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HOSPITAL NEUROLOGY

HEADACHES, ICH, SEIZURES

Abigail Taylor PA-C
Instructor of Neurology
NP PA Neurology Fellowship Program Director

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Nothing to disclose

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

All relevant financial relationships have been mitigated.

LEARNING OBJECTIVES

- Identify headache red flag features using the SNOOP criteria and compile differential diagnosis for secondary headache disorders.
- Review diagnosis, evaluation, management, and complications associated with reversible cerebral vasoconstriction syndrome (RCVS).
- Discuss initial treatment for seizures in hospital and status epilepticus, including adequate dosing of antiseizure medications.
- Review indication for initiation of acyclovir for HSV with empiric antimicrobial regimen for meningitis/encephalitis.
- Highlight the recently updated guidelines for evaluation and management of intracerebral hemorrhage.

CASE 1: MS. SMITH

- 58yo RHD F
- PMHx:
  - DVT/PE (provoked, completed AC)
  - GERD
  - Tobacco and THC use, daily

- New onset recurrent headaches x 4-6 weeks
  - Holocephalic
  - Throbbing
  - Severe
  - + N/V, inability to perform ADLs

MS. SMITH

- Multiple PCP and ED visits
- CTH w/o contrast- normal
- Diagnosed with migraine

- Treatment
  - ED
    - IVF
    - IV Toradol, Dilaudid
    - Antiemetics
  - Home
    - NSAIDS/Tylenol
    - Sumatriptan
    - Fioricet
    - Marijuana

MIGRAINE DIAGNOSTIC CRITERIA: ICHD

- At least 5 or more attacks in a lifetime
- Attack lasting 4-72 hours
- At least 2 out of 4 features
  - Unilateral location
  - Pulsating/throbbing quality
  - Moderate-severe intensity
  - Aggravation by/causing avoidance of routine physical activity
- At least 1 of the following features
  - Nausea and/or vomiting
  - Photophobia
  - Phonophobia

Not better accounted for by another ICHD diagnosis

SNOOP 4 HEADACHE RED FLAGS

SNOOP5		
S	Systemic Secondary Risks	Fever, weight loss, night sweats, Cancer, HIV, immunocompromised state, trauma, OAC
N	Neurologic deficit/abnormal signs	Focal neurologic deficit, confusion, impaired/altered LOC
O	Onset (time course)	Thunderclap (max intensity <60 sec), wakes from sleep
O	Onset (age)	> 50 yo = secondary HA until proven otherwise Consider giant cell arteritis < 5yo
P1	Previous headache history	First headache, different/change in headache
P2	Postural or Positional aggravation	CSF pressure too high or low, inc/dec ICP
P3	Precipitated by Valsalva	Coughing, bending, sneeze, lift, bearing down, exertional
P4	Papilledema or Pulsatile tinnitus	Vision changes/loss, inc ICP, IIH
P5	Pregnancy or Peri-partum	Preeclampsia, hypercoagulable, CSF leaks, treatment selection

Adapted from Dodick DW. Adv Stud Med. 2003;3(6C):S550-S555

MS. SMITH: ADDITIONAL HISTORY

- Thunderclap onset, recurrent
  - HA reaching maximal intensity </= 60 seconds
- Onset at age > 50yo
- Wakes from sleep
- Pattern change
  - Unlike any HA she had previously
- Sneak peak- develops neurologic symptoms as well

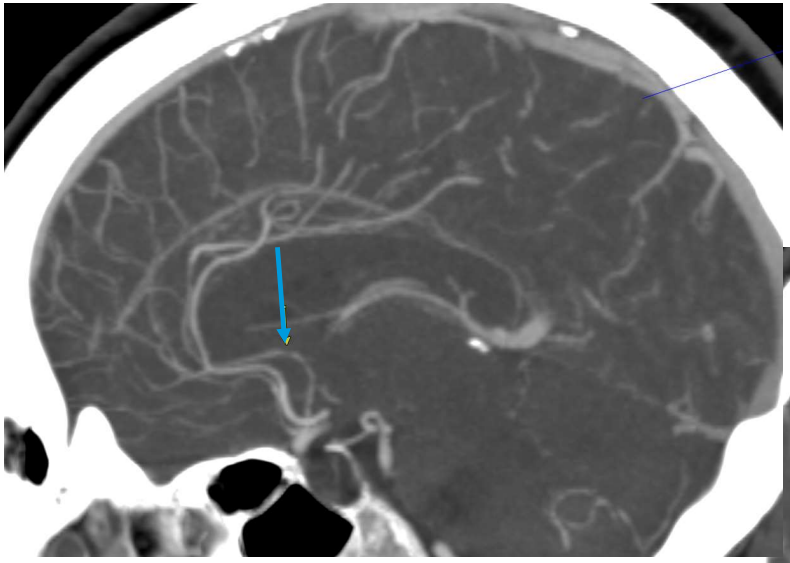
MS. SMITH: PROGRESSION

- New neurologic symptoms
  - R sided weakness/numbness
  - Confusion
    - Often mistaken for aphasia

