Infections of the Central Nervous System

MHD – Neuroscience Module

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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

Lecture outline
• CNS infections:
  – Bacterial
  – Fungal
  – Parasitic
  – Viral
  – Brain abscess
CNS Infections

- **Meningitis**
  - Inflammation within subarachnoid space (between arachnoid and pia matter)
- **Encephalitis/Meningoencephalitis**
  - Inflammation of brain parenchyma
  - Panencephalitis, polioencephalitis, leukoencephalitis
- **Ventriculitis**
- **Brain abscess**
- **Subdural empyema** (space between dura and leptomeninges)
- **Epidural abscess** (space between bone and dura)

Routes of Infection

- **Local extension**: sinuses, ear, dental infection
- **CSF leak**: anatomical defect (spina bifida), trauma (skull fracture)
- **Surgical procedure**
- **Hematogenous**

Meningitis

- **Bacterial** - acute
- **Viral** - acute but self-limiting
- **Fungal** - subacute
  - Immune-compromised
- **Amebic and tuberculous** – subacute granulomatous (usually)
- **Non-Infectious**
  - Chemical (e.g. post-operative)
  - Meningeal carcinomatosis
Bacterial meningitis

- Most common pathogens:
  - *S. pneumoniae*, *N. meningitidis* and *H. influenzae* – together responsible for >80% of all meningitis worldwide
- Classic triad of symptoms: fever, headache, neck stiffness
- Photophobia, altered mental status; seizures in meningoencephalitis
- Diagnosis:
  - Lumbar puncture with CSF cultures
  - Blood cultures

Acute bacterial meningitis

- Etiology
  - < 1 month:
    - *E. coli*
    - Group B streptococci
    - *L. monocytogenes*
  - 1 month – 16 years:
    - *N. meningitidis*
    - *H. influenzae*
    - *S. pneumoniae*
  - Adults (>15 years), immunocompetent:
    - *S. pneumoniae*
    - *Neisseria meningitidis*
  - Immunocompromised (age, diabetes, steroids, alcoholism):
    - *L. monocytogenes*
    - Group B streptococci

CSF Findings

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<thead>
<tr>
<th>ORGANISM</th>
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Gram stain + (60-90%)
Bacterial meningitis = purulent meningitis

Subarachnoid space filled with inflammatory cells.

Acute meningitis

Neutrophils + bacteria
Subacute/Chronic Meningitis

- Causative agents
  - Tuberculous (*Mycobacterium tuberculosis*)
  - Fungal (*Cryptococcus neoformans*, *Histoplasma capsulatum*, *Coccidioides immitis*)
  - Parasitic
    - Syphilis (*Treponema pallidum*)
    - Borreliosis (*Borrelia burgdorferi*)
  - Non-infectious (Neurosarcoid)

CNS tuberculosis

- Rare (<1% of patients with TB; ~ 4% in children)
- Rich foci (Rich nodules): small subpial tubercles that precede development of meningitis
- Clinical presentation:
  - Cranial nerve deficits common
  - Signs of meningeal irritation variable

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In early stages, neutrophils may dominate raising the differential diagnosis of bacterial meningitis.
CNS tuberculosis

• Tuberculous meningitis
• Tuberculoma
• Tuberculous brain abscess
• Vertebral osteomyelitis (Pott’s disease)

Tuberculous meningitis with thick exudate at the base of the brain

Necrotizing Granuloma

Necrosis

Multinucleated giant cells
Tuberculoma

- Caseous center
- Granulomatous inflammation

Space-occupying lesion, common in patients with miliary TB.

Neurosyphilis

- Clinicopathologic patterns:
  - Aseptic meningitis
  - Meningovascular syphilis
  - Parenchymal neurosyphilis
    - General paresis
    - Tabes dorsalis
- CSF shows aseptic meningitis
  - Can be negative in advanced stages
  - CSF VDRL test positive in 20-70%
Neurosyphilis

• Meningovascular syphilis
  – Obliterative endarteritis → thrombosis and infarction → symptoms of stroke (syphilitic stroke)
  – Thickened meninges → hydrocephalus and cranial nerve palsies
  – Months-years after primary infection (7 years on average but earlier in HIV)

Cerebellar gumma:
- Round lesions 1-4 cm
- Hard with necrotic center

Spirochetes within a necrotic area. Modified Steiner stain.

