CNS Infections

Ian A. Cook, M.D.

Pyogenic Infections: sources

- Entry into CNS
  - hematogenous (emboli or thrombi)
  - local extension (ear, nasal sinus, penetrating injury, osteomyelitis of skull, congenital sinus tracts)
  - iatrogenic and/or nosocomial are increasingly common

Hematogenous spread

- Little is known from human autopsy
- In animals, even direct injection of bacteria into tissue frequently does not produce infection
- May need infarction of tissue for seeding to take hold (?)
Spread by Local Extension

• Cranial bones and dura mater provide protection
• Breached if suppuration occurs in middle ear, mastoid cells, or sinus

Common monobacterial infections from hematogenous spread

• Streptococcus pneumoniae
• Neisseria meningitides
• Haemophilus influenzae
• Listeria monocytogenes
• Staphylococcus
• Neonates - E coli and group B strep
• Infants & children - H flu

Mixed Flora

• When septic emboli arrive from lungs, pulmonary AV fistulae, congenital heart lesions
• Direct extension from ears/sinuses
• Difficult to determine mix of aerobic & anaerobic flora even from pus culture
• Use age, setting (post-op, nosocomial, etc), immune status, evidence of systemic vs local disease to guide tx

Acute Bacterial Meningitis

• Inflammation of subarachnoid space -> pia and dura and CSF
• Easy spread -> usually cerebral AND spinal
• Incr vessel permeability -> protein exudate, neutrophils migrate into pia and subarachnoid space
• Neutrophils are replaced with lymphocytes and histiocytes after a few days
• Fibrinogen -> fibrin after a few days, esp more superficially
Acute Bacterial Meningitis

- Subarachnoid arteritis: endothelial cells swell, multiply, crowd lumen -> focal necrosis
- Venous vasculitis: --> focal necrosis, cortical thrombophlebitis
- When fibrinopurulent exudate accumulates, spinal subarachnoid space can be blocked yielding hydrocephalus
- Chronic adhesions can be a delayed sequella

Acute Bacterial Meningitis

- 75% are caused by
  - H. influenzae
  - N. Meningitidis
  - Strep. pneumoniae
  - Listeria is number 4
  - Staph aureus, Group A and D strep

Acute Meningitis

- 1: Pure Pia-arachnoiditis: headache, stiff neck, Kernig and Brudzinski signs (activation of protective reflexes that shorten & immobilize spine; neck extension and hip/knee flexion reduce the stretch, whereas opposite movements increase)

Acute Meningitis

- 2: Subpial encephalopathy: confusion, stupor, coma, convulsions. Tissue below the pus is not penetrated, so change is likely toxic (cytokines). Look for cerebral infarction due to cortical vein thrombosis.
Acute Meningitis

• 3: Inflammatory or vascular involvement of cranial nerve roots: ocular palsies, facial weakness, deafness.

• 4: Thrombosis of meningeal veins: focal seizures, focal cerebral defects (hemiparesis, aphasia) on day 3 - 7 after onset. Look for spinal cord infarction.

• 5: Ependymitis, chroidal plexitis: no clinical signs except for related meningitis and hydrocephalus

• 6: Cerebellar or cerebral hemisphere herniation: due to swelling, causing upper cervical cord compression with quadriplegia or sings of midbrain/3rd nerve compression.
### Subacute & Chronic Meningitis


### Subacute & Chronic Meningitis

2. Subdural effusion: impaired alertness, refusal to eat, vomiting, immobility, bulging fontanels, persistent fever despite clearing of CSF. Consider thromophlebitis with infarction if + fever, nl CSF pressure, and one-sided cerebral signs.

### Subacute & Chronic Meningitis

3. Extensive venous or arterial infarction: unilateral or bilateral hemiplegia, decorticate or decerebrate rigidity, cortical blindness, stupor or coma, with or without seizures.

