EXPLORING **HEADACHE RED FLAGS** WITH SPECIAL FOCUS ON **THUNDERCLAP ONSET**

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DISCLOSURES

- No relevant commercial relationships to disclose.

OBJECTIVES

- Recognize headache red flags using SNOOP4 criteria, focusing on thunderclap onset
- Employ a streamlined diagnostic approach to determine the etiology of your patient's thunderclap headache
- Interpret diagnostic studies (CT head, CT head and neck angiogram, MR brain, CSF) to differentiate between various causes of thunderclap headache

HEADACHE RED FLAGS

AT SNOOP7

Anticoagulation
Trauma

Systemic symptoms/Secondary risk factors (HIV, cancer)
Neurologic symptoms and signs
Focal deficits, blurry vision, seizures
Onset: age of onset > 50 yo or < 5yo
Onset: thunderclap, awakens from sleep
P7

- Precipitation with Valsalva maneuver or exertion
- Positional or postural
- Papilledema
- Pattern change or progressive
- Pulsatile tinnitus
- Pregnancy/peri-partum
- Presenting to an acute care facility

Pearls: headache. Dr. David Dodick. 2010

THUNDERCLAP HEADACHE (TCH)

- Onset: Abrupt
  - *Maximal intensity <1 minute*
- Severity: 10/10
  - *“Worst headache of my life”*
- Character/Quality: Explosion

- Recurrent?
  - *Reversible cerebral vasoconstrictive syndrome (RCVS)*
- Sentinel headache days to weeks before TCH?
  - *Subarachnoid hemorrhage (SAH)*
- Orthostatic worsening?
  - *Intracranial hypotension*

Other signs and symptoms?

- *Fever*
- *Hypertension*
- *ALOC*
- *Seizure*
- *Meningismus*
- *CN abnormalities*
- *Papilledema*
- *Vision changes*
- *Tinnitus*
- *Auditory muffling*
- *Focal weakness/numbness*

DIFFERENTIAL DIAGNOSIS of TCH

Most Common:

- Reversible Cerebral Vasoconstrictive Syndrome (RCVS)
- Subarachnoid hemorrhage (SAH)

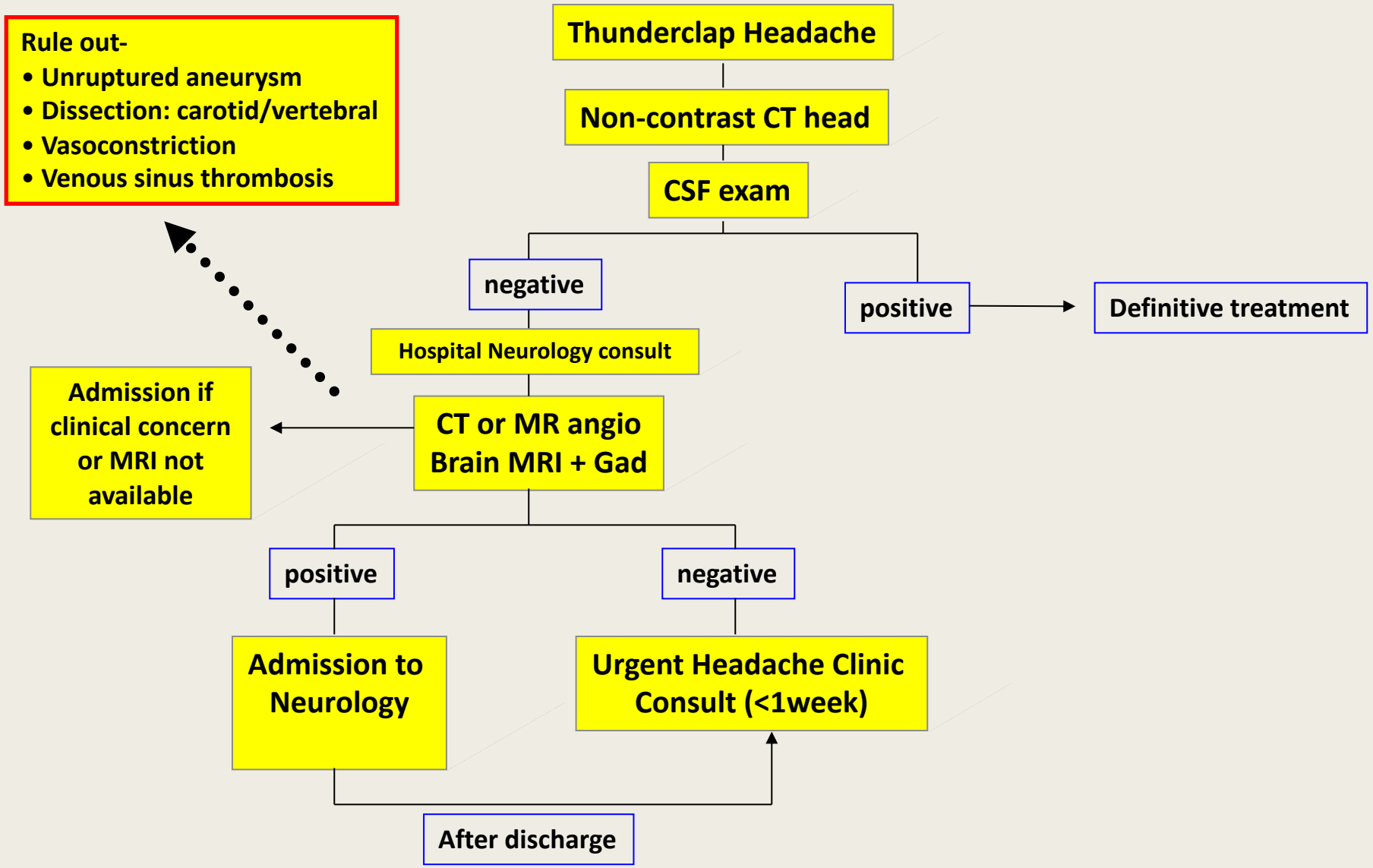
Less Common:

