Disclosures

- I have no disclosures.

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

Neurosyphilis
Question: My patient has neurosyphilis. Does that automatically mean they have late, or like later, or latent syphilis?

Reply: 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

**Reply:** 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 symptoms
- Any stage of syphilis + ocular or otologic disease
- HIV-infected patients PLUS:
  - Late latent syphilis
  - Syphilis of unknown duration
  - Inappropriate serologic response after treatment
  - Consider for any HIV-infected patient with CD4 <350 cells/mm³ and/or RPR ≥ 1:32
Reply: 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?

Syphilis diagnostic testing

<table>
<thead>
<tr>
<th>Test characteristics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SERUM</strong> RPR (non- treponemal tests)</td>
<td></td>
</tr>
<tr>
<td>Sensitivity:</td>
<td>*Titers correspond to disease activity</td>
</tr>
<tr>
<td>1°: 78-86%</td>
<td>*Used to assess treatment response ( \Rightarrow ) 4-fold decline considered to be clinically significant</td>
</tr>
<tr>
<td>2°: Near 100%</td>
<td></td>
</tr>
<tr>
<td>3°/Latent: Varies, ~85%</td>
<td></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><strong>SERUM</strong> Treponemal tests (TPPA, FTA-Abs)</td>
<td></td>
</tr>
<tr>
<td>False positives with other spirochetal infections, malaria, lepromatosis</td>
<td></td>
</tr>
<tr>
<td>False negative in HIV</td>
<td></td>
</tr>
<tr>
<td><strong>CSF VDRL and FTA- Abs</strong></td>
<td></td>
</tr>
<tr>
<td>CSF VDRL Sensitivity: 30-80%, Specificity: 99%</td>
<td>*CSF VDRL at any titer = neurosyphilis</td>
</tr>
<tr>
<td>FTA-abs high sensitivity but low specificity</td>
<td></td>
</tr>
</tbody>
</table>

Beware the ongoing ocular syphilis epidemic


Syphilis Rhinocerebrovasculopathy, MMWR 2015

Woolston et al. MMWR 2015

- Can occur at any stage of syphilis \( \Rightarrow \) most cases now present in early syphilis
- Can involve ANY ocular structure
  - Anterior uveitis (iris, ciliary body)
  - Posterior uveitis (choriorretinitis)
  - Retinitis, retinal detachment
  - Optic neuritis
- ~50% of patients with ocular syphilis will have evidence of meningitis in the CSF
- Treatment is the same as neurosyphilis even if CSF is non-inflammatory
- May have residual vision loss despite treatment
**Reply:** 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 encephalitis?

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**HSV-1 encephalitis**

- HSV is the most frequently identified viral etiology of sporadic encephalitis in the US
- Occurs any time of year
- Bimodal distribution: 1/3 cases <20 y, 2/3 >40 y
- Case fatality rate >70% if untreated; 1/3 of patients may be significantly disabled despite treatment
- CSF: 5-500 WBC/mm³, normal to moderately elevated protein, glucose typically normal
- DWI may be most sensitive sequence early in the course of infection

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**Man flips truck after cold sore virus travels to his brain**

Herpes simplex type 1 is usually a minor annoyance, but in rare cases it can turn deadly

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- Occurs any time of year
- Bimodal distribution: 1/3 cases <20 y, 2/3 >40 y
- Case fatality rate >70% if untreated; 1/3 of patients may be significantly disabled despite treatment
- CSF: 5-500 WBC/mm³, normal to moderately elevated protein, glucose typically normal
- DWI may be most sensitive sequence early in the course of infection
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>No. of days between LP 1 and LP 2</th>
<th>HSV PCR result (where PCR was performed) for sample from LP 1</th>
<th>HSV PCR result (laboratory) for sample from LP 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>4</td>
<td>Negative (A, B, D)</td>
<td>Positive (A, D)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>7</td>
<td>Negative (A, C)</td>
<td>Positive (A, B)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>4</td>
<td>Negative (A)</td>
<td>Positive (A, B)</td>
</tr>
</tbody>
</table>

Weil Clin Infect Dis 2002

Reply: 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 10-15 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

