Identifying and Managing Cerebral Venous Thrombosis and PRES

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74 y/o: Headache x 7 days, Sudden Left Arm Weakness x 20 Hours

• Arterial ischemia? Venous? PRES? Other?
• Management?
74 y/o Cont’d: Headache x 7 days, Sudden Left Arm Weakness x 20 Hours

CVT: Anatomy

Superior sagittal

Inferior sagittal

Straight

Transverse

Sigmoid

Internal jugular

Radiographics 2006;26:S19-S41
CVT: Thrombosis Locations

International Study on Cerebral Vein and Dural Sinus Thrombosis

n=624

- Transverse sinus 86%
- Superior sagittal sinus 62%
- Straight sinus 18%
- Deep venous system 11%
- Cortical veins 17%
- Jugular veins 12%
- Cerebellar veins 0.3%
- Cavernous sinus 1.3%

Stroke 2004;35:664-670

CVT: Most Common Presentations

n=61

- Headache 82%
- Focal neurologic deficit 72%
  - Motor or sensory 52%
  - Visual 28%
  - Aphasia 21%
- Seizures 31%
- Mental status changes 34%

Neurocrit Care 2009;11:330–337
CVT: Headache Presentations

\textit{n=200}

\textbf{Duration}
- Acute (1-3 days) \hspace{1cm} 60\%
- Subacute (4-14 days) \hspace{1cm} 24\%
- Chronic (>14 days) \hspace{1cm} 10\%

\textbf{Quality}
- Band-like \hspace{1cm} 20\%
- Throbbing \hspace{1cm} 9\%
- Thunderclap \hspace{1cm} 5\%
- Other (pounding, exploding, stabbing, etc.) \hspace{1cm} 20\%

\textit{J Headache Pain 2010;11:137-9}

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CVT: Common Findings

\textbf{Isolated intracranial hypertension}
- Mimics pseudotumor cerebri
  - Headache, nausea, visual loss, 6\textsuperscript{th} nerve palsy

\textbf{Focal cerebral signs}
- If acute mimics stroke
  - Absence of well-defined arterial syndrome
  - Presence of seizures
- Subacute can mimic encephalitis or abscess

Both can mimic PRES
CVT: Causes

General
• Lead to venous stasis, increased clotting tendency, and/or changes in the vessel wall

Can be divided into two main groups:
• Regional causes
• Medical causes

CVT: Causes

Regional
• Head trauma, including neurosurgery
• Brain tumors (meningioma, mets)
• Infections
  - Sphenoid or ethmoid sinusitis
  - Dental abscess
  - Otitis media
  - Facial staph aureus leading to cavernous sinus thrombosis
CVT: Causes

Medical
- Malignancies (visceral, lymphoma, leukemia, etc.)
- Inflammatory and connective tissue diseases
  - Behcets, lupus, Chrone’s, ulcerative colitis
- Pregnancy, oral contraceptives
- Hereditary hypercoagulable states
- Cardiac – CHF
- RBC disorders
  - Polycythemia, sickle cell, paroxysmal nocturnal hemoglobinuria

CVT: Tests and Imaging

CSF
- May be done to exclude infection
- CSF WBCs can be increased in 1/3; protein and RBCs increased in 2/3

Imaging
- MRI, MRV can be definitive
- Consider angiography when diagnosis unclear or when interventional treatment considered
CVT: Imaging of Parenchyma

- Abnormalities in as many as 57% of patients
  - Half have regions showing reduced ADC values
    (cytotoxic as well as vasogenic edema)
- Hemorrhage in 1/3 of cases

48 y/o Man: Headache x 2 Days, Brief Leg Weakness

- MRI head was unremarkable
- MRV

RadioGraphics 2006;26:S19-S41
43 y/o Woman With Ulcerative Colitis: Seizures, Quadraparesis Over 4 Days

43 y/o Woman with CVT: Improved Motor Function Post Local tPA
CVT Treatment: Einhaupl Study

