Objectives

- Identify vascular causes of secondary headaches
- Recognize the causes of thunderclap headache
- Diagnose and manage RCVS
What type of Stroke causes headache?

- Traumatic – subdural, epidural hematoma
- Subarachnoid hemorrhage
- Intracerebral hemorrhage
- Ischemic stroke
- Vasculitides
Secondary headaches

**SNOOP**

**Systemic Symptoms**

Fever, myalgia, weight loss, history of systemic illness

**Neurologic Signs and symptoms**

**Onset** - Sudden, with valsalva, positional

**Older Age** : > 50

**Pattern change from prior headaches**
ICHD 3 – The Secondary Headaches
6: Headache attributed to cranial or cervical vascular disorder

- 6.1 Headache due to stroke or TIA
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  - Aneurysm, AVM, dural AV fistula, cavernous angioma, Sturge Weber
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- 6.7 Headache due to other intracranial arterial disorder
  - PRES, RCVS
- 6.8 Headache due to Genetic disorders – CADASIL, CARASIL and MELAS
A 62 year old man presents to the ER with a sudden, severe headache, holocranial with vomiting and vertigo BP: 190/98, neuro exam is normal in stretcher and CT head was normal. He is discharged with diagnosis of benign positional vertigo and when he stands to leave the ER he falls and is unable to stand up.
Right PICA infarct
Ischemic Stroke - Headache

- 27% (7-65%) have headache at onset of stroke
- Headaches are More common in:
  - Women
  - Migraine patients
  - Cerebellar strokes, basilar territory
  - Younger age
- Less common with Lacunar stroke
- Not associated with stroke severity or outcome
- Headache does not predict cause of stroke
76 year old man with atrial fibrillation and hypertension, had the sudden onset of a severe, holocranial headache, right sided weakness and speech difficulty.

What is the most important question for this patient?
Intracerebral hemorrhage
Intracerebral Hemorrhage

- Sudden headache + **focal neurologic symptoms**
- Uncontrolled hypertension is primary cause
- Headache most common with caudate, cerebellar and least with thalamic hemorrhage (< 1/3)
- AVM, aneurysm, vasculitis, venous thrombosis, anticoagulation, trauma, drugs, tumors
- Cortical hemorrhage in elderly => think Amyloid
Pituitary Apoplexy – ICHD II

- Severe, acute retro-orbital or diffuse headache with **at least one of**:
  - Nausea and vomiting
  - Ophthalmoplegia, low VAcuity
  - Decreased LOC

- hypo pituitarism
- hypotension
- fever

- Neuroimaging: acute pituitary hemorrhagic infarction
- Headache occurs with the pituitary hemorrhage
- Headache and symptoms resolve within 1 month
A 26 year old with a history of menstrual migraines is brought to the emergency room with the sudden onset of the worst headache of her life. The headaches reached a 10/10 intensity in about 30 seconds. The really severe pain lasted about 10 minutes but she still has a throbbing, holocranial headache. She reports that this headache feels different than her usual migraine headaches.
Listen to your patients...
Thunderclap Headache

- Very Severe headache
- Abrupt onset, reaching maximum intensity in < 1 minute
- Lasting ≥ 5 minutes

“Worst headache of my life”
Thunderclap Headache
Differential Diagnosis

- Subarachnoid Hemorrhage
- RCVS, PRES
- Intracerebral hemorrhage
- Pituitary apoplexy
- Retroclival hematoma
- Sphenoid sinusitis
- Dural(epi) spinal hematoma
- Primary Exertion Headache
- Aqueductal stenosis
- Primary thunderclap headache

- Arterial Dissection
- Primary cough headache
- Cerebral Venous Thrombosis
- Intracranial Hypotension
- Colloid cyst of III Ventricle
- Meningitis
- Orgasmic headache
- Acute Hypertensive crisis
- Cardiac cephalagia
- Pheochromocytoma
Subarachnoid hemorrhage
Subarachnoid hemorrhage

