

REVERSIBLE CEREBRAL VASOCONSTRICTION SYNDROME

Terminology

- ▣ Migrainous vasospasm or migraine angiitis [1,2]
- ▣ Call-Fleming syndrome (or Call syndrome) [3,4]
- ▣ Thunderclap headache-associated vasospasm [5-7]
- ▣ Drug-induced cerebral arteritis [8]
- ▣ Postpartum cerebral angiopathy [9]
- ▣ Benign angiopathy of the central nervous system [10]
- ▣ Central nervous system pseudovasculitis [11]

Clinical Presentation

- ▣ Thunderclap Headache (94-100%)
 - ❖ Diffuse; associated with nausea and photosensitivity
 - ❖ Pain relief within minutes to hours
 - ❖ Followed by severe recurring exacerbations
 - ❖ Triggers include valsalva like maneuvers (exertion, cough, sex, defecation)
 - ❖ Systolic Hypertension in 33% patients

- ▣ Focal Neurological Deficits (9-63%)
 - ❖ Consequences of complications
 - ❖ 1st week complications include PRES, hemorrhages (cSAH, ICH)
 - ❖ 2nd week complications include TIA, cerebral infarcts

- ▣ Seizures (21%)
 - ❖ Focal/Generalized

Etiologies & Associations

Risk factors, triggers, and other conditions associated with reversible cerebral vasoconstriction syndrome

Changes in estrogen-progesterone levels
Pregnancy
Eclampsia-preeclampsia
Ovarian stimulation
Oral contraceptive medications
Headache disorders
Primary thunderclap headache
Primary cough headache
Primary headache associated with sexual activity
Exercise (exertional) headache
Migraine
Vasoconstrictive agents
Antimigraine agents (triptans, isometheptene, ergotamine tartrate)
Blood products (red blood cell transfusions, erythropoietin)
Cough and cold suppressants (phenylpropanolamine, pseudoephedrine)
Diet pills and energy-enhancing agents (amphetamine derivatives, Hydroxycut)
Antidepressants (selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors)
Adrenergic agents (epinephrine, bromocriptine, lisuride)
Illicit drugs (cocaine, ecstasy, marijuana, lysergic acid diethylamide)
Chemotherapeutic agents (tacrolimus, cyclophosphamide)
Other (indomethacin, interferon alpha, intravenous immune globulin, licorice, ma huang [ephedra], methylephedrine, nicotine patches)
Tumors
Carcinoid, carotid paraganglioma, pheochromocytoma
Metabolic
Hypercalcemia, porphyria
Environmental exposure or trauma
High altitude
Cold water exposure
Swimming
Head trauma
Vascular
Cerebral venous thrombosis
Cervical artery dissection
Postcarotid endarterectomy
Posterior reversible encephalopathy syndrome (PRES)
Neurosurgical manipulation of intracerebral arteries
Spinal subdural hematoma
Unruptured saccular cerebral aneurysm

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

Summary of critical elements for the diagnosis of reversible cerebral vasoconstriction syndromes (RCVS)

1. Single or (most often) recurrent thunderclap headaches.
2. Multifocal segmental cerebral artery vasoconstriction demonstrated on cerebral angiography (with CTA, MRA, or DSA) that usually develops within a week of symptom onset.
3. No evidence for aneurysmal SAH.
4. Brain imaging findings are often normal, or may show vasogenic edema (PRES) and/or FLAIR sulcal hyperintensities (dot sign). Infarcts, if present, are usually symmetric and distributed along border zones of arterial territories. Intraparenchymal hemorrhage and/or nonaneurysmal convexity SAH may be present in some cases of RCVS.

RCVS: reversible cerebral vasoconstriction syndromes; CTA: computed tomography angiography; MRA: magnetic resonance angiography; DSA: digital subtraction angiography; FLAIR: fluid-attenuated inversion recovery; PRES: posterior reversible encephalopathy syndrome; SAH: subarachnoid hemorrhage.

