Reversible cerebral vasoconstriction syndromes, PRES and other acute cerebral complications of pregnancy and delivery

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DISCLOSURES

- None
• 32 yo PRIME. SVD 39 weeks. Uneventful
• Anxiety treated with sertraline.
• Home day 2. NO PP problems
• Home nurse day 3, c/o severe headache. Bp 130/80. Told to come to ER. Declined in favor of sleep.
• Woke up, headache worse, BP 140/90. To ER
Case continued

- ER labs normal
- BP 130/80-150/90
- Urine P/C ratio 0.2
- Anesthesia not spinal HA
- Neuro exam normal.
- Headache improved and almost gone
- Admitted to exclude PEC
- 2 hours after admission, Severe Headache
- Stat CT with ICH and ischemic changes posterior, lateral and midline circulation.
• Airlifted to tertiary center
• Craniotomy for decompression
• Manitol, antihypertensives, Neuro critical care
• Despite normal blood pressure, has recurrent focal deficits with ongoing new bleeds
• Arteriogram with segmental arterial spasm CW RCVS/PCA
• IR for intra-arterial Nicardipine daily for increased TCD studies
• 3 weeks of treatment, spasm stopped.
• Residual deficits with multifocal neuro deficits /Survived
SWI, ADC and T2 FLAIR changes in the Occipital lobe read as possible calcification vs a small vascular malformation on day 1.

MRI CSF flow study – unremarkable on day 2.

Right Parietal and left occipital hemorrhages on CT Head done on day 5, stable hemorrhages.
Normal DWI cuts

- DWI – Right cerebellar infarct
- DWI Bil. Medial Temporal lobe infarcts
- DWI – Left ACA infarct

T2 FLAIR – Bilateral occipital-parietal ICH with surrounding edema

SWI – bilateral occipital hemorrhages

Review of first MRI showing subtle leptomeningeal FLAIR changes

DSA showing vasculopathy in different arterial distribution suggesting Vasculopathy

- Right ACA
- Basilar and bilateral PCA
- Basilar artery
- Left ACA
Reversible Cerebral Vasoconstriction syndrome
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
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.
First case report in 1960

In 1983, French researchers published 11 pt’s- acute benign cerebral angiopathy.

Gregory Call and Marie Fleming - Massachusetts General hospital - 16 pt’s with the characteristic symptoms and abnormal cerebral angiogram findings.

A 2007 review - Calabrese et al. proposed the name reversible cerebral vasoconstriction syndrome used today along with PCA.
• The clear mechanism is not known

• Dysregulation of cerebrovascular tone.

• Severe headache triggers vasoconstriction OR Cerebral vasoconstriction triggers headache

• Same sensory afferents mediate both the headache and vasoconstriction V1 division of trigeminal nerve and C2.

• Ischemic strokes: secondary to severe vasoconstriction

• Hemorrhagic strokes: secondary to reperfusion injury after ischemic stroke.
Pathophysiology

RCVS

PRES

Singhal et al; Bartynski WS and Broadman JF
Abbreviations: PEE = Preeclampsia/Eclampsia, PRES = Posterior reversible encephalopathy syndrome, RCVS = Reversible cerebral vasospasm, BBB = Blood brain barrier, ICH = Intracranial hemorrhage, SAH = Subarachnoid hemorrhage

• True incidence unknown.

• Female to male ratio ranges from 2:1 to 10:1 depending on the case series.

• More than half in peripartum women
• No specific ethnicity is involved.

• Recently being increasingly reported due to
  • increasing awareness.
  • Widespread use of CT and MR angiography
  • vasoconstrictive medications
RISK FACTORS

- Pregnancy
- Migraine
- Vasoactive drugs- SSRI
- Neurosurgical procedures
- Hypocalcemia
- Unruptured saccular aneurysms
- Cervical artery dissection
- Cerebral venous thrombosis
- others
CLINICAL FEATURES

• Thunderclap headache – usually very dramatic - intrapartum or postpartum

• 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 sub acute or low severity headache.
• Absence of Headache at onset is exceptional.

• 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 21% of patients at the time of presentation

• Usually Generalized tonic clonic seizures

• Recurrent seizures are rare
Focal Neurological symptoms

- 9-63% in published case series.
- Hemiplegia
- Tremor
- Hyperreflexia
- Ataxia
- Aphasia
- Visual defects including scotomas, blurring, hemianopia, cortical blindness are common.
- Many patients show features of Balint Syndrome
  - (simultanagnosia, Oculomotor apraxia, optic ataxia

Singhal AB et.al, Walsh RD et.al.
Systemic examination is usually unrevealing.

Vital signs at presentation may show high blood pressure – secondary to pain Vs. associated conditions like eclampsia, cocaine exposure or the disease itself.

- 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.

