Outcome of Untreated Syphilis

Untreated Syphilis

- Clinical Sequelae
- Serology
Clinical Sequelae

The Oslo Study Of The Natural History Of Untreated Syphilis (Gjestland, 1955)

<table>
<thead>
<tr>
<th>Study population</th>
<th>1404 representative cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusions</td>
<td>574 non-Norwegians &amp; non-residents of Oslo</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>Female: Male - 2.1:1</td>
</tr>
<tr>
<td></td>
<td>(958 females, 446 males)</td>
</tr>
</tbody>
</table>

- 259 alive (216 examined)
- 83.4% untreated/no info. as to treatment
Study group categories ($n = 1404$)

1. “Known” - classifiable end point
   ($n = 953$)
2. “Partially known” - some information
   ($n = 194$)
3. “Unknown” - no information
   ($n = 257$)

The Oslo Study Of The Natural History Of Untreated Syphilis (Gjestland, 1955)

Outcome: Secondary Relapse

- **Frequency**: 24% of untreated patients
- **Onset**: 90% within first year
  94% within second year
- **Sites**: Mouth, throat and/or anogenital region in 85% of untreated patients
Outcome: Benign Late Syphilis

- **Frequency**
  - 14% of untreated males
  - 17% of untreated females
- **Onset**
  - 1 - 46 years
- **Sites**
  - Skin 70%
  - Bone 10%
  - Mucosa 10%

Outcome: Cardiovascular Syphilis

**Frequency**
- 13.6% of untreated males
- 7.6% of untreated females
Outcome: Neurosyphilis

Frequency
9.4% of untreated males
5.0% of untreated females

Outcome: Primary Cause of Death

Frequency
15.1% of untreated males
8.3% of untreated females
The Oslo Study Of The Natural History Of Untreated Syphilis (Gjestland, 1955)

Conclusion

“Somewhere between 60 & 70, & probably closer to 60 than 70, out of every 100 untreated syphilitics went through life with little or no inconvenience as a result of the disease.”
Other Studies

- **The Tuskegee Study (1932)**
  412 untreated males with latent syphilis
  Alabama, USA

- **The Rosahn Study (1947)**
  End results in 198 untreated patients

Syphilis: Classification

- **Primary lesion**
  A chancre, the immediate result of contagion

- **Secondary lesions**
  Constitutional poisoning, resulting from that infection

- **Tertiary lesions**
  Gummas which rarely appear before the end of the sixth month and whose development could be delayed for many years *(Ricord, 1856)*
## Classification of Syphilis: Early

<table>
<thead>
<tr>
<th>Time after Exposure</th>
<th>Stage of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 - 90 days</td>
<td>Primary</td>
</tr>
<tr>
<td>6 wks - 6 mths</td>
<td>Secondary</td>
</tr>
<tr>
<td>≤ 2 yrs</td>
<td>Early Latent</td>
</tr>
</tbody>
</table>

## Classification of Syphilis: Late

<table>
<thead>
<tr>
<th>Time after Exposure</th>
<th>Stage of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2 yrs</td>
<td>Late Latent</td>
</tr>
<tr>
<td>3 – 20 yrs</td>
<td>Tertiary</td>
</tr>
<tr>
<td></td>
<td>Gummatous</td>
</tr>
<tr>
<td></td>
<td>(Quartenary)</td>
</tr>
<tr>
<td></td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td>Neurosyphilis</td>
</tr>
</tbody>
</table>
Classification of Syphilis: Congenital

<table>
<thead>
<tr>
<th>Time after Exposure</th>
<th>Stage of Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 yrs since birth</td>
<td>Early (includes SB)</td>
</tr>
<tr>
<td>≥ 2 yrs since birth</td>
<td>Late</td>
</tr>
</tbody>
</table>

Natural History of Syphilis

- Primary Incubation: 25 days
- Secondary Incubation: 46 days
- Secondary Disease: 3.6 months
- Latent Infection

Exposure → First chancre heals → First chancre

(Garnett et al, 1997)
Clinical Interpretation Of Treponemal Serology

Serological Tests for Syphilis: Principles

- Screening
- Confirmation
- Staging of infection
- Retest discrepant results
- Surveillance data (HPA)
Serological Tests for Syphilis