Modified from Annals of Internal Medicine, Calabrese LH, Dodick DW, Schwedt TJ, et al. Narrative review: Reversible cerebral vasoconstriction syndromes, Volume 146, Issue 1, Pages 34-44. Copyright © 2007 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

RCVS₂ score

Criteria	Value
Recurrent or single TCH	
Present	5
Absent	0
Carotid artery (intracranial) narrowing	
Affected	-2
Not affected	0
Vasoconstrictive trigger	
Present	3
Absent	0
Sex	
Female	1
Male	0
Subarachnoid hemorrhage	
Present	1
Absent	0

In a retrospective study of consecutive patients with RCVS (n = 30) or non-RCVS arteriopathy (n = 80), recurrent or single thunderclap headache, vasoconstrictive trigger, female sex, and convexity subarachnoid hemorrhage were predictors of RCVS; intracranial carotid artery involvement (ie, segmental narrowing) was a negative predictor. In the derivation cohort, RCVS₂ scores ≥ 5 had a high specificity and sensitivity (99 and 90%, respectively) for diagnosing RCVS, while scores ≤ 2 had a high specificity and sensitivity (100 and 85%) for excluding RCVS; intermediate scores of 3 to 4 had a lower specificity and sensitivity (86 and 10%) for diagnosing RCVS. Performance was similar in the validation cohort.

RCVS: reversible cerebral vasoconstriction syndrome; TCH: thunderclap headache.

From: Rocha EA, Topcuoglu MA, Silva GS, Singhal AB. RCVS₂ score and diagnostic approach for reversible cerebral vasoconstriction syndrome. *Neurology* 2019; 92:e639. DOI: [10.1212/WNL.0000000000006917](https://doi.org/10.1212/WNL.0000000000006917). Copyright © 2019 American Academy of Neurology. Reproduced with permission from Wolters Kluwer Health. Unauthorized reproduction of this material is prohibited.

RCVS₂ score performance

RCVS ₂ score	Specificity	Sensitivity	PPV	NPV
Derivation cohort				
Score 5 or higher*	99 (93, 100)	90 (73, 98)	96 (82, 100)	96 (90, 99)
Score 3 or 4*	86 (77, 93)	10 (2, 27)	21 (5, 51)	72 (62, 80)
Score 2 or lower†	100 (88, 100)	85 (75, 92)	100 (95, 100)	71 (55, 84)
Validation cohort				
Score 5 or higher*	94 (82, 99)	86 (80, 91)	98 (94, 100)	67 (54, 78)
Score 3 or 4*	83 (69, 92)	11 (6, 17)	68 (46, 85)	22 (16, 28)
Score 2 or lower†	96 (92, 99)	77 (62, 88)	86 (71, 95)	93 (88, 97)

NPV: negative predictive value; PPV: positive predictive value; RCVS: reversible cerebral vasoconstriction syndrome.

* Values for a RCVS diagnosis.

† Values for a non-RCVS diagnosis.

From: Rocha EA, Topcuoglu MA, Silva GS, Singhal AB. RCVS₂ score and diagnostic approach for reversible cerebral vasoconstriction syndrome. *Neurology* 2019; 92:e639. DOI: [10.1212/WNL.0000000000006917](https://doi.org/10.1212/WNL.0000000000006917). Copyright © 2019 American Academy of Neurology. Reproduced with permission from Wolters Kluwer Health. Unauthorized reproduction of this material is prohibited.

