Reversible cerebral vasoconstriction syndrome

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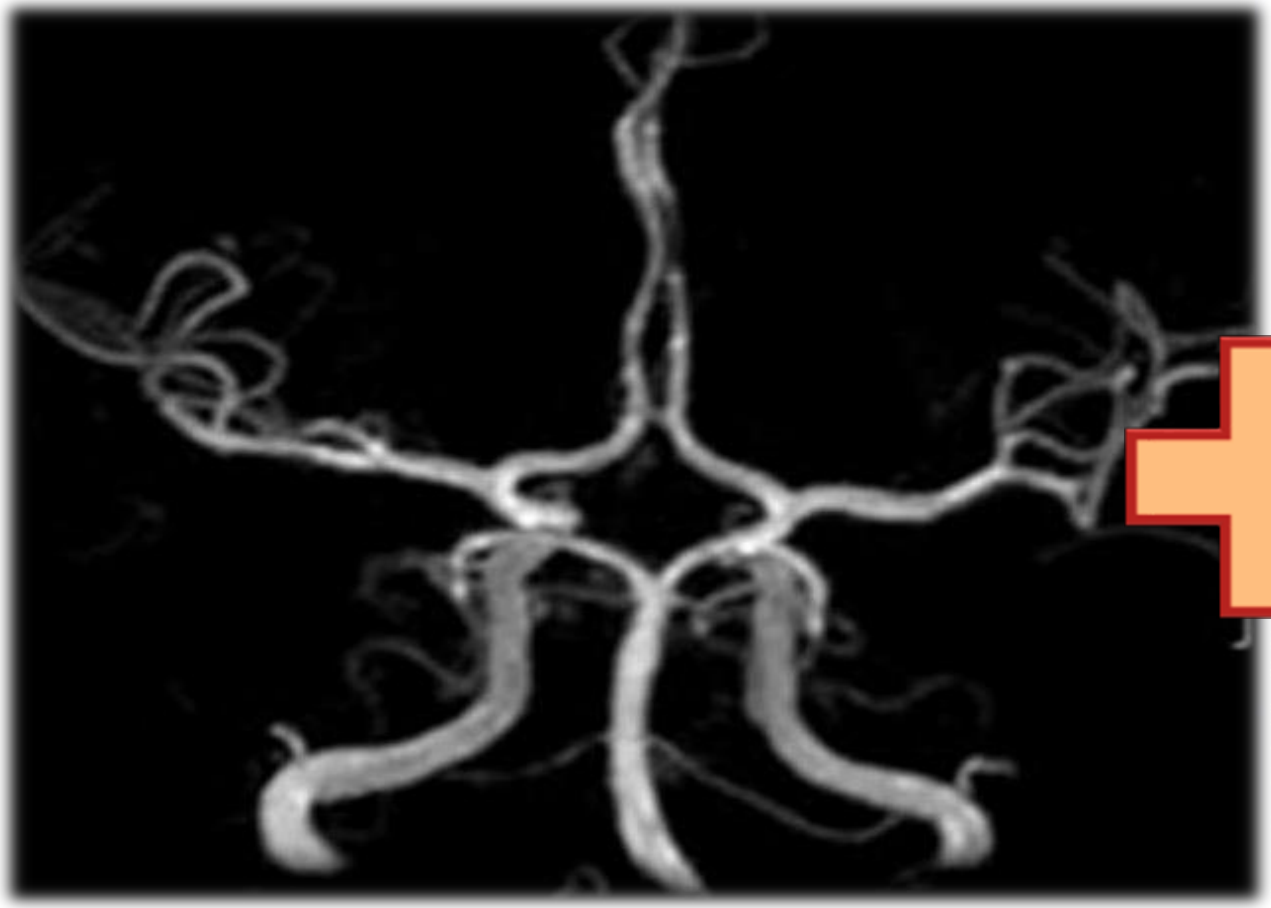


TERMINOLOGY

- Migrainous vasospasm or migraine angitis
- Call-Fleming syndrome(or Call Syndrome)
- Thunderclap headache associated with vasospasm
- Drug-induced cerebral arteritis
- Postpartum cerebral angiopathy
- Benign angiopathy of central nervous system
- Central nervous system pseudovasculitis

OBJECTIVES

- ✓ Introduction
- ✓ Pathophysiology
- ✓ Epidemiology
- ✓ Risk factors
- ✓ Clinical Features
- ✓ Evaluation and Diagnosis
- ✓ Laboratory findings
- ✓ Brain and neurovascular imaging
- ✓ Differential Diagnosis
- ✓ Management

Introduction

- Group of conditions that show reversible vasoconstriction with clinical manifestations that typically include thunderclap headache and less commonly focal neurological deficits related to brain edema, stroke and seizure.
- Clinical outcome is usually benign although major strokes can result in significant disability and death in a minority of patients.

Definition

Severe headaches, with or without other acute neurological symptoms (seizures, strokes, and non-aneurysmal subarachnoid hemorrhage)

AND diffuse segmental constriction of cerebral arteries which resolves spontaneously in 1-3 months

Diagnostic criteria for reversible cerebral vasoconstriction syndrome (adapted from the International Headache Society diagnostic criteria for "acute reversible cerebral angiopathy" and the criteria proposed in 2007 by Calabrese *et al*[1, 2])

- Acute and severe headache (often thunderclap headache) with or without focal neurological deficits or seizures
- Monophasic course without new symptoms more than 1 month after clinical onset
- Segmental vasoconstriction of cerebral arteries demonstrated by angiography (MRA, CTA or catheter)
- Exclusion of subarachnoid haemorrhage due to a ruptured aneurysm
- Normal or near normal CSF (protein <1 g/l, white cells $<15/mm^3$, normal glucose)
- Complete or marked normalisation of arteries demonstrated by a repeat angiogram (MRA, CTA or catheter) after 12 weeks, although they may be normal earlier

HISTORICAL ACCOUNT

- ✓First case report in 1960
- ✓In 1983, French researchers published a case series of 11 patients, terming the condition acute benign cerebral angiopathy.
- ✓Gregory Call and Marie Fleming were the first two authors of a report in which doctors from Massachusetts General hospital, led by C. Miller Fisher, described 4 patients, alongside 12 previous case studies, with the characteristic symptoms and abnormal cerebral angiogram findings.
- ✓A 2007 review by Leonard Calabrese and colleagues proposed the
- ✓name reversible cerebral vasoconstriction syndrome, which has since gained widespread acceptance.

HISTORICAL ACCOUNT

- The adoption of the broad term RCVS, along with its main clinical and imaging features, has encouraged relatively large retrospective and prospective studies that have helped characterize the syndrome.

Pathophysiology

- Key mechanism: Transient alteration in Cerebral Vascular tone

1. Sympathetic overactivity
2. Endothelial dysfunction
3. Oxidative stress

Sympathetic Overactivity

- Supported by association with hypertensive surges, pheochromocytoma and after ingestion of sympathomimetic vasoactive substances

Endothelial Dysfunction

- Endothelial progenitor cells (EPCs) are biomarkers of vascular function
- Patients with RCVS have reduced circulating CD34+KDR+ (EPCs)

Oxidative stress

- Urine 8-iso-prostaglandin F2α is Potent vasoconstrictor and oxidative biomarker
- 8-Iso-prostaglandin F2α is elevated in patients with RCVS.

EPIDEMIOLOGY

- True incidence unknown.
- Female to male ratio ranges from 2:1 to 10:1 depending on the case series.
- Mean age is 42-44 with an age range of 4 months to 65 years.
- No specific ethnicity is involved.
- Cases reported in all continents.
- Recently being increasingly reported due to
  - increasing awareness.
  - Widespread use of CT and MR angiography
  - Escalating use of illicit drugs and vasoconstrictive medications

RISK FACTORS

- ✓Pregnancy
- ✓Migraine
- ✓Vasoactive drugs
- ✓Neurosurgical procedures
- ✓Hypercalcemia
- ✓Unruptured saccular aneurysms
- ✓Cervical artery dissection
- ✓Cerebral venous thrombosis
- ✓others

- No common pathophysiological theme
- May reflect biases of investigators in attributing the risk.
- Epidemiological studies so far did not show any causal relationship between the vasoactive drugs and the proposed mechanism of transient vasculitis or intrathecal inflammation.

BOX 37.1 Conditions Associated With Reversible Cerebral Vasoconstriction Syndrome

IDIOPATHIC

No identifiable associated or precipitating factor
Headache disorders (primary thunderclap headache, primary exertional headache, primary headache associated with sexual activity, primary cough headache, migraine)

EXPOSURE TO MEDICATIONS, DRUGS, AND BLOOD PRODUCTS

Antimigraine medications (triptans, ergot derivatives, isometheptene)
Cough and cold suppressants (phenylpropanolamine, pseudoephedrine)
Antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin-noradrenaline reuptake inhibitors [SNRIs])
Adrenergic medications (epinephrine, methergine, bromocriptine, lisuride)
Illicit drugs (marijuana, cocaine, ecstasy, lysergic acid diethylamide)
Blood products (red blood cell transfusion, erythropoietin, intravenous immune globulin)
Hormonal agents (oral contraceptives, ovarian stimulation)
Chemotherapeutic agents (tacrolimus [FK-506], cyclophosphamide)
Other (licorice, khat leaves, ma huang, Chinese herbal remedies, eucalyptus, methylergonovine, nicotine patches, indomethacin, interferon-α)

PREGNANCY AND PUERPERIUM

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

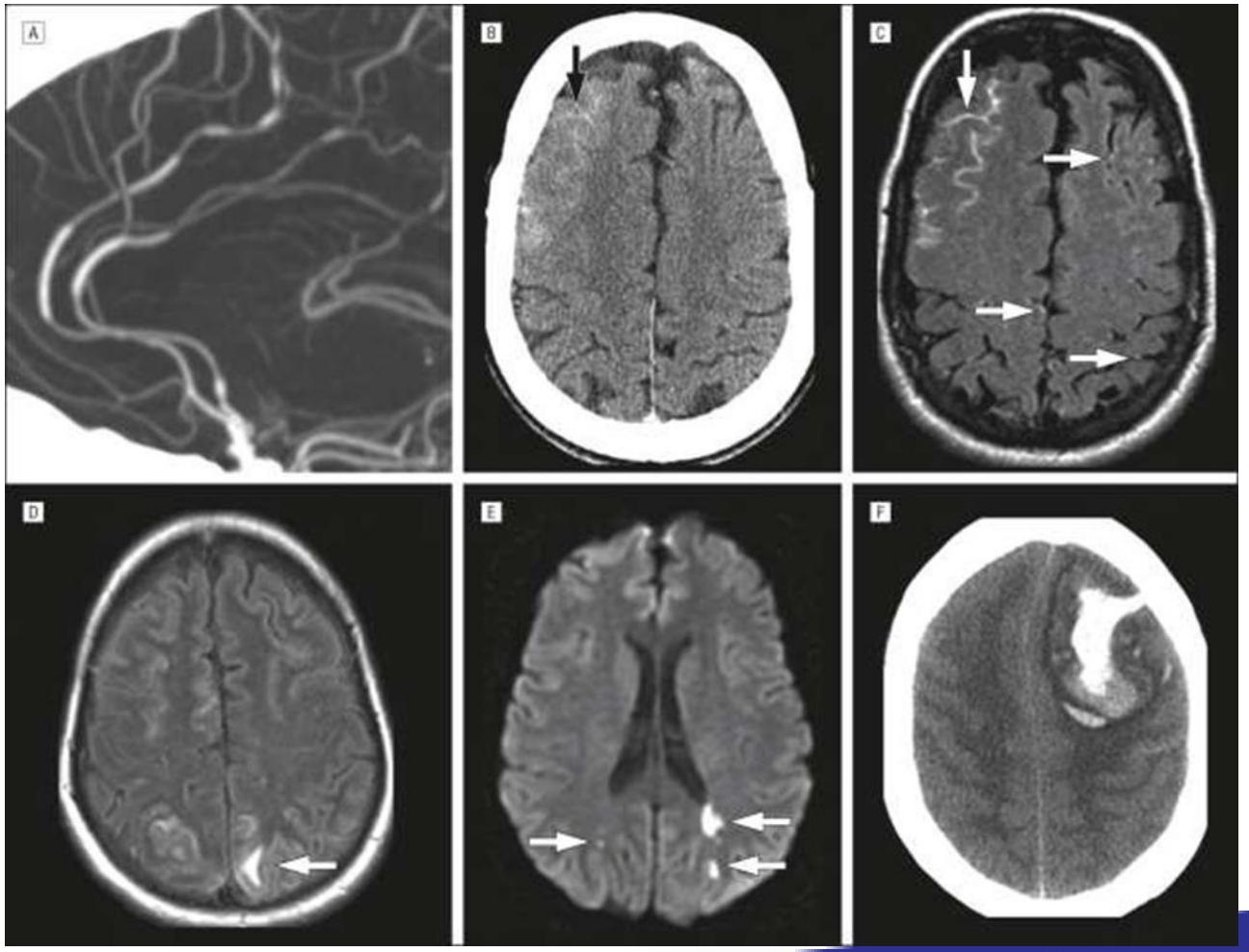
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME

MISCELLANEOUS

High altitude, cold water exposure, hypercalcemia, porphyria, thrombotic thrombocytopenic purpura, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma, cerebral venous sinus thrombosis, post-carotid endarterectomy, neurosurgical procedures, cervical arterial dissection

CLINICAL FEATURES

- **Thunderclap headache – usually very dramatic**
- **Seizures**
- **1/3 patients develop ischemic strokes/Hemorrhagic strokes or reversible cerebral edema**



HEADACHE

- Only symptom in about 50-75% patients.
- Less than 10% of patients will have subacute or low severity headache.
- Absence of Headache at onset is exceptional.

