et al.* 2006a]. Twenty-three of the subjects (including one with postpartum angiopathy) had magnetic resonance angiography (MRA) reversible cerebral vasoconstriction, fulfilling the diagnosis of RCVS. Thirty-four patients were diagnosed to have primary thunderclap headache initially due to lack of evidence of MRA vasoconstriction. Given the potential limitation of MRA in detecting vasoconstrictions in the distal arteriole, some patients with primary thunderclap headache might be diagnosed as having RCVS. Female predominance is distinct in spontaneous RCVS (the female to male ratio ranged from 2.6 : 1 in the French cohort [Ducros *et al.* 2007] to 10 : 1 in the Taiwan cohort [Chen *et al.* 2006a]), while this sex predilection was less significant in secondary RCVS [Ducros *et al.* 2007]. The median age of onset among female patients is about 50 years, while male patients are reported to be younger [Ducros *et al.* 2007; Chen *et al.* 2006a]. Pediatric patients are occasionally seen and all of them have been boys [Liu *et al.* 2009; Kirton *et al.* 2006].

Clinical features

Multiple thunderclap headaches were reported in up to 94–100% of patients with RCVS [Ducros *et al.* 2007; Chen *et al.* 2006a], and they are the most important clinical hallmark of RCVS. Thunderclap headache is defined as a severe headache reaching its maximal intensity within 1 min. When a patient reports having the worst headache that he/she has ever experienced, aneurismal subarachnoid hemorrhage (SAH) and a number of intracranial disorders such as intracranial hemorrhage, cerebral venous sinus thrombosis, pituitary apoplexy, or intracranial hypotension, etc., should also be considered in addition to RCVS [Schwedt, 2007]. However, when the patient experiences multiple thunderclap headaches within 1–2 weeks, RCVS is often the diagnosis.

The thunderclap headaches in patient with RCVS are generally explosive at onset followed by throbbing, with a median duration of around 3 h. Most of the headaches are bilateral and frequently involve the occipital regions. In some cases, the headaches do not match the definition of a thunderclap headache, but they are nonetheless acute and severe. These excruciating headaches prevent patients from carrying out daily activities; for example, 90% of patients with bath-related thunderclap headaches changed bathing habits to prevent attacks [Wang *et al.* 2008].

Besides thunderclap headaches, nearly half of the patients have mild baseline headaches during the course of the disease. Migrainous features, especially nausea, are sometimes mentioned and

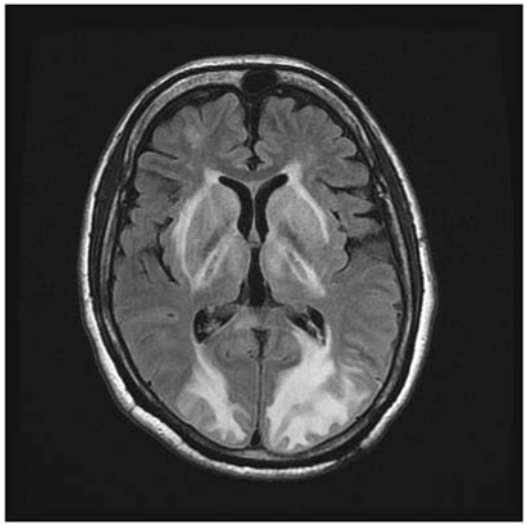

Figure 2. Posterior reversible encephalopathy syndrome on fluid-attenuated inversion recovery image.

patients might have comorbid migraine, but the abruptness of headache onset and excruciating severity distinguish the headaches from migraine. Up to 80% of sufferers have identifiable triggers such as Valsalva-like maneuvers (e.g. exertion, defecation, sex, cough, etc.) or 'bathing' [Ducros *et al.* 2007; Chen *et al.* 2006a; Liao *et al.* 2003]. About one-third of patients have a surge of blood pressure (SBP) (systolic blood pressure >160mmHg) accompanying the headache attacks.

