Central Nervous System Infections

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Etiology

- Bacteria
- Viruses
- Fungi
- Parasites
- Prions

Background

- Pathogenesis
  - initial entry: respiratory tract, GI tract, skin
  - path to CNS: bloodstream, peripheral nerves, adjacent bone, adjacent sinus
- CNS infection is infrequent due to protective mechanisms
  - reticuloendothelial system
  - cellular and humoral immune responses
  - blood-brain barrier
- CNS possesses less immune protection than rest of body

Diagnosis

- Meningeal inflammation is the hallmark of CNS infection
- Time course varies by etiology
  - viruses: hours to 1 day
  - aerobic bacteria: hours to a few days
  - anaerobic bacteria, TB, fungi: days to weeks
  - parasites and syphilis: weeks to years
  - prions: years

Diagnostic steps

- determine site of infection
- obtain culture and sensitivity: blood, CSF, other tissue
- treat expectantly, when indicated
- determine specific etiology and microbial sensitivity and modify therapy

Major Sites

- Meningitis: meninges
- Encephalitis: brain diffusely
- Brain abscess: brain locally
  - brain parenchyma
  - epidural abscess
  - subdural empyema
Meningitis: Clinical Features

- **Early**
  - prodromal illness, fever
  - headache, stiff neck
  - no alteration of mental status, focal neurologic signs or papilledema
- **Late**
  - stupor or coma
  - seizures
  - focal neurologic signs, CN palsies

CSF

- Gram stain detects bacteria
- Cultures: bacteria (1-3 days), viruses (days to weeks), TB and fungi (1-6 weeks)
- Latex agglutination antigen tests: *H. influenzae*, *Strep pneumonieae*, *N. meningitidis*, group A betahemolytic strepococci
- PCR: *M tuberculosis*, enteroviruses, *herpes simplex virus*

**CSF Profiles in CNS Infections**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>WBC</th>
<th>Protein</th>
<th>Glucose</th>
<th>Bacteria</th>
<th>Fungal Culture</th>
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<tbody>
<tr>
<td>Bacterial meningitis</td>
<td>50-10,000 (polys)</td>
<td>increased</td>
<td>low</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>20-1,000 (lymphs)</td>
<td>Slt increased</td>
<td>N</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Fungal/TB meningitis</td>
<td>50-10,000 (polys &amp; lymphs)</td>
<td>Increased</td>
<td>low</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Meningo-vascular syphilis</td>
<td>10-1,000 (lymphs)</td>
<td>Increased</td>
<td>N</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Viral encephalitis</td>
<td>10-200 (lymphs)</td>
<td>Normal or slt increased</td>
<td>N</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Brain abscess</td>
<td>0-10 (lymphs &amp; polys)</td>
<td>Normal</td>
<td>N</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Epidural abscess</td>
<td>0-20 (lymphs)</td>
<td>Normal or slt increased</td>
<td>N</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Subdural empyema</td>
<td>10-1,000 (polys)</td>
<td>Slt increased</td>
<td>N</td>
<td>-</td>
<td></td>
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</tbody>
</table>

Viral Meningitis

- **Etiology**
  - most common: enteroviruses (echoviruses, Coxsackie viruses)
  - less common: Herpes simplex type 2, mumps, HIV
- **Treatment**
  - symptomatic
  - acyclovir and related agents for *Herpes simplex*
- **Prognosis is usually good**

Bacterial Meningitis

- **Etiology**
  - most common: *S. pneumoniae* (except infants), *N. meningitidis, H. influenzae*
  - 0-3 months: *S. agalactiae, E. coli, L. monocytogenes*
- **Prognosis fatal if untreated: 5-25% mortality**

- **Treatment**
  - broad spectrum antibiotics early in course
    - preterm to newborn: ampicillin plus cefotaxime, w/ or w/o gentamicin
    - 2 months to adults: caftaxone or cefotaxime plus vancomycin, ampicillin for suspected *Listeria*
  - corticosteroids provide modest benefit
- **Immunization:** *H. influenzae, N. meningitidis* (some strains)
Postcontrast CT, 
*H. influenzae meningitis*

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**Bacterial Meningitis: Complications**
- Seizures develop in 1/3 of patients
- Focal neurologic signs in 25%
  - CN VIII (hearing loss), III, VI
  - in children: language disorders, developmental delay, mental retardation
- Cerebral infarct
- Hydrocephalus
- Brain abscess
- Note: some bacterial meningitis requires prophylactic treatment of family or close contacts; rifampin
  - *N. meningitidis*
  - *H. influenzae*