- Location: Diffuse or Occipital region or vertex region
- Nausea + photosensitivity
- Usually different character from their migraine headache
- Relapsing remitting course.

Trigger factors for Thunderclap headache in RCVS

- Orgasm
- Physical Exertion
- Acute Stressful or Emotional situations
- Straining
- Coughing
- Sneezing
- Bathing
- Swimming

SEIZURES

- Occurs in 0-21% of patients at the time of presentation
- Usually Generalized tonic clonic seizures
- Recurrent seizures are rare

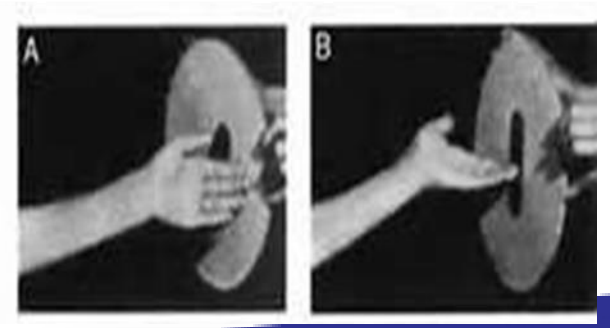
Focal Neurological Syndromes

- %63-9in published case series.
- Higher incidence in inpatient case series

Patients suffering from Simultanagnosia and Balint's syndrome will only report the features they are presently looking at but will not be able to understand the contents of the scene.

- Hemiplegia
- Tremor
- Hyperreflexia
- Ataxia
- Aphasia

- Visual defects including scotomas, blurring, hemianopia, cortical blindness are common.
- Many patients show features of Balint Syndrome.



CLINICAL FEATURES CONTD…

- Systemic examination is usually unrevealing
- Vital signs at presentation may show high blood pressure – secondary

Resolution:

✧**Headache – days to weeks**

✧**Visual and other focal symptoms - days to weeks**

✧**Angiographic resolution – upto 3 months**

✧**<5% experience progressive cerebral arterial vasoconstriction resulting in massive strokes, cerebral edema, severe neurological morbidity or death.**

EVALUATION AND DIAGNOSIS

- Clinical characteristics
- Brain imaging
- Angiographic features

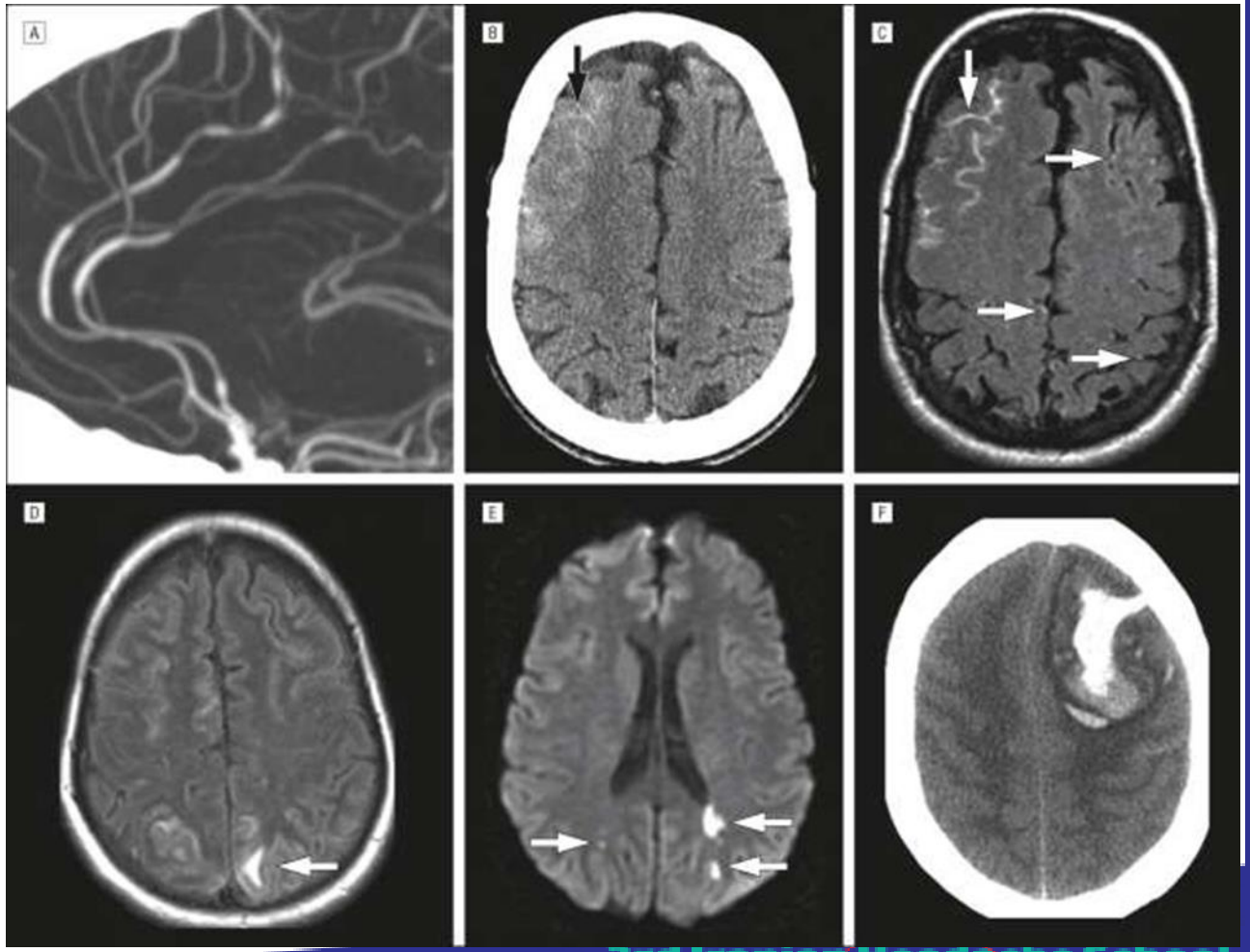
Laboratory Findings

- Routine Blood work and tests for inflammation are typically normal in patients with RCVS.
- Urine Vanillylmandelic acid and 5-Hydroxyindoleacetic acid are useful to rule out systemic diseases and evaluate for vasoactive tumors (Pheochromocytoma, Carcinoid)
- Serum and urine toxicology studies to investigate for vasoactive drugs such as
- methamphetamine and cocaine.
- CSF findings are normal (protein <60 mg/dl, <5WBC/mm3) in more than 85% of patients with minor abnormalities resulting from ischemic and hemorrhagic strokes.
- No role for brain or temporal artery biopsy unless the diagnosis remains unclear despite a thorough evaluation

BRAIN IMAGING

- 30-70% - No abnormality on initial scans despite having widespread cerebral vasoconstriction.
- 75% of admitted patients develop parenchymal lesions.

1. Ischemic stroke
2. Cortical surface subarachnoid hemorrhage
3. Reversible vasogenic brain edema
4. Parenchymal hemorrhage
5. Any combination of above



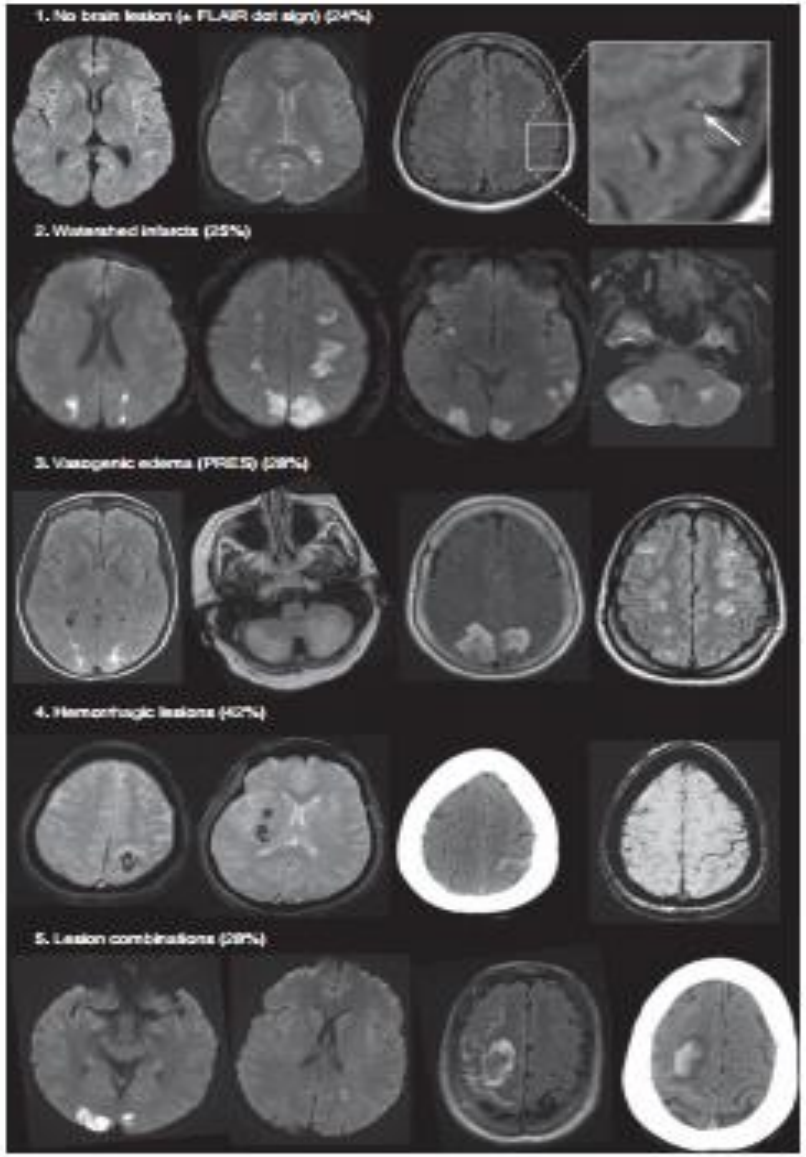
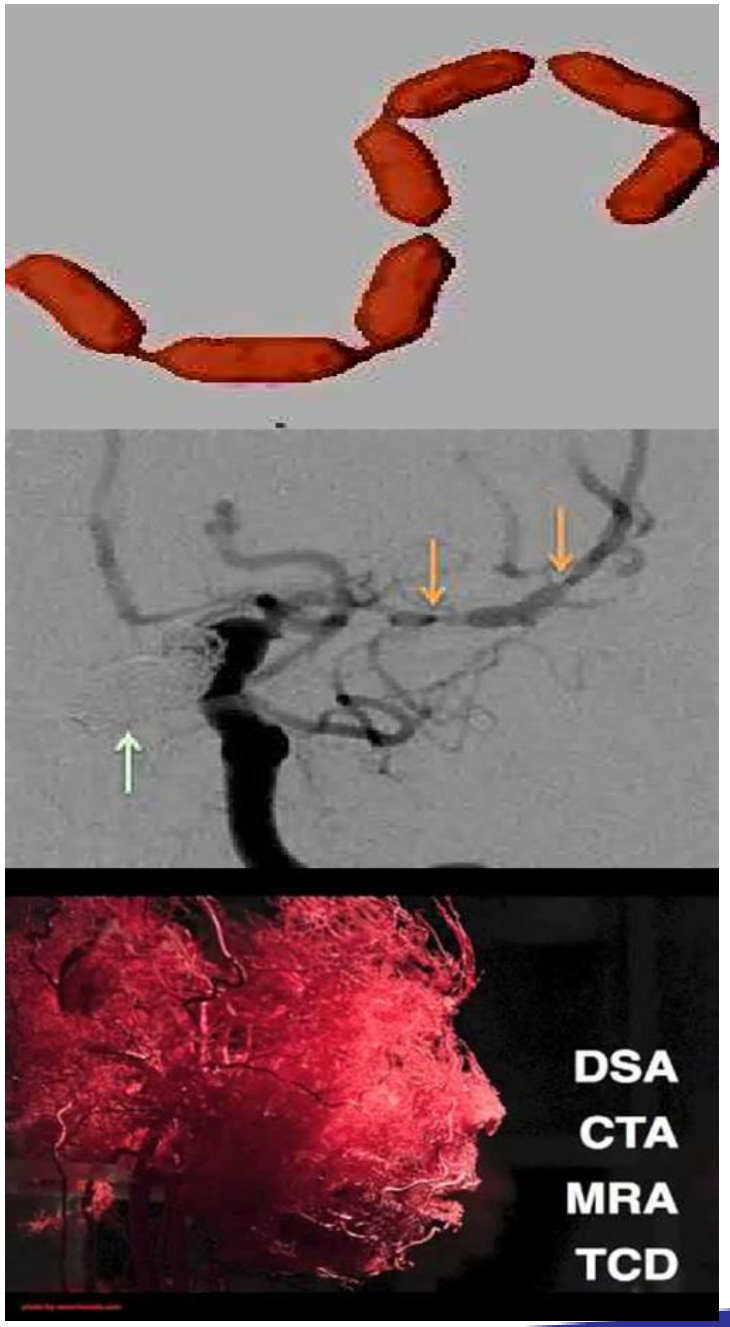


Fig. 97.2. Brain lesions in reversible cerebral vasoconstriction syndrome (RCVS). Representative brain images from patients with RCVS are shown to highlight different lesion patterns. The numbers in parentheses show the percentages of the lesion patterns; totals exceed 100% due to lesion combinations. *Pattern 1 (24%)*, no acute parenchymal lesion. Normal axial diffusion-weighted (DWI), gradient-echo (GRE), and fluid-attenuated inversion recovery (FLAIR) images are shown. The hyperintense dot sign is present on FLAIR (far right, *arrow*). *Pattern 2 (25%)*, *border zone/watershed infarcts*. 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. *Pattern 3 (28%)*, vasogenic edema. Subcortical crescent-shaped T2-hyperintense lesions consistent with the posterior reversible encephalopathy syndrome are seen on FLAIR. *Pattern 4 (42%)*, *hemorrhagic lesions*. The 2 images on the left (axial GRE) show simultaneous lobar and deep intraparenchymal hemorrhages. The 2 images on the right show convexal subarachnoid hemorrhages on computed tomography (CT) and axial GRE. *Pattern 5 (28%)*, *lesion combinations*. The 2 images on the left show bilateral watershed infarcts on DWI, and the 2 images on the right show lobar as well as convexal subarachnoid hemorrhages on axial FLAIR and CT, all in the same patient. (From Singhal AB, Topcuoglu MA, Fok JW, et al. Reversible cerebral vasoconstriction syndromes and primary angiitis of the central nervous system: clinical, imaging, and angiographic comparison. *Ann Neurol*. 2016;79(6):882–894.)



