Third Joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH)

1–4 April 2014

Arena and Convention Centre · Liverpool
Professor Christina Marra
University of Washington School of Medicine, Seattle, WA, USA
Professor Christina Marra  
University of Washington School of Medicine, USA

<table>
<thead>
<tr>
<th>Speaker Name</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof Christina Marra</td>
<td>Dr. Marra's research is supported by the US National Institutes of Health/National Institute of Neurological Disorders and Stroke (NS34235 and NS082120)</td>
</tr>
<tr>
<td>Date</td>
<td>April 2014</td>
</tr>
</tbody>
</table>
Syphilis: Immunology and HIV

Christina M. Marra, MD
Neurology and Medicine (Infectious Diseases)
University of Washington
Seattle, WA
Syphilis: HIV and Immunology
Outline

• Syphilis and HIV
  – Shared epidemiology
  – Poorer serological response to treatment of uncomplicated syphilis
  – Increased likelihood of neurosyphilis
    • Risk factors

• Syphilis immune response and neurosyphilis
  – Innate immunity
  – Bacterial clearance
    • Macrophage activation
    • Opsonophagocytosis
Outline

• Syphilis and HIV
  – Shared epidemiology
  – Poorer serological response to treatment of uncomplicated syphilis
  – Increased likelihood of neurosyphilis
    • Risk factors

• Syphilis immune response and neurosyphilis
  – Innate immunity
  – Bacterial clearance
    • Macrophage activation
    • Opsonophagocytosis
Seattle, WA, USA

Seattle 2010 Census Data

| Population: 608,660 |
| 23rd most populous US city |
| Rainy days per year 149 (6th in US) |
Syphilis in Seattle-King County WA

- Incidence of early syphilis in Seattle-King County in 2011
  - 0.4/100,000 in women
  - 2.4/100,000 in heterosexual men
  - 771/100,000 in MSM
    - 233/100,000 HIV-uninfected MSM
    - 4,083/100,000 HIV-infected MSM
## Treatment Failure After BPG: Systematic Review

<table>
<thead>
<tr>
<th></th>
<th>% Failed</th>
<th>95% CI</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Syphilis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+ (n=167)</td>
<td>12.6</td>
<td>7.6-17.6</td>
<td>0.0003</td>
</tr>
<tr>
<td>HIV- (n=229)</td>
<td>3.1</td>
<td>0.1-5.3</td>
<td></td>
</tr>
<tr>
<td><strong>Late Syphilis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV+ (n=228)</td>
<td>25.4</td>
<td>19.7-31.1</td>
<td>0.12</td>
</tr>
<tr>
<td>HIV- (n=14)</td>
<td>7.1</td>
<td>0-20.6</td>
<td></td>
</tr>
</tbody>
</table>

Blank et al. Sex Transm Infect 2011;87
Symptomatic NS in HIV

• Taylor M et al. (STD 2008;35)
  – Retrospective review of NS in 2001-2004
  – Age 19-65
  – 109 cases

Rate of sx NS in early syphilis in HIV+ 2.1%
Rate of sx NS in early syphilis in HIV- 0.6%
Mechanism of Risk: Neurorelapse?

Musher (JID 1991;163;1201-6)

- Identified 42 cases of neurosyphilis in HIV+
  - Asx neurosyphilis 5
  - Acute meningitis 24
  - Meningovascular 11
  - General paresis 1
Mechanism of Risk: Neurorelapse?

- Musher (JID 1991;163;1201-6)
  - Of the 42 cases of neurosyphilis
    - 16 previously treated with benzathine penicillin
    - 5 (31%) developed neurosyphilis within 6 months of early syphilis treatment
  - Increased risk of neurorelapse
    - Development of neurosyphilis after standard treatment for early syphilis
## Early NS in HIV+ MSM

<table>
<thead>
<tr>
<th>Syndrome, n=49</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 n=26 (53%)
**Previous syphilis treatment n=12 (24%)**
UW Syphilis Study

• Ongoing since July 1996
• Supported by the NINDS
• Study Goals
  – Determine risk factors for neurosyphilis
  – Identify “better” diagnostic tests
  – Determine predictors of neurosyphilis treatment response
Entry Criteria

• Syphilis
• Needs an lumbar puncture (LP) per primary provider
  – Serum RPR titer $\geq 1:32$
  – In HIV, CD4 $\leq 350/ul$
  – Neurological symptoms or signs
Enrollment as of 31 Dec 2013

