CNS Infections, Part 1 and Part 2

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Goals

• Review the clinical presentation, diagnosis, treatment, and complications of the following viral causes of CNS infections:
  • Bacterial meningitis
  • TB meningitis
  • Viral meningitis
  • Herpes Simplex Encephalitis
  • HIV and CNS infections
  • Rabies
What is the difference between “encephalitis” and “meningitis,” anyway?

• “Presence or absence of normal brain function”
• “mental status” changes (MS∆)
• Personality changes
• Focal neurologic deficits
• Speech dysfunction
• Problem is sometimes it’s hard to distinguish...
• ...and there can be “meningoencephalitis” (e.g. *Listeria monocytogenes*), so...
• Always have low threshold to include encephalitis in differential
Case presentation

• 12 yo F
• Severe HA, stiff neck
• Temp 39.5
• Able to answer questions initially
• No bites, trauma
• Differential?
An ID doctor’s way of considering ID Cases

**Non-infectious causes**

- Opportunistic (i.e. HIV)
- "Routine"
- "Weird" (i.e. call ID)

**Infections**

- Gram Positives
- Gram Negatives
- Anaerobes
- Viruses
- Fungi
- Parasites & Protozoa

Other bacteria:
- Intracellular
- Acid Fast/Modified
- Spirochetes & other
Remember: organize your differential

- **Noninfectious**: unlikely—leukemia or lymphoma? SLE?
- **Infectious**:
  - “Standard” bacterial—high likelihood
  - Miscellaneous bacterial—*Rickettsia* infxn? Leptospirosis?
  - Viral—HSV encephalitis? Why less likely? Other viruses?
  - Parasitic—Malaria? *Trypanosoma brucei*? Why less likely?
  - HIV OIs? What are the major CNS infections in advanced HIV?
Bacterial meningitis

- Major causes:
  - Strep pneumoniae
  - Neisseria meningitidis
  - E. coli (newborns... and adults?)
  - Haemophilus influenzae (decreasing with vaccine)
  - and...
  - Listeria monocytogenes (clinically slightly different)
### Table 1. Common Bacterial Pathogens

<table>
<thead>
<tr>
<th>Age/Predisposing Factor</th>
<th>Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 mo</td>
<td><em>GBS, E coli, L monocytogenes</em></td>
</tr>
<tr>
<td>1-3 mo</td>
<td><em>GBS, E coli, L monocytogenes, S pneumoniae, N meningitidis, Hib</em></td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td><em>S pneumoniae, N meningitidis</em></td>
</tr>
<tr>
<td>&gt;50 y</td>
<td><em>S pneumoniae, N meningitidis, L monocytogenes, gram-negative bacilli</em></td>
</tr>
<tr>
<td>Immunocompromised state</td>
<td>*S pneumoniae, N meningitidis, L monocytogenes, gram-negative bacilli (including <em>P aeruginosa)</em></td>
</tr>
<tr>
<td>Post neurosurgical procedure, head trauma</td>
<td>*S aureus, coagulase-negative staphylococci, gram-negative bacilli (including <em>P aeruginosa)</em></td>
</tr>
<tr>
<td>CSF shunt</td>
<td>*Coagulase-negative staphylococci (S epidermidis), S aureus, gram-negative bacilli (including <em>P aeruginosa)</em></td>
</tr>
</tbody>
</table>

*CSF: cerebrospinal fluid; E coli: Escherichia coli; GBS: group B streptococcus; Hib: Haemophilus influenzae type b; L monocytogenes: Listeria monocytogenes; N meningitidis: Neisseria meningitidis; P aeruginosa: Pseudomonas aeruginosa; S aureus: Staphylococcus aureus; S epidermidis: Staphylococcus epidermidis; S pneumoniae: Streptococcus pneumoniae.*

*Source: References 1, 12.*
Meningitis in children (US graph, 1985)

- *H. flu* dramatic decreases with introduction of vaccine; now very rare in US
- *Neisseria* likely to be more common in Liberia than US
Acute meningitis in children: clinical presentation

- In adults, at least one of the following are seen in nearly all cases: fever, HA/MSΔ, neck stiffness
- The **abrupt onset** and **neck stiffness** in this case is what makes bacterial meningitis most likely dx
- In younger children, meningitis can be more difficult to spot, as signs/sx more nonspecific
- 

  - Fever *or* hypothermia
  - Poor feeding
  - Diarrhea
  - Vomiting
  - Lethargy, irritability
  - Seizures
  - Older children may have photophobia, focal neurologic signs
Meningitis: physical exam

- Infants: bulging fontanel
- Older children:
  - Kernig’s Sign
  - Brudzinski’s Sign
- All signs not very sensitive but more specific (helpful if positive, not if negative)
Reconsideration of Case

• 12 yo F, HA, stiff neck, Temp 39.5
• Able to answer questions initially, gradually obtunded
What to do next?