- Arterial Dissection
- Cerebral Venous Sinus Thrombosis (CVST)
- Cerebral infection (meningitis, encephalitis)
- Ischemic stroke
- Intracerebral hemorrhage (ICH)
- Subdural hemorrhage
- Unruptured vascular malformation
- Spontaneous intracranial hypotension
- Complicated sinusitis
- Hypertensive crisis

Even Less Common:

- Brain tumor
- Pheochromocytoma
- Third ventricle colloid cyst
- Pituitary apoplexy
- Aqueductal stenosis
- Retroclival hematoma
- Giant cell arteritis
- Cardiac cephalalgia
- Spontaneous spinal epidural hematoma
- Primary sexual headach

WORKFLOW


Rule out-
• Unruptured aneurysm
• Dissection: carotid/vertebral
• Vasoconstriction
• Venous sinus thrombosis
Thunderclap Headache
Non-contrast CT head
CSF exam
negative
positive
Definitive treatment
Hospital Neurology consult
Admission if clinical concern or MRI not available
CT or MR angio Brain MRI + Gad
positive
negative
Admission to Neurology
Urgent Headache Clinic Consult (<1week)
After discharge

CT HEAD- WITHOUT CONTRAST

TIMING- STAT

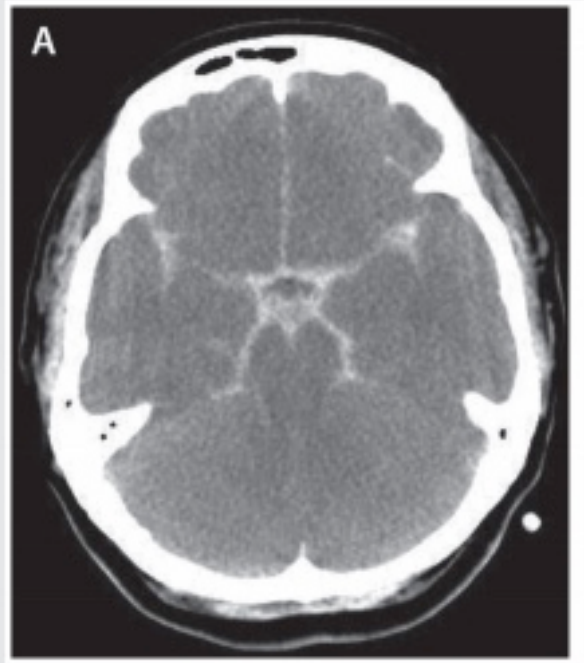
- Diagnosis may require urgent management
- Sensitivity to detect SAH decreases as time passes from event
  - *6hrs- 92-100%*
  - *24hrs- 85-95%*
  - *48hrs- 75%*
  - *5days- 50%*

Attempt to rule out:

- Hemorrhage: subarachnoid, parenchymal, subdural
- Ischemia, subacute
- Cerebral venous sinus thrombosis
- Mass, tumor
- Complicated sinusitis
- Third ventricle colloid cyst

Subarachnoid Hemorrhage (SAH)

Aneurysmal rupture



- Within the sylvian fissures and basal cisterns
- More severe neurologic exam on presentation
- +/- Intraparenchymal hemorrhage, hydrocephalous, cerebral edema, vasospasm

RCVS

- Cortical, hemispheric convexities
- Less severe neurologic exam on presentation
- +/- ischemic stroke, intraparenchymal hemorrhage, posterior reversible encephalopathy syndrome (PRES)

Intraparenchymal Hemorrhage

Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 10598

Subdural Hemorrhage

Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 35891

Early(ish) Ischemic Changes

Case courtesy of Dr David Cuete, Radiopaedia.org, rID: 35732

Mass/tumor

Case courtesy of Dr David Cuete, Radiopaedia.org, rID: 23178

LUMBAR PUNCTURE

- Opening pressure
- Color
- Cell count + differential
  - *Tube 1 and Tube 4, comparison*
- Protein
- Glucose
- Closing pressure
- Other:
  - *Meningitis encephalitis panel*

ANGIOGRAM- CT, MR, Conventional

- Aneurysm
  - *ruptured/unruptured, site, morphology, ? multiple*
- Vasoconstriction
  - *RCVS, vasculitis, intracranial atherosclerosis*
- Dissection
  - *Flame sign*

Case courtesy of Assoc Prof Frank Gaillard, Radiopaedia.org, rID: 5182

Diagnosis of Aneurysmal SAH?