Parenchymal Neurosyphilis

• General paresis
  – 5-25 years after infection
  – Symptoms: psychosis and dementia
  – Neuropathology: cortical atrophy of frontal and temporal lobes
  – Large number of spirochetes present

• Tabes dorsalis (myelopathy)
  – 25-30 years after infection
  – Dorsal columns and posterior spinal roots atrophy
  – T. pallidum cannot be demonstrated
  – Argyll Robertson pupil
  – Optic nerve atrophy with declining visual acuity
  – Ataxia
  – Lightning pains
  – Bladder & bowel dysfunction
Tabes dorsalis

Fungal infections

- Immunocompromised patients
- Majority of fungal CNS infections are **part of systemic infection**:
  - Lung is most common primary site
  - Cutaneous mycosis (in immunocompromised)
  - Sinus or mastoid (Zygomycetes) – direct spread
  - Infected heart valve
  - Acquired (healthcare–associated infection)

Fungal infections – clinicopathologic patterns

- Meningitis
- Encephalitis
- Granuloma or abscess
- Secondary vasculitis with intracerebral hemorrhage – *Aspergillus, Candida, Coccidioides*
  - Vascular invasion and thrombosis → infarction
  - Mycotic aneurysm rupture → hemorrhage
Fungal infections - diagnosis

• Microscopic findings:
  – Mononuclear infiltrate (lymphocytes, macrophages), variably granulomatous (overlaps with TB)

• Special stains for diagnosis:
  – Periodic acid-Schiff (PAS)
  – Grocott methenamine silver (GMS)
  – Mucicarmine (Cryptococcus)

• Molecular diagnosis (PCR)
  – Becoming a gold standard

Fungal meningitis – simplified taxonomy

• Hyphal and pseudo hyphal fungi
  – Candida
  – Aspergillus
  – Zygomycetes
  – Fusarium

• Yeasts
  – Histoplasma
  – Blastomyces
  – Cryptococcus

Fungal infections

Cryptococcus – most common form of fungal meningitis (diagnosed by India Ink stain of CSF)

Present in the soil and bird feces

Infection via respiratory tract
  - initial lung infection may not be clinically apparent

Immunocompromised patient:
  - Lymphoproliferative diseases
  - Transplantation
  - Steroid and cancer therapy
  - Sarcoidosis
Thickened pale meninges

Clear cystic lesions in basal ganglia – "Swiss cheese" effect

Cryptococcus, CSF stained with India ink

Oval budding yeasts with mucoid capsule (stains with mucicarmine)

Inflammation is focal and limited

Infiltration by cryptococci of Virchow-Robin space in the white matter, H&E stain.
Angioinvasive aspergillus, GMS stain

Hemorrhage caused by mycotic aneurysm

Parasitic CNS Infections

- Cysticercosis
- Toxoplasmosis
- Amoebiasis
  - Naegleria fowleri
  - Entamoeba histolytica
  - Balamuthia mandrillaris
Cysticercosis

- Most common cerebral parasite
- Southwestern states and Mexico
- Pork tapeworm, *Taenia solium*
- Seizures are the most common manifestation
- Symptoms usually caused by the death of the parasite

Cysticercosis

- Cysts containing scolex

Cysticercus cellulose

- Cyst wall
- Protoscolex
- Branching body cavity
Toxoplasmosis

- Protozoan *Toxoplasma gondii*
- Cysts in meat or oocysts in cat feces
- Crosses placenta (pregnant women should avoid changing cat litter)
- Most people are infected after childhood and infection is silent
- Reactivation may follow immunosuppression (common in HIV)

Toxoplasmosis

- Brain abscess
  - Seizures and focal neurologic deficits
  - Ring enhancing lesion on MRI
- Congenital toxoplasmosis
  - Part of TORCH infections (Toxoplasmosis, Others, Rubella, CMV, Herpes virus)
  - “Classic triad” of chorioretinitis, hydrocephalus, and intracranial calcifications
- Diagnosis:
  - Serology
  - Toxo PCR
  - Biopsy

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Toxoplasmosis

Bradyzoites within a cyst

Naegleria fowleri

- Free living amoeba
- Swimming in freshwater lakes – enters via cribriform plate
- Fulminant acute meningoencephalitis
  - Usually fatal

Other free-living amoebae: Acanthamoeba and Balamuthia cause granulomatous encephalitis with less fulminant course although still with high mortality