Diagnostic findings for the more common causes of thunderclap headache

Cause	Clinical features	Brain CT	Lumbar puncture	Angiography	Brain MRI
Aneurysmal subarachnoid hemorrhage	Altered consciousness, seizures, meningismus	Subarachnoid blood in basilar cisterns and sylvian fissures	Elevated red blood cells, xanthochromia	Ruptured aneurysm, vasospasm	Subarachnoid blood in basilar cisterns and sylvian fissures
Reversible cerebral vasoconstriction syndrome	Recurrent thunderclap headaches	Normal, or subarachnoid blood along cortical surface/sulci	Normal, mild white blood cell elevation, mild protein elevation	Multifocal multivessel vasoconstriction	Normal, or subarachnoid blood along cortical surface/sulci, ischemic stroke, cerebral edema, intracerebral hemorrhage
Carotid and vertebral artery dissection	Neck pain, symptoms related to cerebral ischemia, Horner syndrome (carotid dissection)	Normal, or ischemic stroke	Normal	Dissected artery, multifocal, segmental vasoconstriction if associated with reversible cerebral vasoconstriction syndrome	Normal, or ischemic stroke
Cerebral venous sinus thrombosis	Focal neurologic deficits, altered mental status, visual changes	Dense triangle sign (clot inside the sinus), cord sign (thrombosed cortical or deep vein), venous hemorrhages	Elevated opening pressure, high protein	Venous sinus thrombosis	Normal, or venous infarctions with hemorrhage; MRI evidence of intraluminal thrombus on T1, T2, and susceptibility-weighted imaging sequences
Spontaneous intracranial hypotension	Orthostatic headache, auditory muffling	Normal, or subdural collections	Low opening pressure	Normal	Pachymeningeal enhancement, sagging brain, subdural collections

CT: computed tomography; MRI: magnetic resonance imaging.

From: Schwedt TJ. Thunderclap Headache. *Continuum (Minneapolis)* 2015; 21:1058. DOI: [10.1212/CON.0000000000000201](https://doi.org/10.1212/CON.0000000000000201). Copyright © 2015 American Academy of Neurology. Reproduced with permission from Lippincott Williams & Wilkins. Unauthorized reproduction of this material is prohibited.

MRI sequences for RCVS

Magnetic resonance sequences	Indications and utility
<i>Necessary</i> T1, T2	<i>Suggested for everyone</i> 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*) DWI/ADC	To evaluate subtle aneurismal SAH or cortical SAH 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
<i>Elective</i> T1 with contrast (axial, coronal and sagittal)	<i>If clinical symptoms/signs are suggestive of alternative diagnosis</i> To exclude spontaneous intracranial hypotension
Cervical T1 fat-saturation + contrast	To exclude cervical artery dissection

ADC, apparent diffusion coefficient; 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.

Representative brain images from patients with RCVS are shown to highlight different lesion patterns. The numbers in parenthesis show the percentages of the lesion patterns; totals exceed 100% due to lesion combinations.

(A) No acute parenchymal lesion (24%). Normal axial DWI, GRE, and FLAIR images are shown. The hyperintense dot sign is present on FLAIR (far right, arrow).

(B) Border zone/watershed infarcts (25%). On the far left, DWI shows typical symmetric, posterior infarcts that spare the cortical ribbon. In the middle and on the far right, DWI shows widespread watershed infarcts.