Neurovascular imaging

- Abnormal cerebral angiography is the primary diagnostic feature.
- Dynamic and progress proximally resulting in a "sausage on a string" appearance.
- Smooth, tapered narrowing followed by abnormal dilated segments of the 2nd and 3rd order cerebral arteries is characteristic.
- CTA, MRA, DSA are preferred.
- TCD might be useful for monitoring the progression of vasoconstriction.
- Angiography can be false negative at the beginning due to distal vasoconstriction.

DIFFERENTIAL DIAGNOSIS

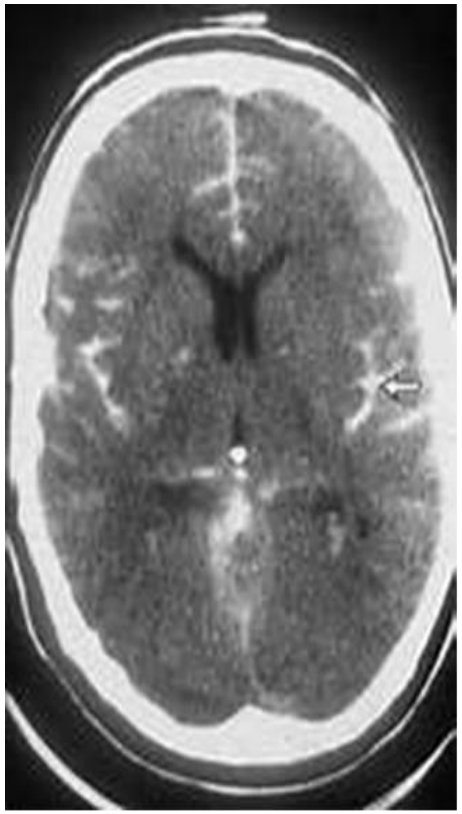
Conditions associated with reversible cerebral vasoconstriction syndromes
Pregnancy ("Postpartum angiopathy")
Headache disorders
Primary thunderclap headache
Migraine
Medications, drugs, and biologics
Antimigraine agents (sumatriptan and other triptans, isometheptene, ergotamine tartrate, methylergonovine maleate)
Cough and cold suppressants (phenylpropanolamine, pseudoephedrine)
Diet pills (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 (erythropoietin, indomethacin, intravenous immune globulin, interferon alpha, nicotine patches, red blood cell transfusions, licorice, ovarian stimulation, oral contraceptive pills)
Miscellaneous
Hypercalcemia, porphyria, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma, carotid endarterectomy, cervical artery dissection, neurosurgical procedures, carotid glomus tumor, tonsillectomy, neck surgery, high altitude, cerebral venous thrombosis

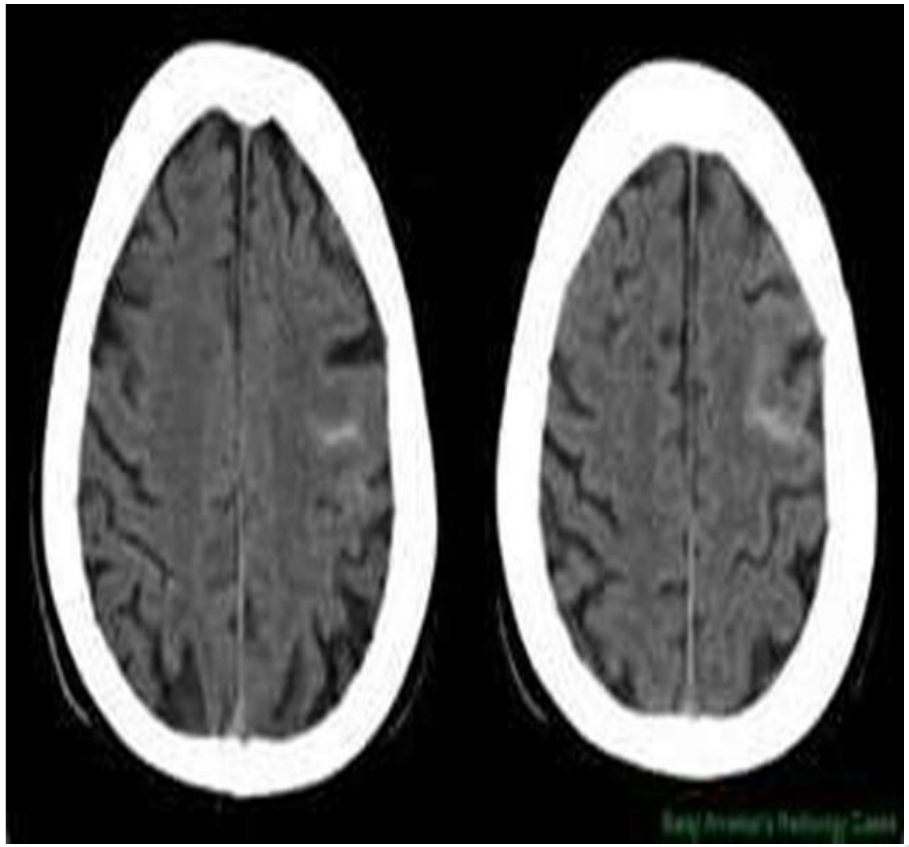
Etiologies of thunderclap headache
Subarachnoid hemorrhage
Sentinel headache
Reversible cerebral vasoconstriction syndromes
Cerebral venous thrombosis
Cervical artery dissection
Spontaneous intracranial hypotension
Pituitary apoplexy
Orgasmic headache associated with sexual activity
Retrodival hematoma
Ischemic stroke
Acute hypertensive crisis
Colloid cyst of the third ventricle
Infections (eg, acute complicated sinusitis)
Primary thunderclap headache

Differences between SAH and RCVS

- Recurrent thunderclap headache favors RCVS.

- Superficial location of small SAH with diffuse cerebral vasoconstriction favors the diagnosis of RCVS





RCVS SAH	Aneurysmal SAH
No evidence of ruptured aneurysm or vascular malformation	Plausible ***target lesion*** identified
Diffuse and disproportionate extent of cerebral vasoconstriction relative to amount of SAH	Severity of ***vasospasm correlates*** with amount of hemorrhage
Sausage on string appearance of alternating areas of segmental vasoconstriction preferentially involving distal 2nd- and 3rd-order cerebral branches	**Smooth, long segmental narrowing** for proximal arteries at circle of Willis
Development of vasoconstriction in first 4–5 days after symptom onset, or **persistence past 3 weeks**	Development of vasospasm peaking between **4and 14 day**s after hemorrhage

Differences between primary thunderclap headache and RCVS

- Both are thought to belong to the same spectrum of disorders.
- Thunderclap headache with no imaging or angiographic vasoconstriction favor the diagnosis of Primary thunderclap headache.

RCVS vs Migraine
Is RCVS simply a severe Migraine attack?

- Migraine is Primary headache; Headache in RCVS is Symptomatic
- Migraine has vascular and neuronal basis
- Angiogram in Migraine is invariably normal
- Migraine recurs for years whereas RCVS rarely recurs
- Only 25% patients with RCVS have prior migraine
- Misdiagnosis can lead to inappropriate use of ant migraine agents like triptans which can exacerbate vasoconstriction and stroke.

RCVS Vs. MIGRAINE

RCVS differentiates from Migraine as

1. it rarely recurs,
2. the abrupt onset of headache is quite different from migraine and
3. brain imaging and angiographic abnormalities are inconsistent with migraine and persist for several weeks.

DDx for ANGIOGRAPHIC ABNORMALITIES

- Intracranial Atherosclerosis
- Infectious arteritis
- Vasculits
- Moyamoya disease
- Fibromuscular dysplasia

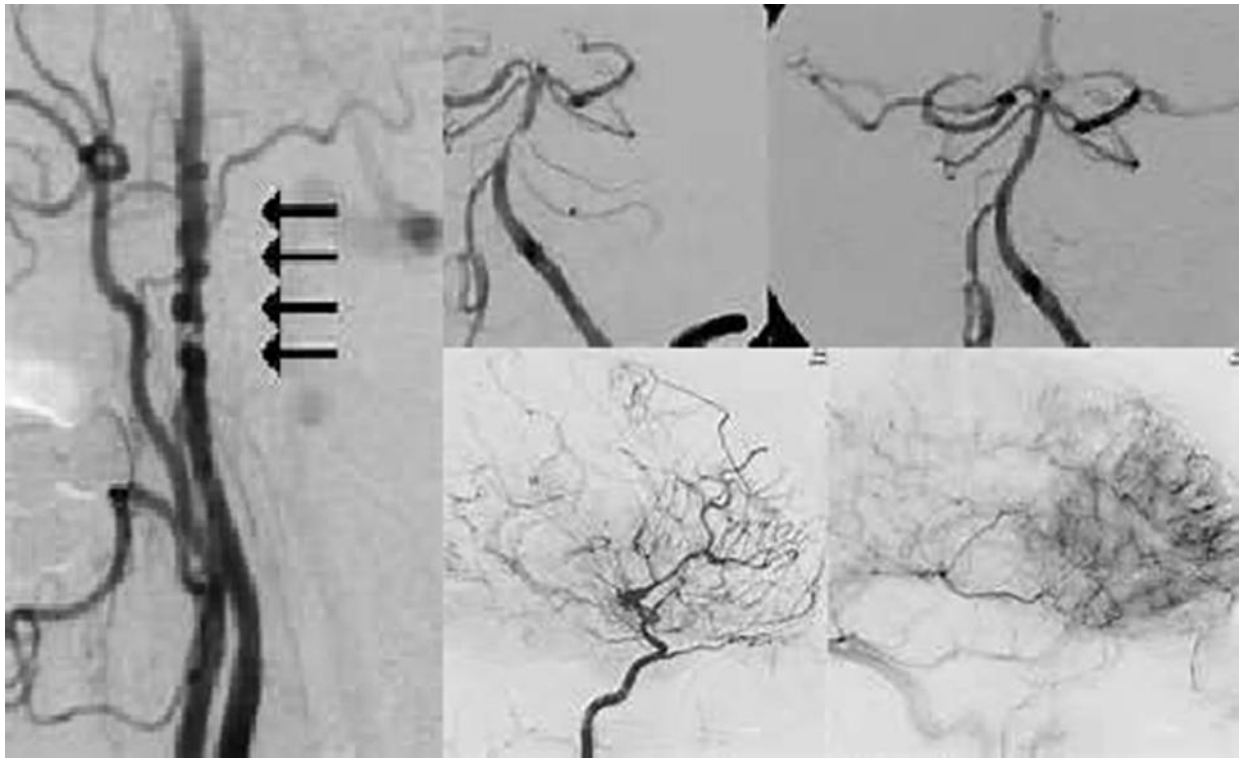
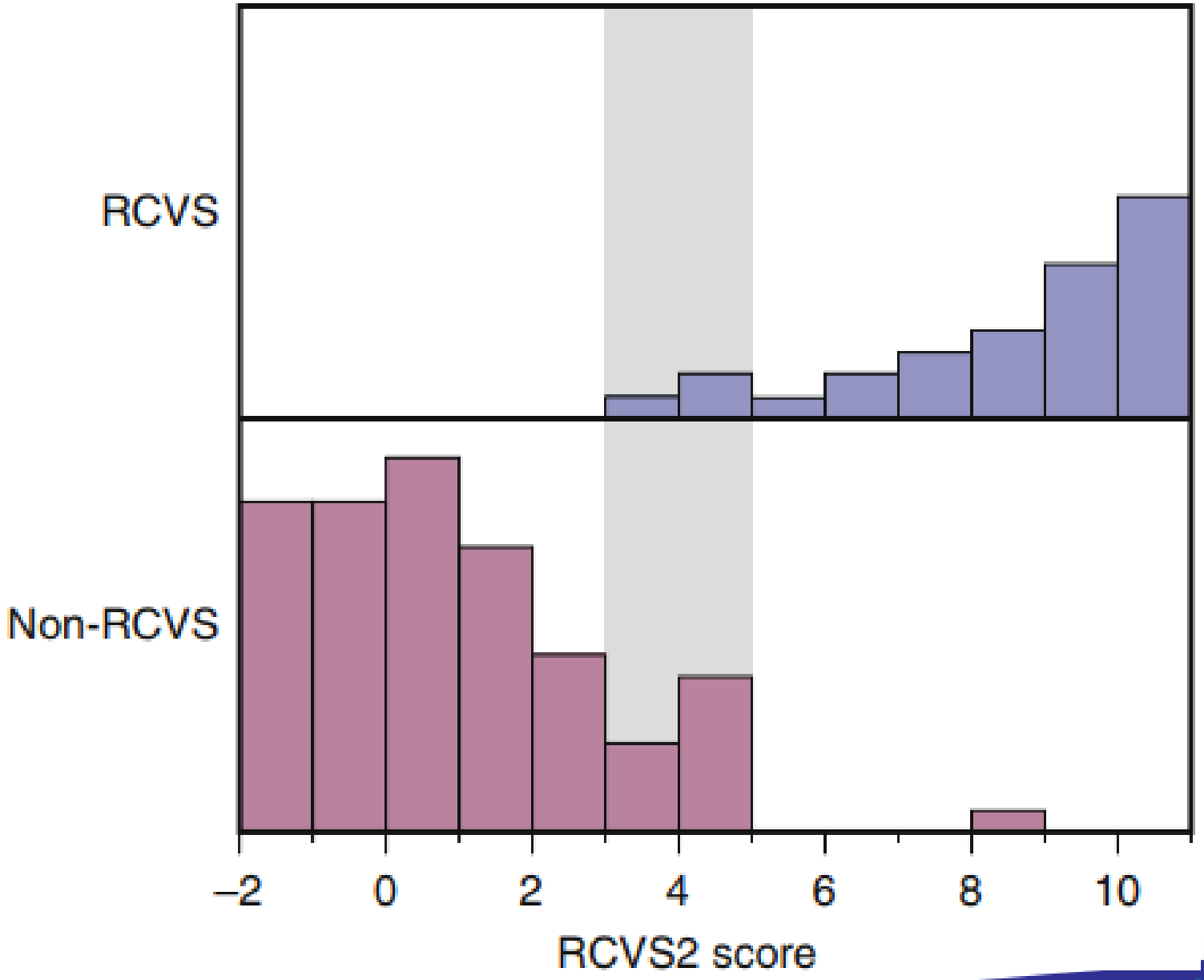