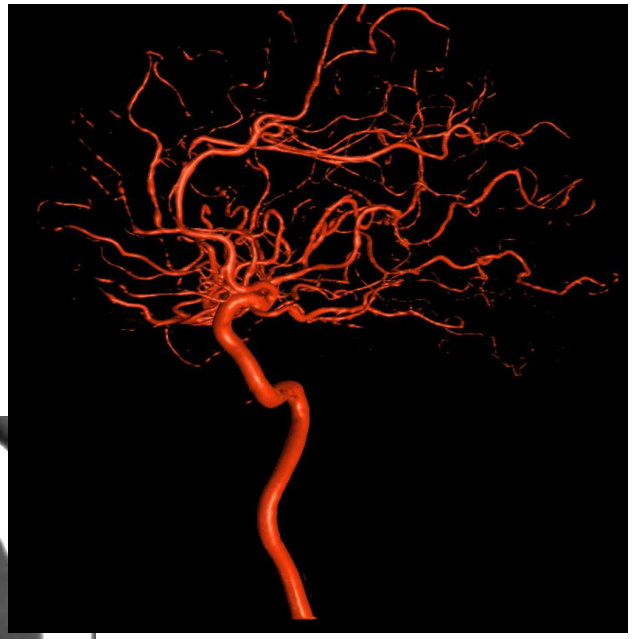
- Re-presents to outside ED
- NIHSS 7
  - Mixed aphasia (2), RUE weakness (1), RLE weakness (1), R face weakness (1), Disoriented (1), Difficulty following commands (1)
- CTH w/o contrast and CTA head/neck- reportedly normal, motion artifact

