CENTRAL NERVOUS SYSTEM INFECTIONS

1. OBJECTIVES
   • Explain the difference between meningitis and encephalitis.
   • Describe routes of parenchymal and meningeal infections.
   • List most common organisms that cause bacterial meningitis in different age groups.
   • Analyze CSF findings in viral, bacterial, and fungal infections.
   • Summarize histologic findings in:
     – Bacterial meningitis and CNS abscess
     – Chronic meningitis (TB)
     – Viral meningoencephalitis
     – Fungal infections
     – Parasitic infections

2. MENINGITIS - Inflammation of the leptomeninges
   a. Bacterial
      - S. pneumoniae, N. meningitidis and H. influenzae cause approx. 80% of cases of bacterial meningitis worldwide
      - Etiological agents associated with bacterial meningitis are age-related
      - Lumbar puncture is the most important investigation in patients with suspected bacterial meningitis. CT or MRI imaging should be done before lumbar puncture to predict the likelihood of brain herniation.
      - CSF is cloudy with numerous neutrophils and low glucose; Gram stain can identify the bacteria.
      - Microscopic: meninges expanded by acute inflammatory infiltrate (purulent meningitis), if brain parenchyma involved = meningoencephalitis
   b. Mycobacterial (Tuberculous)
      - Chronic
      - Thick exudate at the base of brain, entraps cranial nerves and major vessels
      - Can present with cranial nerve involvement or CSF blockade
      - Histopathology:
        Granulomatous inflammation - collections of epithelioid histiocytes, multinucleated giant cells and central caseating necrosis
        Findings are patchy
      - CSF: ↑lymphocytes, moderately high protein, mildly low glucose
   c. Neurosyphilis
      - Meningovascular syphilis:
        - Months or years after primary infection
        - Thickened leptomeninges – hydrocephalus and cranial nerve palsies
        - Obliterative endarteritis causes thrombosis and infarction
- Parenchymal syphilis
  - General paresis – 5-25 after infection; presents with psychosis and dementia; large number of Spirochetes in the brain
  - Tabes dorsalis – atrophy of posterior spinal roots and columns; spirochetes cannot be demonstrated; presents with pupillary abnormalities, optic nerve atrophy, ataxia, and bladder and bowel dysfunction

d. Fungal
  - Chronic
  - Spread from primary pulmonary infection is the most common scenario.
  - Histopathology: mononuclear infiltrate, variably granulomatous (overlaps with Tuberculous meningitis)
  - Special stains: GMS, PAS, Mucicarmine
  - Examples:

  **Cryptococcus** - Budding yeasts with clear mucoid capsule. The capsule stains with India ink and mucicarmine.
  **Aspergillus** - Hyphae branching at 45 degree angles
  **Candida** – Pseudohyphae
  **Zygomycetes** (Mucor) - Direct spread from sinuses

  - **Angioinvasive fungi:**
    - Candida
    - Aspergillus
    - Zygomycetes

- **Mycotic aneurysm:** Term initially used to describe aneurysms associated with bacterial endocarditis (noted to have the appearance of “fresh fungus vegetations”)
  - May be caused by bacteria as well as fungi
  - Septic embolus from the heart can occlude the vasa vasorum of the vessel or the vessel lumen, leading to vascular wall infection and mycotic (pseudo-) aneurysm formation

e. Protozoal
  - Toxoplasmosis
    - Brain abscess (ring-enhancing lesion on MRI)
    - Humans become intermediate hosts through ingestion of oocysts (cat feces, soil)
    - Crosses placenta (pregnant women should avoid changing cat litter)
    - Congenital toxoplasmosis is part of TORCH infections
    - **TORCH** infections
      - Toxoplasmosis, Others, Rubella, CMV, Herpes virus
      - Similar symptoms at birth
      - Classic triad of chorioretinitis, hydrocephalus, and intracranial calcifications
- Maternal infections from these agents are usually asymptomatic!
- Necessity to test for multiple pathogens
  - Diagnosis: serology, PCR, biopsy

- **Naegleria fowleri**
  - Present globally in soil and fresh water; exposure is therefore probably very common but infection is uncommon
  - Invades nasal mucosa and enters brain along olfactory nerves.
  - Rapidly progressive course, usually fatal: hemorrhagic necrosis of grey and white matter
  - Trophozoites are small, about 10 um in tissue. Vacuolated cytoplasm and pale nucleus with prominent nucleolus
  - CSF shows purulent inflammation
  - Diagnosis: wet mount or PCR, but difficult to make in life
  - Other free-living amoebae: Acanthamoeba and Balamuthia cause granulomatous encephalitis and have less fulminant course although still with high mortality

