Neurosyphilis

Richard Dunham, M.D., M.S.
Assistant Professor of Neurology
Washington University in Saint Louis

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Marguerite Urban, Melinda Godfrey, Daniela DiMarco

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None

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SPEAKER DISCLOSURES

None
Objectives

1. Discuss syphilis history, microbiology and recent epidemiology

2. Identify the clinical findings of the various manifestations of neurosyphilis

3. List the treatment recommendations of neurosyphilis

Neurosyphilis History

- Syphilitic gumma considered the most common form of brain tumor. (Bramwell, 1888)

- Neurosyphilis thought to account for 11% of neuropsychiatric admissions in the US in the pre-antibiotic era. (Stokes, 1944)

- Many brainstem stroke syndromes were defined from meningovascular syphilis studies.

- The Romberg test came from tabes dorsalis examination. (Romberg)
Neurosyphilis History (pre-antibiotics)

- Syphilologists recognized the potential of the CNS to act as a reservoir for relapse.

- Early debates about the LP
  - Ravaut recommended NOT examining CSF early to avoid overtreating CNS infections that would resolve spontaneously.

  - Moore recommended early CSF testing to identify severe inflammation and higher risk for developing neurosyphilis.

Neurosyphilis: historical teaching points

- Asymptomatic neurosyphilis always precedes meningeal, vascular and parenchymal syphilis.

- Untreated infection can span decades with multiple stages.

- Risk of progressing to neurosyphilis is related to the degree of CNS inflammation.

- If the spinal fluid remains normal during the first 2 years of infection symptomatic neurosyphilis does not develop (following one dose of benzathine penicillin).
Neurosyphilis History (post-antibiotics)

- *Treponema pallidum* cannot be cultivated.
  - Indirect CSF measures and serologic assays are used for diagnosis.

- *T. pallidum* is exquisitely sensitive to penicillin G.
  - Minimum low serum concentrations of penicillin must be maintained for 7-10 days. One IM benzathine penicillin dose maintains this up to 3-4 weeks.
  - Late syphilis is slowly replicating or nonreplicating and requires longer contact.
  - Enhancing therapy with more doses IM or higher CNS penetration ≠ better outcomes.

Epidemiology

**Figure 35. Syphilis — Rates of Reported Cases by Stage of Infection, United States, 1941–2018**

* Per 100,000.

**NOTE:** See section A1.3 in the Appendix for more information on syphilis case reporting.
Neurosyphilis Microbiology

• CNS invasion is within days in 40-50%, usually asymptomatic.
  ➢ Treponemes can be present without CSF abnormalities.
  ➢ Symptomatic neurosyphilis is rare in primary syphilis.

• Neurosyphilis can occur at any stage.
Natural History of Untreated Syphilis


2018 Syphilis Classification

**Stage**
- Primary
- Secondary
- Early, nonprimary nonsecondary
- Late, or unknown duration

**Clinical Manifestations**
- Neurologic
- Ocular
- Otic
- Late clinical

Report neurosyphilis by stage, as if no neurologic signs
2018 Syphilis Classification

- Primary syphilis
- Secondary syphilis
- Early syphilis, non-primary non-secondary
  - No signs or symptoms of primary or secondary syphilis
  - The initial stage of infection was within the last 12 months (seroconversion, fourfold titer increase, or history).
- Late syphilis, or unknown duration
  - No evidence of having acquired within last 12 months AND either
    - Prior syphilis + current nontreponemal test titer with 4x increase
    - Prior syphilis + neurologic, otic, or late clinical manifestations (cardiovascular, skin, bone)

Neurosyphilis prevalence

- Estimated around 1.8% of people with early syphilis from 2009-2015 from 10 states consistently reporting
- Higher in HIV patients
- US rate of neurosyphilis: 0.47 to 2.1 cases per 100,000 population

De Voux et al 2018. STD 2018;45(1);39-41
Reverse sequence screening

\( T. pallidum \) antibody (TPA) screen (EIA or CIA)

- Reactive/equivocal
- Nonreactive

RPR

- Nonreactive
  - Reactive: Confirmed syphilis, old or new
  - Nonreactive:
    - False positive (syphilis unlikely)
    - Retest in 1 month if high risk

\( T. pallidum \) Particle Agglutination (TP-PA)

Neurosyphilis

Ropper, NEJM 2019;381:1358-1363
### Neurosyphilis: Clinical Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Onset</th>
<th>Signs &amp; symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute meningitis meningomyelitis</td>
<td>Early syphilis</td>
<td>Headaches, neck stiffness, light sensitivity, nausea, vomiting, cranial neuropathies, seizures</td>
</tr>
<tr>
<td>Meningovascular syphilis</td>
<td>Months to years (around 7 years)</td>
<td>Sudden weakness, numbness, difficulty talking, slurred speech, or focal neurologic sign. Acute or chronic meningitis (above). Memory loss.</td>
</tr>
<tr>
<td>Ocular syphilis</td>
<td>Any, usually early</td>
<td>Blurred vision, vision loss, eye pain, eye redness, constricted visual fields.</td>
</tr>
<tr>
<td>Otic syphilis</td>
<td>Any</td>
<td>Asymmetric hearing loss or deafness, tinnitus, vertigo.</td>
</tr>
<tr>
<td>Parenchymatous</td>
<td>General paresis</td>
<td>Cognitive and psychiatric changes, dementia</td>
</tr>
<tr>
<td></td>
<td>Tabes dorsalis</td>
<td>Numbness and unbalance, loss of position and vibration sense, paresthesias, incontinence</td>
</tr>
</tbody>
</table>