Focal neurological deficits, either transient or permanent, are found in 9–63% of sufferers [Calabrese *et al.* 2007; Ducros *et al.* 2007; Chen *et al.* 2006a]. These focal deficits could be consequences of associated complications, such as transient ischemic attacks (TIAs) (up to 16%), posterior reversible encephalopathy syndrome (PRES) (9–14%) (Figure 2), ischemic strokes (4–54%), cortical subarachnoid hemorrhage (cSAH) (up to 22%) or intracerebral hemorrhage (ICH) (up to 6%) [Calabrese *et al.* 2007; Ducros *et al.* 2007; Chen *et al.* 2006a]. Complications occur with different time courses: hemorrhages (cSAH and ICH), and PRES are early events occurring during the first week, while ischemic events including TIAs and cerebral infarcts occur significantly later, during the second week [Ducros *et al.* 2007]. Seizures, either focal or generalized, occur in up to 21% of patients. A recent poster abstract disclosed that hemorrhagic complications could occur in up to 34% of patients [Ducros *et al.* 2009]. Female gender and history of migraine were two independent risk factors for hemorrhagic complications [Ducros *et al.* 2009]. Thunderclap headaches in RCVS tended to resolve within 2–3 weeks, but the recovery of vasoconstrictions might take up to 3 months. In some protracted cases, vasoconstrictions might persist for longer.

Diagnosis

In addition to multiple thunderclap headache, the diagnosis of RCVS requires the demonstration of segmental vessel constriction (string and beads of the vessels) of the cerebral arteries and its reversibility (complete or marked normalization of arteries) within 12 weeks of onset by initial and repeated cerebral angiography, such as MRA, computed tomography angiography (CTA), or conventional angiography.

Imaging studies

In patients who experience a first-ever thunderclap headache, emergent brain CT study is indicated to exclude SAH or other overt intracranial lesions. For those with a negative CT study or those who have experienced multiple thunderclap headaches within a short period, brain MR images including angiography and venography are the studies of choice. The MR sequences should as a minimum include T1, T2, fluid attenuated inversion recovery imaging, gradient-echo (T2*) imaging, diffusion weighted imaging, and apparent diffusion coefficient mapping for differential diagnosis and evaluation of complications. Cervical MR using a T1 fat-saturation sequence with contrast and carotid duplex should be considered if cervical artery dissection is suspected. The rationales for utilizing these MR sequences are summarized in Table 2.

Conventional angiography, by definition, is the gold standard [Calabrese *et al.* 2007]. Catheter angiography however, is invasive and not feasible for frequent follow-ups [Dodick, 2002]. In addition, it was reported that up to 9% of patients experienced transient neurological deficits after catheter angiography in one large series [Ducros *et al.* 2007]. Consequently, we suggest that catheter angiography should not be routinely considered for diagnosis. MRA, surpassing the limitations of conventional angiography, is a non-inferior tool widely used to evaluate vasoconstriction in patients with RCVS [Chen *et al.* 2006a]. A recent large-scale study demonstrated that MRA evaluation in patients with RCVS is valid [Chen *et al.* 2009]. The study also found that vasoconstriction was pervasive and outlasted

Table 2. Recommended magnetic resonance imaging sequences for evaluation and diagnosis of reversible cerebral vasoconstriction syndrome.

Magnetic resonance sequences	Indications and utility
Necessary	*Suggested for everyone*
T1, T2	To exclude intracranial structural lesions that could lead to thunderclap headache, such as pituitary apoplexy, ICH, SAH, etc.
FLAIR	To evaluate white matter lesions, subtle aneurismal SAH, cortical SAH, PRES, and distal hyperintense vessels, etc.
Gradient-echo (T2*)	To evaluate subtle aneurismal SAH or cortical SAH
DWI/ADC	To evaluate vasogenic (PRES) or cytotoxic edema (ischemic stroke or severe PRES)
MRA	To evaluate vasoconstrictions and to exclude cerebral aneurysms or arterial dissections, etc.
MRV	To exclude venosinal thrombosis
Elective	*If clinical symptoms/signs are suggestive of alternative diagnosis*
T1 with contrast (axial, coronal and sagittal)	To exclude spontaneous intracranial hypotension
Cervical T1 fat-saturation + contrast	To exclude cervical artery dissection

