CSF Tests for the Diagnosis of Neurosyphilis in HIV

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Seattle, Washington, USA
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- 736 enrolled
- 694 in dataset, 507 HIV+
- 204 tx for NS
- 150 have at least one followup visit, 120 HIV+
Acknowledgements

- Lauren Tantalo
- April Colina
- Trudy Jones, ARNP
- Rose Fontanilla
- Clare Maxwell, MD
- Sheila Lukehart, PhD
Why Care About Neurosyphilis?

• 12 million cases of syphilis per year world-wide
• Neurosyphilis can occur at any stage of syphilis
Syphilis and HIV Worldwide

North America
Syphilis 100K
HIV 36-54K
HIV Total 790K-1.2M

Caribbean
HIV 45-80K
HIV Total 350-590K

Latin America
Syphilis 3M
HIV 120-180K
HIV Total 1.3-1.9M

Western Europe
Syphilis 140K
HIV 30-40K
HIV Total 520-680K

North Africa & Middle East
Syphilis 370K
HIV 43-67K
HIV Total 470-730K

Sub-Saharan Africa
Syphilis 4M
HIV 3-3.4M
HIV Total 25-28.2M

Eastern Europe & Central Asia
Syphilis 100K
HIV 180-280K
HIV Total 1.2-1.8M

East Asia & Pacific
Syphilis 240K
HIV 150-270K
HIV Total 700K-1.3M

South & Southeast Asia
Syphilis 4M
HIV 610K-1.1M
HIV Total 4.6-8.2M

Australia & New Zealand
Syphilis 10K
HIV 0.7-1K
HIV Total 12-18K

Syphilis
HIV/AIDS
Incidence 12M
4.2-5.8M
Prevalence -- 34-46M
Neurosyphilis Natural History

- Infection
  - 2 - 6 weeks
  - Primary
    - Chancre, regional adenopathy
  - 1 - 3 months
  - Secondary
    - Rash, generalized adenopathy
  - 1 - 3 months
  - Latent
    - Lifetime latency ≥ 70%
  - Tertiary
    - Gumma
    - Cardiovascular

- Neuroinvasion
  - Early Neurosyphilis
  - Late Neurosyphilis
Why Care About Neurosyphilis?

• 10-50% of syphilis patients are HIV+
  – 15-20% of HIV+ syphilis patients have symptomatic neurosyphilis
  – 180,000-1.2 million cases of symptomatic neurosyphilis per year in HIV+ individuals

• It can be cured with penicillin
Neurosyphilis Diagnosis

- CSF-VDRL specific, not sensitive
  - False negatives 30-70%
- Elevated CSF WBCs
  - Can be hard to distinguish from HIV
- CSF-FTA-ABS sensitive, not specific
Neurosyphilis Diagnosis

- CSF-VDRL specific, not sensitive
  - False negatives 30-70%
- Elevated CSF WBCs
  - Can be hard to distinguish from HIV
- CSF-FTA-ABS sensitive, not specific
  - May be result of passive diffusion from serum
Sensitivity and Specificity of CSF-VDRL in UW Study

<table>
<thead>
<tr>
<th>Gold Standard for Diagnosis</th>
<th>CSF WBC &gt;20/ul</th>
<th>Symptomatic NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity of CSF-VDRL</td>
<td>52%</td>
<td>68%</td>
</tr>
<tr>
<td>Specificity of CSF-VDRL</td>
<td>91%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Neurosyphilis Diagnosis

- CSF-VDRL specific, not sensitive
  - False negatives 30-70%
- Elevated CSF WBCs
  - Can be hard to distinguish from HIV
- CSF-FTA-ABS sensitive, not specific
  - May be result of passive diffusion from serum
HIV Alone Causes CSF Pleocytosis

Antiretroviral Use
- Current
- None

White Blood Cells/ul

Percent of Subjects

- 88
- 42
- 12
- 58
## CSF in HIV Without Syphilis

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current use of ARVs</td>
<td>0.17 (0.05-0.54)</td>
<td>0.003</td>
</tr>
<tr>
<td>CD4+ T cells ≤ 200/ul</td>
<td>0.04 (0.006-0.32)</td>
<td>0.002</td>
</tr>
<tr>
<td>Plasma HIV RNA &gt; 50/ml</td>
<td>3.27 (1.14-9.39)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
## CSF Abnormalities in Syphilis by ARV Tx

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Gold Standard for Diagnosis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF WBC &gt; 20 or +CSF-VDRL</td>
<td>+CSF-VDRL</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>32%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Not on ARVs</td>
<td><strong>44%</strong></td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>On ARVs</td>
<td>15%</td>
<td>12%</td>
<td></td>
</tr>
</tbody>
</table>
Neurosyphilis Diagnostic Tests

- Standard diagnostic tests for neurosyphilis all have weaknesses
- HIV status influences CSF measures
  - ARVs
  - CD4
  - Plasma HIV RNA
Alternative CSF Tests in HIV

• Case-control study of assessment of CSF B cells as a diagnostic test
  – 47 HIV-infected cases with syphilis
  – 26 HIV-infected controls
  – Well matched by CD4
Alternative CSF Tests in HIV