- Admission to neurosurgical team
- Angiogram: diagnostic and therapeutic
- Monitor for and management of complications:
  - *Intraparenchymal hemorrhage*
  - *Hydrocephalous*
  - *Cerebral edema*
  - *Vasospasm*

CASE #1

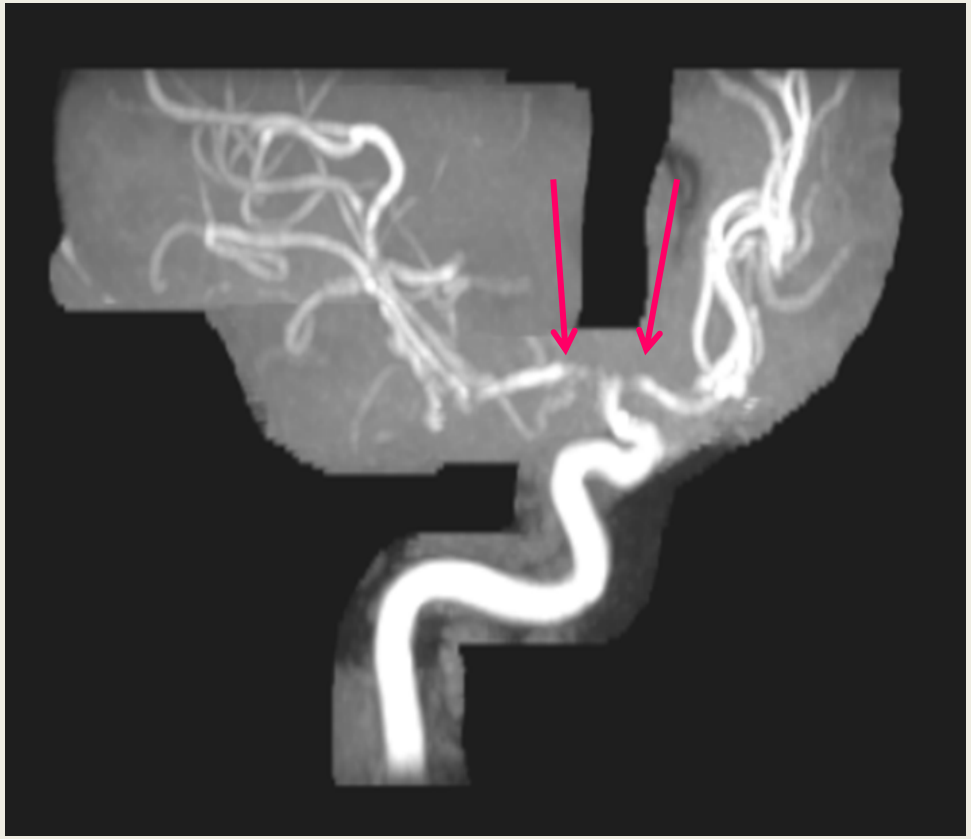
- 33 year old right hand dominant female
- PMHx of migraine taking sumatriptan prn
- She had been drinking heavily & smoking marijuana all evening.
- Developed a thunderclap HA, 10/10, while having sexual intercourse. Very different than her usual migraine HA.
- Associated with dysarthria and left upper extremity weakness, lasting for ~2 hours.
- She went to sleep. Woke up in the morning with persistent 8/10 HA but no dysarthria or weakness. Presents to ED.
- T 37.5 °C , BP 112/62 , HR 70, RR 14.
- Neuro exam: non-focal

Initial Diagnostics

- CT head: within normal limits.
- Lumbar puncture
  - *Opening pressure: wnl*
  - *RBC: 8*
  - *Nucleated cells: 2*
  - *Glucose: 60*
  - *Protein: 40*

Which of the following is the most appropriate next step in management?

A. Cerebrovascular imaging
B. IV thrombolysis
C. Indomethacin
D. Sumatriptan
E. Dexamethasone



REVERSIBLE CEREBRAL VASOCONSTRICTIVE SYNDROME (RCVS)

- Single or recurrent thunderclap headache
- Continuous/ongoing headache
- HA: diffuse or local, severe & throbbing
- Nausea/vomiting
- Photophobia/phonophobia
- Cognitive dysfunction/ALOC
- Seizures
- Focal neuro deficits – transient or persistent
  - *visual defects, hemiplegia, dysarthria/aphasia, ataxia*
- Ischemia can result in transient HTN, sometimes severe

TABLE 8-3 Diagnostic Criteria for Reversible Cerebral Vasoconstriction Syndromes[a]

- Thunderclap headache(s) with or without focal neurologic deficits or seizures
- Monophasic course without new symptoms more than 1 month after initial onset of symptoms
- Multifocal, multivessel, segmental vasoconstriction of cerebral arteries
- Absence of aneurysmal subarachnoid hemorrhage
- Normal or near-normal CSF

  Protein less than 100 mg/dL

  White blood cells less than 15 per mm^3

  Glucose normal
- Complete or substantial normalization of cerebral arteries within 12 weeks of symptom onset

CSF = cerebrospinal fluid.

[a] Data from Calabrese LH, et al, Ann Intern Med,[22] *annals.org/article.aspx?articleid=477594*, Ducros A, Lancet Neurol.[23] *www.thelancet.com/journals/laneur/article/PIIS1474-4422(12)70135-7/fulltext*.