### f. Parasitic
- **Cysticercus**
  - Most common cerebral parasite; presents with seizures
  - Acquired by consuming food contaminated by eggs of pork tapeworm, *Taenia solium*
  - Egg hutches in the gut into oncosphere
  - Oncosphere migrates to other organs and develops into cysticercus (a bladder containing fluid and protoscolex), which lives for a few years before dying
  - Muscle, eyes and CNS are most commonly infected
  - Clinical symptoms of the CNS infection usually caused by the death of the parasite.
  - Cysts eventually resolve into calcified nodules.

### g. Viral
- Aseptic meningitis
- Most common organisms: Enterovirus, Arbovirus, HSV2, West Nile Virus
- Gross and histopathologic abnormalities are scant
- Histopathology: Lymphocytic meningeal infiltrates with perivascular lymphocytic extension along Virchow-Robin spaces
- If + microglial nodules = meningoencephalitis
h. **Non-infectious**
   - Neoplastic meningitis = leptomeningeal carcinomatosis:
     - Tumor cells diffusely infiltrating subarachnoid space causing clinical symptoms and imaging signs that mimic subacute to chronic infectious meningitis
     - Diagnosis made by CSF cytology

3. **ENCEPHALITIS**
   a. Infection of brain parenchyma - neurons and glial cells
   b. Usually accompanied by meningitis (meningitis can occur alone)
   c. Diffuse or focal
   d. **Cytomegalovirus (CMV)**
      - Fetal infection is part of TORCH spectrum
      - Common opportunistic infection in AIDS and other immunocompromised states
      - Histologic findings: obvious meningoencephalitis, cytomegalic inclusions in all cellular elements of the brain, including neurons. Most numerous in the periventricular regions.
      - Postnatal infection: numerous microglial nodules, only occasional cytomegalic cells with inclusions.
   e. **HSV** encephalitis
      - Usually HSV-1
      - Transmitted via saliva with latent infection in trigeminal ganglion
      - Causes medial temporal encephalitis – necrotizing hemorrhagic encephalitis of temporal lobes
      - Microscopic: intranuclear cherry-red inclusions in neurons (“owl’s eye” inclusion)
   f. **Polio** encephalitis
      - Spinal grey matter involvement with destruction of anterior horn cells (lower motor neuron)
      - Mixed inflammatory infiltrate and neuronophagia
   g. **Rabies** encephalitis
      - Rhabdos = rod
      - Bats are the main source in the US
      - Variable incubation time (10 days to >1 year, most commonly 1-3 months)
      - Prodrome of flu-like symptoms and pain at the site of the bite
      - Eosinophilic cytoplasmic inclusions (Negri bodies), easiest to find in neurons of brainstem, hippocampus and Purkinje cells
   h. **Progressive Multifocal Leukoencephalopathy (PML)**
      - JC virus
- Most otherwise healthy adults have serological evidence of polyomavirus infection but PML is largely restricted to immunocompromised hosts
- Productive infection in oligodendrocytes → cell lysis → demyelination
- Histologic findings:
  - loss of myelin
  - foamy macrophages
  - bizarre astrocytes resembling malignant astrocytes
  - oligodendroglial viral inclusions ("ground glass" oligodendrocytes)

i. HIV
- HIV encephalitis (HIVE)
  - widespread microglial nodules with multinucleated giant cells
- HIV leukoencephalopathy
  - subacute onset cognitive impairment
  - diffuse white matter pallor with microglial nodules and multinucleated giant cells
- Vacuolar myelopathy
  - spastic paraparesis with hyperreflexia and ataxia
  - vacuolation of posterior and lateral spinal columns (resembles subacute combined degeneration)

4. BRAIN ABSCESS
- Space-occupying lesion most commonly due to hematogenous spread of infection from the heart (endocarditis, congenital heart defect with shunt) or lung (bronchiectasis)
- Multiple pathogens are common
- Lumbar puncture not helpful unless there is concurrent meningitis
- Neuroimaging is a sensitive diagnostic tool but a definitive diagnosis can be made on biopsy
- Differential diagnosis of a "ring-enhancing" lesion on MRI: abscess, glioblastoma, metastasis