CNS INFECTIONS: PEARLS AND PERILS
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Learning objectives

• Recognize the clinical presentation of common neuroinfectious diseases

• Identify pitfalls of diagnostic testing frequently obtained in the evaluation and management of common neuroinfectious diseases

• Be familiar with the approach to the treatment of common neuroinfectious diseases

Disclosures

• I have no disclosures.

Neurosyphilis

[Image: Skull damage from neurosyphilis]
**Question:** My patient has neurosyphilis. Does that automatically mean they have late, or like later, or latent syphilis?

**Answer:** Neurosyphilis can occur at any stage of infection.

**Question:** I have a patient whose MRI demonstrated a small acute infarct in the internal capsule. He has hypertension and uncontrolled diabetes, and urine tox screen was positive for cocaine. His RPR was 1:64 and was negative 6 months ago. Since strokes in syphilis usually occur as a late presentation and he has many other vascular risk factors, I don’t have to LP him, do I?
Think **meninges, CSF and blood vessels** in early syphilis and **parenchymal disease** in late syphilis

**Answer:** I would recommend an LP for any patient with a newly positive RPR (or positive RPR of unknown duration) and clinical/radiologic evidence of strokes.

**Question:** My clinic patient has uveitis and an RPR of 1:128. Ophtho sent him to clinic for neurological evaluation, but he has no neurological symptoms. I don’t have to LP him, do I?

**Which syphilis patients need an LP?**

- Any stage of syphilis + neurological signs/symptoms
- Any stage of syphilis + ocular or otologic disease
- Tertiary syphilis w/ or w/o neurological signs/symptoms
- Inappropriate serologic response after treatment
- HIV-infected patients PLUS:
  - Consider for HIV-infected patients with CD4 <350 cells/mm³ and/or RPR ≥ 1:32
Which syphilis patients need an LP?

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- Inappropriate serologic response after treatment
- HIV-infected patients PLUS:
  - Consider for HIV-infected patients with CD4 <350 cells/mm³ and/or RPR ≥ 1:32 → Thorough neurologic history and exam

Answer: I would recommend an LP for all patients with ocular syphilis.

Question: My HIV+ patient, intermittently non-adherent to his ARVs, presented to clinic with headaches that are more severe than his usual migraines.

Serum RPR was 1:64. CSF had 20 WBC and a mildly elevated protein, but CSF VDRL was negative. Could this still be neurosyphilis?

No one test has high sensitivity/specificity for neurosyphilis

<table>
<thead>
<tr>
<th>Test characteristics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERUM</strong></td>
<td></td>
</tr>
<tr>
<td>RPR (non-treponemal tests)</td>
<td>Sensitivity: 1°: 78-85%, 2°: Near 100%, 3°/Latent: Varies, ~85%</td>
</tr>
<tr>
<td>False positives 1-2%, usually titer &lt;1:8 (autoimmune disease, IVDU, TB, pregnancy, endocarditis)</td>
<td></td>
</tr>
<tr>
<td>False negatives in HIV, prozone effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*Titer correspond to disease activity</td>
</tr>
<tr>
<td></td>
<td>*Used to assess treatment response → 4-fold decline considered to be clinically significant</td>
</tr>
<tr>
<td><strong>SERUM</strong></td>
<td></td>
</tr>
<tr>
<td>Treponemal tests (TPPA, FTA-Abs)</td>
<td>False positives with other spirochetal infections, malaria, leprosy</td>
</tr>
<tr>
<td>False negative in HIV</td>
<td>*Titer do not correspond to disease activity</td>
</tr>
<tr>
<td></td>
<td>*Most positive for life despite treatment</td>
</tr>
<tr>
<td><strong>CSF VDRL</strong></td>
<td>CSF VDRL Sensitivity: 30-80%, Specificity 99%</td>
</tr>
<tr>
<td>CSF Treponemal tests</td>
<td>*CSF VDRL considered “gold standard” for neurosyphilis</td>
</tr>
<tr>
<td>FTA-Abs/TPPA high sensitivity but low specificity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive CSF VDRL at any titer = neurosyphilis</td>
</tr>
</tbody>
</table>
**Answer:** Yes, CSF VDRL can be insensitive for neurosyphilis. This absolutely could still be neurosyphilis, and based on the clinical data, I would recommend treating him for neurosyphilis with 2 weeks of Penicillin G (4 million units IV q4 hours).

**Question:** We have an inpatient who presented with 2 days of fever, headache and confusion. CSF with 11 WBC (85%L), protein 75 and glucose 53.