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**Tuberculosis and Fungal Meningitis**
- Subacute meningitis
- Fungal etiology: Coccidioides immitis, Histoplasma capsulatum, Cryptococcus neoformans, Aspergillus, Candida
- At risk: immunosuppressed, debilitated, malnourished

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**Tuberculosis and Fungal Meningitis**
- Pulmonary source, <50% have active pulmonary infection
- CSF culture, PCR, serologic tests
- Treatment
  - TB: rifampin, isoniazid, pyrazinamide, and streptomycin or ethambutol
  - fungal: amphotericin B or fluconazole
  - cryptococcal: amphotericin B, plus flucytosine
- Mortality 20-50%
Encephalitis

- **Etiology**
  - 90% viral
  - Arboviruses (togaviruses) most common worldwide, vector born (mosquito, tick) including Eastern, Western, Venezuelan equine
  - Flaviviruses including Japanese B, St. Louis, Murray Valley, West Nile
  - Bunyaviruses including California virus

- **Pathogenesis**
  - hematogenesis
  - neuronal necrosis, glial cell lysis, cerebral edema

Encephalitis: Clinical Features

- **Fever**
- **Headache**
  - meningismus minimal to absent
- **Obtundation and coma**
- **Focal neurologic signs**
- **Seizures**

Encephalitis: Evaluation

- **Imaging:**
  - brain MRI T2: early hyperdense areas of edema
  - head CT or brain MRI: later signs of brain necrosis and hemorrhage
  - herpes simplex encephalitis: mesial temporal lobar lesions

Spirochete Meningitis

- **Lyme disease:** *Borrelia burgdorferi*
  - Chronic meningitis
  - CN palsies, esp CN VII
  - CSF Lyme titer
- **Syphilis:** *Treponema pallidum*
  - Chronic meningitis
  - CSF VDRL
- **Treatment:** penicillin, ceftriaxone
Encephalitis: Evaluation

- EEG: diffuse bilateral slowing, seizures
- CSF
- Serologic tests:
  - IgM-antibody-capture enzyme-linked immunosorbent assay (MacELISA): serum and CSF arboviruses
  - CSF PCR: Herpes simplex

Encephalitis: Management

- Symptomatic
  - seizures
  - increased ICP
- Corticosteroid use is controversial
- Antivirals
  - acyclovir for encephalitis of unknown cause
  - ganciclovir for cytomegalovirus
  - famciclovir for varicella-zoster

Encephalitis: Management

- Prognosis depends on etiology
  - mumps and Venezuelan equine encephalitis: excellent
  - West Nile, western equine, St. Louis, California encephalitis: 2-15% mortality, 25% morbidity (dementia, seizures, focal neurologic deficits)
  - eastern equine, Japanese B, Murray Valley encephalitis: 20-40% mortality
  - herpes simplex encephalitis: 20% mortality treated with acyclovir, 50% morbidity
  - rabies encephalitis: fatal
Brain Abscess

- **Pathogenesis**
  - extension from within cranium (sinusitis, mastoiditis), following skull fracture or craniotomy, or blood born metastasis
  - begins as localized encephalitis, necrosis, and inflammation
  - fibroblasts at the periphery form a capsule wall
  - cerebral edema surrounds the abscess

Brain Abscess

- **Etiology**
  - bacteria:
    - 50% anaerobic; anaerobic streptococci and *Bacteroides fragilis*
    - *S. aureus* after head trauma or craniotomy
  - fungi
  - parasites: cysticercosis

Brain Abscess: Clinical Features

- Symptoms subacute
- HA, lethargy
- Fever
- Seizures, focal or generalized
- Focal neurologic signs
- Increased ICP

Brain Abscess: Evaluation

- **Imaging**
  - head CT: lesion with hypodense center and contrast-enhancing capsule with surrounding edema
  - brain MRI: similar
- **EEG**: localized slowing, seizures
- Note that LP is potentially dangerous due to risk of brain herniation

Postcontrast CT

Right frontal bacterial abscess

Postcontrast T1W MRI

Left periventricular bacterial abscess with ventricular rupture and ventriculitis
Brain Abscess: Management
- Broad spectrum antibiotics for both anaerobic and aerobic bacteria
  - cefotaxime, ceftriaxone plus metronidazole, chloramphenicol
  - staphylococci: nafcillin
- Surgical aspiration
  - gram stain and culture
- Cerebral edema: corticosteroids, mannitol
- Prognosis: 30-65% mortality, 50% morbidity