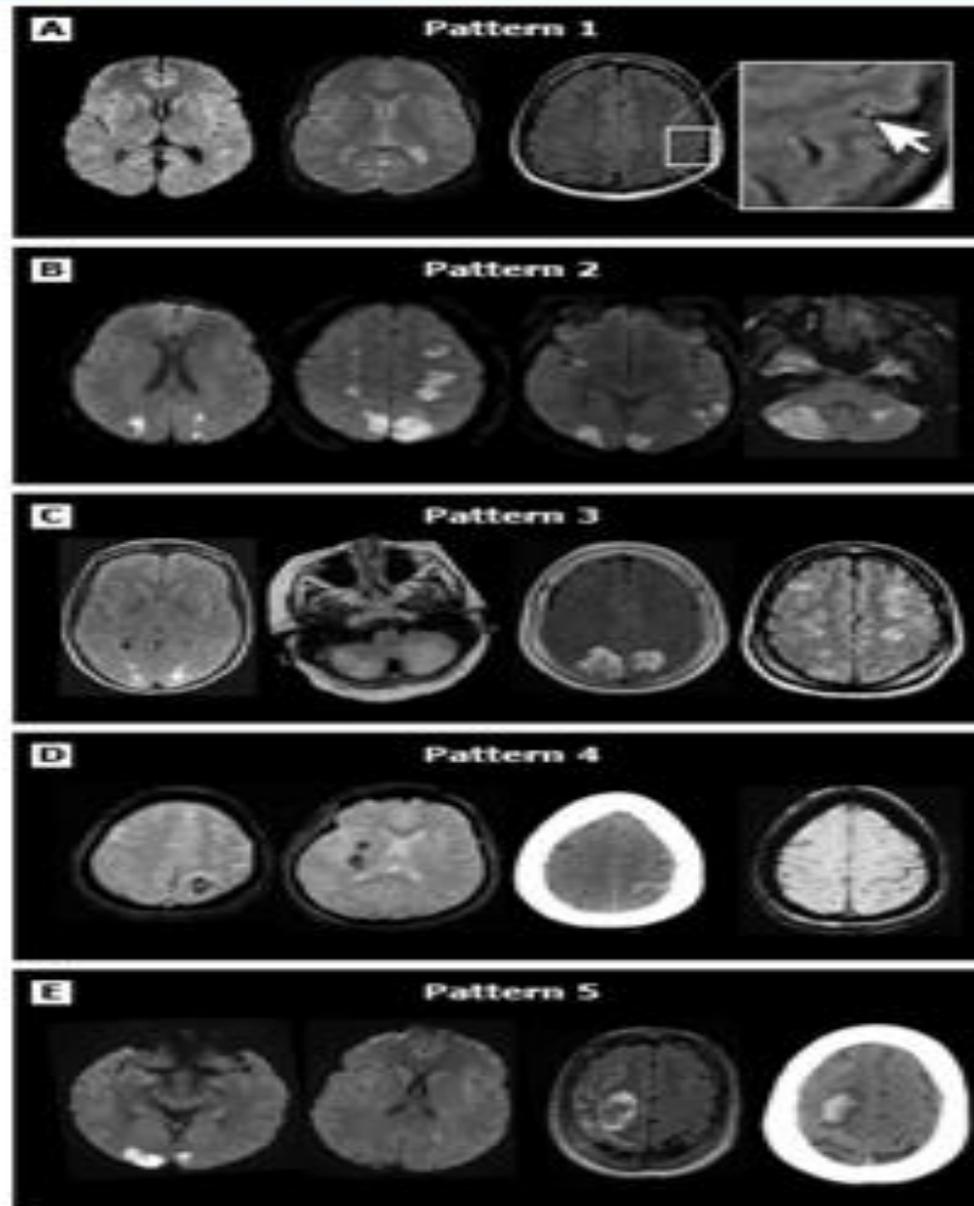
(C) Vasogenic edema (28%). Subcortical crescent-shaped T2-hyperintense lesions consistent with the posterior reversible encephalopathy syndrome are seen on FLAIR.

(D) Hemorrhagic lesions (42%). The two images on the left (axial GRE) show simultaneous lobar and deep intraparenchymal hemorrhages. The two images on the right show convexal subarachnoid hemorrhages on CT and axial GRE.