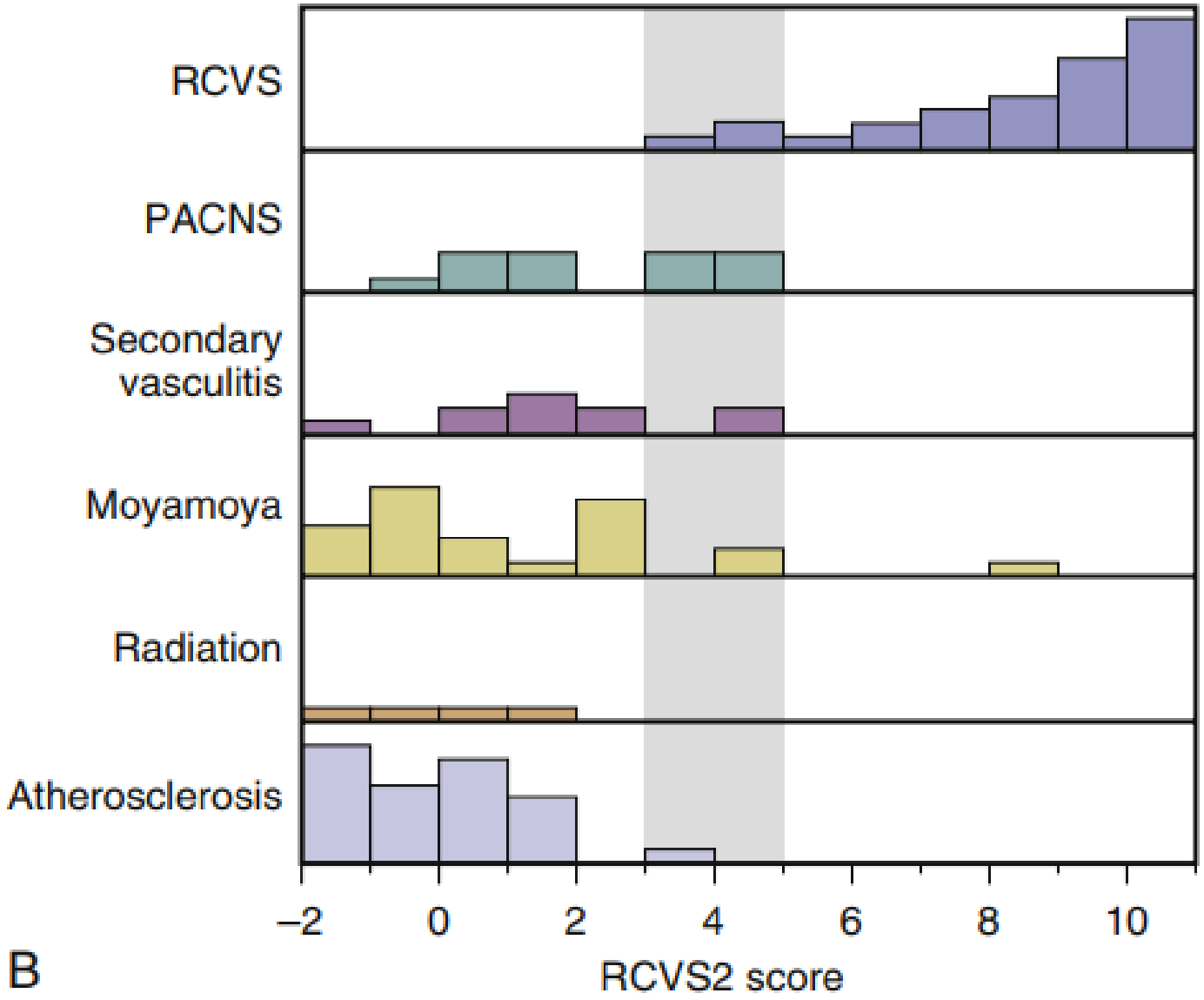
TABLE 37.1 The RCVS2 Score.

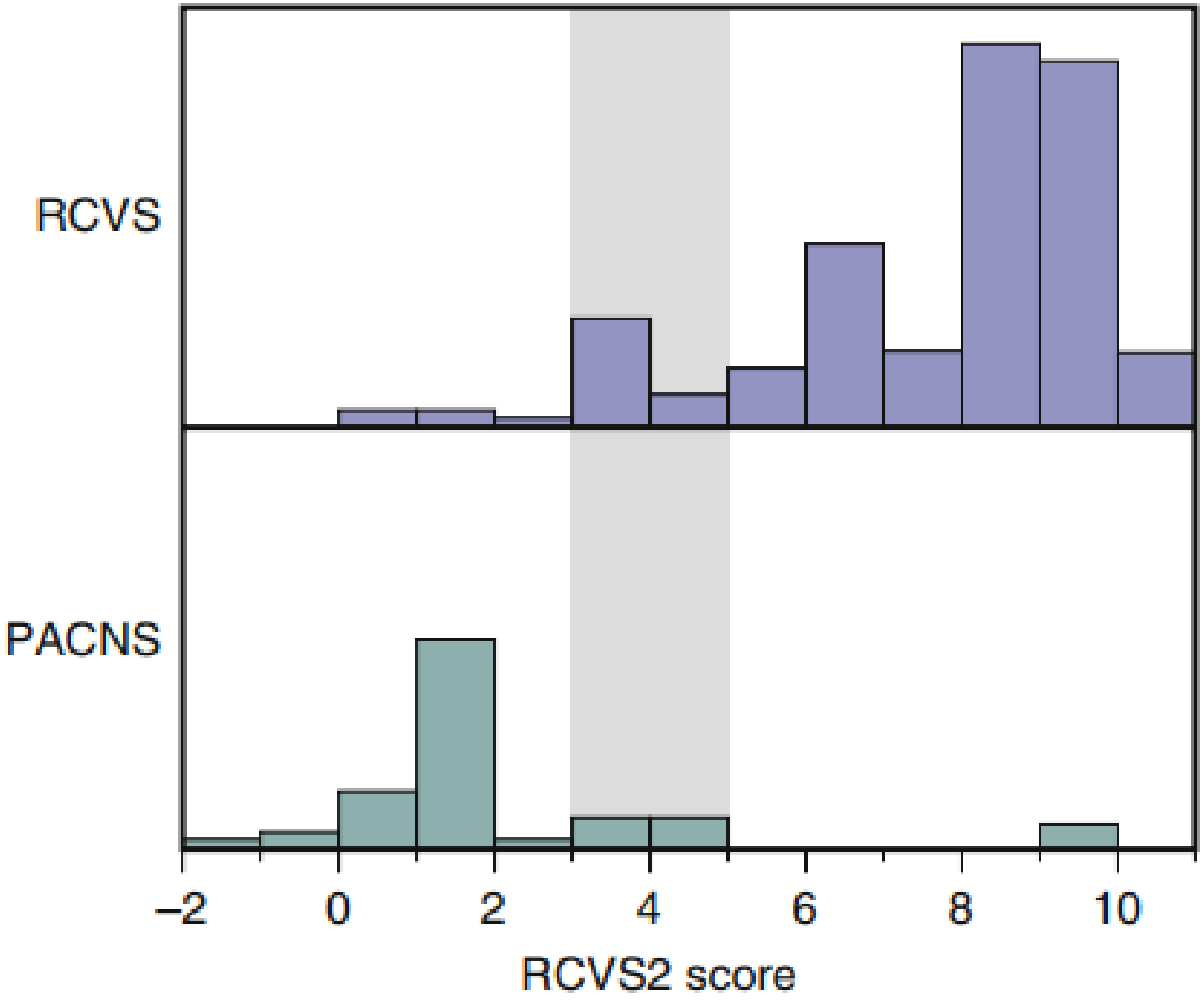
Criteria	Value
RECURRENT OR SINGLE TCH	
Present	5
Absent	0
CAROTID ARTERY (INTRACRANIAL)	
Affected	–2
Not affected	0
VASOCONSTRICTIVE TRIGGER	
Present	3
Absent	0
SEX	
Female	1
Male	0
SUBARACHNOID HEMORRHAGE	
Present	1
Absent	0

RCVS, Reversible cerebral vasoconstriction syndromes; *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[7]:e639–e647.