Ropper, NEJM 2019;381:1358-1363

### Meningitis

- Basilar leptomeningeal inflammation with cranial nerve palsies
- Symptomatic or asymptomatic
- Can be associated with progressive myelitis over weeks to months

Fisher and Poser. Arch Neurol 1977; 34:785
AIDS wasting, encephalopathy, seizures, numbness
RPR 1:512, later up to 1:2048
CSF: cells 16, protein 61, VDRL +

1-3 years later with recurrent intracranial hemorrhages

Meningovascular syphilis

- Small and medium vessel CNS vasculitis
- Diffuse thickening and lymphocytic infiltration of the meninges
- Ischemic strokes
- Intracerebral hemorrhages
- Ischemic myelitis
Severe acute L>R vision loss
Panuveits, chorioretinal
lesions, perineuritis

HIV+, RPR 1:128
CSF cells 120, protein 154,
VDRL+

• Posterior uveitis and panuveitis is the most common
• Usually occurs during early syphilis
• Unilateral or bilateral
• CSF can be normal
• Immediate ophthalmology referral
• Treat for neurosyphilis
• Report ocular syphilis within 24 hours
Ocular neurosyphilis

- Episcleritis, scleritis
- Anterior, intermediate or posterior uveitis
- Choroid and retinal disease
- Keratitis (corneal inflammation)
  - Ghost vessels
- Lens dislocation
- Cataracts
- Optic neuritis
  - Disc pallor
- Argyll Robertson pupil

20 year old with subacute dizziness and microvascular disease

THEN

3 months later with, headaches, seizures, meningoencephalitis, hearing loss, and blurred vision

HIV neg
RPR 1:32
CSF: cells 500, VDRL +
Argyll Robertson pupils

Osman and Clark NEJM 2016; 375e40

Otic neurosyphilis

- Two mechanisms
  1. Osteitis of the temporal bone with destruction of the membranous cochlea and labyrinth
  2. Inflammation of CN VIII

- Acute or slowly progressive, often with syphilitic meningitis
- Unilateral or bilateral sensorineural hearing loss
- Tinnitus
- Vertigo
- Unbalance
Late Clinical Neurologic Manifestations

- Usually slowly progressive, destructive inflammatory process years after the initial infection

- "General paresis" or chronic encephalitis
- Tabes dorsalis
- Gummas of the CNS

Horowitz et al. NEJM 1994; 331:1488-1491

"General paresis"

- Starts 15 – 30 years after initial infection, progressive and fatal
- Younger (40 – 60 years)
- Frontal and temporal lobes more affected
- Slowly progressive cognitive impairment leading to paralysis and incontinence
- Neuropsychiatric (delusions, psychosis, disorientation)
- Personality changes
- 20% have seizures
- Penicillin treatment may stop progression but will not fully reverse cognitive impairment

Lair and Naidech. Neurology 2004; 63(7)
Tabes dorsalis

- 15-30 years after initial infection

- Chronic myelopathy involving posterior columns
  - Demyelination and axonal loss

- Chronic inflammation of posterior roots and meninges, more severe in lumbar
  - Meningeal and root fibrosis
  - Degeneration of sensory ganglia

Tabes dorsalis: clinical findings

- Numbness
  - Especially loss of vibration and proprioception in the legs
  - Regions of reduced sensation (central face, nipples, ulnar forearms, peroneal legs) leads to painless ulceration and joint damage (Hitzig zones)
  - Wide based unsteady walking

- Hyporeflexia

- Shooting pains in the abdomen and limbs

- Visceral crisis

- Incontinence
CNS Gumma

- Necrotizing granulomatous lesion
- Direct extension of the syphilitic meningovascular inflammation into parenchyma, but can occur anywhere in the brain
- Usually involving the convexities
- T1 hypointense, occasionally isointense
- T2 hyperintense with perilesional edema
- Diffuse enhancement, but occasionally ring enhancing (21%)
- Some with adjacent meningeal enhancement (35%)

Fargen et al. Neurosurgery 2009; 64(3):568-75

Neurosyphilis & HIV

- Significant overlap
  - HIV can cause progressive neurologic disease
  - CSF in HIV can have similar abnormalities
- Higher incidence of false positives
- Higher RPR titers at presentation and remain elevated after treatment.
- Serological tests for syphilis are accurate.
- Treatment is the same
Neurosyphilis review of systems

- Eye redness
- Vision changes
- Headaches
- Neck stiffness
- Sensitivity to light
- Slurred speech
- Hearing loss
- Dizziness
- Seizures
- Weakness
- Numbness
- Unsteadiness or difficulty walking
- Urinary urgency or frequency
- Incontinence
- Memory and thinking difficulty
- Hallucinations
- Changes in personality

Who should have an LP?