### Late Effects of Meningitis

1. Meningeal fibrosis around optic nerves, around spinal cord & roots: blindness & optic atrophy (opticochiasmatic arachnoiditis), spastic paresis with sensory loss of lower segments of body (meningomyelitis).
Late Effects of Meningitis

2: Chronic meningoencephalitis with hydrocephalus: dementia, stupor or coma, paralysis (e.g. general paresis of the insane). If lumbosacral posterior roots are involved, a tabetic syndrome results

Late Effects of Meningitis

3: Persistent hydrocephalus in the child: blindness, arrest of all mental activity, bilateral spastic hemiplegia

Spinal Fluid Exam

- If there is clinical evidence of a focal lesion with increased ICP, then CT scan for mass lesion is prudent but ordinarily should not delay antibiotic treatment
- Opening Pressure
  - if normal - think blocked needle
  - > 400 mmH2O - herniation potential - mannitol
- Pleocytosis is diagnostic
- Protein > 45 in 90% (more often 100-500mg/dl)
- Glucose Low <40 mg/dl or <40% of serum
- Gram stain & culture

Imaging

- Chest film - pneumonitis or abscess
- Sinus or skull film or CT - cranial osteomyelitis, paranasal sinusitis, mastoiditis
- CT for erosive lesions, abscess, subdural empyema
- MRI with Gd enhancement - meningeal exudate, cortical reaction
- Venous occlusions and adjacent infarction
Differential Diagnosis

- All febrile patients with even lowgrade fever should be considered if they have headache, lethargy, or confusion of sudden onset.
- Think of this in confused febrile ICU patients
- Likewise worry for immunocompromised alcoholic patients
- DDX
  - viral meningitis (also EBV, HSV)
  - subarachnoid hemorrhage
  - chemical meningitis
  - TB, leptospiral, sarcoid, fungal

Treatment

- Bacterial meningitis is a medical emergency.
- Manage septic shock
- Begin antibiotic regimen empirically while awaiting test results
- Tailor once identified
- Treat I.V. for 10-14 days unless persistent parameningeal focus of infection
- Go longer if fever is prolonged or if late appearance of signs/sx (drowsiness, hemiparesis)

Treatment

- Steroids - old vs new literature: use in kids or if very high O.P. (Dex 0.15mg/kg QID x 4d)
- Osmotic agents (mannitol, urea) - only with high OP (>400mm)
- Anticonvulsants - not routinely given; use if a seizure has occurred or for evidence of cortical venous occlusion
- Prophylaxis - household contact of meningococcal meningitis (or rifampin)
Prognosis
• Fatal if untreated
• Especially in infants and the elderly
• Bad prognostic features include - bacteremia, coma, seizures, alcoholism, diabetes, multiple myeloma, head trauma
• Residual neurological deficits are rare with meningococcal infections; >25% of children with H flu, up to 30% of children/adults with pneumococcal meningitis (~10% behavioral abnl)

Bacterial Encephalitides
• Mycoplasma pneumoniae
• Listeria monocytogenes
• Legionella pneumophila
• Whipple disease

Mycoplasma
• 10-20% of pneumonias
• Associated with Guillain-Barre polyneuritis, cranial neuritis, acute myositis, aseptic meningitis, seizures, transverse myelitis, global encephalitis
• CSF with few lymphos/monos, culture of resp tract, IgG/IgM, PCR
• Erythromycin & tetracyclines

Listeria
• Immunocompromised or debilitated
• Rhomboencephalitis
  • headache, fever, nausea, vomiting x days, followed by asym CN palsies, cerebellar dysfunction, hemi- or quadriplegia, or sensory loss
• Organism is difficult to detect
• Ampicillin + tobramycin
**Legionella**
- Pulmonary infection
- HA, obtundation, confusion, high fever, tremor, nystagmus, ataxia, gaze palsies, dysarthria, SIADH
- CSF usually normal; CT negative
- Serum Ab to bacillus
- Erythromycin or azithromycin + ciprofloxacin

**Brucellosis**
- From livestock, esp. raw milk
- CSF lymphocytic pleocytosis, incr protein, elevated titres in blood & CSF
- Rifampin, cotrimoxazole, doxycycline

**Whipple Disease**
- Rare disease, mostly middle-aged men
- Weight loss, fever, anemia, steatorrhea, abdominal pain/distension, arthralgia, lymphadenopathy, hyperpigmentation, progressive dementia, ataxia, sz, myoclonus, supernuclear ophthalmoplegia (vertical)
- *Tropheryma whipelii* - bx jejunum
- Periodic acid-Schiff (PAS) pos. organism
- PCN + Steptomycin followed by Bactrim or ceftriaxone x 1 yr

**Septic Thrombophlebitis**
- Dural sinuses: lateral (transverse), cavernous, petrous, longitudinal
- Usually related to nasal sinus, middle ear, or skin around upper lip/eye/nose
- Skin and sinus flora
- HA papilledema
- ICP, cerebral venography
- Antibiotics, often anticoagulants
**Brain Abscess**