CSF HSV 1 PCR negative. Could this still be HSV-1 encephalitis?
What is the utility of HSV-1 PCR in the CSF?

• 54 patients with biopsy-proven HSE underwent HSV-1 PCR from CSF
  • Sensitivity 98%
  • Specificity 94%

Lakeman J Infect Dis 1995

Sensitivity of CSF HSV-1 PCR is lower early in the course of HSV encephalitis

Patients with Suspected Herpes Simplex Encephalitis: Rethinking an Initial Negative Polymerase Chain Reaction Result

Table 2. Results of PCR analysis of CSF samples obtained from patients who had an initial negative PCR result.

<table>
<thead>
<tr>
<th>Patient</th>
<th>No. of days between onset of CNS symptoms and LP 1</th>
<th>HSV PCR result (laboratory where PCR was performed) for sample from LP 1</th>
<th>No. of days between LP 1 and LP 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>Negative (A, B, D)</td>
<td>Positive (A, D)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>Negative (A, C)</td>
<td>Positive (A, B)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Negative (A)</td>
<td>Positive (A, B)</td>
</tr>
</tbody>
</table>

Lakeman J Infect Dis 1995

Answer: Yes, this could definitely still be HSV-1 encephalitis. I recommend you repeat the lumbar puncture, resend an HSV-1 PCR from the CSF and start IV acyclovir 10 mg/kg every 8 hours as you await the results.

Question: The repeat CSF HSV-1 PCR was positive. She received 3 weeks of IV acyclovir but is still quite impaired, far from her baseline. Should we discharge her on oral antiviral therapy?
No significant cognitive benefit of oral therapy after IV acyclovir

- 87 HSE patients randomized to valacyclovir 2 g TID versus placebo x 90 days
- Excluded individuals with life expectancy <90 d and those who couldn’t take PO
- Primary outcome was survival with no/mild impairment at 12 months

Answer: No, unfortunately there is no evidence that a longer course of oral antiviral therapy after completing IV acyclovir is beneficial.

Question: We have a 55-year-old man on the inpatient service with no past medical history other than “possible meningitis” over 5 years ago, who presented with 5 days of fever, chills, malaise and severe headache. One day prior to presentation, he developed bilateral hip and buttocks pain and paresthesias along with urinary retention.

On exam, his temperature is 101, and there is meningismus. Neurologic exam is notable for decreased sensation in an S3-S5 distribution.

Question: CSF demonstrated normal opening pressure with 310 WBC (84% lymphocytes), glucose 40, and protein 91. CSF HSV-2 PCR returned positive. What route and duration of acyclovir would you recommend, and should he be discharged on suppressive oral antiviral therapy?
Lumbosacral myeloradiculitis associated most commonly with HSV-2 reactivation

- Typically present with lower back/buttocks pain, paresthesias in lumbosacral distribution and bowel/bladder symptoms
- CSF profile consistent with viral meningitis
- MRI may be normal or may show root/lower spinal cord edema with enlargement, T2/FLAIR hyperintensity and contrast enhancement
- Treatment: IV acyclovir 10 mg/kg q8h x 2 weeks

Eberhardt et al. Neurology 2004

101 patients with HSV-2 meningitis randomized to valacyclovir 500 mg BID or placebo x 1 year after completing treatment for acute meningitis

Aurelius et al. CID 2012

- In Year 1, 14 cases of recurrent meningitis in valacyclovir group (29%) vs. 8 cases in placebo group (16%), p=0.12
- In Year 2, 12 cases in valacyclovir group (24%) vs. 4 in placebo (8%), p=0.03

Answer: Although there are no data to guide therapy for HSV or VZV meningitis, I generally treat severe or complicated cases (e.g., meningoencephalitis, myelitis, meningoradiculitis), even in immunocompetent patients, with a full 2-week course of IV acyclovir. From the perspective of preventing recurrent HSV-2 meningitis, there are no data to support use of long-term suppressive valacyclovir.
Question: Our patient with newly diagnosed HIV infection (CD4 count 90 cells/mm³, viral load 75K) presented with progressive right sided weakness and confusion. Brain MRI demonstrates several ring-enhancing lesions with surrounding edema and mass effect.

I know the serum toxoplasma antibody status of an HIV+ patient with focal brain lesions is important. The patient’s serum toxo IgM ELISA is negative, so does this rule out toxoplasmosis?