• **Serology**
  Indirect confirmation of treponemal infection by antibody detection

• **Antibody detection**
  Nontreponemal: phospholipid or cardiolipin abs [nonspecific]
  Treponemal: cannot differentiate between *T. pallidum* & other pathogenic infections

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Serological Tests for Syphilis

• **Serology**
  Indirect confirmation of treponemal infection by antibody detection

• **Antibody detection**
  Nontreponemal: **VDRL/RPR**
  Treponemal: **TPPA/TPHA/EIA/FTA-Abs**
Can *T. pallidum* be differentiated from *T. pertenue*

- Yes but not by serological tests.
- The flanking region sequences of the 15-kDa lipoprotein gene differentiate pathogenic treponemes.


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*T. pallidum* genome sequencing

- Complete Genome sequenced

Potentials:
- Novel diagnostic & vaccine targets
- DNA typing for resistance
- Insights on pathogenesis

Fraser CM et al. Science 1998; 281:375-88
STS+: Yaws or Syphilis?

- **History**: Born & brought up in endemic area e.g. Caribbean: Yaws as a child
- **Clinical**: Tissue paper scars on shins
  Exclude signs of syphilis
- **Serology**: VDRL/TPPA >1:8 \(\Rightarrow\) Syphilis likely

STS+: Acquired or Congenital Syphilis?

- **History**: Patient: ‘Misty Vision’ as a child
  Clutton joints
  Family history: Parents/Siblings
- **Clinical**: Stigmata of Congenital Syphilis
  Slit lamp
  CVS -> acquired syphilis
EIA+ TPPA+ VDRL+ RPR+

- Treated or Untreated Syphilis: any stage

EIA+ TPPA+ VDRL- RPR-

- Untreated Syphilis: Primary, late latent & late syphilis
- Untreated Secondary/Early latent Syphilis with prozone
- Treated Syphilis: any stage
EIA+ TPPA- VDRL- RPR-

- Untreated Syphilis: Primary
- Treated syphilis
- False Positive

Less common scenarios:
Think what is most likely to explain
Think in context of history, examination and investigations

EIA- TPPA- VDRL+ RPR+

- Untreated Syphilis: Primary
- Treated syphilis
- Biological False Positive (BFP)

Less common scenarios:
Think what is most likely to explain
Think in context of history, examination and investigations
EIA-  TPPA+  VDRL-  RPR-

- Untreated Syphilis: Primary
- Treated syphilis
- False positive

Less common scenarios:
Think what is most likely to explain
Think in context of history, examination and investigations

Inno-LIA.........
Interpretation: Summary

- **Decide whether**
  - Syphilis or Yaws?
  - Acquired or Congenital?
  - Treated or Untreated?

- **Which stage?**
  - History
  - Clinical examination
  - Investigations

Serological Response to Antibiotic Treatment

- First or repeat infection
- Titre of non treponemal test
- Stage of infection
- HIV status
Serological “Cure”

- At 6/12 following therapy
  - Negative RPR (Seroreversion) OR 4 fold decrease in titre

- Evaluations
  - VDRL: declines 4 fold (2 dilutions) @ 3/12 & 8 fold (3 dilutions) @ 6/12 in early syphilis [Brown et al, 1985]
  - RPR: declines 4 fold (2 dilutions) @ 6/12 & 8 fold (3 dilutions) @ 1 yr [Romanowski et al, 1991]

- Remain serofast.....
  - No change in RPR or 2 fold decrease or increase in titre following initial therapy or retreatment

RPR Seroreversion Following Treatment at 3 years

<table>
<thead>
<tr>
<th>Stage of Infection</th>
<th>% Seroreversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>72</td>
</tr>
<tr>
<td>Secondary</td>
<td>56</td>
</tr>
<tr>
<td>Early latent</td>
<td>26</td>
</tr>
<tr>
<td>Overall</td>
<td>63</td>
</tr>
</tbody>
</table>

(Romanowski et al 1991)
Interpretation: Summary

- **Decide whether**  Syphilis or Yaws?  
  Acquired or Congenital?  
  Treated or Untreated?

- **Which stage?**  History  
  Clinical examination  
  Investigations

Conclusion

- Reactive screening tests require confirmation with a different treponemal test of equal sensitivity & (greater) specificity

- Discrepant treponemal test results need further testing