- Extension (2/3) or hematogenous (1/3)
- Endocarditis (SBE, acute), congenital heart disease
- Consider the site to select antibiotics while waiting for lab results
- HA, drowsiness, confusion, seizures, focal motor/sensory/speech disorders. Fever less consistent.
- Neuroimaging
- IV antibx, mannitol, Dex, aspiration

**Subdural Empyema**

- Intracranial suppurative process between inner surface of dura and outer surface of arachnoid
- Usually from sinus, middle ear, mastoids
- Sinus esp in young men (strep)
- Hx of chronic sinusitis/mastoiditis
- Incr CSF OP, pleocytosis with PMNs, nl glu
- CT scan for lesions/erosion
- Burr hole drainage, PCN+Ceph3+Flagyl

**HIV in the CNS**

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- HIV infection is a global epidemic
- CNS infection is common among patients with HIV
- Neuropsychiatric disability is a common consequence
**HIV and the CNS**

- HIV-associated dementia (HAD) became part of definition of AIDS in 1987 by CDC.
- Also called AIDS dementia complex (ADC), HIV dementia (HIVD)
- Dementia, delirium, and “milder” cognitive impairments

**The Numbers ...**

- Annual prevalence of HAD 7-15%
- Ann. prevalence of milder cognitive impairments ~35% of people with AIDS, 50% of those infected with HIV

**Leading causes of death in Africa, 1999**

<table>
<thead>
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<th>Rank</th>
<th>Cause</th>
<th>% of total</th>
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<tr>
<td>1</td>
<td>HIV/AIDS</td>
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<td>Diarrhoeal diseases</td>
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<td>Tuberculosis</td>
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<td>8</td>
<td>Cerebrovascular disease</td>
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<td>Ischaemic heart disease</td>
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Leading causes of death globally, 1999

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Neuro Consequences of HIV

• Early
  • acute viral syndrome with initial infection
  • MS-like illness
  • aseptic meningitis
  • demyelinating neuropathies

• Late
  • Dementia (HAD, ADC, HIV encephalopathy)
  • Vacuolar myelopathy
  • Peripheral neuropathy
  • Myopathies
  • Cerebrovascular complications
  • Seizures
  • Opportunistic Infections

HAD Clinical Manifestations

• Behavioral
  • apathy
  • social withdrawal
  • irritability
  • depression
  • personality changes

• Cognition
  • short term memory
  • concentration
  • mental slowing

• Motor
  • fine motor clumsiness & slowing
  • tremor
  • leg weakness

Van Gorp J Clin Exp Neuropsychol 1989
**Neuropsychological Deficits**

- MACRO exam
  - memory
  - attention
  - construction
  - psychomotor speed (timed gait, grooved pegboard, trails A & B, fingertapping)

**Clinical Correlates**

- NP-impaired are more likely to be unemployed, have more psychosocial morbidity
- Major depression is common (5-10% of HIV+ men) regardless of illness severity; dysthymia is common
- Pain & sensory neuropathies

**Macrophages/Microglia**
Antiretroviral Agents

Psychopharmacology

- Delirium
  - Low dose haloperidol or chlorpromazine
- Psychosis
  - haloperidol, thioridazine
- Depression
  - SSRIs, venlafaxine, mirtazapine, nefazodone
  - IPT, supportive + IMI (Markowitz ‘98)
  - Depression, apathy, anergia, cognitive impairment
    - methylphenidate, dextroamphetamine

Psychopharmacology

- Mood instability
  - Lithium, Valproate, Carbamazepine, Gabapentin, Lamotrigine, Topiramate
- Anxiety
  - SSRIs, benzos, buspirone
- Wasting
  - Dronabinol (a cannabinoid), Oxandrolone (anabolic steroid), Megestrol (derivative of progesterone), Somatotropin, Thalidomide, Testosterone
- Pain
  - opiates

CyP450 Interactions

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<th>CyP450 Isoenzyme Inhibited</th>
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<tr>
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Evidence-based URLs

- APA Practice Guideline on HIV/AIDS
  http://www.psych.org/psych_pract/treatg/pg/prac_guide.cfm
- Dave Flockhart’s Drug-Drug Interaction Tables
  http://medicine.iupui.edu/flockhart/
  http://www.drug-interactions.com/

Clinical Management Summary

- Watch for subtle cognitive deficits, regardless of whether HAD is the chief complaint; consider neuropsych testing to follow changes
- Treat other psychiatric complaints with common sense approaches
- Watch vigilantly for drug-drug interactions
- Psychotherapy plus pharmacotherapy