- Transferred to our hospital for higher level of care

MS. SMITH: VASCULAR IMAGING

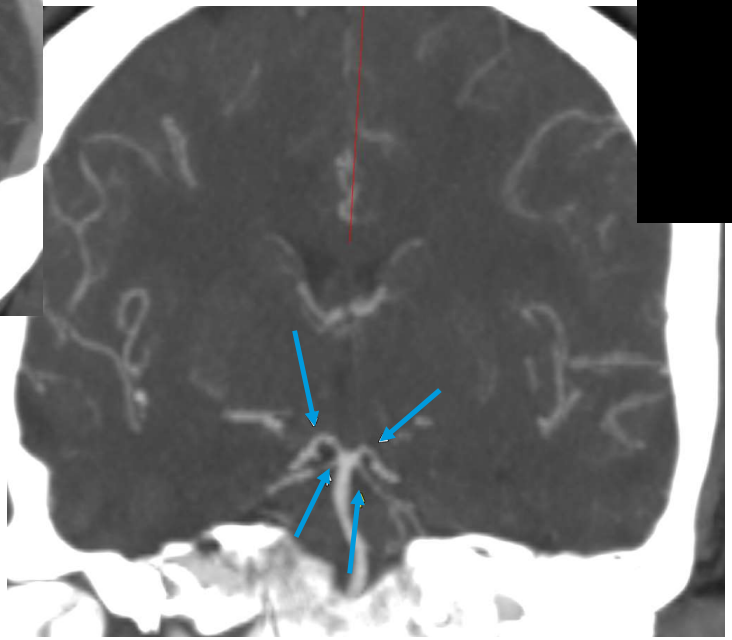


CTA head



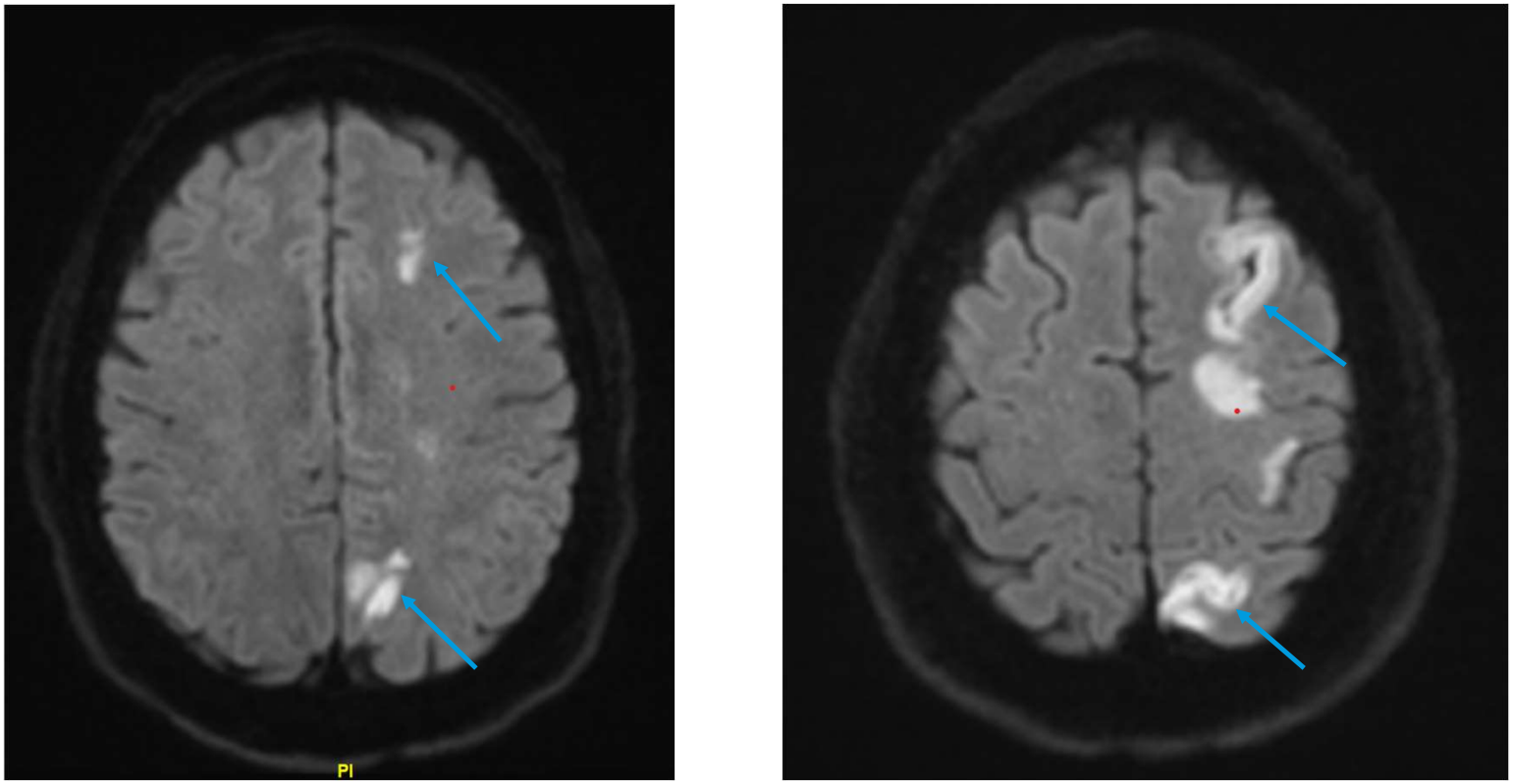
Conventional angiogram

Vascular irregularities in various intracranial vessels



CTA head

MS. SMITH: MRI BRAIN, DWI



Ischemic strokes: scattered in left hemisphere

MS. SMITH: ADDITIONAL EVALUATION

- MR Venogram: No cerebral venous sinus thrombosis
- LP/CSF analysis: Unremarkable
- EEG: Left hemispheric slowing, no irritability or seizures
  - Empiric levetiracetam (Keppra) discontinued

QUESTION: WHAT IS THE MOST LIKELY ETIOLOGY OF MS. SMITH'S ISCHEMIC STROKES?

1. Vasculitis 2/2 CNS infection
2. Primary CNS Vasculitis
3. Multifocal intracranial atherosclerosis
4. Reversible cerebral vasoconstrictive syndrome (RCVS)

REVERSIBLE CEREBRAL VASOCONSTRICTIVE SYNDROME (RCVS)

- Presentation
  - Thunderclap headache(s), recurrent is hallmark
  - Headache can have migrainous features
  - Focal neurologic deficits, seizures

- Risk factors:
  - Pregnancy, post-partum, pre-eclampsia
  - ETOH use, binge drinking
  - Drugs: marijuana, cocaine, ecstasy, amphetamine
  - Meds: antidepressants (SSRI), stimulants (Adderall), cold medications (pseudoephedrine), triptans, immunosuppressants
  - Migraine

RCVS EVALUATION

- Vascular imaging- CTA, MRA
  - Multifocal, multivessel, segmental vasoconstriction of cerebral arteries
  - Peak onset at 2-3 weeks
  - Reversibility demonstrated in 12 weeks

- CSF to rule out alternate cause of vascular abnormalities or TCH
  - Normal/near normal

- Consider MRI and/or EEG to evaluate for complications

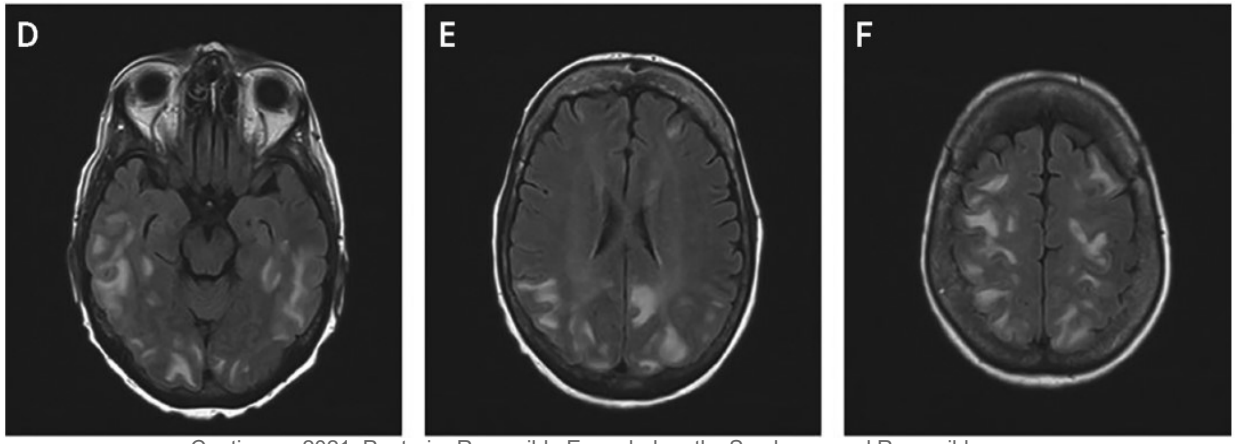
MS. SMITH: RCVS MANAGEMENT

- Calcium channel blockers
  - Nimodipine → verapamil
  - Titrate as able, avoiding hypotension/bradycardia
- Conventional angio w/ IA CCB, improvement of vasospasm

