Emerging Issues in Neurosyphilis

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Outline

• Recent syphilis epidemiology
• Recent neurosyphilis epidemiology
• Identifying those at greatest risk
• Surrogates for monitoring treatment success
Magnitude of the Problem

“Rumors of the demise of syphilis seem to have been greatly exaggerated”

– Fisman DN. Lancet 2007
Syphilis in China

Chen et al. Lancet 2007
Syphilis in Guangxi Province

- Wong et al. STI 2007
  - Dec 2004-Feb 2006 -> 11,473 patients at 14 outpatient STD clinic sites
  - 1,297 (12%) syphilis seropositive
  - 752 primary or secondary
  - 2% also HIV+
Syphilis in Guangxi Province

• Wong et al. STI 2007
  – Odds syphilis higher
    • Women
    • Lower education
    • Higher annual income
Neurosyphilis Natural Hx

CNS Invasion

- Clearance
- Transient Meningitis
  - Clearance
  - Persistent Meningitis
    - =Asx Meningitis (Early)
      - Early Sx NS
        - Wks - Mos - Yrs
          - Sx Meningitis
            - HA, SN, N/V
            - Hearing Loss
            - Visual Loss
          - Meningovascular
            - Stroke + Meningitis
          - General Paresis
            - Dementia
            - Pers Chng
          - Tabes Dorsalis
            - Spinal Cord
            - Sensory Ataxia
            - Incontinence

- Late Sx NS
  - Yrs - Decades
  - Rare
CSF in Neurosyphilis

- Pleocytosis
  - >10 WBC/ul
    - Mononuclear
  - Difficult to distinguish from HIV
- Protein concentration
  - > 45 mg/dL
- CSF-VDRL
  - Specific, but not sensitive
Tertiary (NS) Syphilis in China

Chen et al. Lancet 2007
Early NS in HIV+ in US

- MMWR June 29, 2007
  - Neurosyphilis not a reportable disease
  - HIV+ MSM with early sx neurosyphilis
    - Los Angeles, San Diego, Chicago, NY
      - Convenience sample in Chicago and NY
Early NS in HIV+ MSM

• MMWR June 29, 2007
  – Retrospective chart review +/- physician interview
    • Neurologic sx/signs + CSF exam OR tx for NS
  – Case definition
    • Confirmed = any stage, + CSF-VDRL
    • Probable = any stage, - CSF-VDRL, protein > 40 OR WBC > 5, and sx/signs
## Early NS in HIV+ MSM

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial nerve</td>
<td>34</td>
</tr>
<tr>
<td>Meningitis</td>
<td>6</td>
</tr>
<tr>
<td>Meningovascular</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
</tr>
</tbody>
</table>

Median CD4, 312/ul
No signs of non-neurosyphilis, 26 (53%)
Previous syphilis tx, 12 (24%)
Early NS in HIV+ MSM

- MMWR June 29, 2007
  - Risk of symptomatic early NS 1.7%
  - Risk of persistent sx after treatment 0.5%
UW Neurosyphilis Study

Criterion for NS Diagnosis

- CDC Sx NS
- Sx NS
- +CSF-VDRL
- Any Sx NS

Percent of HIV+ Subjects

- 84/577
- 31/215
- 77/574
- 37/214

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Routine LP in Early Syphilis

**NO**

(2006 CDC STD Tx Guidelines)

- CSF abnormalities common in early syphilis and in HIV
- Clinical and prognostic significance of CSF abnormalities in HIV+ patients with primary or secondary syphilis is unknown

**YES**

- Asx neurosyphilis precedes sx
- Asx NS occurs at any time after infection
- Identification and tx of asx neurosyphilis will prevent progression to sx disease
Reconciling NO vs YES

• Ideal study
  – HIV+, any stage of syphilis
  – Examine CSF
  – Randomize asx with abnormal CSF to NS vs non-NS treatment
  – Follow for development of symptomatic neurosyphilis
• Barriers
  • + CSF-VDRL = NS
  • n~850
  • Cost
Days After BPG