- The most common cause of thunderclap headache
- 80% from ruptured saccular aneurysms
- Other causes: AVM, dural AV fistula, drugs/cocaine, vertebral dissection,
- 95% CT head shows hemorrhage
  - CT head sensitivity highest 6-12 hours after SAH
  - Sensitivity decreases to 75% by day 3, 58% by day 5
  - 5% CT is negative acutely – need to do a LP
- Need Angiography – CT angiogram, ? 4 vessel angiogram
  - 14-22% angiogram is negative
ICHDI II – Part Two – The Secondary Headaches

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   - RCVS
   - Genetic disorders – CADASIL, CARASIL and MELAS
Temporal Arteritis

- Age > 55 years, usually > 60
- Primary presentation is **headache**, can be any type
- Other features predicting positive biopsy
  - Transient monocular vision loss
  - Jaw claudication
  - Elevated ESR, C reactive protein
  - Can also have -myalgia, fever, fatigue, anemia
- After first eye involved, second involved ≤ 1 week
Temporal Arteritis

- Biopsy at least 3 cm, consider bilateral biopsies
- Immediate prednisone: 1 mg/kg, do not wait for biopsy
  - Biopsy still be positive up to weeks after starting steroids
- Temporal artery biopsy is 85% sensitive
  - Increased if all clinical features present and esr/crp elevated
- Imaging studies
  - Contrast enhanced MRI of the temporal artery
  - Ultrasound to look for halo (only 40-69% sensitive)
Primary and Secondary CNS Angiitis

- Secondary - + ANCA, SLE, RA, Behçet's, PAN, Sjogren's,
- Headache in 50-80%, diffuse, not sudden onset
- **Encephalic signs:**
  - Stroke
  - Seizures
  - Change in LOC, confusion
- Headache improves with immunosuppressants
- Subacute, stepwise presentation
- MRI with strokes of different ages
*Absence* of headache + CSF pleocytosis- Diagnosis unlikely
A 28 year old, with a history of migraines, has had a prolonged labor and has transient loss of vision in right eye and severe right sided headache. Labor continues and four hours after delivery she has onset of left hemiplegia and lethargy.
Peri-partum stroke with Headache

- Cerebral venous thrombosis
- Pre-eclampsia/eclampsia
- Cerebral artery dissection
- RCVS
Right Carotid Artery Dissection
Left Carotid Artery Dissection
Carotid Artery Dissection

- Carotid and vertebral arteries are pain sensitive
- Pain is referred to the face/head
- Carotid dissection usually causes headache
  - Ipsilateral **Headache in 55 – 100%**
  - Often precedes ischemic symptoms
- Ipsilateral Horner’s, Pulsatile tinnitus, carotid bruit
- Ipsilateral neck pain is also common

*Cerebral artery dissection- increased in migraine patients*
Vertebral artery dissection

- Headache in 50 – 70%
- SAH with intradural vertebral artery dissection
- Sudden headache in occiput, nape of neck
- Stroke, SAH can occur 1-10 days after headache
- If detected at onset of headache, may prevent stroke
Cervical Artery dissection - Imaging

- CT angiogram, MR angiogram – usually adequate
- Need intracranial and extra cranial angiograms
- MRI neck with fat saturation protocol
  - Intramural blood, crescent sign,
- Angiogram
  - Long tapered or flame shape
    - stenosis - 48%
    - occlusion – 35% (can recanalize later)
  - Intimal flap
  - Double lumen
  - Later: pseudoaneurysm
Right Vertebral Artery Dissection
Right Vertebral Artery dissection
Cerebral Venous Thrombosis

- Headache usually is the presenting feature
- Can have:
  - Papilledema, vision loss due to increased ICP
  - Seizures
  - Focal neuro deficits, confusion, decreased LOC
- Often has a hemorrhagic component + edema
  - Does not conform to an arterial territory, need CT Venogram
- MR venogram - can overestimate, transverse sinus with anatomic variation is very common- CT venogram is better!
- Causes: postpartum, hereditary thrombophilias
- 23% progress, can herniate -> anticoagulation, thrombolysis
Empty Delta Sign
Cerebral venous thrombosis
Sagittal Sinus Thrombosis
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A 79 year old man with hypertension and renal insufficiency woke up with a holocranial headache and mild confusion. His wife called 911. In the ER his blood pressure is 240/140. You are called to see him when he begins to have recurrent generalized seizures.
PRES – Posterior Reversible Encephalopathy syndrome
Clinical Features