- Discontinue triptan, Fioricet, and marijuana use
- Avoid triggers
  - Valsalva
  - Orgasm
  - Intense emotions
  - Hot showers

RCVS COMPLICATIONS

- Ischemic stroke
- Subarachnoid hemorrhage, nonaneurysmal locations
- Seizures
- Posterior reversible encephalopathy syndrome (PRES)
  - Often seen in conjunction with RCVS, look for it



Continuum 2021: Posterior Reversible Encephalopathy Syndrome and Reversible Cerebral Vasoconstriction Syndrome as Syndromes of Cerebrovascular Dysregulation

SYMPTOMATIC TREATMENT FOR HEADACHE

- Daily
  - Normal saline 1L IV bolus
  - Magnesium sulfate 1-2g IV

- Q8 hrs
  - “Cocktails”
  - Pain control
    - Toradol 15-30mg
    - Tylenol 650-1000mg PO or IV
    - Avoid opiates
  - Anti-emetic
    - Compazine 5-10mg IV*
    - Phenergan 12.5-25mg*
    - Zofran 4mg IV
    - Ativan 0.5-1mg IV
  - Benadryl 12.5-25mg IV
    - Give with anti-emetics* to avoid adverse reaction

- Other options
  - Steroids: Dexamethasone 4-8mg IV x1
  - Valproic acid (Depacon) 500mg IV x1
  - Nerve blocks: supraorbital, temporoauricular, occipital

Consider:
- Organ function/other issues (kidney, liver, coagulation)
- Side effect profile (sedation, qtc prolongation)

CASE 2: MRS. SHANNON

- 63 yo LHD F
- PMHx:
  - Breast cancer s/p resection and chemotherapy last administered 3 months ago
  - Depression

- Presented to our ED via ambulance
  - HA and “feeling off” yesterday
  - Slow to wake, confused, garbled speech
  - Seizure, “GTC”

MRS. SHANNON: EXAM

- VS: T 38.8
- General: Lethargic. Disoriented. Difficulty following commands.
- Language: Mixed (expressive and receptive) aphasia. Paraphasic errors. Impaired fluency.
- CN: Decreased blink to threat on R side.

MRS. SHANNON: SEIZURES

- Another seizure in the ED, witnessed by nursing
  - Head and eyes forced to the R side
  - RUE twitching
  - 2 minutes
  - Somnolent, confused/mumbled responses, groaning to pain

- 3 minutes later, another seizure
  - Unresponsive
  - RUE and face twitching
  - 1 minute

QUESTION: MRS. SHANNON (66 KG) HAS ALREADY RECEIVED BENZODIAZEPINES X2 DOSES. HOW MUCH LEVETIRACETAM (KEPPRA) SHOULD WE ADMINISTER?

1. 1500 mg IV x1
2. 3000 mg IV x1
3. 4000 mg IV x1
4. 5000 mg IV x1

STATUS EPILEPTICUS

- Convulsive/nonconvulsive
  - One of the following
    - 5+ minutes of continuous and/or electrographic seizure activity
    - 2 or more discrete seizures between which there is incomplete recovery of consciousness

- Refractory
- Super refractory

STATUS EPILEPTICUS MANAGEMENT

- ABCs!
- Benzo- Lorazepam (Ativan)
  - 0.1-0.2mg/kg
    - Max: 4mg
    - Repeat x1
- Load an antiseizure medication (ASM)

- Don’t under dose medications
- Start routine dosing of chosen ASM

- Fosphenytoin
  - 20mg/kg
  - Max: 1500mg
  - Hypotension
- Valproic acid
  - 40mg/kg
  - Max 3000mg
  - Liver, platelet dysfunction
- Levetiracetam
  - 60mg/kg
  - Max 4500mg

MRS. SHANNON: NEXT STEPS

- Levetiracetam
  - 4000mg IV x1
  - 750mg IV BID, starting tonight
- EEG: Periodic lateralizing discharges (PLEDS), improved
- Starting to wake up, following simple commands, answering questions

- Etiology of seizures?
  - HA, fevers, confusion
  - Consider CNS infection

- Blood cultures
- LP/CSF
- Antimicrobials
- Neuroimaging

CT HEAD BEFORE LP

- When:
  - Immunocompromised host
  - >60yo
  - Focal neurologic signs/symptoms
  - Seizure
  - AMS
  - Papilledema
  - Hx of neurologic disease

- Why:
  - Rule out a mass lesion
    - May increase risk of herniation with LP/CSF removal

LP Checklist

- Antithrombotic use, last dose

- CBC, platelet count, coags

EMPIRIC ANTIMICROBIAL TREATMENT

- Third generation cephalosporin
  - Ceftriaxone 2g IV Q 12hrs OR ceftoxamine 2g IV Q 4-6 hrs
- Vancomycin 15-20mg/kg Q 8-12hrs

- Special populations:
  - >50yo/immunocompromised/ETOH abuse?
    - Add Ampicillin 2g IV Q 4hrs
  - Neurosurgical intervention/indwelling device/penetrating trauma?
    - Drop third generation cephalosporin
    - Add cefepime, meropenem, or ceftazidime
  - Concern for viral encephalitis/temporal lobe dysfunction?
    - Add acyclovir 10mg/kg Q8hrs