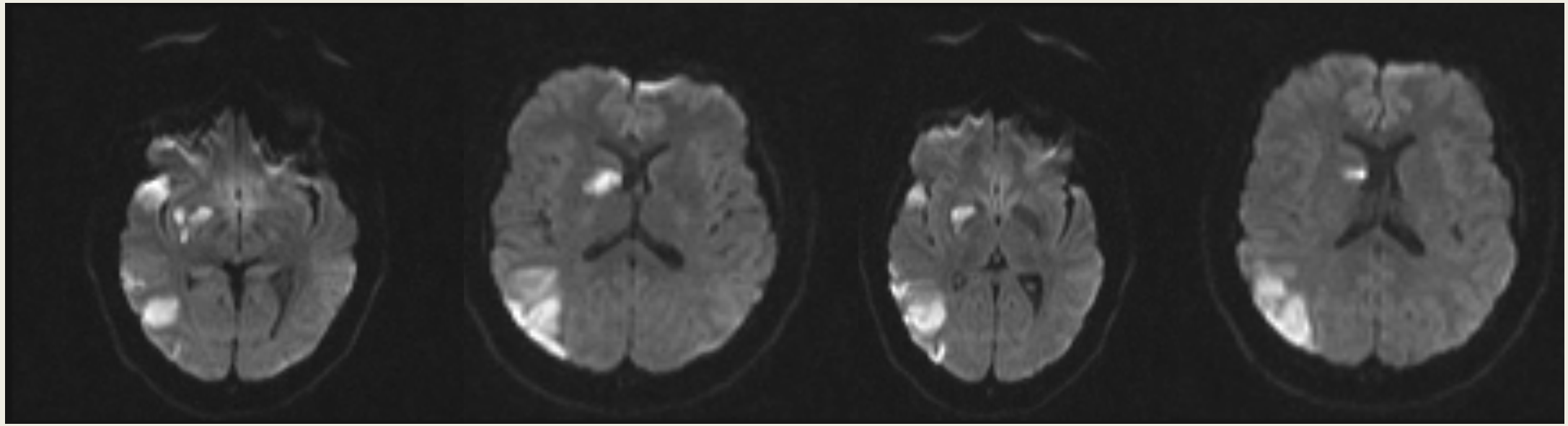
Risk factors:

- Female gender
- Pregnancy, post-partum, preeclampsia
- Use of serotonergic and sympathomimetic substances
- Drugs: marijuana, cocaine, ecstasy, amphetamine
- ETOH use, binge drinking
- Medications:
  - *Antidepressants, SSRI*
  - *Stimulants*
  - *Cold medications, pseudoephedrine*
  - *Triptans, ergotamine*
  - *Cyclophosphamide*
  - *Tacrolimus*
  - *IVIG*
  - *Erythropoietin*
- Migraine

Potential triggers:

- Valsalva: cough, straining BM, bending
- Showering/ bathing
- Urinating
- Sexual activity
- Strong emotions, anger
- Head trauma
- Hypercalcemia
- Pheochromocytoma