- Slow onset headache, but may have a thunderclap headache
- Confusion, decreased level of consciousness
- Visual Changes, focal neurologic symptoms
- Seizures!
- 75% have moderate to severe hypertension, 25% do Not!
PRES
Associated Disorders

- Hypertensive encephalopathy
- Eclampsia
- Acute and Chronic Renal disease, Dialysis
- Hypercalcemia, hypo magnesium, hypo natremia
- Blood products – RBC transfusion, ivIg
- Contrast media – intra arterial
- Sepsis, H1N1 A, ischemic bowel disease
- TTP, hemolytic uremia syndrome
- Vasculitis – SLE, PAN, Wegners, cryoglobulinemia,
- Porphyria
Medications that can cause PRES

- Immunosuppressant drugs
  - Cyclosporine A
  - Tacrolimus
  - Sirolimus
  - Bevacizumab
  - Cisplatin
  - Cytarabine
  - Gemcitabine
  - Ipilimumab
  - Vincristine
  - Interferon alpha
  - Methotrexate
  - Rituximab

- Tyrosine kinase inhibitors—sorafenib, sunitinib

- Granulocyte colony stimulating factor
Clinical Spectrum of PRES
Lee VH et al Arch Neurol 2008; 65: 205-210

- Retrospective review of 36 patients with PRES
- 20 F, 16 M, mean age: 45 years

- 68% had hypertension
- 11% had eclampsia
- 21% on dialysis
- 24% s/p bone marrow or solid organ transplant
- 32% had malignancies
Clinical Spectrum of PRES
Lee VH et al  Arch Neurol 2008; 65: 205-210

- Seizures  87%
- Encephalopathy  92%
- Headache  53%
- Visual change  39%
- Intubation  39%
- Mean systolic BP  187 mm Hg

- 5/36 died
- 28/36 with mean f/u of 1.8 years – full recovery, no seizures
PRES Imaging

- Symmetric WM hyper intensities- + DWI, no mismatch
  - Restricted diffusion in 11-26%- cytotoxic edema vs infarction
- Border zone regions – cortex, subcortical and deep WM
- Primarily posterior –parietal/ occipital-spares calcarine cortex
- Can be holo hemispheric – ie ACA/MCA borderzone
- Gyriform signal enhancement with gadolinium can occur
- Can look similar to post seizure MRI if mild
- **Brainstem and cerebellum are often involved**
- Severe cases: anterior cortex, basal ganglia
PRES
Pathophysiology

- Impaired **autoregulation** and **Dysfunctional endothelium**
- Possible mechanisms
  - Brain hyper perfusion, Vasogenic edema
  - Breakdown of BBB
  - Extravasation of fluid/blood products
  - Arterial border zone – capillary level
  - GM more packed than WM, resists edema
  - Posterior circulation has less sympathetic innervation
  - immune system (T cell) and endothelial cell activation with vasoconstriction with hypo perfusion and activation of coagulation and leukocyte trafficking
  - cytotoxic meds – may have direct toxicity on endothelium
A 44 year old with chronic migraine without aura, calls your office on a Friday afternoon to report that 2 hours previously she had the sudden onset of a bilateral severe headache, “the worst of her life” that reached peak intensity in less than 1 minute. She took a maxalt and repeated it in 2 hours and it is slowly resolving. Of note, her psychiatrist just increased her Zoloft to 200 mg and she has been taking Claritin D for an upper respiratory infection and sometimes for her anxiety, she smokes marijuana.
Thunderclap Headache
Thunderclap Headache (TCH)