Resolution:

Singhal AB et.al, Buckle RM et.al, Williams TL et.al, Fugate JE et.al
EVALUATION AND DIAGNOSIS

- Clinical characteristics
- Brain imaging
- Angiographic features
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

Singhal AB et al; Archives of Neurology 2011
• 30-70% - No abnormality on initial scans despite having widespread cerebral vasoconstriction.
• 75% of admitted patients develop parenchymal lesions.
• Most frequent lesions are

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

Most common lesion
Neurovascular imaging

- Abnormal cerebral angiography
- “sausage on a string” appearance.
- Smooth, tapered narrowing followed by abnormal dilated segments
- CTA, MRA, DSA are preferred.
- TCD monitoring progression and guide therapy
- Angiography can be false negative initially
<table>
<thead>
<tr>
<th></th>
<th>Preeclampsia</th>
<th>PRES</th>
<th>PPA/RCVS</th>
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<tbody>
<tr>
<td>Neuro SX</td>
<td>Y</td>
<td>Y</td>
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<td>Hypertension</td>
<td>Y</td>
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<tr>
<td>ICH</td>
<td>Y</td>
<td>N ?</td>
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<td>Proteinuria</td>
<td>Y</td>
<td>N</td>
<td>N</td>
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<td>Hemoconcentration</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<td>Very High BNP</td>
<td>N</td>
<td>Y</td>
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<td>Renal abn</td>
<td>Y</td>
<td>N</td>
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<td>Resolution</td>
<td>Del</td>
<td>Days</td>
<td>w/m</td>
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<td>Recurrent CVA common</td>
<td>N</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Hear rate</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>CT</td>
<td>Mulifocal at onset of bleed or seizure-bilateral in almost all</td>
<td>Edema only</td>
<td>Bleed or infarction then multifocal</td>
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<tr>
<td>Variable</td>
<td>RCVS/PCA</td>
<td>PACNS</td>
<td>SAH</td>
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<tr>
<td>SEX-F to M</td>
<td>2-3:1</td>
<td>1:1</td>
<td>1.6:1</td>
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<tr>
<td>ONSET</td>
<td>Acute</td>
<td>Sub-acute/Chronic</td>
<td>Acute</td>
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<tr>
<td>Headache</td>
<td>Severe/Dull/Throbbing/Thunderclap</td>
<td>Progressive/Thunderclap/Dull</td>
<td>Thunderclap</td>
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<tr>
<td>CSF findings</td>
<td>Normal</td>
<td>Abnormal</td>
<td>Abnormal</td>
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<tr>
<td>Imaging-Parenchymal</td>
<td>May be normal/infarcts and SAH</td>
<td>Abnormal in most/ small infarcts</td>
<td>SAH-Site specific</td>
</tr>
<tr>
<td>Imaging-Neurovascular</td>
<td>Dilation and Spasm, multifocal</td>
<td>Often Normal Can see arterial irregularities</td>
<td>Saccular Aneurism in many.</td>
</tr>
</tbody>
</table>
RCVS SAH

**No evidence** of ruptured aneurysm or vascular malformation

**Diffuse and disproportionate** extent of cerebral vasoconstriction relative to amount of SAH

**Sausage on string** appearance of alternating areas of segmental vasoconstriction preferentially involving distal 2nd- and 3rd-order cerebral branches

Development of vasoconstriction in first 4–5 days after symptom onset, or **persistence past 3 weeks**

Aneurismal SAH

Plausible **target lesion** identified

Severity of **vasospasm correlates** with amount of hemorrhage

**Smooth, long segmental narrowing** for proximal arteries at circle of Willis

Development of vasospasm peaking between **4 and 14 days** after hemorrhage
• Misdiagnosis can lead to inappropriate use of antimigraine agents like triptans which can exacerbate vasoconstriction and stroke.

• RCVS vs Migraine
  1. RSVS rarely recurs, no hx migraine
  2. abrupt onset of headache different from migraine
  3. brain imaging and angiographic abnormalities are inconsistent with migraine and persist for several weeks.
DD for ANGIOGRAPHIC ABNORMALITIES

- Intracranial Atherosclerosis
- Infectious arteritis
- Vasculits
- Moyamoya disease
- Fibromuscular dysplasia
• Arterial narrowing is irregular
• Accumulating T2-hyperintense brain lesions on neuroimaging
• Leptomeningeal enhancement
• Scattered deep infarcts
RCVS Vs. PACNS

- Recurrent thunderclap headache.
- CSF abnormal in 80-90% PACNS

- 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 - 97% ABNORMAL)

**Specificity of 98-100% and a similarly high PPV**

**Can be used as a bedside tool without cerebral angiography**
• No proven established therapy

• Most patients recover with time

• Upto 1/3 patients have transient symptoms and rare cases develop progressive clinical course

• Reasonable to admit for observation, pain control and supportive care for the first few days after symptom onset.
• Admit to NSICU
• 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.**
  - No methergine, Hemabate/PIT miso OK

• Treat seizures symptomatically. Rarely recur.
  - PP pts go on mag given DDX PEC
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, Magnesium sulphate, nicardipine
Nimodipine

• Two prospective case control
  • no effect on time course of cerebral vasoconstriction
• Improved headache frequency and intensity.

• Proven effects on smaller vasculature which is difficult to image by angiography.
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.
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
  • has been proposed as a diagnostic test for RCVS.

• Risk of reperfusion injury.
Angiogram before IA therapy
Angiogram after IA therapy
Avoid exposure to precipitating factors/ discontinue SSRI, vasoactive substances.

Avoid physical exertion, valsalva maneuver and known triggers of recurrent headaches for a few weeks. (no intercourse)

Secondary prophylaxis for stroke is not indicated.

No genetic implications of RCVS
15-20% - residual deficits

chronic migraine like headaches and depression following RCVS are common.
CONCLUSIONS

1. RCVS is group of conditions characterized by reversible cerebral constriction – dilation of cerebral arteries
2. ~90% have recurrent thunderclap headaches
3. ~1/3rd of patients develop ischemic or hemorrhagic strokes or reversible brain edema on brain imaging
4. Exclusion of CNS vasculitis and demonstrating reversibility is key to diagnosis
5. Sympathomimetics, serotonergic drugs, immunosuppressive as well as postpartum status are important precipitants
6. Most important treatment principle is identification and removal of potential precipitants
Thank you