Days Difference Between BPG and LP

- 7 (5-10) days
- 23 (19-43) days
- 119 (102-134) days

Days Difference Between BPG and LP

N = 69 30 8
1-14d 15d-3mo >3mo-6mo
NS and Initial RPR Titer

Days Difference Between BPG and LP

<table>
<thead>
<tr>
<th></th>
<th>No NS</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 d-3 mo</td>
<td>n=25</td>
<td>n=5</td>
</tr>
<tr>
<td>&gt;3-6 mo</td>
<td>n=7</td>
<td>n=1</td>
</tr>
</tbody>
</table>
Value of Early LP

• Assume that those with neurosyphilis after BPG initially were asx and had CSF abnormalities
  – Asx NS precedes sx neurosyphilis
  – Odds of CSF abnormalities c/w neurosyphilis are ~ 6-fold higher when serum RPR titer $> 1:32$
Value of Early LP

- Asymptomatic, RPR ≥ 1:32 0-15 days after BPG
  - N=70
- Initial RPR ≥ 1:32, studied 15 d-6 mo after BPG
  - N=28
- Number of LPs to identify 6 subsequent sx NS = 98
LP for RPR $\geq$ 1:32

- Sx NS does occur after BPG treatment
- May be more likely to develop sx NS after treatment if initial serum RPR $\geq$ 1:32
- Need to perform $\sim$ 16 LPs in asx syphilis patients with RPR $\geq$ 1:32 to identify 1 subsequent case of sx NS
- Ideally, alternate markers could be identified to further decrease # LPs required
Evaluation of NS Tx Success

• Normalization of CSF abnormalities
• Can change in serum RPR be used as a surrogate for CSF normalization after NS tx?
  – 72 subjects with CSF WBC > 20/ul
  – Treated for NS
  – LP 3 months after treatment, ± 6, 12 months
  – CSF normalization ≤ 20 cells/ul
  – RPR normalization 4-fold decline in titer or reversion to nonreactive
# Subject Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38</td>
</tr>
<tr>
<td>Male</td>
<td>99%</td>
</tr>
<tr>
<td>Syphilis Stage</td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>68%</td>
</tr>
<tr>
<td>Late or Unknown</td>
<td>32%</td>
</tr>
<tr>
<td>Serum RPR Titer</td>
<td>1:128</td>
</tr>
<tr>
<td>CSF WBCs/ul</td>
<td>44</td>
</tr>
<tr>
<td>CSF-VDRL+</td>
<td>45%</td>
</tr>
<tr>
<td>CD4/ul</td>
<td>388</td>
</tr>
<tr>
<td>Log Plasma HIV RNA</td>
<td>4.44</td>
</tr>
</tbody>
</table>
Predictive Value of RPR Normalization

- After neurosyphilis treatment, RPR normalization correctly predicted CSF WBC normalization
  - 88% of the time at 4 months
  - 89% of the time at 7 months
  - 97% of the time at 13 months

<table>
<thead>
<tr>
<th>Months After Tx</th>
<th>N</th>
<th># Normalized RPR</th>
<th>Positive Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>70</td>
<td>40</td>
<td>88%</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>48</td>
<td>89%</td>
</tr>
<tr>
<td>13</td>
<td>63</td>
<td>57</td>
<td>97%</td>
</tr>
</tbody>
</table>
Normalization of Serum RPR

- Taking into account baseline serum RPR
- 57-fold greater odds of normalizing CSF WBC when serum RPR normalized
Using RPR as Surrogate for Treatment Success

- Patients whose RPR normalizes at 3-12 (+1) months after neurosyphilis treatment do not need to undergo LP to confirm treatment success

- Patients who do not normalize serum RPR need to undergo follow-up LP

- Data do not apply to non-NS treatment
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