• A. Start cloxacillin.
• B. Start chloramphenicol.
• C. Order CXR.
• D. Start griseofulvin.
• E. Perform spinal tap.
• F. Start ceftriaxone 1 gram daily.
• Cloxacillin is best used for staph.
• A chest XR will not help you in further diagnosis.
• Griseofulvin is good for ringworm, not meningitis.
• Meningitis dose Ceftriaxone is 2 grams q12hr, not 1 gram q24.
• Chloramphenicol (IV, PO) will cover relevant organisms—which are...?
• Under ideal conditions, a spinal tap is critical in patients with HA, fever +/- MSΔ.
Which of the following is most likely suggestive of Pneumococcal or Meningococcal meningitis?

- A. “turbid,” WBC 2000 (90% PMN), prot 300, glu 16
- B. “clear,” WBC 5, RBC 250, prot 45, glu 60
- C. “cloudy,” WBC 250 (40% PMN / 60% lymphocyte), prot 300, glu 30
- D. “cloudy,” WBC 150 (80% Eo), prot 100, glu 60
- E. “cloudy,” WBC 100 (“atypical cells”), prot 100, glu 60
Gram-negative meningitis

- Clinically identical to pneumococcal & Neisseria meningitis
- *E coli* most common Gram negative
- Seen most often in neonates
- Can also be seen in elderly or immunosuppressed
• In adults, *E coli* meningitis should prompt what additional measure?
• Give ivermectin—gram-negative meningitis can be due to *strongyloides* moving through gut wall, causing transient bacteremia & seeding of CNS.
Case #2: 16 yo F

• HA x 3 weeks
• Some intermittent fevers, wt loss
• Unremarkable vitals, physical exam
• CSF: yellow, viscous, WBC 500 (90% L), Prot 300 mg/dL (3 g/L), Glu 22
While you wait for culture results, what action(s) would be reasonable to take?

• A. Give chloramphenicol.
• B. Start rifampin, isoniazid, pyrazinamide, ethambutol, methylprednisolone, and Vitamin B6.
• C. Consider psychiatric issue; headaches don’t last that long, she’s making it up.
• D. Send HIV serology (“spot”).
• E. Place PPD.
Tuberculous meningitis (TBM)
  • Exact incidence hard to know
  • May account for ~5% of extrapulmonary TB
  • Can have acute or indolent course (several weeks to 9 months)
  • Diagnosis difficult; often made clinically
  • PPD not useful in dx
  • Classic TBM tap: ↑WBC, mostly lymphs, ↑prot, ↓glu (bacteria’s food is glucose!)
  • Tx with anti-TB meds plus steroids initially
  • HIV testing in pts with suspected TBM.
What would be the major differences in the spinal tap of a patient with TBM and a patient with fungal meningitis?

• A. TBM usually has low glucose; fungal meningitis rarely does.
• B. TBM usually has high protein; fungal meningitis has normal protein.
• C. TBM usually has lymphocytes and high WBC; fungal meningitis has high WBC but with neutrophils.
• D. There are no major differences.
Fungal meningitis

- Major concern is *Cryptococcus neoformans*
- Also Candida, aspergillus (rare)
- Crypto dx: India Ink, serum/CSF Crypto Ag
- ~10% of pts in sub-Saharan Africa with CD4 <100 are + for Crypto Ag & should be on prophylactic Fluconazole
- Major problem in IRIS in Africa—heavy cause of mortality in pts beginning ARVs
- Ampho B drug of choice; fluconazole
India Ink in CSF
9 yo M

- HA 3 days, fever
- Temp 38.2 in exam room
- + Meningismus; Kernig’s & Brudzinski’s negative
- CSF: 32 WBC, 100% lymph, glu 63, prot 50, clear fluid
What do you want to do?