ADC, apparent diffusion coefficiency; DWI, diffusion weighted image; FLAIR, fluid-attenuated inversion recovery; ICH, intracerebral hemorrhage; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; PRES, posterior reversible encephalopathy syndrome; SAH, subarachnoid hemorrhage.

headache resolution in patients with RCVS. CTA has been reported to be a highly sensitive and specific tool in evaluating intracranial vasculature [Forsting, 2005], and could be a useful tool in evaluating vasoconstrictions in RCVS; however, radiation exposure and contrast medium are concerns if the patient requires frequent follow-ups.

Transcranial color-coded sonography

Transcranial color-coded sonography (TCCS) has been widely applied and validated in the study of vasospasm of intracranial vessels [Sloan *et al.* 2004; Aaslid, 2002; Lysakowski *et al.* 2001] and is ideally suited for monitoring hemodynamic changes in patients with RCVS. Our recent publication on TCCS in patients with RCVS proved its utility [Chen *et al.* 2008] and demonstrated that the risk of PRES or ischemic stroke was high in those with a mean flow velocity of the middle cerebral artery (MCA) greater than 120 m/s and a Lindegaard index greater than 3 [Chen *et al.* 2008]. Additionally, we found that patients with RCVS experienced prolonged vasoconstriction, making the risk of PRES and ischemic strokes outlast headache resolution. Based on the study results and easy accessibility of TCCS, we suggest routine neurosonographic follow-up beyond 1 month of headache remission until a consistent flow decrement approaches normal. However, TCCS is limited in patients with bilateral transtemporal window thickening.

Cerebrospinal fluid studies

Spinal tapping should be considered, especially when SAH is suspected in a patient with a negative brain CT scan. It is also valuable in helping to exclude infection or inflammation of the central nervous system (CNS). However, when a patient has experienced multiple thunderclap headaches but no neck stiffness, and his/her MRA has demonstrated multifocal segmental vasoconstrictions in the absence of aneurism, a cerebrospinal fluid (CSF) study seldom increases the diagnostic yield.

Diagnostic criteria

Diagnostic criteria for the eponymic syndrome of RCVS 'headache attributed to benign (or reversible) angiopathy of the central nervous system (code 6.7.3)' were proposed in the *International Classification of Headache Disorders*, 2nd edition [Headache Classification Subcommittee of the International Headache Society, 2004] (Table 3) prior to the proposal of RCVS as the unifying term. Calabrese and co-workers also summarized the critical elements for the diagnosis of RCVS upon the proposal of RCVS [Calabrese *et al.* 2007] (Table 3). Most patients with RCVS could generally fulfill these criteria. However, we proposed that CSF studies might not be necessary if the clinical presentation and angiographic findings are characteristic of RCVS. In addition, the duration criterion and definition of reversibility need to be refined. Normalization of vasoconstrictions within 3 months is found in the majority of patients; however, we noticed that

Table 3. Diagnostic criteria for reversible cerebral vasoconstriction syndrome.

Current diagnostic criteria of benign (or reversible) angiopathy of the central nervous system in the International Classification of Headache Disorders, 2nd edition

1. Diffuse, severe headache of abrupt or progressive onset, with or without focal neurological deficits and/or seizures and fulfilling criteria 3 and 4.
2. 'Strings and beads' appearance on angiography and subarachnoid hemorrhage ruled out by appropriate investigations.
3. One or both of the following:
   (a) headache develops simultaneously with neurological deficits and/or seizures;
   (b) headache leads to angiography and discovery of 'strings and beads' appearance.
4. Headache (and neurological deficits, if present) resolves spontaneously within 2 months.

Diagnosis criteria of reversible cerebral vasoconstriction syndrome proposed by Calabrese et al. (2007)

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

some patients would have a more protracted course. If the vasoconstrictions had improved greatly by 3 months, even though not completely normalized, 'reversibility' could still be claimed in our opinion.