MRS. SHANNON: DIAGNOSTICS/INITIAL PLAN

- CTH prior to LP
  - Immunocompromised statue, seizure, focal neuro deficits
- Do not delay initiation of treatment for CTH and LP/CSF
- Blood cultures
- Initiate antimicrobials
  - Ceftriaxone and vancomycin
  - Added acyclovir- concern for viral encephalitis
  - Added ampicillin- immunocompromised state and age
- Steroid administration
- CTH w/o contrast
  - No mass lesion, ischemia, or hemorrhage

MRS. SHANNON: LP AND CSF ANALYSIS

- NC 379 (H)
  - Lymphocytes 76%
- RBCs 808 (H)
  - Equal in tube 1 and 4- not a traumatic tap
- Protein 76 (H)
- Glucose 63

- Meningitis/Encephalitis panel: all negative
  - CMV, EV, HSV-1, HSV-2, HHV-6, HPeV, VZV

MRS. SHANNON: NEXT STEPS

- CSF results
  - Gram stain negative
  - Bacterial culture x48 hrs negative
- Antimicrobial therapy
  - D/C Ceftriaxone, Vancomycin, and Ampicillin
  - Continue Acyclovir, high suspicion for HSV encephalitis
- Discontinue steroids
- Repeat LP/CSF analysis
  - HSV1 PCR positive
  - May be negative early in course, first 72 hours
- If HSV is suspected, continue acyclovir and repeat CSF PCR in 3-7 days.

Join: **vevox.app** ID: **XXX-XXX-XXX**

POLL OPEN

QUESTION: WHICH PART MRS. SHANNON'S CNS IS MOST LIKELY TO BE AFFECTED?

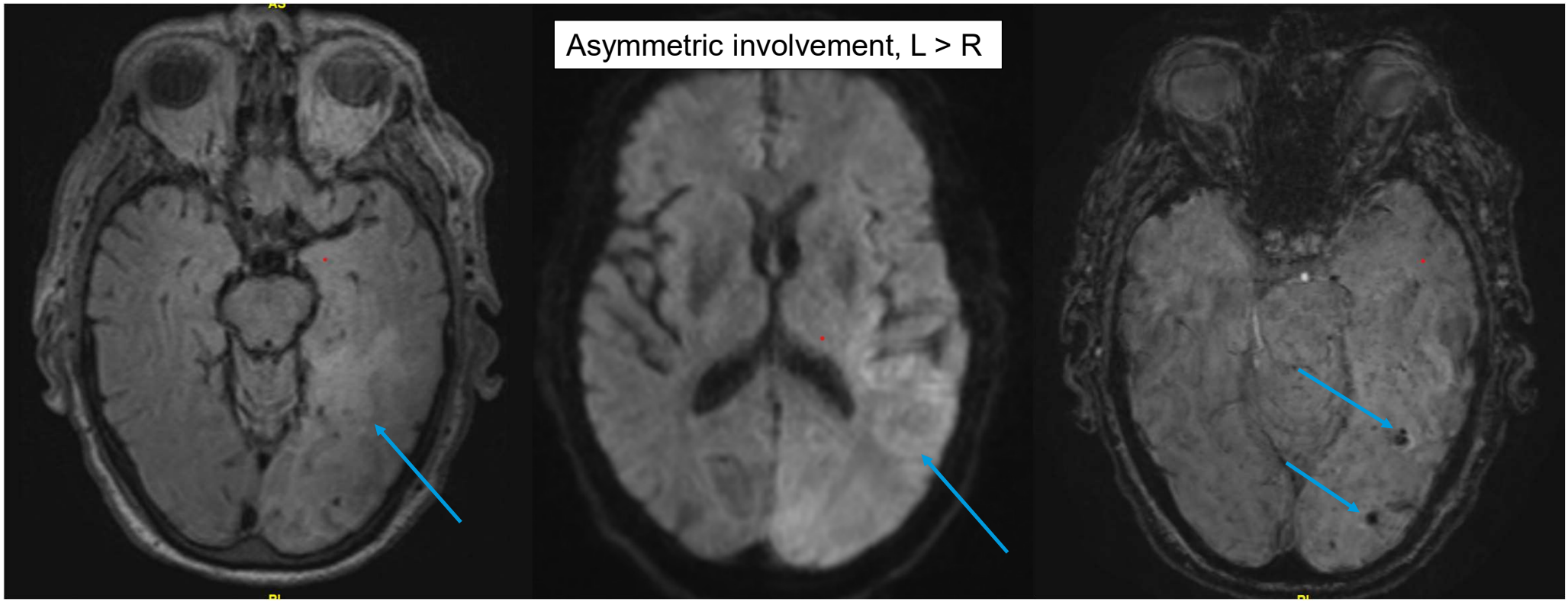
✓ 1. Temporal Lobe

2. Basal Ganglia

3. Brainstem

4. Spinal Cord

MRS. SHANNON: MRI BRAIN W/WO CONTRAST



T2 FLAIR
Hyperintensity

DWI
Hyperintensity

SWI
Hypodensity

HSV1 ENCEPHALITIS TREATMENT/PROGNOSIS

- Acyclovir IV x10-14 days
  - Monitor for AKI, hydration
  - Early initiation is key