Parasites
- Protozoa
  - Plasmodium falciparum (malaria)
  - Toxoplasma gondii
  - Naegleria fowleri (primary amebic meningoencephalitis)
- Acanthamoeba or Hartmanella species (granulomatous amebic encephalitis)

Parasites
- Helminths
  - Taenia solium (cysticercosis)
  - Angiostrongylus cantonensis (eosinophilic meningitis)
- Rickettsia
  - Rickettsia rickettsii (Rocky Mountain spotted fever)

Prion diseases
- Creutzfeldt-Jacob disease (CJD)
  - most common prion disease, 1/1,000,000/year
- Gerstmann-Straussler syndrome
- Fatal familial insomnia
- Kuru
Prion Diseases

Pathogenesis
- no nucleic agent identified
- protein normally made by neurons, malformed into abnormal infectious particle

Clinical presentation
- do not present with typical signs of infection
- lack fever and elevated WBC
- subacute to chronic dementia, 6 months to 2 years
- myoclonic jerks common
- CSF appears normal by standard tests
- prions not killed by ethanol, formalin or boiling
- prions killed by autoclaving

Prion Diseases: Transmission
- Prions present: CSF, brain, pituitary gland, peripheral nerves inervate dura and cornea
- Prions not present: saliva, perspiration, urine, stool
- Blood considered infectious, but no human case from blood transfusion
- Transmission: cornea, dura, pituitary, surgical instruments, heredity (GSS, FFI)
- Most cases sporadic, with transmission not identified

Prion Diseases: CJD variant (vCJD)
- United Kingdom
- Transmitted from infected cattle with bovine spongiform encephalopathy (BSE, mad cow disease)

CJD Diagnosis
- Clinical: rapidly progressive dementia, myoclinic jerks, normal CSF
- CSF electrophoresis: 14-3-3 protein in many patients
- Brain MRI atrophy, basal ganglia enhancement
- EEG: quasiperiodic discharges

HIV: History
- 1981: CDC reported uncommon opportunistic infections and malignancies in young homosexual men
- Later: Acquired Immunodeficiency Syndrome (AIDS)
- 1983: Human immunodeficiency virus, a retrovirus, isolated; later HIV-1
- Later: HIV-2 identified in West Africa
HIV: Epidemiology
- 50% of persons infected with HIV develop symptomatic neurologic disease
- 90% of persons dying of AIDS show neuro-pathologic abnormalities
- Neurologic disease more frequent when CD4 < 20 cells/mm³, but may occur at any time
- Neurologic disease may be a direct effect of HIV or secondary infection
- Any part of the nervous system and muscles may be affected, sometimes resulting in two or more coexisting neurologic conditions

HIV
- Brain disease without mass effect
  - HIV encephalopathy
  - cytomegalovirus (CMV) encephalitis
  - progressive multifocal leukoencephalopathy (PML)

HIV Dementia
- Nomenclature: AIDS dementia complex (ADC), HIV encephalopathy, HIV-associated major cognitive/motor disorder
- Incidence uncertain, > 1/3 AIDS patients at death
- 3 categories of symptoms, onset insidiousness
  - cognitive: decreased memory and concentration
  - behavioral: social withdrawal
  - motor: clumsiness, imbalance, tremor

HIV Dementia
- Neurologic exam
  - Impaired mental states
  - Ocular motor saccades and pursuit abnormal
  - Coordination and rapid alternating movements impaired
  - Frontal release signs common
  - May progress to akinetic mutism, paraparesis, and incontinence

HIV Dementia
- Evaluation
  - brain MRI: atrophy, diffuse T2 hyperintense white matter signal
  - CSF: pleocytosis, mononuclear, < 20 cells/mm³, increased protein, < 65 mg/dl
    - HIV-1 30% patients
    - HIV-1 p24 core protein 50% patients

HIV Dementia
- Evaluation (cont)
  - laboratory, exclude other causes: renal, liver, electrolytes, syphilis, vitamin B12 and folate
- neurophysiological testing

HIV Dementia
- Treatment
  - zidovudine (AZT)
  - HAART (highly active antiretroviral therapy)
  - symptomatic
HIV: Cytomegalovirus