Differential diagnosis

Aneurismal SAH should be recognized early because of its devastating outcome. Multiple thunderclap headaches and absence of neck stiffness are the most convincing clinical characteristics to help in distinguishing RCVS from SAH prior to neuroimaging studies. In other words, if the patient presents with a first attack of thunderclap headache or neck stiffness, enthusiastic work-up for SAH should be carried out. cSAH is not infrequent in patients with RCVS, but these superficial SAHs are usually few, overlying a few cortical sulci, with disproportionate widespread short-segmental vasoconstriction [Ducros *et al.* 2007]. In contrast, the location and severity of delayed vasospasm in aneurismal SAH tend to be long-segmental and have a close spatial relationship with the bleeding site [Calabrese *et al.* 2007]. In primary angiitis of the CNS (PACNS) the angiographic findings resemble RCVS. In PACNS, there is often small vessel involvement (92%), but large vessel involvement is not uncommon (71%) [Salvarani *et al.* 2007]. Hence, it is difficult to make a distinction between these two syndromes at an early stage based solely on angiographic findings. Nonetheless, repetitive thunderclap headaches have never been reported in PACNS. In doubtful cases, CSF studies or even brain biopsy may provide an ancillary diagnostic yield. Cervical arterial dissection is frequently considered to be a secondary cause of thunderclap headache. However, it was recently identified that cervical artery dissection could be a comorbid condition of RCVS, and should be carefully sought in patients with suspected RCVS [Ducros *et al.* 2007]. It is uncertain whether the arterial dissection is the cause or consequence of RCVS. More studies are required to elucidate this enigma. The comparison of RCVS with these disorders is summarized in Table 4.

Pathophysiology of RCVS

Despite gradual delineation of its clinical presentations, the exact pathophysiology of RCVS remains enigmatic. As RCVS is a collection of similar clinico-radiological syndromes, the underlying mechanisms could be multi-factorial. Some pathophysiological mechanisms have been proposed (Figure 3).

Dysfunctional regulation of vascular tone

A disturbance in the control of cerebral vascular tone seems to be a critical element in the pathogenesis of RCVS. This alteration in vascular tone may be spontaneous or evoked by various exogenous or endogenous factors, one of which is aberrant sympathetic response [Dodick, 2002]. Heightened sympathetic activities are plausible with observations of SBP and triggers with elevated sympathetic tone in a great proportion of spontaneous RCVS patients [Ducros *et al.* 2007; Chen *et al.* 2006a]. In addition, evidence from secondary RCVS, such as patients with pheochromocytoma [Heo *et al.* 2009; Im and Kim, 2008; Armstrong and Hayes, 1961], acute

Table 4. Differential diagnosis of disorders that may mimic or be comorbid with reversible cerebral vasoconstriction syndrome.

	Reversible cerebral vasoconstriction syndrome	Aneurismal: subarachnoid hemorrhage	Primary angiitis of the central nervous system	Cervical artery dissection
Incidence	?, (<1% in headache clinic)	1/10,000	2.4/1,000,000	2.6/10,000
Age, median, years	40–60	50–60	40–60	40–50
Sex	F ≫ M	F/M = 2/1	M > F	M = F
Headache characteristics	Multiple TCH	TCH	63% headache, insidious and progressive	80% head or neck pain, 13% as TCH
Cerebrospinal fluid studies	Mostly normal, some have slight elevation of RBC, WBC, or protein	High opening pressure, increased RBC, xanthochromia	80–90% abnormal, modest elevation of WBC and protein	Normal
Brain computed tomography/magnetic resonance imaging	Mostly normal, some complicated with posterior reversible encephalopathy syndromes, borderzone ischemic stroke, ICH, cortical SAH	SAH (5% computed tomography negative), cerebral edema, delayed ischemic infarction and/or hydrocephalus subsequently	97% abnormal, including infarction (53%), ICH, gadolinium-enhancing lesions (1/3)	around 60% infarction; crescentic intramural hematoma may be seen
Angiographic findings	Multifocal short-segmental narrowing, mostly in medium to large vessels, sometimes with adjacent focal dilatation; takes weeks to months to resolve	Vasospasm develops 3–12 days after SAH, long-segmental, with spatial correlation with hemorrhage; resolves with time, but some are irreversible	50–90% angiography positive, string and beads appearance, 92% small vessel changes, 71% large vessel changes; variable course, mostly irreversible	Long-segmental tapered narrowing, double lumen, intimal flaps; 10–20% multi-vessel involvement; could comorbid with reversible cerebral vasoconstriction syndromes and thus has multifocal short-segmental narrowing