• A. Start fluconazole.
• B. Observe; provide IVF.
• C. Order Toxoplasmosis IgM serology.
• D. Start ceftriaxone 2 grams IV q12hr.
• E. Begin cimetidine.
Viral meningitis, aka “Aseptic meningitis”

- Many potential causes
- Major players are enteroviruses & herpesviruses
  (HSV2>VZV>CMV>HSV1>HHV6)
- CSF low WBC, lymph>>neutrophil, protein normal or slightly elevated, glu normal
- Supportive treatment
- Adults: recurrent meningitis caused by HSV2 aka “Mollaret’s meningitis”
CSF analysis: know your CSF

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal/TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (cmH2O)</td>
<td>5-20</td>
<td>&gt; 30</td>
<td>Normal or mildly increased</td>
<td></td>
</tr>
<tr>
<td>Appearance</td>
<td>Normal</td>
<td>Turbid</td>
<td>Clear</td>
<td>Fibrin web</td>
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<tr>
<td>Protein (g/L)</td>
<td>0.18-0.45</td>
<td>&gt; 1</td>
<td>&lt; 1</td>
<td>0.1-0.5</td>
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<tr>
<td>Glucose (mmol/L)</td>
<td>2.5-3.5</td>
<td>&lt; 2.2</td>
<td>Normal</td>
<td>1.6-2.5</td>
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<tr>
<td>Gram stain</td>
<td>Normal</td>
<td>60-90% Positive</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Glucose - CSF:Serum Ratio</td>
<td>0.6</td>
<td>&lt; 0.4</td>
<td>&gt; 0.6</td>
<td>&lt; 0.4</td>
</tr>
<tr>
<td>WCC</td>
<td>&lt; 3</td>
<td>&gt; 500</td>
<td>&lt; 1000</td>
<td>100-500</td>
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<tr>
<td>Other</td>
<td></td>
<td>90% PMN</td>
<td>Monocytes</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>10% have &gt;90% PMN</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>30% have &gt;50% PMN</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monocytes</td>
<td></td>
</tr>
</tbody>
</table>
56 yo F with lethargy x72 hours

• Intermittent fevers
• Speech difficulties—looks like stroke
• No gross motor deficits
• Temp on exam 38.0, vitals otherwise stable
• No meningismus
What do you want to do next?

• Obtain CXR.
• Start atenolol for hypertensive CVA.
• Test for HIV.
• Obtain CSF.
• Send sputum for AFB.
CSF

• WBC 120 (50 N, 50 L)
• Glu 28
• Prot 60
• Gram Stain:
What do you want to do now?

• Start ARVs (for HIV).
• Increase atenolol for CVA.
• Start IV ampicillin.
• Start 4-drug TB treatment.
• Start Flagyl.
Listeria

• “Meningoencephalitis”—can present either as meningitis, or encephalitis, or both

• Likes to live on meats & cheeses left out in warm weather

• Gradual or abrupt onset

• Very young or old (>60); also in HIV!

• Often with CVA-like sx in adults

• High mortality if not treated

• Tx: ampicillin
Referred to ER from clinic

• 35 yo M with focal neurologic deficits
• Sx worsened 4-6 wks; brought in by family
• R sided weakness lower extremity
• Confusion
• Vitals: 36.6, 100, 106/60, RR 22, 98%
• Exam: cachexia, heart/lungs/abdomen all normal; difficulty standing, cannot walk without assistance
Which of the following statements are true?

• A. A careful evaluation of this patient’s oral cavity may give clues to the diagnosis.
• B. The rapid administration of ampicillin and gentamicin is likely to help.
• C. This patient probably has a CVA.
• D. A chest x-ray should be ordered.
• E. The most likely diagnosis is TB meningitis.
The patient has thrush. Which of the following organisms are likely causes of this presentation?

- A. Strongyloides stercoralis.
- B. Toxoplasma gondii.
- C. Actinomyces israelii.
- D. Cryptococcus neoformans.
- E. Rift Valley Fever.
- F. A complication of EBV infection.
- G. JK Virus.
- H. PCP
An ID doctor’s approach to DDx in febrile illness

Fever & Sx

Non Infectious Cause?
-PE (long trip, coagulopathy?)
-Malignancy (leukemia, lymphoma)
-Drug fever, chemical exposure

Then...