Viral Infections

- Meningitis most common
- Causes of viral meningitis:

<table>
<thead>
<tr>
<th>Common</th>
<th>Intermediate to uncommon</th>
<th>Rare</th>
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<tbody>
<tr>
<td>Enteroviruses *</td>
<td>HSV 1</td>
<td>Adenoviruses</td>
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<tr>
<td>Adenoviruses</td>
<td>EBV</td>
<td>CMV</td>
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<tr>
<td>HSV 2</td>
<td>VZV</td>
<td>Influenza A, B</td>
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<tr>
<td>WNV</td>
<td>HIV</td>
<td>Measles, mumps, rubella</td>
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<tr>
<td></td>
<td>HIV-6</td>
<td>Parainfluenza</td>
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<td>Rotavirus</td>
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* Accounts for >75% of cases for which specific etiology can be identified.
Viral Meningitis - CSF Findings

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PCR-based testing of CSF or serum or CSF serology is often necessary to document specific viral cause.

Viral Meningitis

- Gross examination usually normal
  - May be: hyperemia, congestion, and edema of brain
- Microscopic changes subtle:
  - Lymphocytic meningeal infiltrates
  - Perivascular lymphocytic extension along Virchow-Robin spaces

![Meningeal and scanty perivascular infiltrates of lymphocytes](image)
Encephalitis

- Inflammation of brain parenchyma, diffuse or regional
- Usually accompanied by meningitis = meningoencephalitis (meningitis can occur alone)
- Diffuse or focal
- Most caused by viruses

CNS targets of particular viruses

<table>
<thead>
<tr>
<th>Meninges</th>
<th>Mumps</th>
<th>Enterovirus</th>
<th>Coxsackie</th>
<th>HIV</th>
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<tbody>
<tr>
<td>Motor neurons</td>
<td>Polio</td>
<td>Enterovirus</td>
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<tr>
<td>Neurons and glia</td>
<td>Herpes virus</td>
<td>Rabies</td>
<td>Measles</td>
<td></td>
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<tr>
<td>Neurons, glia and endothelium</td>
<td>CMV (in immunocompromised)</td>
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<tr>
<td>Oligodendroglia</td>
<td>Papovavirus (usually immunocompromised)</td>
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<tr>
<td>Microglia</td>
<td>HPV</td>
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<tr>
<td>Dorsal root ganglia</td>
<td>HSV, VZV</td>
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<tr>
<td>Fetal nervous system</td>
<td>Rubella, CMV</td>
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Seasonal Prevalence of Viral Encephalitis

<table>
<thead>
<tr>
<th>Summer/Early Fall</th>
<th>Fall and Winter</th>
<th>Winter and Spring</th>
<th>Any Season</th>
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<tbody>
<tr>
<td>Arboviruses (West Nile virus)</td>
<td>Lymphocytic choriomeningitis virus (LCMV)</td>
<td>Mumps</td>
<td>Herpes simplex virus EBV, CMV</td>
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<tr>
<td>Enteroviruses</td>
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<tr>
<td>Rocky Mountain spotted fever</td>
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<td>Leptospirosis</td>
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| * Nonviral infections that can mimic viral encephalitis

Perry A. Practical Surgical Neuropathology.
Viral Encephalitis

- Greater grey matter than white matter involvement
  - Diffuse or focal
- Microscopic findings:
  - Perivascular inflammation
  - Leptomeningeal inflammation
  - Microglial clusters (microglial nodules)
  - Neuronophagia
- T-lymphocytes predominate (some PMNs can be present in acute phase)
West Nile Virus Encephalitis

- Mosquito born infection
- Most WNV infections are asymptomatic
- Polioencephalomyelitis
- Parkinsonism
- Predilection for certain groups of neurons:
  - Anterior horn cells
  - Nigral neurons
  - Purkinje cells

Polio Encephalitis

- Poliovirus (Enterovirus)
- Still endemic in South Asia and Africa
- Fecal-oral transmission – replicates in oropharynx and small intestine
- Virus recovered from stool or throat
- Clinical features:
  - Asymmetrical paralysis (lower limbs>>upper limbs>trunk)
  - Cranial nerve palsies (IX, X)
  - Bulbar disease
  - Reticular formation (cardiac arrhythmia, sleep apnea, abnormal breathing patterns)
**Polio Encephalitis**