ICH, intracerebral hemorrhage; RBC, red blood cells; SAH, subarachnoid hemorrhage; TCH, thunderclap headache; WBC, white blood cells. (Modified from Calabrese *et al.* [2007]; additional information quoted from: Birnbaum and Hellmann [2009]; Brisman *et al.* [2006]; Chen *et al.* [2006a]; Ducros *et al.* [2007]; Lee *et al.* [2006]; Salvarani *et al.* [2007].)

hypertensive crises [Tang-Wai *et al.* 2001], or ingestion of sympathomimetic drugs [Kaye and Fainstat, 1987; Margolis and Newton, 1971], also support the significance of excessive sympathetic activity or an abnormal vascular response to circulating catecholamines. However, since the vasoconstrictions persist for a protracted course beyond headache resolution [Chen *et al.* 2008; 2009], there should be some factors regulating vascular tone other than heightened sympathetic activity participating in the pathogenesis. Although the absence of blood in the subarachnoid space basically distinguishes RCVS from SAH, it is conceivable that numerous immunologic and biochemical factors known to regulate vascular tone from studies of SAH-related vasospasm might play some roles in the pathophysiology of vasoconstriction in RCVS [Nishizawa and Laher, 2005; Pluta, 2005; Dietrich and Dacey, 2000].

Pathophysiology of PRES suggests causal links

The presence of PRES or watershed zone infarcts in severe cases stresses the role of vasoconstriction and its underlying pathogenic factors [Chen *et al.* 2006b; 2008; 2009; Singhal, 2004; Dodick *et al.* 2003]. Hypertensive encephalopathy constitutes a substantial proportion of PRES; however, 20–30% of patients with PRES are normotensive on disease occurrence [Bartynski, 2008]. In our latest study in which 77 RCVS patients were recruited, 19 (24.7%) had a history of hypertension, and 35 (45.5%) had SBP during thunderclap headache attacks [Chen *et al.* 2009]. The mean maximal systolic blood pressure during the headache attacks was 156.9 ± 30.2 mmHg (range 101–220 mmHg). PRES was noted in seven patients (9.1%); six of them had ictal SBP. It was likely that hypertension was a bystander as a stress response to the excruciating headaches but could also be a player in the