CNS toxoplasmosis

- Most common focal brain lesion in HIV+ w/ CD4 < 200 in US
- Presentation usually evolves over weeks to months
- TMP/SMX prophylaxis reduces risk of toxoplasmosis
- Ddx: CNS lymphoma, pyogenic abscess, tuberculoma, cryptococcoma

Utility of toxoplasma serology

- Toxoplasmosis seropositivity in general population in the US is estimated to be 10-40%
- Toxoplasmosis in HIV is typically reactivation of prior infection (i.e., IgM antibodies less helpful)
- Serum IgG is positive in most HIV patients with CNS toxoplasmosis
- CSF toxoplasma PCR is very specific but sensitivity varies

Answer: The serum toxoplasma IgG is more informative in an HIV patient in whom you are worried about CNS toxoplasmosis. Send the IgG and, if safe, do a lumbar puncture and send the CSF for toxoplasma PCR.

Question: Serum toxo IgG was positive. CSF demonstrated 23 WBC (80%L), 27 RBC, glucose 47 and protein 58. CSF toxoplasma and EBV PCR are pending. What else can help us to distinguish between toxo and CNS lymphoma?

Toxoplasmosis versus CNS lymphoma in HIV

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<th>Clinical presentation</th>
<th>Radiologic findings</th>
</tr>
</thead>
<tbody>
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<td>Focal s/sx (~75%), HA (~50%), fever (~50%); sx evolve faster than CNSL</td>
<td>Basal ganglia, thalamus, grey-white junction. Usually multiple lesions (75%) with ring or nodular enhancement + Mass effect and edema</td>
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<tr>
<td>At risk with CD4 count &lt;200</td>
<td>Periventricular, deep white matter. Can be solitary/few lesions with solid/homogeneous enhancement; in patients with HIV, can ring-enhance + Mass effect and edema</td>
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Raffi et al. AIDS 1997
**Toxoplasmosis versus CNS lymphoma in HIV**

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<tr>
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<th>Toxoplasmosis</th>
<th>Primary CNS Lymphoma</th>
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</thead>
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<tr>
<td><strong>Clinical presentation</strong></td>
<td>Focal s/sx (~75%), HA (~50%), fever (~50%); sx evolve faster than CNSL</td>
<td>Focal s/sx including hemiparesis, aphasia, visual field deficit</td>
</tr>
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<td>+Mass effect and edema</td>
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</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Pyrimethamine (w/ leucovorin) and sulfadiazine</td>
<td>Corticosteroids, methotrexate, rituximab, XRT, ARVs</td>
</tr>
<tr>
<td></td>
<td>Avoid steroids if possible!</td>
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</table>

**Question:** My patient, originally from Mexico, was referred for evaluation of a single ring-enhancing right frontal lesion. While in the ED with her husband who was being seen for chest pain, she had a witnessed convulsive spell and was confused for hours afterward.

**Blood cultures, HIV test, PPD and chest/abdomen/pelvis CT were negative. Serum cysticercal ELISA was also negative. Could this still be cysticercosis?**
Neurocysticercosis (NCC)

- Infection of the nervous system with larval stage of the helminth, *Taenia solium*
- 50+ million people affected worldwide
- One of the most common causes of acquired epilepsy in developing world

Location, location, location

- Intraparenchymal (70%)
  - Cortical (>90%)
  - Deep gray matter (5%)
  - Brainstem/infratentorial (Uncommon)
- Extraparenchymal (30%)
  - Sylvian fissure
  - Basal cisterns
  - Spine
  - Intraventricular

Stages of neurocysticercosis

- Viable cyst
- Degenerating cyst
- Dead cyst

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  - Intraventricular

Serological diagnosis of NCC

- Enzyme-linked immunotransfer blot
  - Sensitivity near 100% for multiple parenchymal, ventricular, or subarachnoid cysts; specificity 100%
  - Performs as well (or better) in serum as CSF
  - Sensitivity much lower in patients w/ single or calcified lesions (<50%)
- ELISA
  - Sensitivity and specificity lower than EITB
  - Sensitivity even lower for single or calcified lesions (<50%)
- Neither can be used to distinguish prior from active infection
"We recommend serologic testing with enzyme-linked immunotransfer blot as a confirmatory test in patients with suspected neurocysticercosis. Enzyme-linked immunosorbent assays (ELISAs) using crude antigen should be avoided due to poor sensitivity and specificity."

**Answer:** The epidemiology, clinical presentation and radiology findings are all highly suggestive of NCC. The ELISA has lower sensitivity, I would send a serum enzyme immunotransfer blot (EITB) for cysticercosis, keeping in mind, though, that this patient may still have a false negative EITB.