<table>
<thead>
<tr>
<th>Level of Impairment</th>
<th>Total</th>
<th>UCIV</th>
<th>Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (begin study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe (n=125)</td>
<td>27 (9.6)</td>
<td>11 (3.2)</td>
<td>16 (2.5)</td>
<td>.0009</td>
</tr>
<tr>
<td>Severe (n=247)</td>
<td>48 (9.4)</td>
<td>23 (4.7)</td>
<td>25 (5.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Day 90 (complete study)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe (n=125)</td>
<td>12 (15.8)</td>
<td>6 (7.1)</td>
<td>4 (4.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Severe (n=247)</td>
<td>64 (8.4)</td>
<td>29 (2.3)</td>
<td>35 (5.3)</td>
<td>.01</td>
</tr>
<tr>
<td>12 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe (n=125)</td>
<td>5 (11.8)</td>
<td>5 (4.5)</td>
<td>4 (3.8)</td>
<td>.02</td>
</tr>
<tr>
<td>Severe (n=247)</td>
<td>61 (10.2)</td>
<td>30 (9.5)</td>
<td>31 (6.2)</td>
<td>.01</td>
</tr>
<tr>
<td>24 mo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate/severe (n=125)</td>
<td>6 (13.8)</td>
<td>4 (11.4)</td>
<td>2 (9.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Severe (n=247)</td>
<td>66 (10.2)</td>
<td>31 (9.6)</td>
<td>35 (6.2)</td>
<td>.01</td>
</tr>
</tbody>
</table>

Reply: No, unfortunately there is no evidence that a longer course of oral antiviral therapy after completing IV acyclovir is beneficial, and I do not recommend she be discharged on oral therapy.

Question: Our HSV-1 encephalitis patient was readmitted from rehab 4 weeks after she was discharged with worsening confusion. Could this be recurrent HSV infection?

Relapsing symptoms after HSV encephalitis

- ~15-25% of patients have early relapsing symptoms after completing acyclovir
- More common in children
- More common in children ➔ chorea, dystonia, fever, AMS, behavioral changes, seizures
- Adults ➔ movement symptoms less common
- CSF pleocytosis and elevated protein; contrast enhancement on MRI
- Immune-mediated hypothesis supported by recent discovery of NMDAR and other antibodies in patients with relapsing symptoms
Diagnostic approach to relapsing symptoms in HSV

**RELAPSING NEUROLOGICAL SYMPTOMS**
(e.g., CHOREOATHETOSIS, CONFUSION, AGGRESSION, AGITATION, SEIZURES)

CSF HSV-1 PCR
- **PCR +**
  - **ACYCLOVIR**
- **PCR -**
  - **ANTIBODY RESULTS**
    - **NEGATIVE**
      - **CONSIDER IMMUNOTHERAPY**
    - **POSITIVE**
      - **IMMUNOTHERAPY**

**Reply:** I would repeat a lumbar puncture and resend the CSF HSV-1 PCR. If the HSV-1 PCR is negative, I would NOT restart IV acyclovir and would consider serum/CSF evaluation for NMDAR antibodies if there is no identified cause for a persistent decline.

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**Toxoplasmosis**

**Question:** Our patient with newly diagnosed HIV infection (CD4 count 90 cells/mm³, viral load 75K) presented with progressive right sided weakness and confusion.
I know the serum toxoplasma antibody status of an HIV+ patient with focal brain lesions is key. 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 Toxo IgG and PCR are very specific but sensitivity varies

Reply: The serum toxoplasma IgG is typically more informative in an HIV patient in whom you are worried about toxoplasmosis. Send the IgG and, if safe, do a lumbar puncture and send the CSF for toxoplasma IgG and/or toxo PCR.
**Question:** Serum toxo IgG was positive. CSF demonstrated 23 WBC (80%), 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?