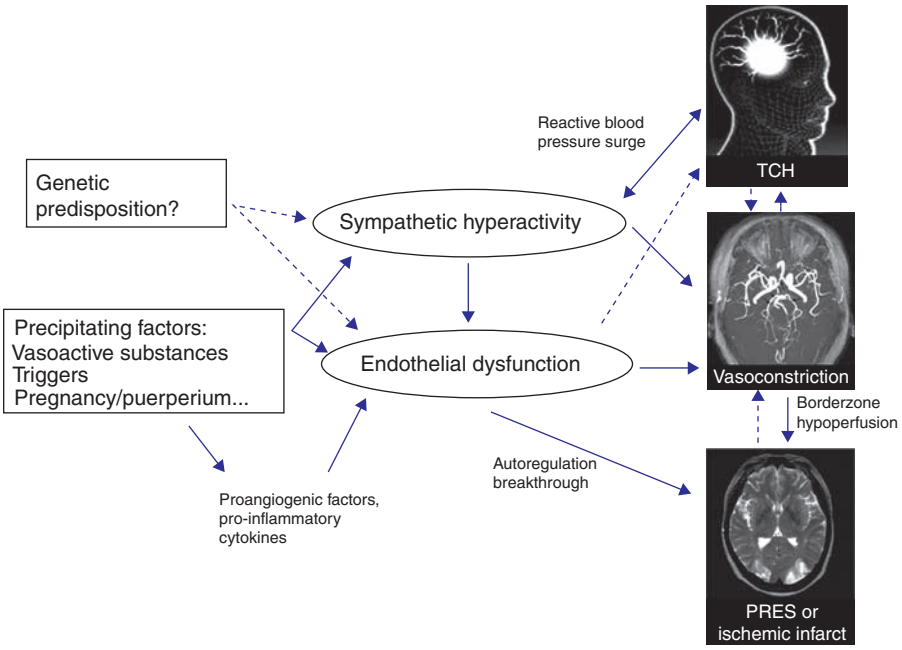

Figure 3. Proposed pathophysiology of reversible cerebral vasoconstriction syndrome. PRES, posterior reversible encephalopathy syndrome; TCH, thunderclap headache.

pathogenesis of PRES. It has been proposed that in PRES the endothelial control of vascular tone is overwhelmed as a result of autoregulation breakthrough, which progresses into a vicious cycle of homeostatic failure, leading to progressive increase of vascular resistance and, which, in turn, further worsens endothelial dysfunction. Increased vascular permeability, attributed to endothelial dysfunction, may contribute partly to the vasogenic edema in PRES [Bartynski, 2008; Bartynski and Boardman, 2008; Chen *et al.* 2006b; Singhal, 2004; Dodick *et al.* 2003]. In contrast, the progressive increase of vascular resistance phenomenologically presents itself as diffuse vasoconstriction, and when severe, may lead to irreversible ischemic change, especially over the watershed zones with posterior preponderance [Bartynski and Boardman, 2008; Chen *et al.* 2006b]. We found that more severe vasoconstrictions in the M1 segment of MCA and the P2 segment of the posterior cerebral artery contributed to a higher risk of PRES in patients with RCVS [Chen *et al.* 2009], which was consistent with the concept. In addition, our study noticed that a history of hypertension may make P2 more inert to vasoconstriction, but a sudden SBP during a thunderclap headache attack was associated with a more severe vasoconstriction of P2 [Chen *et al.* 2009]. The latter might be explained by the relative paucity of sympathetic innervations and defective autoregulation of the posterior circulation [Beausang-Linder and Bill, 1981].

Overlap between postpartum angiopathy and eclampsia

As one variant of RCVS, postpartum angiopathy, has many clinical, laboratory and radiographical features overlapping with eclampsia and pre-eclampsia, it has been proposed that these disorders might belong to the same disease spectrum and have some shared pathophysiological mechanisms [Fletcher *et al.* 2009; Singhal and Bernstein, 2005; Donaldson, 2000]. Recent studies have demonstrated that placental growth factor (PlGF), soluble PlGF receptor (sFlt-1) [Rana *et al.* 2007; Levine *et al.* 2004], and a soluble transforming growth factor β1 receptor (soluble endoglin) [Levine *et al.* 2006] correlate with the presence of eclampsia and also predict its development. It was also found that the ratio of sFlt-1 to PIGF could be used to predict the occurrence of pre-eclampsia [Rana *et al.* 2007]. It is uncertain whether the balance of these anti-angiogenic and pro-angiogenic factors could also play a role in postpartum angiopathy; however, a recent case report had drawn a link between them [Singhal *et al.* 2009]. Nonetheless, these mechanisms might not be applicable to patients with RCVS not related to pregnancy or puerperium.