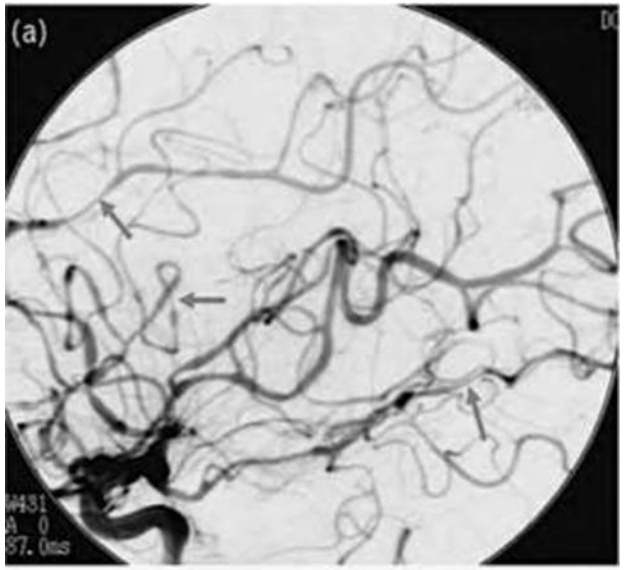


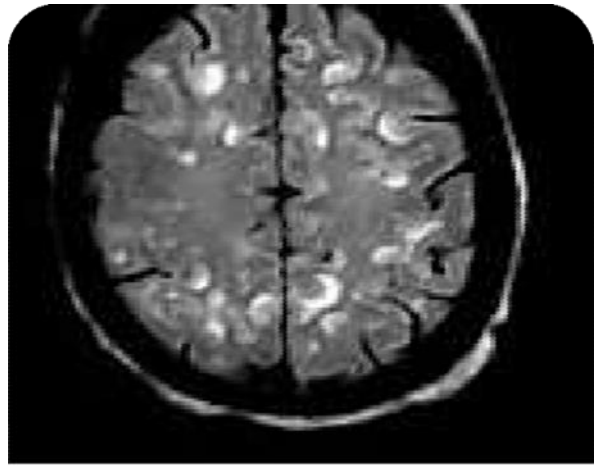


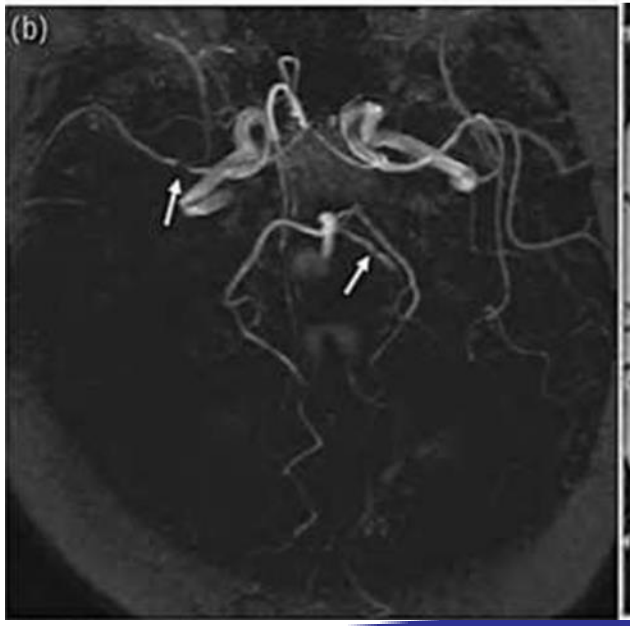


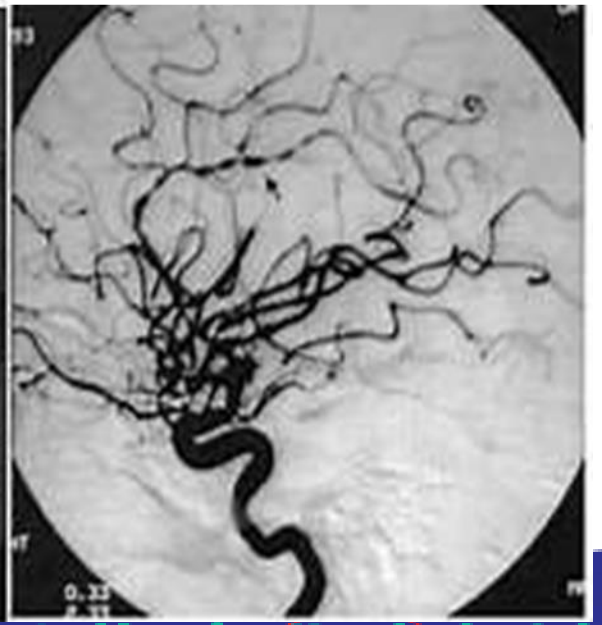
PACNS

- Arterial narrowing is irregular
- Accumulating T2-hyperintense brain lesions on neuroimaging
- Leptomeningeal enhancement
- Scattered deep infarcts





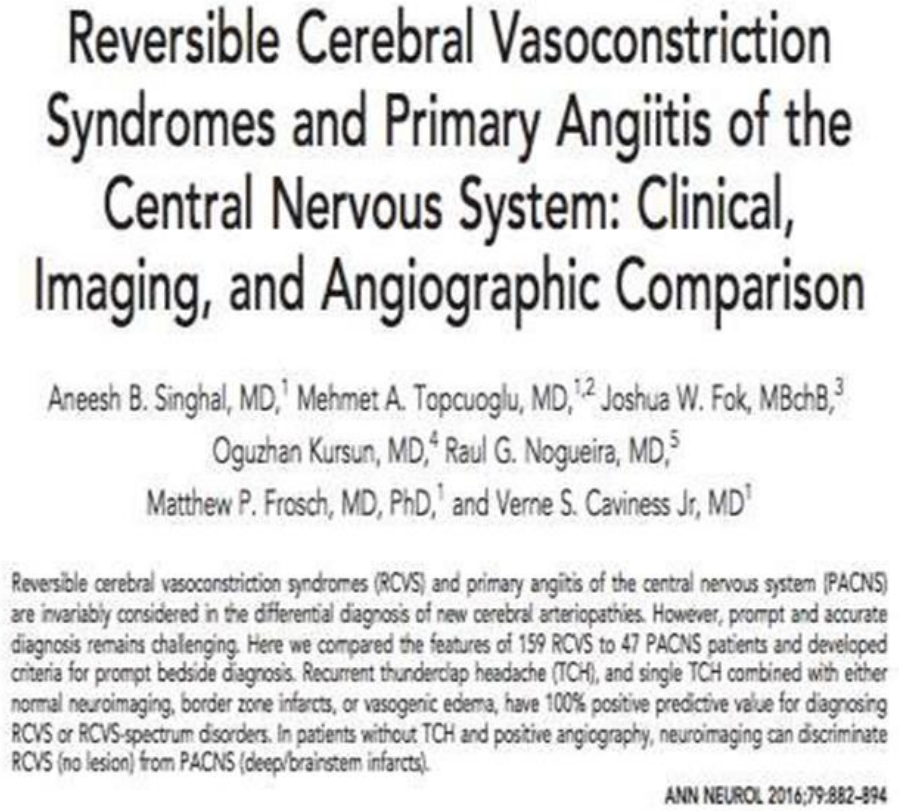




RCVS VS. PACNS

- Recurrent thunderclap headache.
- Single thunderclap headache combined with either normal neuroimaging or borderzone infarcts or vasogenic edema.
- No thunderclap headache but abnormal angiography and no brain lesions on neuroimaging(the absence of brain lesions virtually rules out PACNS).

**Specificity of 98-100% and a similarly high PPV
**Can be used as a bedside tool without cerebral angiography



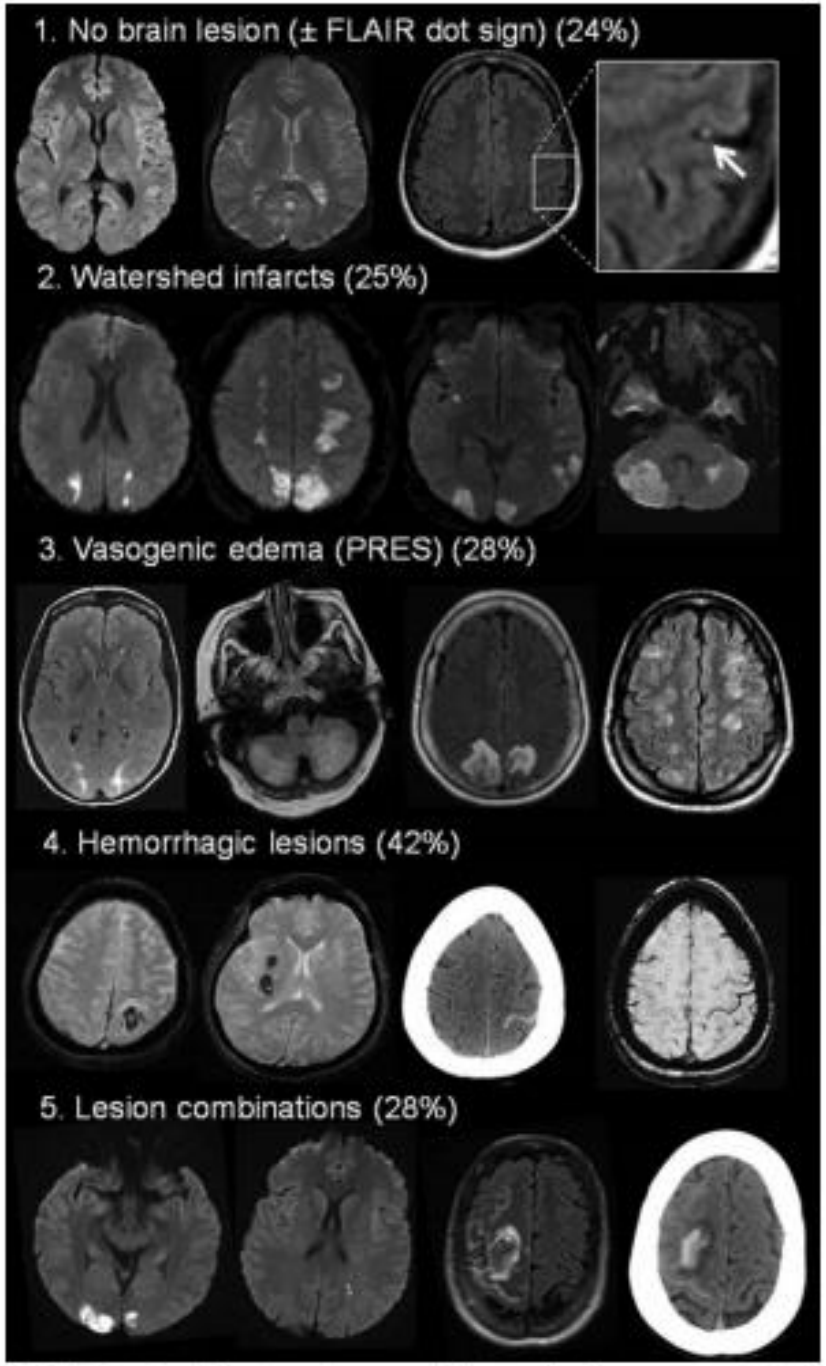
Reversible Cerebral Vasoconstriction Syndromes and Primary Angiitis of the Central Nervous System: Clinical, Imaging, and Angiographic Comparison

Aneesh B. Singhal, MD,[1] Mehmet A. Topcuoglu, MD,[1,2] Joshua W. Fok, MBchB,[3] Oguzhan Kursun, MD,[4] Raul G. Nogueira, MD,[5] Matthew P. Frosch, MD, PhD,[1] and Verne S. Caviness Jr, MD[1]

Reversible cerebral vasoconstriction syndromes (RCVS) and primary angiitis of the central nervous system (PACNS) are invariably considered in the differential diagnosis of new cerebral arteriopathies. However, prompt and accurate diagnosis remains challenging. Here we compared the features of 159 RCVS to 47 PACNS patients and developed criteria for prompt bedside diagnosis. Recurrent thunderclap headache (TCH), and single TCH combined with either normal neuroimaging, border zone infarcts, or vasogenic edema, have 100% positive predictive value for diagnosing RCVS or RCVS-spectrum disorders. In patients without TCH and positive angiography, neuroimaging can discriminate RCVS (no lesion) from PACNS (deep/brainstem infarcts).

ANN NEUROL 2016;79:882–894

Variable	RCVS	PACNS
Incidence	?	2.4/1,000,000
Age	40-20	60-40
Sex	F>>M	M>F
Onset	Acute (sec to min)	Typically subacute to chronic
Headache	Often Thunderclap	Dull aching
CSF analysis	Normal or near normal	Abnormal 80-90%
CT/MRI	Normal in Majority If complicated show watershed infarcts, ICH, SAH , PRES	%97abnormal, infarction ()53% ICH, Gadolinium enhancing lesions ()33.3%
Neurovascular Imaging	Sausage on a string appearace Reversible	%90-50angiography positive String and bead appearance Mostly Irreversible
Brain biopsy	Always negative	Gold standard for diagnosis



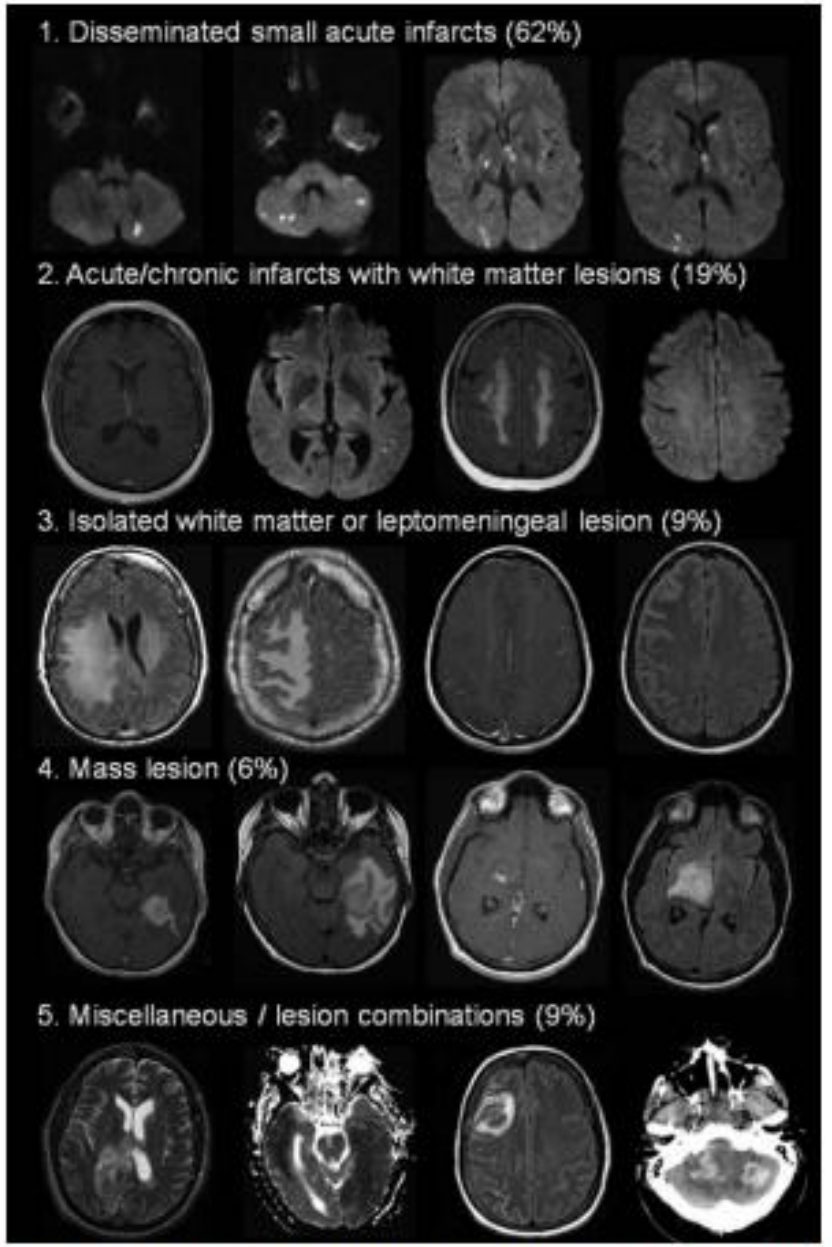


FIGURE 2: Brain lesions in primary angiitis of the central nervous system (PACNS). Representative brain images from patients with PACNS highlight different lesion patterns. The