Number of Patients

New Enrollment
Re-enrollment

Yearly Enrollment Trends
T. Pallidum Strain Types
Seattle 2001-2010

Grimes M et al. Sex Transm Dis 2012;39
Strain Type and Neurosyphilis Risk

- Tp0548 type f: 30%
- Other Types: 10%

P = 0.001
Neurosyphilis Risk

• Neurosyphilis
  – Reactive CSF-VDRL

• Controls
  – Normal CSF measures
  – No symptoms

• Multivariate model
  – Age per decade
  – Late vs. early stage
  – RPR titer ≥1:32 vs. <1:32
  – Treated for uncomplicated syphilis vs. not
  – Year <2005 vs. ≥2005
  – On ARVs vs. not
# Neurosyphilis Risk: Demographics

<table>
<thead>
<tr>
<th></th>
<th>HIV-uninfected n=177</th>
<th>HIV-infected n=384</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>105 (88%)</td>
<td>381 (99%)***</td>
</tr>
<tr>
<td>Age</td>
<td>35</td>
<td>38**</td>
</tr>
<tr>
<td>Late stage</td>
<td>56 (47%)</td>
<td>93 (25%)***</td>
</tr>
<tr>
<td>RPR titer</td>
<td>1:64</td>
<td>1:64</td>
</tr>
<tr>
<td>Treated</td>
<td>67 (56%)</td>
<td>155 (40%)**</td>
</tr>
<tr>
<td>CSF-VDRL+</td>
<td>31 (26%)</td>
<td>93 (24%)</td>
</tr>
<tr>
<td>On ARVs</td>
<td>NA</td>
<td>204 (64%)</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001
### Neurosyphilis Risk

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratios</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIV-uninfected</td>
<td>HIV-infected</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>NS</td>
<td>1.7*</td>
<td></td>
</tr>
<tr>
<td>Late stage</td>
<td>3.3*</td>
<td>3.6***</td>
<td></td>
</tr>
<tr>
<td>RPR ≥1:32</td>
<td>13.1**</td>
<td>21.3***</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>0.4*</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Year &lt;2005</td>
<td>NS</td>
<td>5.0**</td>
<td></td>
</tr>
<tr>
<td>On ARVs</td>
<td>NA</td>
<td>0.2***</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001
Outline

• Syphilis and HIV
  – Shared epidemiology
  – Poorer serological response to treatment of uncomplicated syphilis
  – Increased likelihood of neurosyphilis
    • Risk factors

• Syphilis immune response and neurosyphilis
  – Innate immunity
  – Bacterial clearance
    • Macrophage activation
    • Opsonophagocytosis
Toll-like Receptor (TLR) Gene Single Nucleotide Polymorphisms (SNPs) and Neurosyphilis

- TLRs important in initiating innate immune response
  - TLR 2_G2258A SNP confers decreased signaling in 293T cells stimulated with lipidated P47 (Lorenz E et al. Infect Immun 2000;68)
- TLR2 forms heterodimers with TLR1 and TLR6
TLR SNPs and Neurosyphilis

• Three common TLR SNPs
  – TLR1_T1805G
    • “Deficient” 1805GG
  – TLR2_G2258A
    • “Deficient” 2258GA
  – TLR6_C745T
    • “Deficient” 745CT/TT
TLR SNPs and Neurosyphilis

• Restricted to Caucasians
• Neurosyphilis
  – Reactive CSF-VDRL
• Controls
  – Normal CSF measures
  – No symptoms
TLR SNPs and Neurosyphilis: Demographics

<table>
<thead>
<tr>
<th></th>
<th>Controls n=256</th>
<th>Neurosyphilis n=91</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>251 (98%)</td>
<td>90 (99%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td><strong>HIV-infected</strong></td>
<td>200 (78%)</td>
<td>70 (77%)</td>
</tr>
<tr>
<td><strong>Late stage</strong></td>
<td>57 (23%)</td>
<td>29 (32%)</td>
</tr>
<tr>
<td><strong>RPR titer</strong></td>
<td>1:32</td>
<td>1:256***</td>
</tr>
<tr>
<td><strong>Treated</strong></td>
<td>130 (51%)</td>
<td>31 (34%)**</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001
TLR SNPs and Neurosyphilis

![Bar chart showing proportions of TLR SNPs deficient in control and +CSF-VDRL conditions.](chart)