MRI Brain: Ischemia

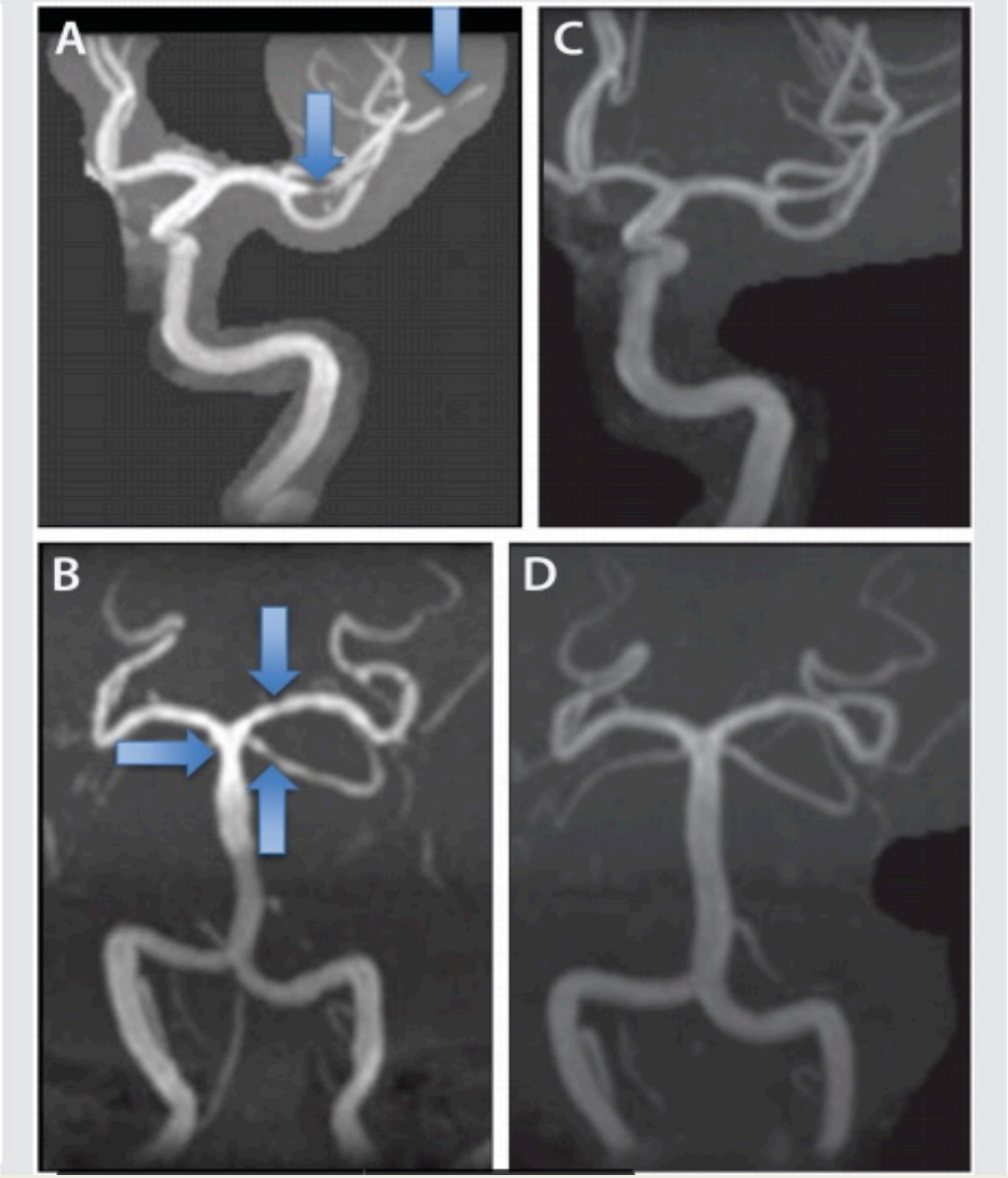


Complications of RCVS

- Ischemic stroke/TIA
  - Typically occurs during the 2nd week
- Hemorrhagic stroke
  - Occurs in 1/3
  - SAH most common but also ICH and SDH
  - Risk factors: female and migraine
- Posterior reversible encephalopathy syndrome (PRES)

Treatment of RCVS

- Guided by observational data given no randomized controlled trials
- Calcium channel blockers:
  - Parenteral (neurologic sx, abnl MR brain, severe hypertension)
    - Nimodipine [IV 0.5–2 mg/kg/h]
    - Nicardipine [IV 5-15mg/kg/h]
    - Prostacyclin [IV 0.9ng/kg/min]
    - Milrinone [IA 0.5ug/kg/min]
  - Oral
    - Nimodipine [30-60mg Q4-8h]
    - Verapamil [40-120 mg Q8h]
  - Duration: 4-12 weeks
- Stop offending agent
- Avoid Valsalva, sexual intercourse, and other triggers for weeks