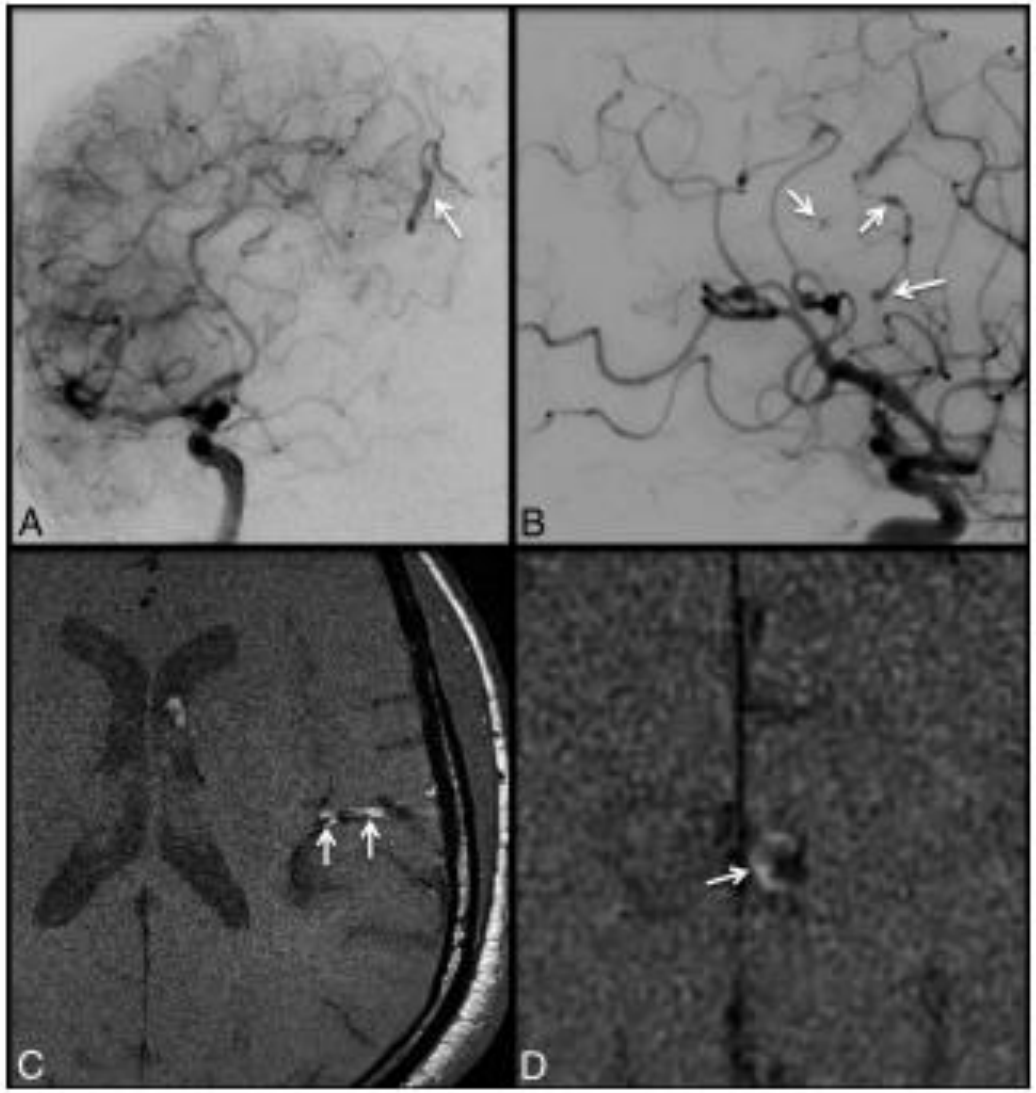


FIG 4. A 59-year-old man with a history of seizures, who was subsequently found to have multifocal infarcts in several vascular territories (not shown). Subsequent catheter angiograms (*A* and *B*) demonstrate marked irregularity of branches of the distal right anterior cerebral artery (*white arrow, A*) and left MCA (*white arrows, B*), with multifocal areas of narrowing and saccular and fusiform dilation. On axial T1 precontrast high-resolution VWI (*C*), there is intrinsic T1 mural hyperintensity in involved MCA (*white arrows*) and anterior cerebral artery branches. On axial T1 postcontrast high-resolution VWI (*D*), there are accompanying areas of eccentric vessel wall enhancement (*white arrow, D*).

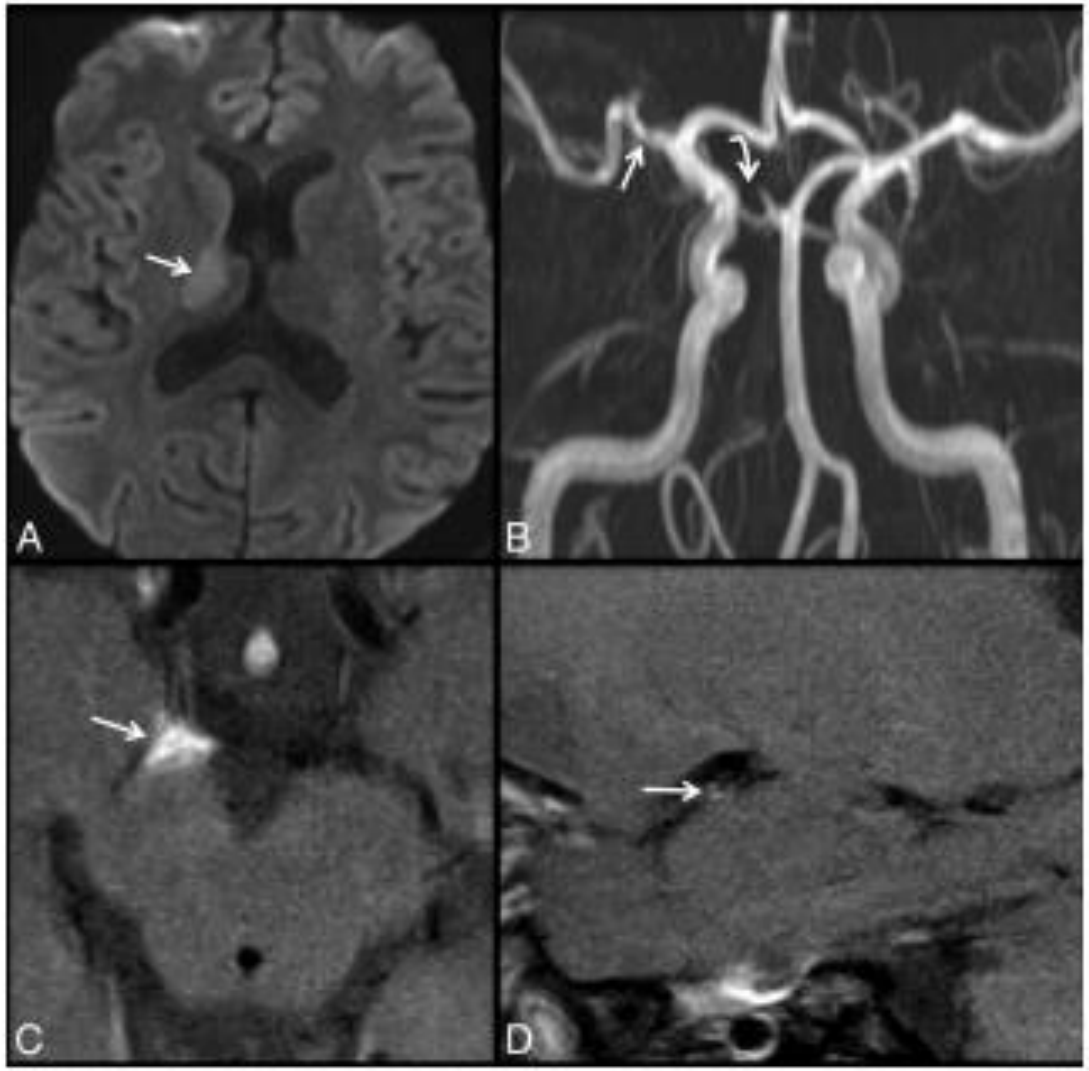


FIG 2. A 35-year-old man with a history of Behçet vasculitis who presented with left-sided weakness. DWI (*A*) demonstrates an acute infarct involving the right thalamus and posterior limb of the internal capsule (*white arrow*). Coronal 3D reformat of TOF MRA (*B*) reveals irregularity and narrowing of the M1 arterial segment of the right MCA (*white arrow*) and occlusion or high-grade stenosis of the P1 arterial segment of the right PCA (*curved white arrow*). On axial T1 postcontrast high-resolution VWI (*C*), there is prominent enhancement and enlargement of the right posterior cerebral artery (*white arrow*). Sagittal T1 postcontrast VWI (*D*) demonstrates typical tram-track, circumferential enhancement of the right M1 MCA (*white arrow*), consistent with vasculitic inflammation.

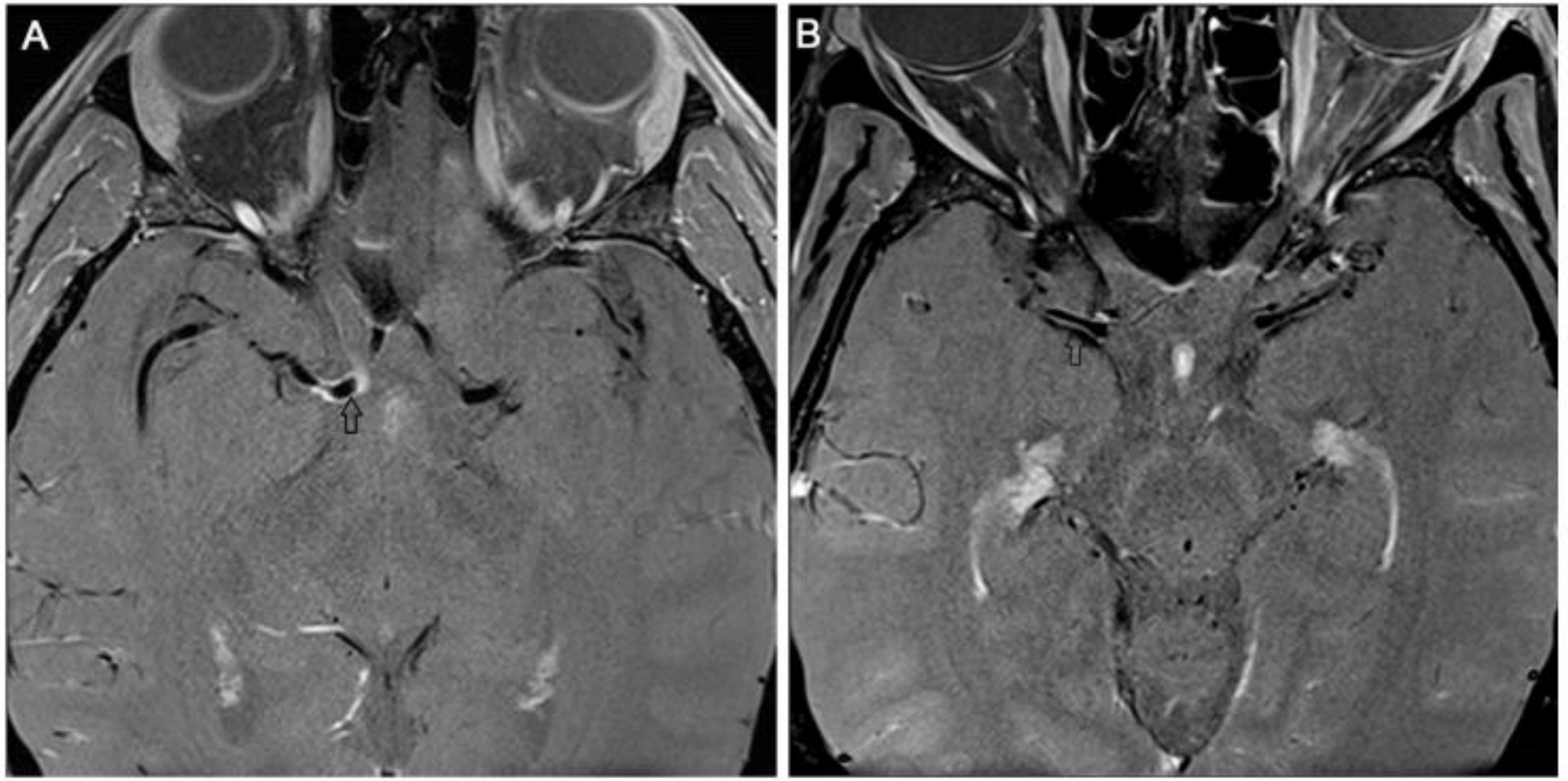


Fig. 1 HR-MRI brain axial section post gadolinium contrast: Vasculitis patient (**a**) shows vessel wall enhancement and thickening (arrow) while RCVS patient (**b**) shows minimal wall enhancement (arrow)