- TLR1: P=0.02
- TLR2: P=0.02
- TLR6: P=0.04
Multivariate Odds Neurosyphilis

TLR1 Deficient
RPR ≥1:32
Year <2005
Late Stage
Syph Tx
ARV Use

Adjusted OR
All
HIV-infected

**
***
*
**
*
***
***
*

TLR6 Deficient
RPR ≥1:32
Year <2005
Late Stage
Syph Tx
ARV Use
Age

Adjusted OR
All
HIV-infected

**
***
*
**
*
***
***
*
Bacterial Clearance

Treponema pallidum

LOCAL SPREAD
EPIDERMIS
DERMIS

BLOODSTREAM
DISSEMINATION
& SYSTEMIC SPREAD

T & B CELL
ACTIVATION

IMMUNE RESPONSE

OPSONIZATION, PHAGOCYTOSIS
& BACTERIAL CLEARANCE

TNF & IFN
Plasma cell
M

IL-1, IL-6
IL-12, TNF
DC

Ho EL and Lukehart SA. Prokaryotes 4th Ed. 2013
Immune Activation and Neurosyphilis

• Serum TNF-a and IFN-g by ELISA
• Neurosyphilis
  – Reactive CSF-VDRL
• Controls
  – Normal CSF measures
  – No symptoms
## Immune Activation and Neurosyphilis: Demographics

<table>
<thead>
<tr>
<th></th>
<th>Controls n=62</th>
<th>Neurosyphilis n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td>57 (92%)</td>
<td>47 (94%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td><strong>HIV-infected</strong></td>
<td>43 (69%)</td>
<td>37 (74%)</td>
</tr>
<tr>
<td><strong>Late stage</strong></td>
<td>19 (31%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td><strong>RPR titer</strong></td>
<td>1:32</td>
<td>1:256***</td>
</tr>
<tr>
<td><strong>Treated</strong></td>
<td>25 (40%)</td>
<td>12 (24%)</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001
Immune Activation and Neurosyphilis

Serum TNF-α pg/ml

- HIV-uninfected
- HIV-infected

Serum IFN-γ pg/ml

- HIV-uninfected
- HIV-infected

P<0.001
P=NS
P=0.003

Controls
Neurosyphilis

P=NS
P=0.003
Opsonic Capacity of Sera

- Monocyte derived macrophages (MDMs) derived from normal donor blood monocytes
- Incubated with *T. pallidum* and source of opsonic antibody
  - Patient sera
  - Negative and positive control sera
- Percent MDMs ingesting opsonized *T. pallidum* normalized to pool of immune sera
Opsonic Capacity of Sera: Demographics

<table>
<thead>
<tr>
<th></th>
<th>HIV-uninfected n=37</th>
<th>HIV-infected n=83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>36 (97%)</td>
<td>82 (99%)</td>
</tr>
<tr>
<td>Age</td>
<td>37</td>
<td>41*</td>
</tr>
<tr>
<td>Late stage</td>
<td>12 (34%)</td>
<td>18 (22%)</td>
</tr>
<tr>
<td>RPR titer</td>
<td>1:64</td>
<td>1:128**</td>
</tr>
<tr>
<td>Treated</td>
<td>25 (68%)</td>
<td>35 (42%)*</td>
</tr>
<tr>
<td>Opsonic capacity of sera</td>
<td>0.62</td>
<td>0.47*</td>
</tr>
</tbody>
</table>

*P<0.05, **P<0.01, ***P<0.001
Opsonic Capacity of Sera

- Median Opsonic Capacity of Sera

- Not treated for syphilis before entry
- Treated for syphilis before entry

- HIV-uninfected
- HIV-infected

- P=0.002
- P=NS
- P=0.03
- P=NS
Summary: Host Immunity Impacts Neurosyphilis Risk

• ARVs protect against neurosyphilis in HIV
• Defects in innate immunity increase neurosyphilis risk in HIV-infected and -uninfected patients
• HIV infection may impair opsonic antibody production or function
  – Blunted response to therapy for uncomplicated syphilis
    • Treatment for uncomplicated syphilis doesn’t decrease neurosyphilis risk in HIV
Acknowledgements

• Lauren Tantalo
• Sharon Sahi
• Trudy Jones
• Sheila Dunaway
• Emily Ho
• Clare Maxwell
• Sheila Lukehart
• Arturo Centurion
• Tom Hawn
• Our patients and referring providers
• NIH/NS34235, NIH/NS082120
Third Joint Conference
of the
British HIV Association (BHIVA)
with the
British Association for Sexual Health and HIV (BASHH)

1–4 April 2014

Arena and Convention Centre · Liverpool