**NOT, Recommended**

- primary and secondary syphilis without neurologic signs or symptoms

**YES, Recommended**

- Neurologic signs or symptoms
- Treatment failure at any stage or re-infection
- Evidence of tertiary disease (gumma, aortitis, iritis)
- Ocular
Neurosyphilis Diagnosis

- Lumbar puncture supportive findings
  - Elevated cells (> 5 cells/mm\(^3\))
  - Elevated protein (> 50 mg/dL)
  - Reactive CSF VDRL, if the fluid is not bloody

- There is no single test adequate for diagnosing neurosyphilis
  - CSF-FTA has high negative predictive value but is not standardized

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**Neurosyphilis Diagnosis Flowchart:**

- **Serum Screening (RPR, treponemal test)**
  - Reactive, no neuro:
    - Treat 1\(^{st}\) or 2\(^{nd}\) syphilis
    - No CSF testing indicated
  - Reactive AND neurologic, ocular, or otic signs of NS
    - Both nonreactive
      - Unlikely syphilis
    - Reactive VDRL:
      - Confirmed neurosyphilis, old or new
    - VDRL, abnormal CSF
      - CSF treponemal test? (not recommended by CDC)
        - Reactive CSF treponemal:
          - Previous treated neurosyphilis
          - Untreated neurosyphilis
          - False positive
        - Nonreactive CSF treponemal:
          - Unlikely neurosyphilis
          - Other etiologies of neurologic symptoms?
  - (-) VDRL, normal CSF
    - NS still possible if high suspicion
    - Tx failure

*Just guidance
No single test is adequate*
Neurosyphilis Lab Guideposts

- Neurosyphilis exceedingly unlikely if serum treponemal and RPR tests are negative

- Examining the CSF in early syphilis without neurologic signs will lead to false positives

- Positive CSF VDRL = neurosyphilis
  - Specific but not sensitive (40% in late neurosyphilis)
  - Can remain positive after treatment
  - Falsely positive in bloody tap

Treatment for ocular, otic or neurosyphilis

- IV aqueous crystalline PCN-G 18-24 million units/day IV administered as 3-4 million units IV q4 hours or continuous x 10-14 days

  USE IF NECESSARY:
  - Procaine penicillin G 2.5 million units IM once daily + probenecid 500mg PO QID, both for 10-14 days

  - Steroids do not have a clear role
Monitoring following treatment

• Repeat RPR titer
  - At 6, 12, and 24 months
  - If HIV+, then at 3, 6, 9, 12, 24 months

• If adequate RPR response, repeat CSF not needed for HIV negative or HIV on ART

• Repeat CSF?
  - In 6 months if the CSF had pleocytosis initially, until normal
    ▶ If the CSF cell count has not decreased at 6 months consider retreatment
    ▶ If the CSF cell count or protein are not normal at 2 years, consider retreatment

Treatment failures that require CSF testing

• Inadequate serological response after treatment
  ▶ Lack of fourfold decline
    • 12 months after primary, secondary, or early latent
    • 24 months after late latent or unknown
    • 12-24 months for neurosyphilis

• Fourfold increase in titer (may not occur at low titers)

• Persistent or recurrent symptoms
Summary

• Latent syphilis does not mean quiescent syphilis

• Do not screen with CSF unless there are clinical signs suggestive of neurosyphilis

• Diagnose and treat HIV neurosyphilis cases the same as non-HIV

• The American Academy of Neurology no longer recommends screening for syphilis as a general dementia evaluation

4/13/2021  Knopman et al Neurology 2001; 56(9)

Educational Resources

• Clinical Education Initiative: https://ceitraining.org/

• The national STD curriculum educational series through the NYC prevention training center https://www.std.uw.edu/

• CDC 2021 STI treatment guidelines (coming soon)
Next in the syphilis series

Part 3: Congenital Syphilis - Treatment & Prevention from Pregnancy to Delivery
April 20, 2021, 7:00-1:00 pm

Jason Zucker, MD, MS
Faculty
New York City RTD Prevention Training Center (NYC PTC)
New York University School of Medicine

Discuss clinical features, microbiology & recent epidemiology
Identify the clinical picture and treatments for congenital syphilis
Discuss the screening recommendations for syphilis in pregnancy

REGISTER for April 20

Part 4: Syphilis Case Discussions
April 27, 2021, 12:00-1:30 pm

Daniela E. O'Marco, MD, MPH
Assistant Professor of Medicine
Division of Infectious Disease
University of Rochester School of Medicine
Rochester, NY

Marguerite A. Urban, MD
Assistant Professor of Medicine
Infectious Disease Division
University of Rochester School of Medicine and Dentistry
Rochester, NY

Jason Zucker, MD, MS
New York City RTD Prevention Training Center (NYC PTC)
New York University School of Medicine

QUESTIONS?
Richard Dunham, MD
dunhamsr@wustl.edu

NYS Sexual Health Center of Excellence
853 West Main St. Rochester, New York
585.274.3044