- **Pathophysiology**
  - reactivation of latent infection
  - retinitis most common presentation
  - any portion of neuraxis may be affected
- **Symptoms and signs:** acute to subacute altered mental status, coma, meningismus, seizures, CN palsies

HIV: Progressive Multifocal Leukoencephalopathy

- **Evaluation**
  - CSF: normal or pleocytosis (PMN's), increased protein, CMV PCR
  - head CT/Brain MRI: subependymal enhancement and ventriculitis
- **Median survival 5 weeks**
- **Treatment:** ganciclovir, Foscarnet

HIV: Brain disease with mass affect

- **Toxoplasma encephalitis** – most common
- **Lymphoma** – next most common
- **Opportunistic infections:**
  - Abscess: pyogenic, candida, nocardia, cryptococcal, fungal
  - Syphilitic gumma
  - Parasites
- **Vascular occlusive disease**
**HIV: Toxoplasmosis**

- **Pathophysiology and Epidemiology**
  - *Toxoplasma gondii*: intracellular protozoa
  - 5-25% AIDS patients develop toxoplasma encephalitis
  - propensity for basal ganglia, causing chorea
- **Clinical presentation: days to weeks**
  - fever, malaise
  - focal cortical neurologic symptoms and signs
  - altered mental status

- **Evaluation**
  - CT/MRI: single or multiple, nodular or ring enhancing lesions with edema
  - DDx single lesion: primary CNS lymphoma, SPECT may distinguish
  - LP contraindicated if mass affect
  - CSF nonspecific: 1/3 mononuclear pleocytosis < 100 cell/mm³, elevated protein 50-200 mg/dl; *T. gondii* PCR
- **Treatment**: sulfadiazine, pyrimethamine
  - 90% patients respond in 2-4 weeks

**HIV: Primary CNS Lymphoma**

- **Pathophysiology and Epidemiology**
  - a non-Hodgkins lymphoma arising in and confined to CNS
  - 2-13% AIDS patients develop PCNSL
    - 2nd most common brain mass in adults AIDS patients
    - most common brain mass in pediatric AIDS patients
- **Clinical presentation: altered mental status, focal neurologic symptoms/signs, seizures, CN palsies**

- **Evaluation**
  - CT/MRI: solitary or multiple, hyperdense ring or nodular enhancement, or isodense and with variable edema
  - DDx: toxoplasmosis, SPECT may distinguish
  - LP contraindicated if mass affect
    - CSF: 25% positive cytology, Epstein-Barr virus PCR
- **Treatment**: radiotherapy
  - leptomeningeal PCNSL, chemotherapy

**HIV: Cerebrovascular Disease**

- **Pathophysiology**
  - ischemia or hemorrhage
    - 19% autopsy series
  - due to: underlying infection, marantic endocarditis, infectious vasculitis (esp syphilis), vasculitis due to HIV, hypercoagulable state
- **Treatment similar to other patients with stroke**
HIV: Meningitis

- Cryptococcal: most common
  - 2-10% AIDS patients
- Other: TB, syphilis, Listeria, meningeal lymphomatosis

HIV: Myelopathy

- HIV-related vascular myelopathy
  - 20% AIDS autopsies
  - clinical presentation: spastic paraparesis, hyperreflexia, bowel and bladder incontinence, sensory level uncommon
  - evaluation: MRI normal or shows spinal cord atrophy or T2 hyperdensities
  - pathology: loss of myelin, spongy degeneration of dorsal and lateral columns
  - treatment: none yet proven effective

HIV: Myelopathy

- Other: infections including HTLV-1; epidural, intradural, and intramedullary tumors including lymphoma; demyelination; ischemia; B12 deficiency

HIV: Neuropathies and Myopathies

- Often concomitant with CNS infection
  - Complicates clinical presentation
- Neuropathies
  - Distal symmetric polyneuropathies
  - Acute and chronic inflammatory demyelinating polyneuropathy (A/C IDP)
  - Mononeuropathy multiplex
  - Autonomic polyneuropathy
  - Toxic neuropathies
  - Cytomegalovirus polyradiculopathy

HIV: Myopathies

- Myopathies
  - HIV associated myositis
  - zidovudine myopathy
  - HIV wasting syndrome

Summary

- Sites affected
  - Meningitis
  - Encephalitis
  - Brain abscess
- Etiologies
  - Viruses including HIV
  - Bacteria
  - Fungi
  - Parasites
  - Prions