Prognosis

Despite substantial risks of ischemic or hemorrhagic complications, permanent neurological deficits were noted in only 3–6% of patients in two large prospective series [Chen *et al.* 2009; Ducros *et al.* 2007]. In a retrospective study using the Barthel index for long-term assessment, it was found that 29% had mild disability and none had severe disability after a mean follow-up of 35 months [Hajj-Ali *et al.* 2002]. However, mortality has been noted in some case reports [Singhal *et al.* 2009; Singhal, 2002]. In the French series, no angiographically proven recurrence had been identified after a mean follow-up of 3.2 years (range 26–62 months) [Ducros *et al.* 2007]. However, in a subsequent review, two patients experiencing recurrence of multiple thunderclap headaches were identified, one after smoking cannabis and the other after using SSRIs [Ducros and Bousser, 2009]. In our experience, recurrence was noted in 6 out of 77 (8%) RCVS patients at a median follow-up of 25 months. All reported a clinical recurrence with multiple thunderclap headaches and their MRAs showed reversible vasoconstrictions [Chen *et al.* 2009]. Nonetheless, no definite prognostic indicators have been identified.

Treatment

Given the risks of potential complications, RCVS should be treated as an emergent condition. All of the diagnostic evaluations including neuroimaging studies and/or spinal taps should be carried out as soon as possible. Interventions should be employed immediately after a tentative diagnosis of RCVS is made, starting with the avoidance of triggers and withdrawal of secondary causes. Regarding pharmacological treatment, unfortunately no treatment has gained enough evidence of efficacy. Our previous open-labeled trials suggest that thunderclap headaches in patients with RCVS might be responsive to the calcium channel blocker nimodipine within 2 days [Lu *et al.* 2004]. The patients were given oral nimodipine 30–60 mg every 4 h, adjusted according to the severity of vasoconstriction. When oral nimodipine was ineffective, exacerbated vasoconstrictions disclosed by sequential MRA or TCCS, or the presence of PRES or ischemic stroke, intravenous nimodipine (0.5–2 mg/h) was administered via a central venous line, with blood pressure monitored every 2–4 h. The efficacy of nimodipine in aborting thunderclap headache ranged from 64% [Ducros *et al.* 2007] to 83% [Chen *et al.* 2006a]. It should be stressed that any efficacy of nimodipine has not been proven against the hemorrhagic and ischemic complications of RCVS, and increasing the dose of nimodipine could possibly be deleterious in patients with ischemic complications due to the lowering effect on blood pressure [Ducros *et al.* 2007]. Close blood pressure monitoring and avoidance of hypotension should be exercised during dose escalation. Hypotension (systolic blood pressure <100 mmHg) should be corrected immediately by dose tapering and hydration. Dizziness, nausea, facial flushing, tachycardia, or allergies were other potential adverse effects [Liu *et al.* 2009; Chen *et al.* 2006a; Lu *et al.* 2004]. Other calcium channel blockers such as nicardipine [Liu *et al*. 2009] or verapmil [Bouchard *et al.* 2009] had been tried, but their efficacy and safety remain to be established. Magnesium sulfate has been tried in the treatment of eclampsia/pre-eclampsia in a small subset of patients with postpartum angiography with acceptable outcomes [Chik *et al.* 2009]. Prospective, large-scaled, randomized, placebo-controlled trials are required to investigate the efficacy of the above drugs in patients with RCVS.

Prophylaxis

No studies have specifically investigated prophylactic measures for RCVS. Given the possibility of recurrence, it is advisable, as prophylaxis, for patients to avoid further exposure to possible implicated substances or conditions (Table 2). However, evidence is still lacking on which substances should be avoided. Studies employing pharmacogenetics might be helpful.

Future therapeutic approaches

In patients with refractory vasoconstrictions, intra-arterial therapy might be considered. Calcium channel blockers such as nimodipine [Elstner *et al.* 2009; Klein *et al.* 2009] or the phosphodiesterase inhibitor milrinone [Bouchard *et al.* 2009] have been employed in some cases and led to satisfactory outcomes. However, more studies are required. In addition, the risk of reperfusion injury should be considered [Singhal *et al.* 2009]. It may still be speculative, but considering the potential pathophysiological implications, therapies targeted at the restoration of endothelial function might be promising and deserve further investigation.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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