**Design**
- RCT, single center, blinded outcome assessment
- N=20 (stopped when better outcomes in heparin arm)
- Diagnosis by catheter angiogram
- Primary endpoint: CVT severity score

**Intervention**
- Heparin bolus 3000U then PTT goal 2x baseline

**Findings**
- **Placebo**
  - 3 dead; 6 minor deficit; 1 complete recovery
  - Two new ICHs developed
- **Heparin**
  - 2 minor deficit; 8 complete recovery
  - No new ICHs developed (3/10 had prior ICH)

Einhaupl Lancet 1991;338:597-600

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CVT Treatment: CVST Study Group

**Design**
- RCT (multi-center; double blind)
- N=59
- Diagnosis by catheter angiogram or MRI/MRV
- Primary endpoint: Barthel, stroke handicap scale, death

**Intervention**
- LMWH (nadroparin) 180 anti-factor Xa U/Kg/24h bid x 3wk then warfarin x 10wk

**Findings**
- **Placebo**
  - 6/29 dead/dependent (4 dead; 2 dependent)
- **Nadroparin**
  - 4/30 dead/dependent (2 dead; 2 dependent)
  - No new ICH (15/30 with ICH at baseline)

Bruijn Stroke 1999;338:484-488
CVT Treatment: Cochrane Meta-analysis

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Death</td>
<td>2</td>
<td>79</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.33 [0.08, 1.28]</td>
</tr>
<tr>
<td>2 Death or dependency</td>
<td>2</td>
<td>79</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.46 [0.16, 1.31]</td>
</tr>
</tbody>
</table>

Authors’ conclusions

Based upon the limited evidence available, anticoagulant treatment for cerebral sinus thrombosis appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency which did not each statistical significance.

Cochrane Database of Systematic Reviews

CVT Treatment: AHA Guidelines 2006

Recommendation

For patients with cerebral venous sinus thrombosis, UFH or LMWH is reasonable even in the presence of hemorrhagic infarction (Class IIa, Level of Evidence B). Continuation of anticoagulation with an oral anticoagulant agent is reasonable for 3-6 months, followed by antiplatelet therapy (Class IIa, Level of Evidence C)

In the ISCVT prospective observational study, steroids were not useful in acute CVT and were instead detrimental.

Stroke 2006;87:577-617; Stroke 2008;39:105-110
CVT Treatment

CVT: Prognosis Per ISCVT Study

Outcome at 6 months
• 78% favorable (mRS 0-1)
• 14% death or dependency (mRS > 2)

Other
• Recurrence 2.2%
• Complete or partial recanalization 90% \(^2\)

Stroke 2004;35;664-670; \(^2\)Neurocrit Care 2009;11:330–337
35 y/o: Headache, Visual Blurring x 2 days

- Arterial ischemia? Venous? PRES? Other?
  - Management?

PRES = RPLS

PRES
- Posterior reversible encephalopathy syndrome

RPLS
- Reversible posterior leukencephalopathy syndrome

*NEJM* 1996;334:484-50;
*Arch Neurol* 2008;65:205-210
PRES Pathophysiology

Capillary leak due to affected endothelium
• May be caused by increased blood pressure
• May be due to drugs or other mechanisms

Arch Neurol 2008;65:205-210;
Arch Neurol 2008;65:175-176

PRES Imaging

Reversible vasogenic subcortical edema generally without infarction
• T2 abnormalities, most conspicuous on FLAIR
• DWI only slightly increased signal or isointense
  - ADCs not decreased

Arch Neurol 2008;65:205-210;
Arch Neurol 2008;65:175-176
PRES: Imaging

Areas of high T2 signal
- Bilateral
- Posterior head regions preferentially involved
  - Sparse sympathetic innervation in V-B territory may have more disruption of autoregulatory mechanisms
- Subcortical white matter more than grey matter

PRES: Atypical Imaging

- Unilateral cerebellar high T2 signal
- Mild mass effect
- Grey and white matter involvement
- Abnormal enhancement
PRES: Signs and Symptoms