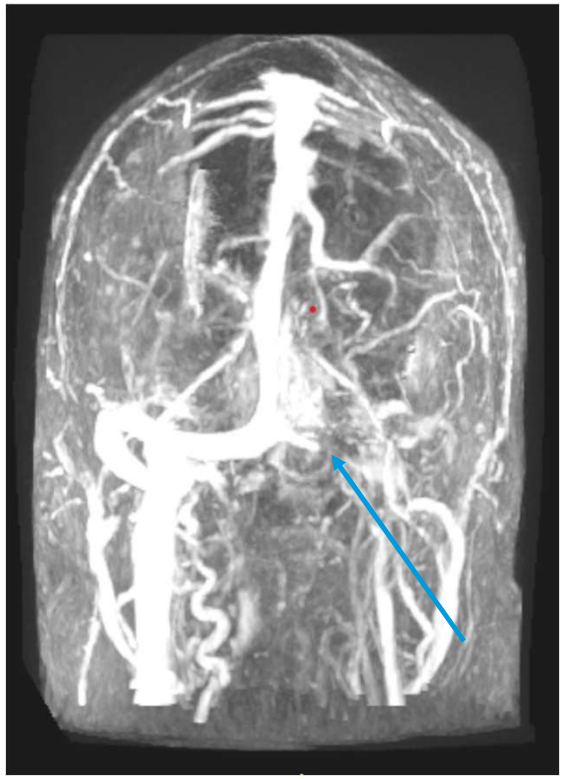
- #1 Cause of fatal viral encephalitis
  - Fatal if untreated
  - Mortality < 20% with appropriate treatment

- Monitor for complications

MRS. SHANNON COMPLICATIONS

- Worsening aphasia and headache
- CTH: venous infarction
- MRV: CVST in the transverse and sigmoid sinus w/ extension to IJ

CTH



MR Venogram

HERPES VIRUSES COMPLICATIONS

- Seizures
- Stroke
  - Ischemic
  - Hemorrhagic
  - Venous
- Cerebral venous sinus thrombosis (CVST)
- Vasculitis, VZV
- Necrosis
- Associated with secondary autoimmune encephalitis (NMDA)

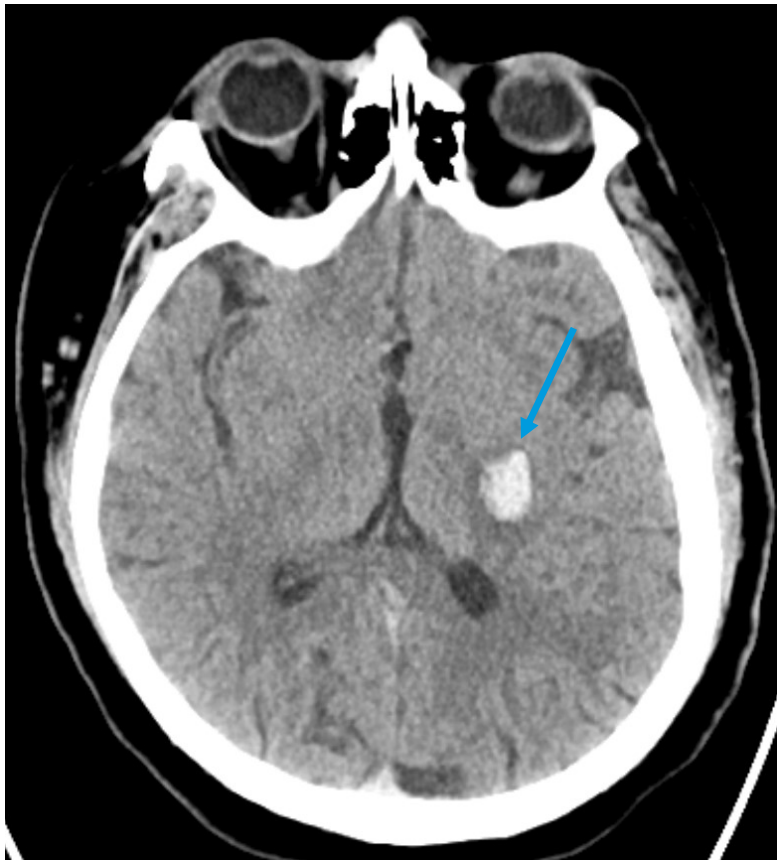
Initiate specific targeted treatment

CASE 3: MR. JONES

- 51 yo RHD M
- PMHx:
  - Hypertension not on medications

- Stroke alert activated by EMS en route to ED
  - Headache since waking this morning
  - R face, arm, and leg weakness and slurred speech
  - BP 208/96
  - NIHSS 8
    - R facial droop (2), R arm drift (2), R leg drift (2), dysarthria (1)