Treatment Effect: CCB for RCVS

Conventional Angiogram

- A/B: on presentation
- C/D: 10 weeks later

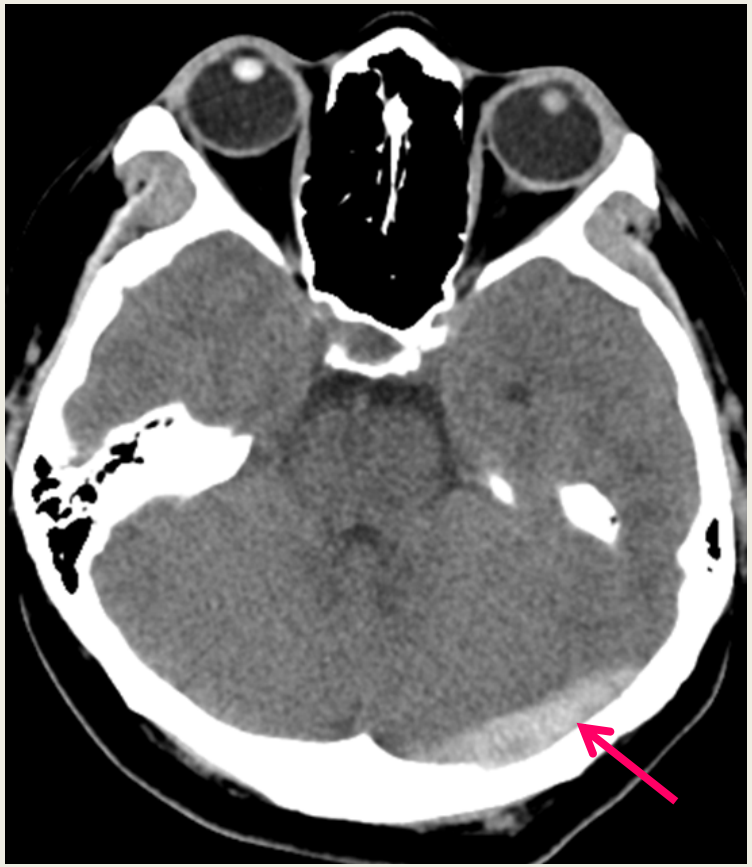
CASE #2

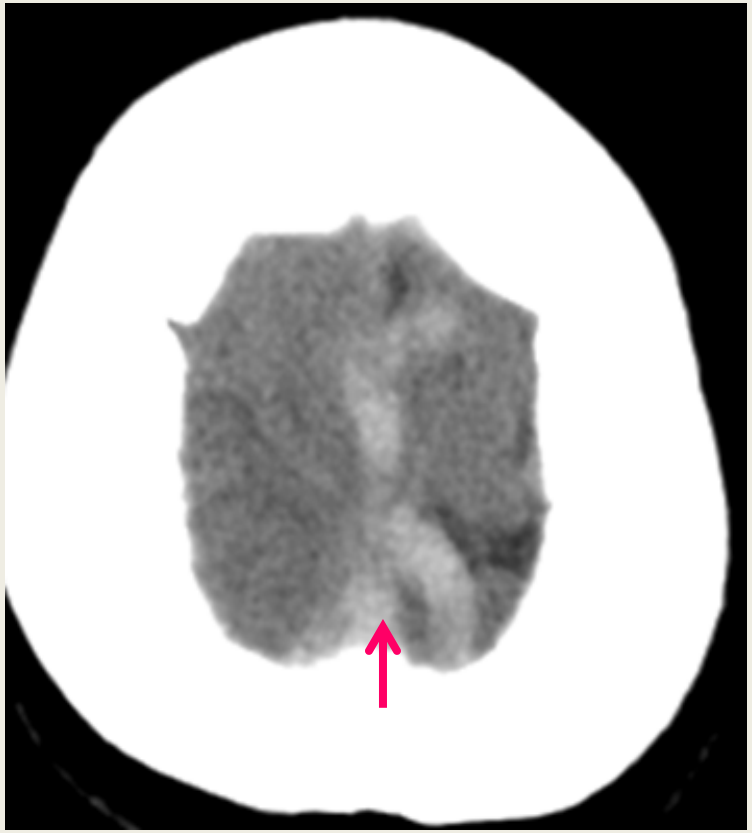
- 32 year old right hand dominant female, previously healthy.
- Meds: oral contraceptive pill, started 1 wk prior to presentation.
- Developed a thunderclap headache, nausea, and vomiting while driving home from work.
- Headache persisted at moderate intensity with repeated episodes of emesis over the next 2 days.
- On day #3, she woke up with left sided weakness & presented to the ED.
- BP 136/66, HR 103, T 37.3.
- In the ED, she has a witnessed generalized tonic clonic (GTC) seizure, lasting 30 seconds
  - *IV lorazepam & IV fosphenytoin.*
- Neuro exam: depressed level of consciousness & flaccid left hemiplegia.

CT Head Without Contrast

Dense clot sign/dense triangle sign
With contrast can see empty delta sign

Venous infarct: Posterior right parietal lobe





Extensive venous sinus thrombosis:
Superior sagittal, left transverse, and left sigmoid

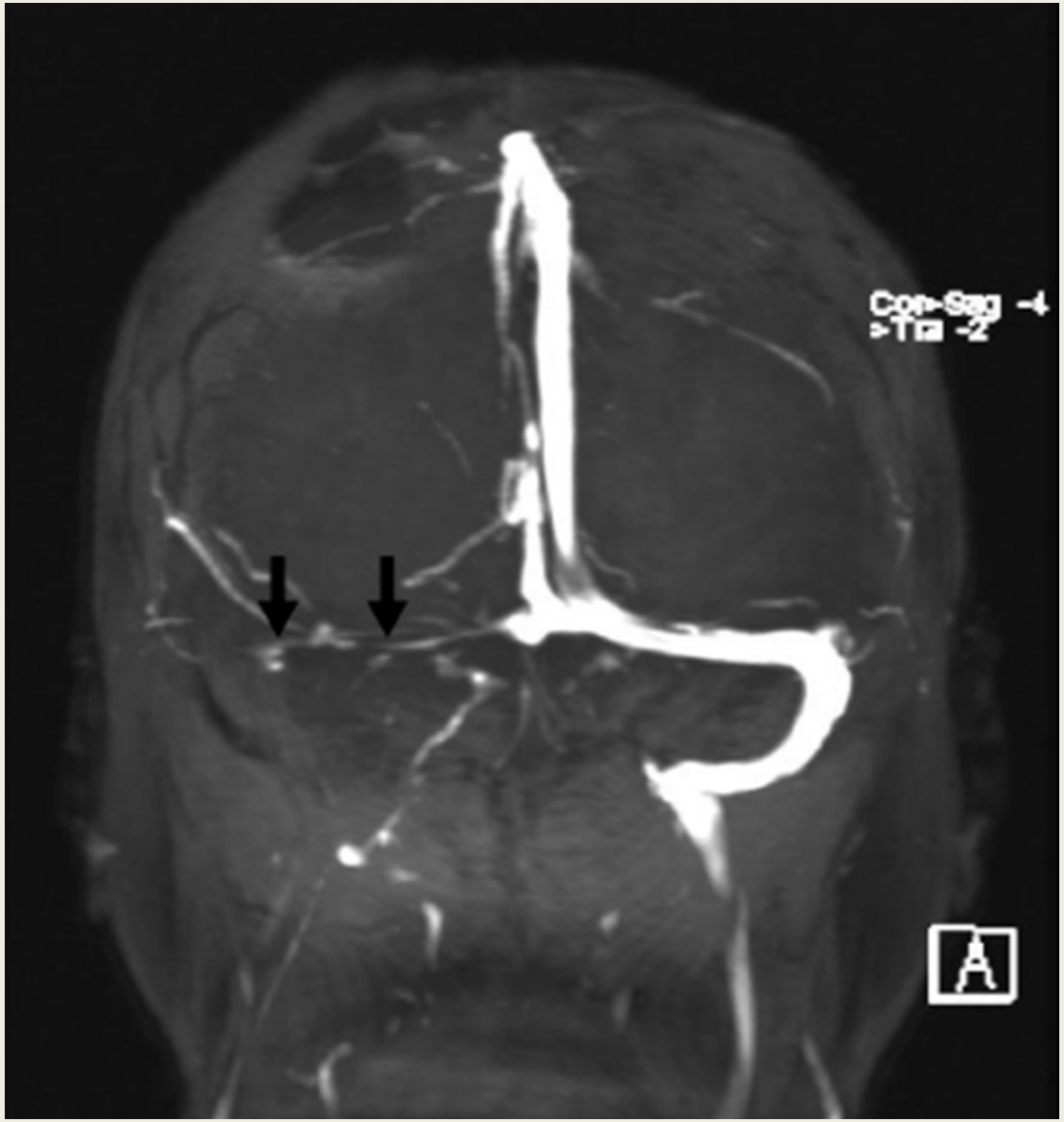
Which of the following diagnostic tests is the most appropriate next step?