Table 2 Differentiating PACNS and RCVS

	PACNS	RCVS
Gender and mean age of onset	Male, 50 years	Female, 42 years
Clinical presentation	Insidious with subacute onset of headache with focal and non-focal deficit	Acute onset of thunderclap headache with or without neurological deficit
Clinical course	Chronic, relapsing	Remission within one month, monophasic
CSF findings	Lymphocytic pleocytosis and elevated protein levels	Normal
Common neuroimaging findings	-Ischemic, high intensity T2/FLAIR lesions -Abnormal MRI images in 100 % of cases	-Ischemic, edema, cSAH, ICH -Normal MRI images in 20 % of cases
Vascular findings	Normal in one-third of cases	Abnormal in all cases
Histologic findings	Vasculitic changes	Normal
Immunosuppressive therapy	Essential	Not indicated
Prognosis	Improved with immunosuppressive therapy	Excellent

Abbreviations: *PACNS:* primary angiitis of the central nervous system, *RCVS:* reversible cerebral vasoconstriction syndrome, *CSF:* cerebrospinal fluid, *cSAH*: convexity subarachnoid hemorrhage, *FLAIR*: fluid-attenuated inversion recovery, *ICH:* intracranial hemorrhage

Adopted with permission from Hammad et al. [66••]

TABLE 3. Cerebral Angiogram Features

Variable	RCVS, n = 159	PACNS, n = 47	p
Cerebral angiography performed	99%[a]	96%	0.012
DSA	40%	67%	<0.001
CTA	88%	41%	<0.001
MRA	78%	32%	<0.001
Abnormal result	100%	56%	<0.001
Artery involved			
Intracranial ICA	17%	9%	0.238
Middle cerebral artery	89%	50%	<0.001
Anterior cerebral artery	84%	40%	<0.001
Posterior cerebral artery	79%	36%	<0.001
Vertebral or basilar arteries	48%	16%	<0.001
AICA/PICA/SCA	53%	22%	<0.001
Extracranial ICA or vertebral	8%	2%	0.201
Arterial segment involvement			
Proximal (A1, M1, P1, V, B)	81%	41%	<0.001
Middle (A2, M2, P2, SCA, AICA, PICA)	92%	56%	<0.001
Smaller distal branches	86%	50%	<0.001
Morphology (DSA or CTA only)			
Concentric, smooth taper (sausaging)	68%	8%	<0.001
Eccentric narrowing, irregular/notched	13%	50%	<0.001
Segmental dilatation	50%	5%	<0.001
Symmetric involvement	82%	16%	<0.001
Mean severity score	22 ± 15	9 ± 12	<0.001
≥1 segment with >50% narrowing	83%	56%	0.001

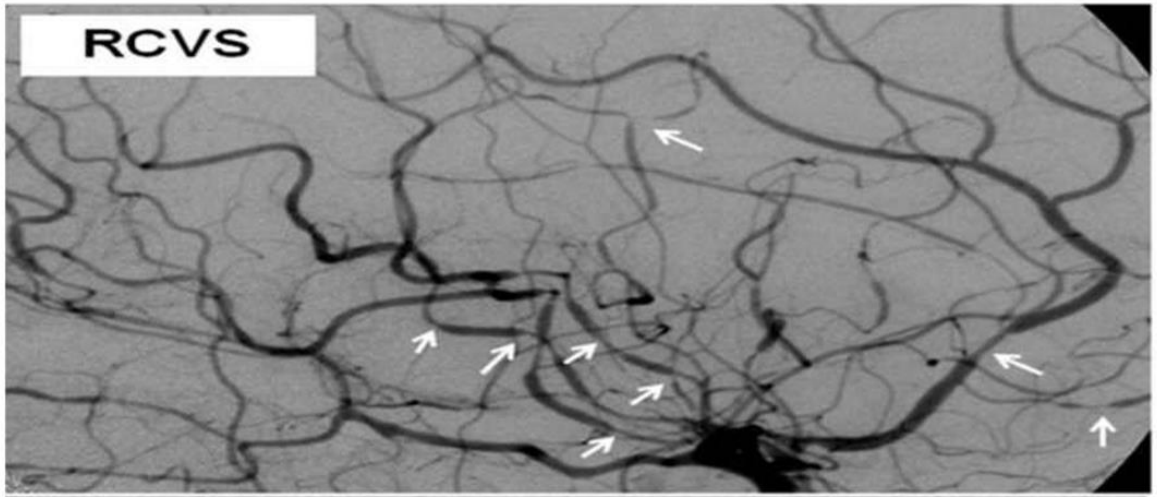
[a]One RCVS patient was diagnosed on the basis of transcranial Doppler ultrasound.
A1 = 1st segment of anterior cerebral artery; A2 = 2nd segment of anterior cerebral artery; AICA = anterior–inferior cerebellar artery; B = basilar artery; CTA = computed tomographic angiography; DSA = digital subtraction angiography; ICA = internal carotid artery; M1 = 1st segment of middle cerebral artery; M2 = 2nd segment of middle cerebral artery; MRA = magnetic resonance angiography; P1 = 1st segment of posterior cerebral artery; P2 = 2nd segment of posterior cerebral artery; PACNS = primary angiitis of the central nervous system; PICA = posterior–inferior cerebellar artery; RCVS = reversible cerebral vasoconstriction syndrome; SCA = superior cerebellar artery; V = vertebral artery.

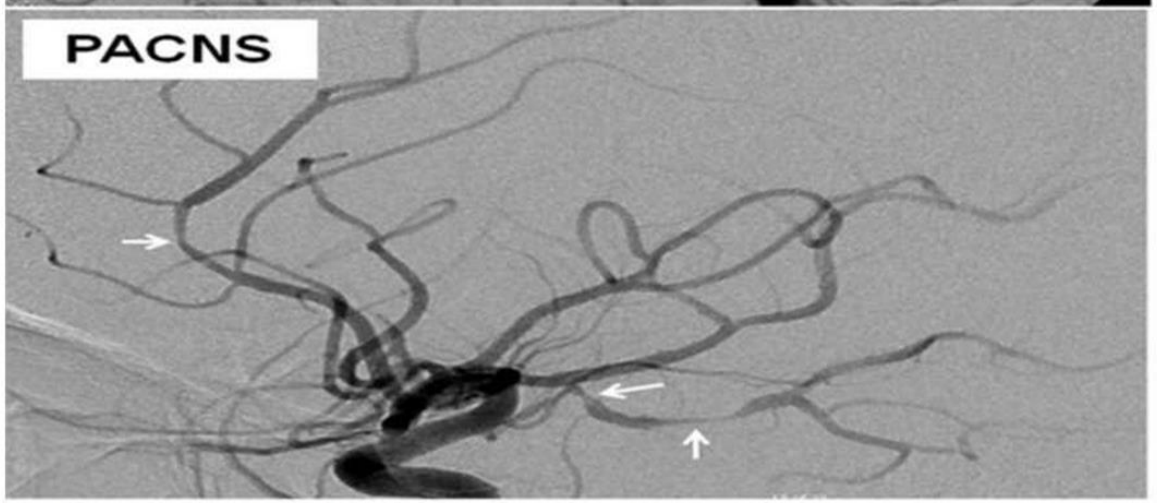
TABLE 5. Distinguishing RCVS from PACNS

Variable	Sensitivity	Specificity	PPV	NPV
Recurrent TCH[a]	74 [67–81]	98 [89–100]	99 [95–100]	53 [43–64]
Single TCH[a]	15 [10–22]	96 [85–99]	92 [75–99]	25 [19–32]
Plus normal brain MRI	2 [0–5]	100 [92–100]	100 [30–100]	23 [18–30]
Plus FLAIR dot sign	10 [6–16]	100 [92–100]	100 [79–100]	25 [19–32]
Plus border zone–only infarcts	3 [1–6]	100 [92–100]	100 [40–100]	23 [18–30]
Plus vasogenic edema (PRES)	4 [1–8]	100 [92–100]	100 [54–100]	24 [18–30]
Plus ICH or cSAH	9 [5–15]	96 [85–99]	88 [64–98]	24 [18–31]
No TCH; positive angiogram	11 [6–17]	49 [34–64]	42 [23–58]	14 [9–20]
For the diagnosis of RCVS				
Plus normal brain MRI	1 [0–3]	100 [92–100]	100 [17–100]	23 [17–29]
Plus border zone–only infarcts	5 [2–9]	98 [89–100]	88 [47–98]	23 [18–30]
Plus ICH or cSAH	3 [1–6]	98 [89–100]	80 [29–97]	23 [17–29]
Plus vasogenic edema (PRES)	3 [1–7]	100 [92–100]	100 [48–100]	23 [18–30]
Plus FLAIR dot sign	6 [3–11]	94 [83–99]	75 [43–94]	23 [18–30]
For the diagnosis of PACNS				
Plus deep/brainstem infarcts	38 [35–54]	100 [98–100]	100 [81–100]	85 [79–89]
Plus CSF abnormal[b]	28 [16–43]	99 [95–100]	87 [60–98]	82 [76–88]
Plus both of the above	28 [16–43]	100 [98–100]	100 [75–100]	83 [77–87]

[a]Values shown are for the diagnosis of RCVS. Numbers in brackets are 95% confidence intervals.
[b]Abnormal is >5 cells and >80mg/dl.
cSAH = convexal subarachnoid hemorrhage; CSF = cerebrospinal fluid; FLAIR = fluid-attenuated inversion recovery; ICH =

Typical Angiographic features of RCVS





MANAGEMENT

- No proven established therapy
- Most patients recover with time
- Up to 1/3 patients have transient symptoms and rare cases develop progressive clinical course
- Reasonable to admit for observation, pain control and supportive care

Management

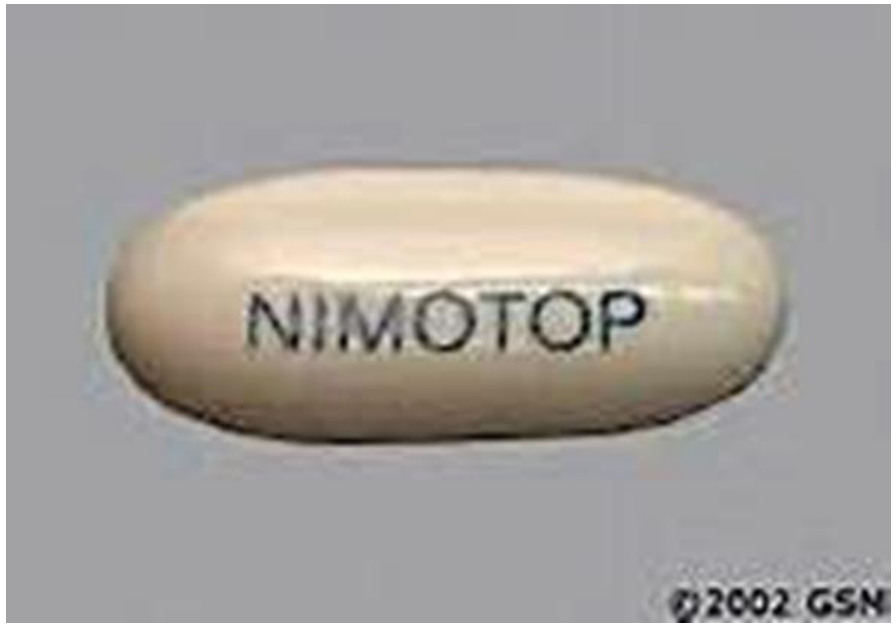
- ✓ An acute and self-limiting course without new symptoms after 1 month
- ✓ Identification and elimination of any precipitating or aggravating factors
- ✓ Rest and sexual activity, physical exertion, Valsalva maneuvers, and other headache triggers avoidance for a few days to a few weeks
- ✓ Analgesics, antiepileptic drugs for seizures, monitoring of blood pressure, and admission to intensive-care units in severe cases
- ✓ Nimodipine, verapamil and magnesium sulphate

Management

- Glucocorticoids should be avoided
- In severe cases, intra-arterial administration of milrinone, nimodipine, and epoprostenol and balloon angioplasty

Nimodipine

- Two prospective case control studies didn’t show any effect on time course of cerebral vasoconstriction
- but
- It helped with headache frequency and intensity.
- Proven effects on smaller vasculature which is difficult to image by angiography.



Nimodipine

- ✓ No randomized clinical trials
- ✓ The most widely employed treatment
- ✓ Intravenously or orally
- ✓ The dose : varying from 30-60 mg every 4-8 h
- ✓ Duration : from 4 to 12 weeks
- ✓ Reduces the number and intensity of headaches within 48 h
- ✓ Terminates the headache in 64–83%
- ✓ No definite effect on the hemorrhagic and ischemic complications

Supportive care

- Admit to NICU
- Q1h Neurochecks and Blood pressure management.
- Hypertension leads to hemorrhagic stroke by worsening vasoconstriction and even mild hypotension leads to ischemic stroke.
- Pain management: Round the clock opioid analgesics. Triptans and ergot derivatives are contraindicated.
- Treat seizures symptomatically. Rarely recur

Vasoconstriction

Guided by observational data and expert opinion.