**Question:** I saw a patient in clinic, originally from Mexico, currently working as a construction foreman, who complained of 1 month of worsening headaches and several episodes of left arm/leg shaking followed confusion.

Serum cysticercal ELISA was positive. My practice is to treat with albendazole + steroids, but dual antihelminthic therapy seems to be all the rage. Is that a good idea for this patient?
Extraparenchymal NCC

- Less common form of infection with proliferating, invasive membranous structures
- Associated with more protracted course and worse prognosis
- Complications, particularly of basal subarachnoid disease, include:
  - Hydrocephalus and elevated ICP
  - Vasculitis +/- infarcts and hemorrhages

Should I treat with dual therapy?

- Double-blind, placebo-controlled randomized controlled trial
- Inclusion: 1-20 viable cysts
- Exclusion: Subarachnoid NCC at base of brain, most intraventricular cysts, cysts in brainstem, larger cysts (>30 mm), ocular cysts
- Three arms, all 10 days of therapy:
  1. Albendazole alone (15 mg/kg/day)
  2. Albendazole + praziquantel
  3. High-dose albendazole (22.5 mg/kg/day)

- Primary outcome: Cyst resolution at 6 months

Answer: A recent RCT showing benefit of dual anti-helminthic therapy for NCC patients excluded most patients with subarachnoid disease. Dual anti-helminthic therapy is still reasonable in this patient, but steroids should be initiated before starting treatment, and he should be observed carefully for complications (e.g. ↑ICP, seizures).
Treatment summary

<table>
<thead>
<tr>
<th>CALCIFIED CYSTS</th>
<th>Viable Cysts</th>
<th>Degenerating Cysts</th>
<th>Subarachnoid Cysts</th>
<th>Ocular Cysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>No antiparasitic therapy</td>
<td>1-2 lesions: albendazole x 10-14 d +/- steroids</td>
<td>Single lesion: albendazole x 7-14 d +/- steroids</td>
<td>ABZ +/- PZQ +/- steroids +/- resection</td>
<td>Surgical resection</td>
</tr>
<tr>
<td></td>
<td>&gt;2 lesions: albendazole + praziquantel x 10-14 d +/- steroids</td>
<td>Multiple lesions: albendazole + praziquantel x 10-14 d + steroids</td>
<td>+/− resection</td>
<td>Antihelminthic therapy may result in loss of vision secondary to inflammation</td>
</tr>
</tbody>
</table>

Question: I am seeing a middle-aged African American man from Modesto with a 6 week history of progressive headache, confusion and lethargy. CSF demonstrates 290 cells/mm³, protein is 100 and glucose 36. CSF gram stain and fungal stains are negative.

Question: Coccidioidal meningitis is high on my differential diagnosis. What testing on the CSF is most sensitive to make the diagnosis?
Coccidioidomycosis

- Most primary infections (pulmonary) are asymptomatic (~2/3)
- CNS dissemination (1%) occurs weeks to months after 1st infection

Risk factors for extrapulmonary/disseminated disease:
- African or Filipino ancestry
- Immune compromise (HIV, malignancy, DM, SOT, steroids)
- Pregnancy

Imaging:
- Meningeal enhancement
- Hydrocephalus
- Focal lesion (e.g., infarct, abscess)
- Spinal arachnoiditis also common

Performance of Cocci testing in CSF

<table>
<thead>
<tr>
<th>CSF Parameter</th>
<th>Sens (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal culture</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Immunodiffusion (ID)</td>
<td>67</td>
<td>99</td>
</tr>
<tr>
<td>Complement fixation (CF)</td>
<td>70</td>
<td>100</td>
</tr>
<tr>
<td>Antigen</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>Antigen, ID, CF</td>
<td>98</td>
<td>99</td>
</tr>
</tbody>
</table>

Performance of Cocci testing in CSF

Answer: If you suspect Cocci meningitis, in addition to checking an opening pressure, cell count, glucose, protein and fungal culture, send a CSF Cocci immunodiffusion, complement fixation and antigen.
Treatment for Cocci meningitis

- **1st line**: **Lifelong** fluconazole 400 to 1200 mg/day

- If disease progression on 1st line therapy:
  1. Increase dose of fluconazole as tolerated
  2. Consider another azole (e.g., voriconazole, posaconazole, isavuconazonium)
  3. Consider IT amphotericin B

- Hydrocephalus is a common complication → neurosurgery evaluation for shunt

- Consider adjunctive steroids in patients with vasculitis and infarcts

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**Useful references**


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THANK YOU

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