Infections by Category of Organism:
—“Routine” bacteria, e.g. Staph, Strep, Gram Neg Rods, anaerobes
—“Odd” bacteria, e.g. vibrios, filamentous Gram +s, spirochetes, intracellular organisms (Neisseria)
—Mycobacteria
—Viruses
—Fungi
—Parasites (protozoa & helminths)

Then...

Could this be an opportunistic infection in the setting of HIV or leukemia/lymphoma?

Then...

Think about opportunistic organisms by the same set of categories, e.g. “odd” bacteria of Nocardia, fungi such as PCP, parasites like toxoplasmosis, etc.
CNS infections in HIV

• HIV can have subtle presentations, but thrush is essentially diagnostic

• Always suspect HIV in pts with wasting or cachexia or recurrent illness

• If you diagnose HIV in setting of one illness (e.g. CNS disease), remember that HIV patients can also have other diseases as well—this patient had RR of 22, which is tachypnea! Consider lung infections like PCP or TB!
CNS infections in HIV con’t: most common OIs

- CD4 <250: CNS lymphoma *2nd*ary to EBV
- CD4 <200: cryptococcosis
- CD4 <100: toxoplasmosis
- CD4 <50: Progressive Multifocal Leukoencephalopathy (PML) due to JK virus
Diagnosis

• CNS lymphoma: CT scan
• Cryptococcosis: India Ink prep of CSF; also spinal tap typically very high pressure, fluid “shoots out”
• Toxoplasmosis: serology
• PML dx requires MRI
Treatment

- CNS lymphoma: none, ARVs may help
- Crypto: ampho B or fluconazole, serial spinal taps in patients with ongoing HA or blurry vision (to ↓ intracranial pressure)
- Toxo: pyrimethamine/sulfa
- PML: ARVs, no specific treatment (anywhere)
Dog bite

- 15 yo M bitten by dog yesterday
- Dog ran away
- Hand is red, swollen, tender; elbow tender as well
- Remainder of exam is normal
Further treatment includes?

- A. IV ampicillin and gentamicin.
- B. This patient does not have rabies & can be sent home.
- C. This patient does have rabies, nothing can be done, send him home.
- D. Start rabies PEP (rabies vaccine).
- E. PO fluconazole for *Candida canimorsus*, a known fungal pathogen from dogs.
Rabies virus

- In Rhabdovirus family (Lyssavirus)—nonsegmented negative-sense RNA virus in bullet-shaped envelope
- ~30,000 – 70,000 deaths each year (still!)
- Retrograde passage through peripheral nerves to CNS
- Mainly affects brainstem
Rabies: clinical

- Incubation usu ~1-3 months
- Prodrome: nonspecific; paresthesias @ bite site
- Encephalitic or “Furious” rabies (~80%): hydrophobia/aerophobia, pharyngeal spasms, hyperactivity, aggression
- Flaccid or “Dumb” rabies (~20%): quadriplegia—similar to GBS
- Death in ~2-3 wks from prodrome; almost universally fatal (one known survivor—Jeanna Giese pictured previously)
- Clinical dx
Post-Exposure Prophylaxis (PEP) in USA

• Two interventions:
  • Rabies vaccine (IM only—not intradermal)
  • Rabies Immune Globulin (HRIG)—given locally at wound site and distantly IM
• 5 doses: day 0, 3, 7, 14, 28 in deltoid
50 yo M

- Presents with SZR, FVR, confusion
- 3 days PTA has FVR/HA/confusion
- 1 day PTA had SZR, lost consciousness 10-15 mins
Exam
• 37.8, 110/90, 66, 18 with 90% RA sats
• Neck supple, no lymphadenopathy
• Lungs clear
• III/VI SEM with radiation to carotids
• Abd benign, no LE edema, no rash
• Neuro: normal except for confusion
Data

- Lytes: 132 / 3.5 / 102 / 26
- WBC: 14.2 (82 N, 6 Bands, 10 L, 1 Atypical lymph, 1 M)
- Hct: 47
- Plt: 267
- CXR: bibasilar atelectasis
What do you want to do next?