Empiric therapy is not warranted without justifying vasoconstriction by cerebral angiography.

90% patients will have resolution spontaneously, we don’t need to use any vasodilators.

Nimodipine, Verapamil, and Magnesium sulphate were tried.

Glucocorticoids

- Used in the clinical dilemma for PACNS but with the established criteria it is easy to differentiate between the two.
- Delaying the therapy for a few days in PACNS is not associated with increased morbidity or mortality in challenging cases.
- Recent study showed glucocorticoids were associated with worse outcomes.

Reversible Cerebral Vasoconstriction Syndromes

Analysis of 139 Cases

Aneesh B. Singhal, MD; Rula A. Hajj-Ali, MD; Mehmet A. Topcuoglu, MD; Joshua Fok, MD; James Bena, MS; Donsheng Yang, MS; Leonard H. Calabrese, DO

Objectives: To compare the clinical, laboratory, and imaging features of patients with reversible cerebral vasoconstriction syndromes evaluated at 2 academic centers, compare subgroups, and investigate treatment effects.

Design: Retrospective analysis.

Setting: Massachusetts General Hospital (n=84) or Cleveland Clinic (n=55).

Patients: One hundred thirty-nine patients with reversible cerebral vasoconstriction syndromes.

Main Outcome Measures: Clinical, laboratory, and imaging features; treatment; and outcomes.

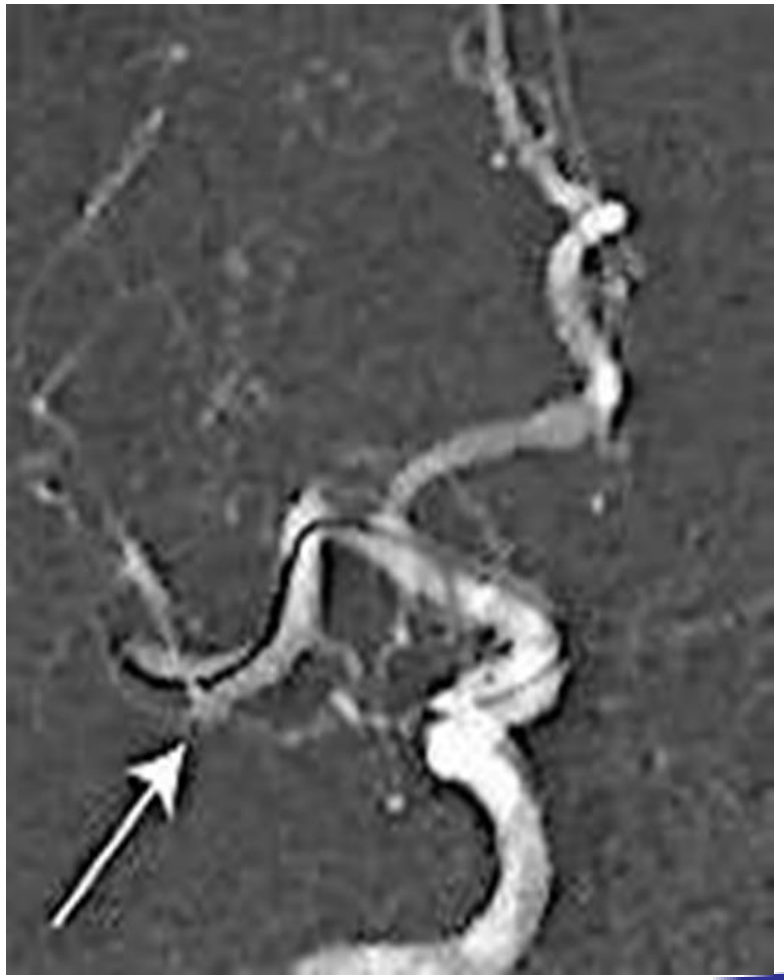
Results: The mean age was 42.5 years, and 81% were women. Onset with thunderclap headache was documented in 85% and 43% developed neurological deficits. Prior migraine was documented in 40%, vasoconstrictive drug exposure in 42%, and recent pregnancy in 9%. Admission computed tomography or magnetic resonance imaging was normal in 55%; however, 81% ultimately developed brain lesions including infarcts (39%), convexity subarachnoid hemorrhage (34%), lobar hemorrhage (20%), and brain edema (38%). Cerebral angiographic abnormalities typically normalized within 2 months. Nearly 90% had good clinical outcome; 9% developed severe deficits; and 2% died. In the combined cohort, calcium channel blocker therapy and symptomatic therapy alone showed no significant effect on outcome; however, glucocorticoid therapy showed a trend for poor outcome ($P=.08$). Subgroup comparisons based on prior headache status and identified triggers (vasoconstrictive drugs, pregnancy, other) showed no major differences.

Conclusion: Patients with reversible cerebral vasoconstriction syndromes have a unique set of clinical imaging features, with no significant differences between subgroups. Prospective studies are warranted to determine the effects of empirical treatment with calcium channel blockers and glucocorticoids.

Arch Neurol. 2011;68(8):1005-1012. Published online April 11, 2011. doi:10.1001/archneurol.2011.68

Intra-arterial therapy

- Balloon angioplasty and direct IA Nicardipine, Papaverine, Milrinone and Nimodipine have been used with variable success.
- IA infusion of the vasodilators into a single constricted artery can promptly reverse the vasoconstriction in multiple cerebral arteries including the contralateral arteries.
- This response is rarely observed in PACNS and intracranial atherosclerosis and has been proposed as a diagnostic test for RCVS.
- Not routinely used due to the risk of reperfusion injury.



Prevention and Counseling

- Avoid exposure to precipitating factors.
- Avoid physical exertion, valsalva maneuver and known triggers of recurrent headaches for a few weeks.
- Secondary prophylaxis for stroke is not indicated.
- No genetic implications of RCVS

Prognosis

- 15-20% of patients will have residual deficits from stroke but mild with mRS of 0-2 in 90-95% of patients at discharge.

- Some patients may continue to have chronic migraine like headaches and depression following RCVS.

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Long-term outcomes after reversible cerebral vasoconstriction syndrome

Seby John[1], Aneesh B Singhal[2], Leonard Calabrese[3], Ken Uchino[1], Tariq Hammad[3], Stewart Tepper[4], Mark Stillman[4], Brittany Mills[2], Tijy Thankachan[2] and Rula A Hajj-Ali[3]

Abstract

Background: Long-term outcomes of reversible cerebral vasoconstriction syndrome (RCVS) have not been systematically investigated.

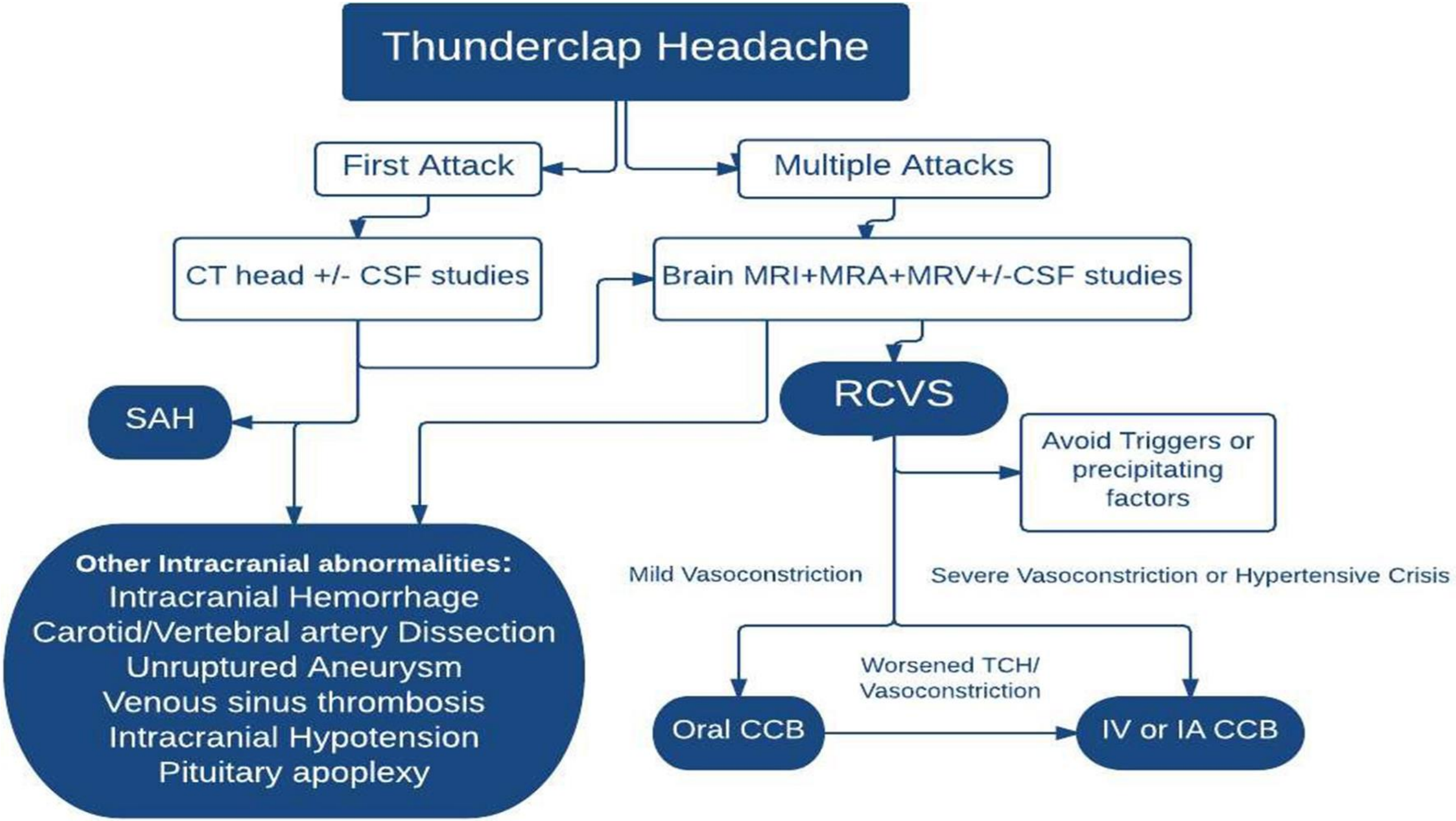
Methods: The following validated questionnaires were mailed to patients recruited from the RCVS registries of two academic hospitals: headache screening form, Headache Impact Test, Migraine Disability Assessment Test, Barthel Index (BI), EuroQoL (EQ-5D-5L) and Patient Health Questionnaire (PHQ-9).

Results: Of the 191 patients in the registries, 109 could be contacted and 45 responded. Median follow-up time after symptom onset was 78 months. After RCVS resolution, 24 (53%) patients continued to have headache, but the majority (88%) reported improvement in its severity. Thirteen of the 24 patients with persistent headache had a history of migraine prior to RCVS diagnosis. The majority (97.5%) of respondents were functionally independent based on BI scores. EQ-5D-5L showed better scores in the domains of mobility, self-care and usual activities, as compared to pain and anxiety/depression. Patients with persistent headache had significantly higher levels of EQ-5D-5L pain scores. PHQ-9 scores revealed only one patient (3%) with severe depression.

Conclusion: More than half of RCVS patients will continue to have chronic headaches of mild to moderate intensity that are distinct from the "thunderclap" headaches at RCVS onset. The vast majority regain complete functional ability. However, pain and anxiety/depression are frequent, often aggravated by concomitant chronic headaches, and may be associated with lower quality of life.

Prognosis

- ✓Long-term prognosis : by the occurrence of stroke
- ✓Most with strokes gradually improve for several weeks and few have residual deficits
- ✓Life-threatening forms : Less than 5%
- ✓Recurrence : possible (about 8%)
- ✓71% had no evidence of any long-term disability
- ✓29% had only minor disability


Thunderclap Headache
First Attack
Multiple Attacks
CT head +/- CSF studies
Brain MRI+MRA+MRV+/-CSF studies
SAH
RCVS
Avoid Triggers or precipitating factors
Other Intracranial abnormalities:
Intracranial Hemorrhage
Carotid/Vertebral artery Dissection
Unruptured Aneurysm
Venous sinus thrombosis
Intracranial Hypotension
Pituitary apoplexy
Mild Vasoconstriction
Severe Vasoconstriction or Hypertensive Crisis
Worsened TCH/ Vasoconstriction
Oral CCB
IV or IA CCB

Take Home Message

- RCVS is group of conditions characterized by reversible cerebral constriction –dilation of cerebral arteries
- ~90% have recurrent thunderclap headaches
- ~1/3rd of patients develop ischemic or hemorrhagic strokes or reversible brain edema on brain imaging
- Exclusion of CNS vasculitis and demonstrating reversibility is key to diagnosis
- Sympathomimetics, serotonergic drugs, immunosuppressive as well as postpartum status are important precipitants
- Most important treatment principle is identification and removal of potential precipitants

Clues

- Recurrent thunderclap headache for a few days
- Convexity subarachnoid hemorrhage
- Cryptogenic stroke plus headache especially post partum or after the use of vasoactive drugs
- Dynamic nature of clinicoradiological features
- Diffuse segmental vasoconstriction


Thank you