- **Subarachnoid hemorrhage**
  - 10-43% have sentinel thunderclap like headache
  - 12% have worst headache of life with SAH
- **RCVS** – 85-95% present with thunderclap
- **Cerebral venous thrombosis** - 75% with headache
  - 2-13% have a TCH at onset
- **Arterial dissection** - 75% present with headache
  - TCH in up to 20%, ipsilateral to the dissection
- **Spontaneous intracranial hypotension**
  - 14% with TCH
- **Meningitis** - 2.7% with TCH
RCVS eponyms
Reversible cerebral vasoconstriction syndrome

- Crash migraine
- Benign angiopathy of the CNS
- Migrainous vasospasm, migraine angiitis
- Call-Fleming syndrome
- Post partum angiopathy
- Bath headache
- Isolated benign cerebral vasculitis
- Drug-induced cerebral vasoconstriction
- Vasospasm in fatal migrainous infarction
Headache due to RCVS
ICHD 3 criteria

- Headache with either or both:
  - Recurrent during ≤ 1 month with thunderclap onset
  - Triggered by sexual activity, exertion, valsalva, emotion, bathing

- Angiogram with “Strings and beads” or Sausages on a string
- Angiographic findings resolve spontaneously in 2-3 months
- No other ICHD diagnosis and SAH has been excluded
RCVS Features

- Headache – severe, acute, thunderclap, recurrent
- SAH ruled out – CT, LP (protein < 80, WBC < 10)
- MRA/CTA – more severe angiographic findings => increase risk of stroke
- MRI DWI - can have PRES changes, watershed infarction
The Thunderclap Headache of RCVS and its Triggers

- RCVS
  - Primary: 1/3
  - Secondary: 2/3

- Recurrent Thunderclap headache is hallmark (mean: 4-8)

- 80% have a trigger including: sexual activity, defecation, stressful situation, urination, coughing, sneezing, laughing, sudden bending down, singing
Secondary RCVS

- Pregnancy and post partum
- Drugs: phenylpropanoloamine, ephedrine, pseudoephedrine, ergotamine, methergine, bromocriptine, SSRIs, lisuride, sumatriptan, isometheptine, cocaine, ecstasy, amphetamines, cannabis, LSD, tacrolimis, cytoxan, erythropoietin, amphetamine, ecstasy, bromocriptine, cannabis
- Blood products: iv Ig, red blood cell transfusions
- Metabolic: hypercalcemia, pheochromacytoma, porphyria, carcinoid tumors, unruptured aneurysms, head trauma, neurosurgery, endarterectomy, spinal subdural hematoma,
The clinical and radiological spectrum of RCVS- A prospective series of 67 patients
Ducros A et al   Brain 2007:130:3091-3101

- Prospective study, single center, same neurologist
- RCVS diagnostic criteria:
  - Sudden, severe headache, +/- neuro deficits/seizures
  - Cerebral vasoconstriction on MRA or angiogram with at least 2 narrowings per artery, on two different intracranial arteries
  - Disappearance of artery narrowing in less than 3 months
RCVS- clinical features
Ducros et al

- Average age: 42.5 years
- Women > Men - 43 female, 24 male
- RCVS was primary in 37% and secondary: 63%
- Focal neurologic deficits: 14/67 patients
  - transient: 11 cases > 24 hours: 5 cases
- Seizures: 2/67
- BP >160/90 in 22 (only 2 had prior hypertension)
Clinical symptoms of RCVS
Ducros A et al  Brain 2007:130:3091-3101

- TCH was presenting symptom in all and was bilateral
- 76% TCH was the only symptom
- 63 (93%) had recurrent TCH- mean: 4.5 days after first
- 13 patients had h/o migraine – all noted TCH different
- 79% had trigger- primarily valsalva-cough, sneeze, sex
- Nausea/vomit: 57%
- Agitation: 32%
- Photophobia: 30%
Secondary causes of RCVS
Ducros A et al  Brain 2007:130:3091-3101

- 25 patients no precipitating factor
- 5 women were postpartum - 1 had bromocriptine
- 37 patients used vasoactive substances
  - Cannabis: 20
  - SSRIs: 13
  - OTC decongestants: 8
  - Cocaine: 3
  - Interferon: 2
  - Nicotine patch: 1
- Cannabis more in men and SSRI more in women
MRI in RCVS
Ducros et al