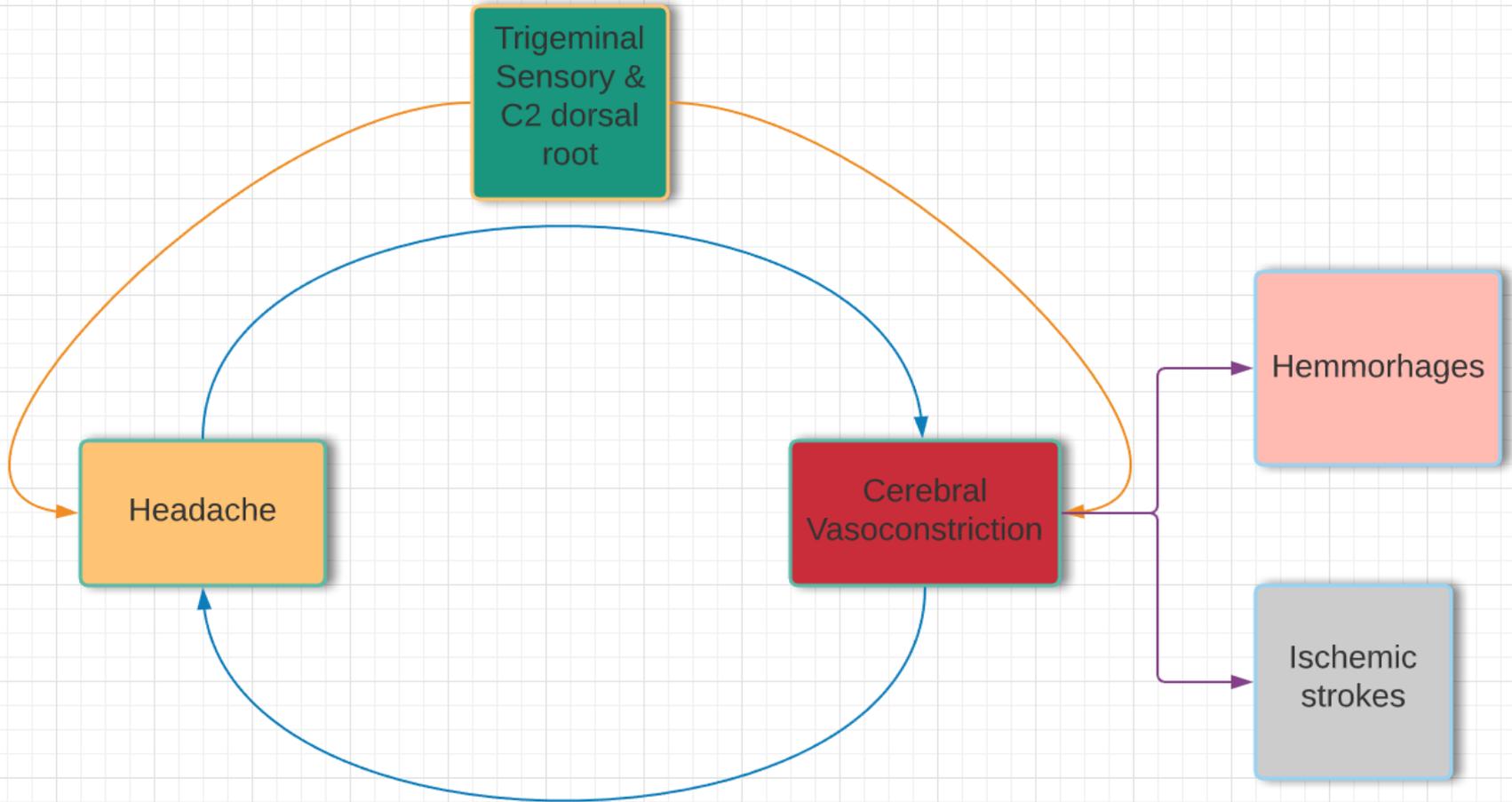
(E) Lesion combinations (28%). The two images on the left show bilateral watershed infarcts on DWI and the two images on the right show lobar as well as convexal subarachnoid hemorrhages on axial FLAIR and CT, all in the same patient.

RCVS: reversible cerebral vasoconstriction syndrome; DWI: diffusion-weighted images; GRE: gradient-echo; FLAIR: fluid-attenuated inversion recovery.

Brain lesions in reversible cerebral vasoconstriction syndrome (RCVS)



Pathogenesis



Management

- ❑ RCVS has no established therapy
- ❑ Symptomatic Therapy include:
 - ❑ Blood pressure control (Labetalol, Nicardipine)
 - ❑ Analgesics (NSAID's, Opioids)
 - ❑ Avoid Triggers
- ❑ Vasoconstriction: Relieved by pharmacological and intra-arterial vasodilation
 - ❑ Pharmacological : Brief course of Dantrolene and Serotonin antagonists
 - ❑ Vasodilation:
 - Intra-arterial administration of calcium blockers (Nicardipine, nimodipine) and PDE inhibitors (Milrinone)
 - Balloon angioplasty

Clinical Course & Prognosis

- ▣ Symptoms usually resolve within days to weeks
- ▣ Complications from stroke in 15-20 %
- ▣ Modified Rankin scale score of 0-2 at discharge
- ▣ Severe complication only in less than 5% cases.
- ▣ Complications include massive stroke, brain edema , severe morbidity and death.
- ▣ Recurrence occurs in approximately 5-6 % cases

Thank

You