• A. Send for psych +/- neuro consult for acute psychosis.
• B. Begin halol; you do not require psych consult to treat this syndrome.
• C. Obtain lumbar puncture.
• D. Begin IV amphotericin B.
Tap

- CSF clear
- 9 RBC
- 138 WBC (44 N, 23 L, 33 M)
- Glu 83
- Prot 45
- Gram stain: monos & neuts, no organisms
MRI FLAIR (axial)
MRI FLAIR (coronal)
Diagnosis?
Herpes Simplex Encephalitis (HSE)

- Almost exclusively HSV-1
- Acute inflammation, congestion and/or hemorrhage of brain *predominantly in temporal lobes*
- Can be primary or recurrent (primary in ~33% of cases, most of those <18 yo)
- Pathogenesis not perfectly understood
HSV con’t

• Most common cause of sporadic viral encephalitis in world
• 1 per 300,000 individuals
• ~10-20% of all viral encephalitides
• *Throughout the year, pts of all ages*
• In US, Caucasians>African Americans
Clinical presentation

•Usu acute (<1 wk)
•**FVR** +/- (any of) MSΔ, ↓LOC, dysphasia/aphasia, focal CN deficits, SZR seen in ~90% of pts
•Can also see specific syndromes:
  •Hypomania
  •Klüver-Bucy syndrome
  •Amnesia

<table>
<thead>
<tr>
<th>Number (%) of patients</th>
<th>Brain-positive $(n = 113)^a$</th>
<th>Brain negative $(n = 85)^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical findings</td>
<td></td>
<td></td>
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<tr>
<td>Alteration of consciousness</td>
<td>109/112 (97)</td>
<td>82/84 (98)</td>
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<tr>
<td>CSF pleocytosis</td>
<td>107/110 (97)</td>
<td>71/82 (87)</td>
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<tr>
<td>Fever</td>
<td>101/112 (90)</td>
<td>68/85 (78)</td>
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<tr>
<td>Headache</td>
<td>89/110 (81)</td>
<td>56/73 (77)</td>
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<tr>
<td>Personality change</td>
<td>62/87 (71)</td>
<td>44/65 (68)</td>
</tr>
<tr>
<td>Seizures</td>
<td>73/109 (67)</td>
<td>48/81 (59)</td>
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<tr>
<td>Vomiting</td>
<td>51/111 (46)</td>
<td>38/82 (46)</td>
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<tr>
<td>Hemiparesis</td>
<td>33/100 (33)</td>
<td>19/72 (26)</td>
</tr>
<tr>
<td>Memory loss</td>
<td>14/59 (24)</td>
<td>9/47 (19)</td>
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<tr>
<td>Clinical findings at presentation</td>
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<tr>
<td>Fever</td>
<td>101/110 (92)</td>
<td>84/79 (81)</td>
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<tr>
<td>Personality change</td>
<td>69/81 (85)</td>
<td>43/58 (74)</td>
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<tr>
<td>Dysphasia</td>
<td>58/76 (76)</td>
<td>36/54 (67)</td>
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<tr>
<td>Autonomic dysfunction</td>
<td>53/88 (60)</td>
<td>40/71 (56)</td>
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<td>Ataxia</td>
<td>22/55 (40)</td>
<td>18/45 (40)</td>
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<tr>
<td>Hemiparesis</td>
<td>41/107 (38)</td>
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<tr>
<td>Seizures</td>
<td>43/112 (38)</td>
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<td>Focal</td>
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<td>Generalized</td>
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<td>14</td>
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<tr>
<td>Both</td>
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<td>13</td>
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<tr>
<td>Cranial nerve defects</td>
<td>34/105 (32)</td>
<td>27/81 (33)</td>
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<tr>
<td>Visual field loss</td>
<td>8/58 (14)</td>
<td>4/33 (12)</td>
</tr>
<tr>
<td>Papilledema</td>
<td>16/111 (14)</td>
<td>9/84 (11)</td>
</tr>
</tbody>
</table>

$^a$ Of 202 patients assessed.
HSE: Dx

• Avg CSF WBC ~100; protein ~100
• CSF RBC is not diagnostic for HSE (and likewise lack of CSF RBC doesn’t rule it out)
• (MRI with temporal lobe enhancement in appropriate clinical picture is highly suggestive)
• In resource-abundant settings HSV PCR (~94% sens, ~98% specific) is primary means of diagnosis
Tx and Prognosis

• IV acyclovir 10 mg/kg q8hr, dose adjust for renal insufficiency; if no IV, give po (limited data supporting use)

• Total duration 14-21 days

• Mortality: untreated 70%

• Mortality with treatment ~20%, but...

• About half of pts with some moderate to serious neurologic deficit