A. MRI Brain

B. MRA Neck

C. MR Venogram

D. US of the lower extremities


A

CEREBRAL VENOUS SINUS THROMBOSIS (CVST)

- Onset- acute, subacute, or chronic
- Headache- most frequent and typically the first symptom
- Encephalopathy, ALOC
- Seizures
  - *Focal, generalized, status epilepticus*
  - *More frequent than in other types of stroke*
- Focal neurologic symptoms
  - *Motor weakness- most frequent*
  - *Aphasia- involvement of left transverse/lateral sinus*

CVST Etiology: Major Risk Factors

Transient

- Infection
  - *CNS, sinus, systemic*
- Pregnancy & peri-partum
- Dehydration
- Mechanical precipitants
  - *head injury, neurosurgery, LP, jugular catheter occlusion*
- Drugs
  - *OCPs, Hormones, Asparaginase, tamoxifen, glucocorticoids*

Permanent

- Inflammatory disease
  - *Sarcoid, SLE, IBD, Wegener's*
- Malignancy
  - *CNS, hematologic, solid tumor*
- Hematologic
  - *Prothrombotic states (genetic or acquired), polycythemia, anemia*

Which of the following is recommended as the initial treatment of CVST?

A. IV recombinant tissue-type plasminogen activator (rtPA)

B. Unfractionated heparin IV, therapeutic

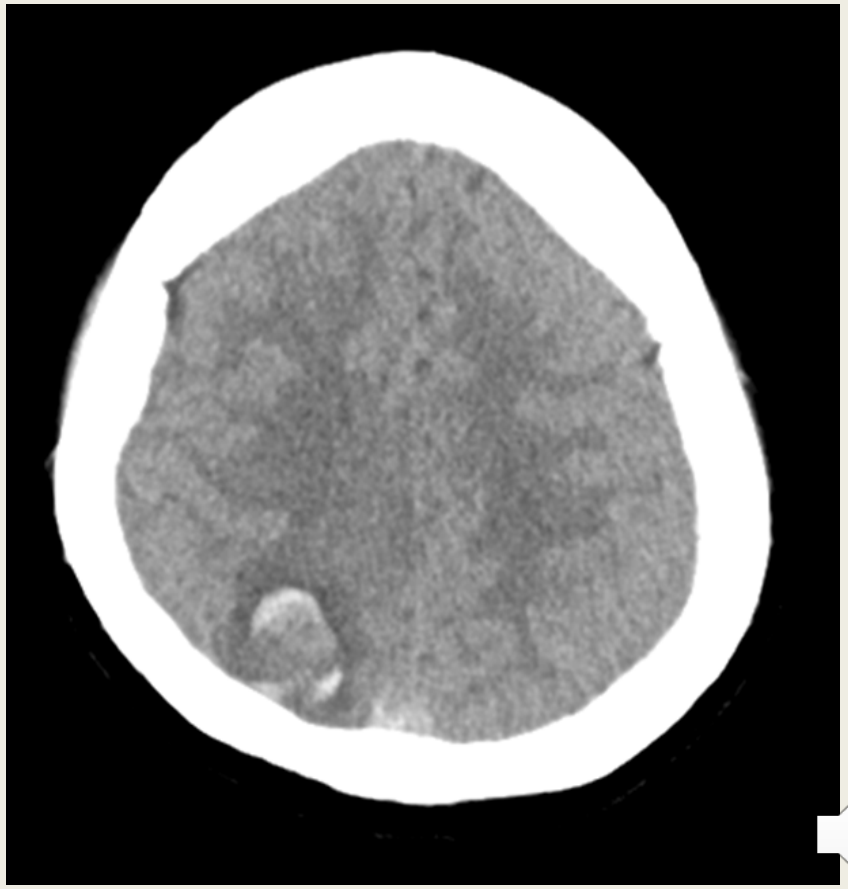
C. Aspirin

D. IV dexamethasone

Repeat CTH shows small amount of hemorrhage has developed in the area of venous infarct in the R parietal lobe.

Which of the following would you recommended as initial intervention?

A. Reverse anticoagulation
B. Continue unfractionated heparin
C. IV dexamethasone
D. Nicardipine



Complications of CVST

- Stroke
  - *Venous infarction*
    - Venous congestion⟶ insufficient blood supply ⟶ damage to brain tissue
  - *CVST is an uncommon cause of CVA*
    - Represents 0.5% - 1% of all strokes
  - *Usually affecting young individuals (<50 yrs)*
- Hemorrhage
- Increased ICP
  - *Decreased CSF absorption*
- Seizures

CVST: Treatment Goals

- **Re-canalize** the occluded sinus/vein
- **Prevent propagation/extension** of the thrombus
- **Treat the underlying prothrombotic condition** in order to prevent further thrombosis in other areas
- **Prevent recurrence** of the CVST