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**Toxoplasmosis versus CNS lymphoma in HIV**

<table>
<thead>
<tr>
<th></th>
<th>Toxoplasmosis</th>
<th>Primary CNS Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical presentation</strong></td>
<td>Focal sx (~75%), HA (~50%), fever (~50%), sx evolve faster than CNSL</td>
<td>Focal sx including hemiparesis, aphasia, visual field deficit</td>
</tr>
<tr>
<td></td>
<td>At risk with CD4 count &lt;200</td>
<td>At risk with CD4 count &lt;50</td>
</tr>
<tr>
<td><strong>Radiologic findings</strong></td>
<td>Basal ganglia, thalamus, grey-white junction</td>
<td>Periventricular, deep white matter</td>
</tr>
<tr>
<td></td>
<td>Usually multiple lesions (75%) with ring or nodular enhancement</td>
<td>Can be solitary/few lesions with solid/homogeneous enhancement; in patients with HIV, can ring-enhance</td>
</tr>
<tr>
<td></td>
<td>+Mass effect and edema</td>
<td>+Mass effect and edema</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Serum IgG (reactivation), CSF IgG and PCR; response to empiric Rx</td>
<td>CSF EBV PCR (Sé 90-100%), brain biopsy; cytology has poor sensitivity (&lt;20%)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Pyrimethamine (w/ leucovorin) and sulfadiazine or clindamycin; AVOID steroids if possible!</td>
<td>Corticosteroids, XRT, methotrexate and other chemotherapy</td>
</tr>
</tbody>
</table>

**Question:** CSF toxoplasma PCR was positive. The patient was started on pyrimethamine, sulfadiazine and leucovorin 10 days ago and has been clinically improving. When is it safe to start ARVs?
Over a 9-year period, 65 cases of CNS toxo diagnosed

0 cases of paradoxical CNS toxo IRIS

Reply: It is reasonable to start ARVs in a patient who is on appropriate toxoplasmosis treatment and stable x ~7-14 days

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

Stages of neurocysticercosis

- Viable cyst
- Degenerating cyst
- Dead cyst

Location, location, location

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

Serological diagnosis of NCC

- **ELISA**
  - Serum sensitivity 75-80%, specificity 75%
  - CSF sensitivity higher than serum (>85%) and nearly 100% for subarachnoid disease
  - Sensitivity MUCH lower for single or calcified lesions (<50%)
- **Western blot** (available through CDC)
  - Sensitivity 80-100%, specificity 100%
  - Performs as well in serum as CSF
  - Sensitivity much lower in patients w/ single or calcified lesions (<50%) and higher (100%) for subarachnoid disease
- Neither can be used to distinguish prior from active infection
Reply: The epidemiology, clinical presentation and radiology findings are all highly suggestive of NCC, and this is exactly the type of patient in whom the ELISA might be less sensitive. I would send a CSF ELISA and western blot.

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 w/ 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
**Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial**

- Double-blind, placebo-controlled RCT
- Inclusion: 1-20 viable cysts
- Exclusion: **Subarachnoid NCC at base of brain, most IV cysts, cysts in brainstem, larger cysts (>30 mm), ocular cysts**
- Albendazole + praziquantel vs albendazole vs high-dose albendazole x 10 days
- Primary outcome: Cyst resolution at 6 months

**Reply:** 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**

- **Calcified Cysts:** No antiparasitic therapy
- **Viable Cysts:** Single/few lesions: ABZ +/- steroids
  - Multiple lesions: ABZ + PZQ + steroids
- **Degenerating Cysts:** Single lesion: ABZ +/- steroids vs no therapy
  - Multiple lesions: ABZ + PZQ + steroids
- **Subarachnoid Cysts:** ABZ +/- PZQ + steroids +/- resection
  - Often requires prolonged and multiple courses of therapy
- **Ocular Cysts:** Surgical resection
  - Anthelmintic therapy may result in loss of vision secondary to inflammation
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 40 (serum 100). CSF gram stain and fungal stains are negative.

Question: Cocci menigitis 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>Immunodiff (ID) IgM/IgG</td>
<td>67</td>
<td>99</td>
</tr>
<tr>
<td>Complement fixation (CF) IgG</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>

Kassis Clin Infect Dis 2015
Galgiani Clin Infect Dis 2016

Reply: If you suspect Cocci meningitis, in addition to checking an opening pressure, cell count, glucose, protein and fungal culture, I recommend you 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)
  3. Consider IT amphotericin B
- Hydrocephalus is a common complication → neurosurgery evaluation for shunt
- Infarcts → adjunctive steroids

Useful references