Retrospective study in which all had follow-up imaging $n=36$

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Encephalopathy</td>
<td>92%</td>
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<tr>
<td>Seizure</td>
<td>87%</td>
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<tr>
<td>Headache</td>
<td>53%</td>
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<tr>
<td>Visual changes</td>
<td>39%</td>
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<tr>
<td>Blurred vision</td>
<td></td>
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<tr>
<td>Cortical blindness</td>
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</tbody>
</table>

*Arch Neurol 2008;65:205-210*

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PRES: Predisposing Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>53%</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td></td>
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<tr>
<td>Hypertensive encephalopathy</td>
<td></td>
</tr>
<tr>
<td>BP may be $&lt;140/90$ but elevated compared to normal BP</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>45%</td>
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<tr>
<td>Dialysis dependency</td>
<td>21%</td>
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<tr>
<td>Malignancy</td>
<td>32%</td>
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<tr>
<td>- Chemotherapeutic or cytotoxic drugs</td>
<td></td>
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<tr>
<td>Transplantation</td>
<td>24%</td>
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<tr>
<td>- Immunosuppressive drugs</td>
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</tbody>
</table>

*Arch Neurol 2008;65:205-210; Arch Neurol 2008;65:175-176*
## PRES: Predisposing Conditions

<table>
<thead>
<tr>
<th>Conditions at risk for PRES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditions</td>
</tr>
<tr>
<td>Toxemia of pregnancy (preeclampsia/eclampsia)</td>
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<tr>
<td>Posttransplantation:</td>
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<tr>
<td>NHx RTM</td>
</tr>
<tr>
<td>SHT</td>
</tr>
<tr>
<td>Immune suppression:</td>
</tr>
<tr>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Tacrolimus (FK-506)</td>
</tr>
<tr>
<td>Infection/sepsis/shock</td>
</tr>
<tr>
<td>Systemic inflammatory response syndrome</td>
</tr>
<tr>
<td>Multiorgan dysfunction syndrome</td>
</tr>
<tr>
<td>Autoimmune diseases:</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Systemic sclerosis (scleroderma)</td>
</tr>
<tr>
<td>Wegener’s</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
</tr>
<tr>
<td>Status-post cancer chemotherapy</td>
</tr>
<tr>
<td>Combination high-dose chemotherapy</td>
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<tr>
<td>Reported miscellaneous drugs</td>
</tr>
<tr>
<td>Cytarabine&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cisplatin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ganciclovir&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tiazoquin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Kinase inhibitor BAY 54-9006&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Miscellaneous reported associations</td>
</tr>
<tr>
<td>Hypomagnesemia&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypercalcemia&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hypocholesterolemia&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Intravenous immunoglobulin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Guillain-Barré syndrome&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ephedra overdose&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Diethylamine/erythrocyte&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Triple-H therapy&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tumor lysis syndrome&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hydrogen peroxide&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dimethyl sulfoxide stem cells&lt;sup&gt;1&lt;/sup&gt;</td>
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**AJNR Am J Neuroradiol** 2008;29:1036–1042

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## PRES: Treatment

- Treat blood pressure (15-25% per day)
- Discontinue offending drug or decrease the dose
- Treat seizures

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**NEJM** 1996;334:494-500
PRES: Prognosis

Clinical symptoms often resolve
- Mean 5.3 days

Imaging resolution
- Earliest in one study 5 days
- Range probably several days to weeks
- Lesions suggestive of small residual infarcts may persist

Arch Neurol 2008;65:205-210

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PRES: Prognosis

Not universally favorable
- Delay in diagnosis or treatment
  or recalcitrant PRES can have poor outcomes:
  - Hemorrhage
  - Infarction
  - Herniation
  - Death
PRES vs Venous Ischemia?  
MRI Characterization

• Careful diagnostic imaging can resolve this question
• With MRI, need to do specific sequences:
  - DWI/ADC (always)
  - MRV (always)
  - (Plus GRE, enhanced thin section T1 SPGR vs enhanced MR venography)