- Cervical artery dissection - 4/67 patients
- 19 (28%) had abnormal MRI
  - C SAH 15
  - ICH 4
  - Infarct with symptoms 2
  - Silent infarct 1
  - RPLS/PRES 6
RCVS- Vascular Imaging

- MRA showed diffuse, segmental artery constriction in 59 (88%)
  - 6- vasoconstriction only on second MRA – 14 days later
  - TCD in 64 - 44 (69%) had increased velocities MCA, carotid
- Angiogram – 45/67 patients
  - All had multifocal segmental artery constrictions
  - Including those with normal MRA and 6 with normal TCD
- Other arterial abnormalities in 7
  - 4 with small unruptured aneurysms – (2-3.8 mm)
    - None of these patients had SAH on MRI or CSF exam
  - 4 had vertebral artery dissection
Time Course of RCVS

- Monophasic course, no new symptoms after 1 month
- Days 1-7  Thunderclap headache, can be recurrent
- Days 7-21  Peak of vasoconstriction
- Week 12  Resolution of Vasoconstriction

**Stroke complications: 5-10%**

- RISK factors for stroke: h/o migraine, severe vasoconstriction
- Week 1-2 : SAH, ICH, seizures, PRES
- Week 2-3: TIAs and Ischemic stroke
RCVS - Diagnostic Testing

- Listen to the patient!
- Review medication list!
- CT head
- Toxicology screen
- LP - Check opening pressure
  - r/o SAH, meningitis, inflammatory/vasculitis
- MRI brain with and without
- MRA/V and/or CTA/V
- If negative- consider 4 vessel angiogram but…..
  - 9% -transient neurologic deficits after angiogram
**RCVS - Pathophysiology**

- Unknown- transient deregulation of cerebral arterial tone resulting in Vasoconstriction

Possibly due to:

  - Endothelial dysfunction
  - Increased sympathetic tone
  - Oxidative stress

- Possible hormonal component

- c SAH occurs early – suggesting small vessel involvement first

- Stroke/TIAs later in course suggest larger vessels involved later

- Genetic polymorphism – BDNF gene
RCVS treatment

- Stop all vasoactive drugs
- Monitor BP, avoid high or low BP
- Nimodipine – 30-60 mg q 4-8 hours for 4-12 weeks
  - This reduces the thunderclap headaches within 48 hours
  - Does not change the time course of vasoconstriction
  - Can also use verapamil, magnesium
- Avoid glucocorticoids – can worsen, increase sympathetic tone
- Angiogram can cause transient neurologic symptoms in 9%
CADASIL
Cerebral Autosomal dominant Arteriopathy with Subcortical Infarcts and leukoencephalopathy

- Missense mutation in the NOTCH 3 gene on chromosome 19p13 – over 50 mutations
- Migraine with aura, including hemiplegia, in 30-40- 3rd decade
- MRI WM abnormalities – ages 30-40- 2/3 micro bleeds
- 85% have stroke or TIA by their 5th decade
- Subcortical dementia in 60s
- Psychiatric Sx in 20-30%, depression, bipolar
Migraine that Mimics Stroke
Familial Hemiplegic Migraine

- 3 genes have been identified
- Slowly progressive hemiparesis
- Hemisensory loss, can have aphasia
- Visual aura or homonymous vision loss
- Sx spread slowly 30-60 minutes
- Severe pounding headache, contralateral follows symptoms
- Can have drowsiness, coma, symptoms can be prolonged
MELAS- Mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes

- Mutation in MtDNA – maternally inherited
- Stroke like events, strokes
- Lactic acidosis, ragged red fibers – muscle
- Migraine with/ without aura, hemiplegic
- Seizures can occur
- CoQ10 may help
Conclusions

- Sudden severe headache - think secondary headache
  - Most Often vascular – SAH, CVT, Dissection, RCVS
  - Intracranial hypotension
- Secondary headaches often without neurologic deficits
- Migraine patients – at increased risk of dissection, RCVS
- Recurrent thunderclap headache suggests RCVS - image!
- The correct diagnosis is essential!
THE END
Thank you