Acute Treatment of CVST

- Systemic anticoagulation:
  - *Unfractionated heparin, low molecular weight heparin*
  - *Oral anticoagulation with vitamin K antagonists*
  - *<u>REGARDLESS</u> of the presence of ICH*
- Steroids NOT recommended; enhance hypercoagulability
- Seizure + parenchymal lesion, add antiepileptic drug
  - In the absence of seizure, routine use of AEDs is NOT recommended

AHA/ASA guidelines 2011

Length of Anticoagulation for CVST

- **PROVOKED**
  - *Associated with a transient risk factor*
  - *Vitamin K antagonists for 3-6 months*
- **UNPROVOKED**
  - *No risk factor identified*
  - *Vit K antagonists for 6-12 months*
- **RECURRENT** CVST, VTE after CVST, or first CVST with severe thrombophilia/permanent risk factor
  - *Vit K antagonists indefinitely*
  - *Severe thrombophilia: homozygous prothrombin G20210A, homozygous factor V Leiden, Protein C or S deficiency, antiphospholipid syndrome, combined thrombophilia defect*

CASE #3

- 34 year old right hand dominant female
- Previously healthy, no medications
- Developed thunderclap headache, neck pain, vertigo, N/V while doing a “squat-snatch” at the gym
- Presented to the ED within 2 hours of onset
- Blood pressure is 161/92. Otherwise HDS, afebrile.
- Neuro exam: right sided sensory loss and left sided incoordination/ataxia

Initial Diagnostics

- CT head: normal
- LP not performed given clinical suspicion of brainstem CVA
- CTA head/neck: left vertebral artery dissection, extracranial.
- INR 1.0, PTT 27.2, platelet 256

Case courtesy of Dr Henry Knipe, Radiopaedia.org, rID: 48493

What is the most appropriate next step?

A. MR brain

B. Administer tPA

C. Unfractionated heparin

D. Aspirin

What is the most appropriate next step?

A. MR brain

B. Administer tPA

"IV alteplase in AIS known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 h and probably recommended."

AHA/ASA guidelines 2019

ARTERIAL DISSECTION

Internal carotid 3x more common than vertebral
Extracranial > intracranial
Men = women

Vertebral Artery:

- Pain: head (occipital), neck
- Headache: gradual or thunderclap in onset
- Ischemic symptoms in 90% of patients
  - *Cerebral- posterior circulation Dizziness, dysarthria, ataxia*
  - *Cranial nerve palsies*
  - *Lateral medullary syndrome is common*

Internal Carotid Artery:

- Pain: head, face, neck
- Headache: gradual or thunderclap in onset
- Pulsatile tinnitus in 25%
- Ischemic symptoms in 50-90% of patients
  - *Cerebral- anterior circulation*
  - *Retinal*
- Cranial nerve palsies, compression

Tapered, flame-like occlusion typical of acute dissection

Arterial Dissection Etiology: Predisposing Factors

- Genetic:
  - *Fibromuscular dysplasia—most common*
  - *Ehlers–Danlos syndrome type IV*
  - *Marfan's syndrome*
  - *Type 1 collagen point mutation*
  - *Osteogenesis imperfecta type 1*
  - *Cystic medial necrosis*
  - *Autosomal dominant polycystic kidney disease*
  - *Alpha-1 antitrypsin deficiency*
  - *Pseudoxanthoma elasticum*
  - *Moyamoya*
  - *Reticular fiber deficiency*
  - *Homocystinuria*
- **Trauma:**
  - *Motor vehicle accident*
  - *Sports injury*
  - *Vigorous coughing*
  - *Chiropractic manipulation*
  - *Iatrogenic*
- Infection (URTI)
- Smoking
- HTN
- OCP
- RCVS

Complications of Arterial Dissection

- Ischemic stroke
  - *Overall, relatively uncommon cause of stroke*
    - Approximately 2% of all ischemic strokes
    - 10-25% of strokes in young pts
- Direct/local compression of cranial nerves
  - *Dissection/aneurysmal dilatation*
  - *Can be painful*

Treatment of Arterial Dissection

- Antithrombotic therapy
- Antiplatelet or anticoagulation?
  - CADISS- Cervical Artery Dissection in Stroke Study, 2015
    - Patients randomized, antiplatelet or anticoagulation x3 months
    - Primary endpoint: ipsilateral stroke or death within 3 months
    - No significant difference between the two treatment groups
- AHA/ASA Guidelines:
  - For pts with ischemic stroke/TIA and extracranial carotid or vertebral arterial dissection, the use of antithrombotic therapy with either antiplatelet or anticoagulant therapy for at least 3-6 months is reasonable.

TABLE 8-2 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, subarachnoid blood along cortical surface/sulci	Normal, mild white blood cell elevation, mild protein elevation	Multifocal multivessel vasoconstriction	Normal, 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, ischemic stroke	Normal	Dissected artery, multifocal, segmental vasoconstriction if associated with reversible cerebral vasoconstriction syndrome	Normal, 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, 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, subdural collections	Low opening pressure	Normal	Pachymeningeal enhancement, sagging brain, subdural collections

CT = computed tomography; MRI = magnetic resonance imaging.

TAKE HOME POINTS

- Consider secondary causes of headache and ask your patients about headache red flags.
- Pursue further diagnostic evaluation with CT head, angiogram, lumbar puncture, and/or MRI as indicated.
- Initiate treatment as soon as possible. Monitor closely.
- Ask for help from your friendly neurology collegues if needed ☺

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QUESTIONS?

- Please reach out to me via email with any questions
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