- Disease restricted to grey matter
- Infection and destruction of **anterior horn cells** (lower motor neuron)
- Old lesions:
  - loss of motor neurons
  - anterior nerve root atrophy
  - neurogenic atrophy of corresponding muscles

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**Polio Encephalitis**

Mixed inflammatory infiltrate in spinal grey matter with acute poliomyelitis

Neuronophagia (inferior olive)

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**Rabies**

- Exposure to rabid dogs most common cause worldwide (in US: bat, raccoon, skunk)
- Incubation can be last from 10 days to more than one year depending on bite location
- Prodrome of flu-like symptoms
- **Negri bodies** (cytoplasmic inclusions) seen in neurons of brainstem, hippocampus and cerebellum (Purkinje cells)

Bullet-shaped Rhabdovirus
Herpes Encephalitis

- Usually HSV-1
- Transmitted via saliva
- Latent infection in trigeminal ganglion
- Example of focal encephalitis:
  - Medial temporal lobes - edema, hemorrhage and necrosis (acutely)
Gross findings:
- bilateral, usually asymmetrical hemorrhagic necrosis of temporal lobes, especially anteriorly and inferiorly, and, to a lesser extent, the insulae, cingulate gyri, and thalamus
- usually accompanying brain edema

HSV-1 intranuclear inclusion ("owl's eye")

"Burnt-out" herpes encephalitis - chronic phase:
- hemorrhagic necrosis will progress to cavitation and atrophy
- in long-term survivors affected parts of the brain appear shrivelled and brown
**Cytomegalovirus (CMV)**

- Particularly important in fetal/neonate population – TORCH
  - *Toxoplasma*, *Rubella*, *CMV*, *Herpes simplex*
- Common opportunistic infection in AIDS, affecting the CNS in 10-20% of cases
- Large intracytoplasmic and intranuclear inclusions

**Congenital CMV Encephalitis**

- Moderately dilated ventricles and several foci of calcifications in the periventricular region.
- Microscopic:
  - 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.
Progressive Multifocal Leukoencephalopathy (PML)

- Caused by JC virus, genus Polyomavirus (also BK virus and SV40 but only JCV associated with CNS disease)
- Usually affects immunocompromised
  - Reversal of immunosuppression can stop the progression of PML
- Histology
  - Loss of myelin (with axonal sparing)
  - Bizarre astrocytes
  - Oligodendroglial inclusions

Multiple small or larger confluent foci of grey discoloration in the white matter (*) and at the junction of white matter and cerebral cortex (green arrow)
HIV pathology

• **HIV encephalitis (HIVE)**
  – Widespread microglial nodular encephalitis with *multinucleated giant cells* with predilection to grey matter

• **HIV leukoencephalopathy**
  – Subacute onset cognitive impairment and apathy
  – Diffuse white matter myelin pallor with microglial nodules and multinucleated giant cells
  – Oligodendrocytes are not infected - etiology uncertain

• **Vacuolar myelopathy**
  – Spastic paraparesis with hyperreflexia and ataxia
  – Vacuolation of spinal cord white matter
Multinucleated Giant Cell - HIVE

Vacuolar myelopathy: myelin pallor in dorsal and lateral columns
Brain Abscess

• Space-occupying, focal CNS infection
• Predisposition:
  – Hematogenous spread most common
    • Heart (endocarditis, congenital heart defect with shunt)
    • Lung (bronchiectasis)
  – Local extension
    • Teeth, ear (otitis, mastoiditis), frontal sinus
  – Direct introduction of organisms
    • Penetrating head trauma, neurosurgery
• Usual suspects (diabetes, EtOH etc)

Brain Abscess

• Multiple pathogens common
• Lumbar puncture is not helpful unless there is concurrent meningitis or ventriculitis
  – May cause herniation!
• Neuroimaging
• Definite diagnosis and pathogen identification can be achieved by stereotactic biopsy

Post-contrast MRI: “ring-enhancing” lesion

Other “ring-enhancing” lesions:
- Glioblastoma
- Metastasis
Well-circumscribed areas of softening at grey-white junction or in white matter, where the collateral circulation is poorest

Evolution of an Abscess

1) Early cerebritis (days 1-3)
   - Focal encephalitis
2) Late cerebritis (day 4-9)
   - Necrotic center surrounded by rim of inflammatory cells
   - Microvascular damage
3) Early encapsulation (days 10-13)
4) Late encapsulation (2 weeks +)
Thank you!