- % CSF lymphocytes that are B cells
  - CD19+ by FACS
- Opted for specificity
  - Augment CSF-VDRL
- Set cut-offs based on values in subjects with normal CSF measures
  - Elevated CSF % B cells defined as ≥ 20%
<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19% &gt; 20</td>
<td>43%</td>
<td>100%</td>
</tr>
</tbody>
</table>

CSF Diagnostic Tests

Gold Standard
+CSF-VDRL
## Validation Study

<table>
<thead>
<tr>
<th></th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD19%</strong></td>
<td>129 (90%)</td>
<td>15 (10%)</td>
</tr>
<tr>
<td><strong>CSF-VDRL</strong></td>
<td>117 (78%)</td>
<td>33 (22%)</td>
</tr>
</tbody>
</table>
## Validation Study

<table>
<thead>
<tr>
<th>Gold Standard +CSF-VDRL</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD19% $&gt; 20$</td>
<td>21%</td>
<td>93%</td>
</tr>
</tbody>
</table>
## Validation Study

<table>
<thead>
<tr>
<th>Gold Standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic NS</td>
<td>64%</td>
<td>89%</td>
</tr>
<tr>
<td>+CSF-VDRL</td>
<td>64%</td>
<td>89%</td>
</tr>
<tr>
<td>CD19% &gt; 20</td>
<td>25%</td>
<td>90%</td>
</tr>
</tbody>
</table>
Neurosyphilis Diagnosis

![Bar chart showing the percent of subjects with Neurosyphilis (NS) and those without (No NS) for CSF-VDRL+ and CD19+ conditions. The chart indicates a higher percentage of subjects with Neurosyphilis for CSF-VDRL+ compared to CD19+.](chart.jpg)
## CSF CD19% in HIV+ with Syphilis by ARV Tx

<table>
<thead>
<tr>
<th>Subjects</th>
<th>CD19% ≥ 20</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Not on ARVs</td>
<td>5%</td>
<td>0.46</td>
</tr>
<tr>
<td>On ARVs</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>
Normalization of CD19%

CSF CD19%, n = 16

CSF-VDRL, n = 26
Assessment of %CD19+ Cells

- Specific but not sensitive
- Can augment CSF-VDRL assessment
- Not influenced by ARV use
- Declines after neurosyphilis treatment
- Complex, not readily used or available
Our Diagnostic Approach to Neurosyphilis in HIV+

- NS diagnosed if...
  - Neurological or ocular sx/signs
  - Reactive CSF-VDRL

- If WBC > 20/ul but nonreactive CSF-VDRL
  - Consider ARV tx, CD4, HIV RNA, CSF FTA-ABS, + CD19%
Point of Care CSF Tests

• Immunochromatographic strip tests (ICTs)
  – Detect IgG, IgM and IgA antibodies to recombinant treponemal proteins
  – Intended for use on blood
  – Sensitive (85-97%) and specific (94-98%) in field trials
  – Goal is specificity over sensitivity

• RPR/TRUST
  – Detect IgG and IgM to lipoid material
  – Not recommended for CSF
ICTs Tested

• Optimized and assessed readability on a test CSF panel
  – SD Bioline Syphilis 3.0 (Korea)
  – Syphicheck-WB (India)
  – Visitect (Scotland)
Bioline Test on CSF

Unused

Negative

Weak Positive

Strong Positive
## CSF ICTs

<table>
<thead>
<tr>
<th></th>
<th>Gold Standard</th>
<th>+CSF-VDRL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Bioline</td>
<td>100%</td>
<td>68%</td>
</tr>
<tr>
<td>Syphicheck</td>
<td>89%</td>
<td>80%</td>
</tr>
<tr>
<td>Visitect</td>
<td>97%</td>
<td>66%</td>
</tr>
</tbody>
</table>
# CSF ICTs

<table>
<thead>
<tr>
<th></th>
<th>Gold Standard</th>
<th>Symptomatic NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Bioline</td>
<td>84%</td>
<td>63%</td>
</tr>
<tr>
<td>Syphicheck</td>
<td>84%</td>
<td>79%</td>
</tr>
<tr>
<td>Visitect</td>
<td>84%</td>
<td>66%</td>
</tr>
<tr>
<td>CSF-VDRL</td>
<td>63%</td>
<td>89%</td>
</tr>
</tbody>
</table>
### Bioline Titer $> 1:8$

<table>
<thead>
<tr>
<th>Gold Standard</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF-VDRL+</td>
<td>67%</td>
<td>98%</td>
</tr>
<tr>
<td>Symptomatic NS</td>
<td>60%</td>
<td>96%</td>
</tr>
</tbody>
</table>
## Bioline Test

<table>
<thead>
<tr>
<th>Gold Standard</th>
<th>Symptomatic</th>
<th>NS</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioline undiluted</td>
<td>84%</td>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioline &gt; 1:8</td>
<td>60%</td>
<td>96%</td>
<td></td>
<td></td>
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</tbody>
</table>
Normalization of ICTs

Bioline ICST, n = 41

CSF-VDRL, n = 31
Future Studies

- Determine whether CSF B cells are making treponemal antibodies
- Complete studies to determine the “best” ICT
- Determine whether titers of treponemal antibodies measured by ICTs decline in serum in parallel with CSF titers
- Optimize the RPR/TRUST for use on CSF
- “Field trial” of point of care tests in our STD clinic