STAT CTH W/O CONTRAST

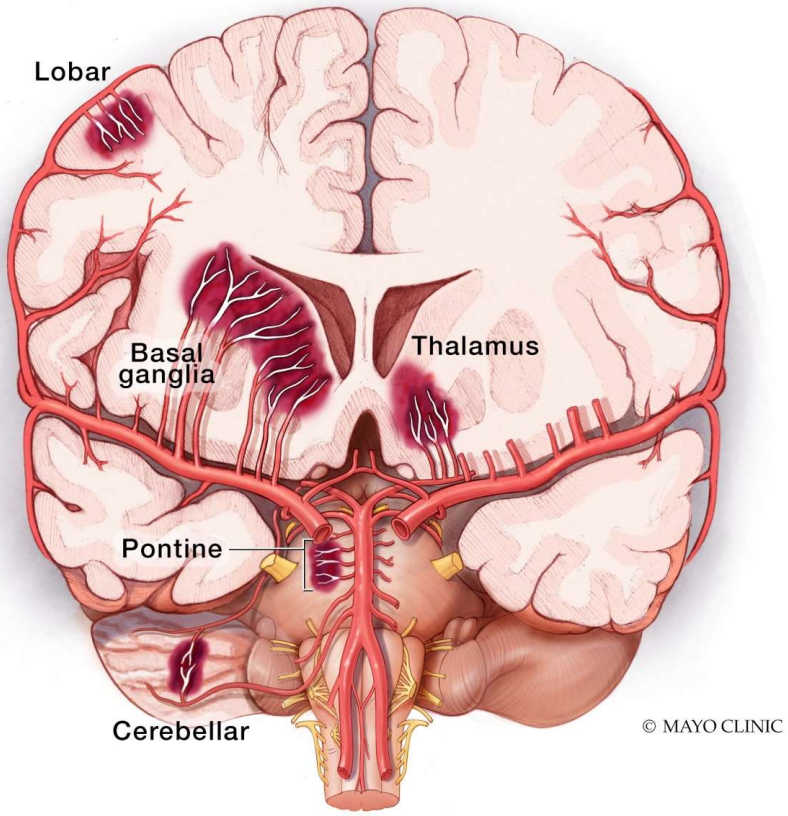


Intraparenchymal hemorrhage, L basal ganglia

NONTRAUMATIC ICH: ETIOLOGIES

- **Hypertensive**
- **Cerebral Amyloid Angiopathy**
- Vascular malformations
- CNS infection (HSV encephalitis)
- Hemorrhagic infarction (including cerebral venous sinus thrombosis)
- Brain tumors
- Bleeding disorders, antithrombotic therapy
- Vasculitis
- Septic embolism, mycotic aneurysm
- Moyamoya
- Drugs: cocaine, amphetamines

HTN HEMORRHAGE



- Classic locations
  - "Blood pressure causes trouble"
  - Basal Ganglia
  - Pons
  - Cerebellum
  - Thalamus

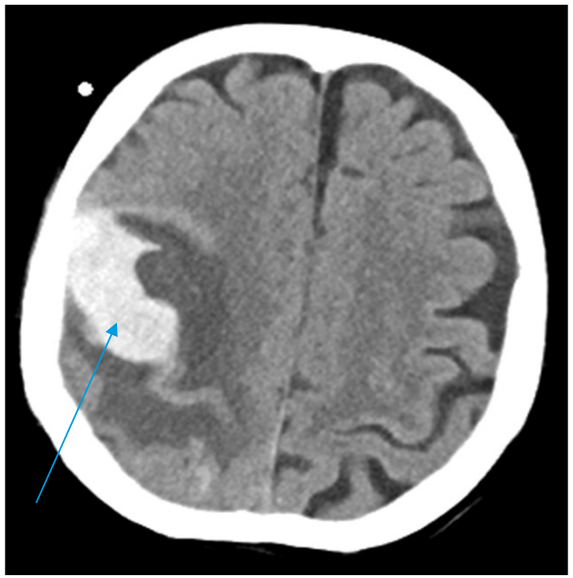
- Penetrator arteries
  - 90º to parent vessel
  - High pressures w/o gradual decrease in vessel caliber
  - Long-term- lipohyalinosis and focal necrosis
    - Lacunar strokes

CEREBRAL AMYLOID ANGIOPATHY (CAA)

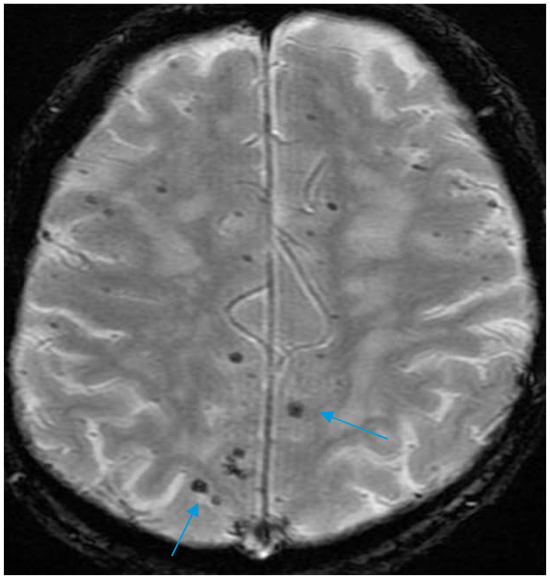
- Presentation:
  - Usually asymptomatic
  - Lobar hemorrhage in older patients, >60 yo
  - Cognitive impairment

- Pathogenesis
  - Deposition of amyloid beta peptide
    - Small to medium-sized cerebral blood vessels
  - Weakens the structure of the vessel walls
    - Prone to bleeding

CAA IMAGING



CTH: lobar hemorrhage



CTH: lobar hemorrhage

MRI GRE/SWI: Cerebral microhemorrhages in the cortex and/or “grey-white” junction

QUESTION: MR. JONES LIKELY HAS A HTN HEMORRHAGE. WHAT IS OUR TARGET SBP?

1. 100-120 mmHg
2. 120-140 mmHg
3. 130-150 mmHg
4. 160-180 mmHg

BLOOD PRESSURE RECOMMENDATIONS

2022 AHA/ASA GUIDELINES

Mild to moderate ICH

- SBP goal: 140
  - Range: 130-150
  - Sustained, avoid fluctuations
  - Lowering <130 is potentially harmful
  - ASAP
    - Initiate treatment <2 hours
    - Reach goal within 1 hour

Large or severe ICH, surgical decompression

- SBP goal not well established

Stroke. 2022 Jul;53(7):e282-e361

MANAGEMENT OF COAGULOPATHY

2022 AHA/ASA GUIDELINES

- "ICH while anticoagulated has extremely high mortality and morbidity."

- All anticoagulant and antiplatelet drugs should be discontinued and anticoagulant effect reversed immediately — *Class 1 rec*

Stroke. 2022 Jul;53(7):e282-e361

REVERSAL OF ANTICOAGULATION-ASSOCIATED ICH

	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban	UFH	LMWH
Dosing	Once daily	BID	BID	Once daily	Once daily	Continuous	BID or once daily
Mechanism	Vitamin K antagonist	Direct Thrombin Inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	AT-mediated inhibition anti-Xa/anti-IIa	AT-mediated inhibition anti-Xa/anti-IIa
Half-life (h)	20-60	12-17; longer in CKD	8-15	5-9; 11-13 in elderly	10-14	1-2	4.5-7
Onset of action	24-72 h Therapeutic 5-7 d	1-2 h	3-4 h	2-4 h	1-2 h	IV, immediate	SubQ, 3-5 h
Lab	PT/INR	TT, aPTT, anti-IIa, ECT	Anti-Xa assay	Anti-Xa assay	Anti-Xa assay	APTT	Anti-Xa assay
Reversal	Vit K 10mg IV; over 30 min and FFP 15mL/kg OR 4F-PCC if INR: 2-3.9, 25U/kg 4-6, 35U/kg >6, 50U/kg	Idarucizumab 5g; Two 2.5g vials consecutive infusions	Andexanet alfa *Low dose: bolus 400mg @ 30mg/min, followed by 480mg infusion @ 4mg/min for up to 120 min †High dose: bolus 800mg @ 30mg/min, followed by 960mg infusion @ 8mg/min for up to 120 min	Andexanet alfa *Low dose: bolus 400mg @ 30mg/min, followed by 480mg infusion @ 4mg/min for up to 120 min †High dose: bolus 800mg @ 30mg/min, followed by 960mg infusion @ 8mg/min for up to 120 min	Andexanet alfa (Not FDA approved)	Protamine sulfate 1mg per 100 U of heparin (max protamine dose of 50mg)	If last LMWH <8h, Protamine 1mg/mg LMWH If last dose of LMWH >8 h, Protamine 0.5mg/mg LMWH (max protamine dose of 50mg)

Content created by Dr. Cumara O'Carroll

STEROIDS, HYPEROSMOLAR THERAPY, PLATELETS

2022 AHA/ASA GUIDELINES

- "Several in-hospital therapies that have historically been used to treat ICH patients appear to confer either no benefit or harm."

- No benefit for outcome:
  - Prophylactic corticosteroids
  - Continuous hyperosmolar therapy

- Worsen outcome:
  - Platelet transfusions outside the setting of
    - ASA use and emergency surgery
    - Severe thrombocytopenia

Stroke. 2022 Jul;53(7):e282-e361

DVT AND SEIZURE PROPHYLAXIS

2022 AHA/ASA GUIDELINES

- Similar considerations apply to some prophylactic treatments historically used to prevent medical complications following ICH.

- DVT prophylaxis
  - Compression stockings alone are <u>not enough</u>
  - Chemical DVT ppx: 24-48 hours after ICH, if stable

- Seizure prophylaxis
  - <u>Does not</u> improve long-term seizure control or functional outcome

Stroke. 2022 Jul;53(7):e282-e361

MR. JONES: HYPERTENSIVE HEMORRHAGE

- Monitor for hematoma expansion
- BP control
  - Nicardipine gtt x 24-48 hours, SBP goal 130-150
  - Lisinopril and amlodipine initiated
- 48 hours after admission
  - Clinically and radiographically stable
  - DVT ppx initiated
- Rehab

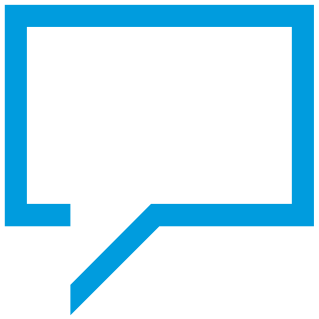
- What more can we do?
  - Ongoing trials, hopefully more to come!

SUMMARY

- Use SNOOP criteria to look for headache red flags. Rule out secondary causes of headache when indicated. Consider RCVS. CTA may not show vascular abnl for 2-3 weeks.
- Keep a high index of suspicion for status epilepticus in patients with recurrent seizures/not returning to baseline. Start/load adequate doses of ASM.
- HSV is the #1 cause of fatal encephalitis, associated with significant complications. Start acyclovir early. PCR may be falsely negative in first 72 hours.
- ICH can be associated with high morbidity and mortality. SBP goal is 130-150 for mild-mod ICH. Many things we have historically done to/for our patients are either of no benefit or potentially harmful.
  - New AHA/ASA guidelines 2022, top things to know

QUESTIONS & DISCUSSION

Taylor.Abigail@mayo.edu



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