Lec. 4 | CNS Infection

Meningitis

A 45-year-old man is brought to the ED with 1–2 days of fever, headache, nausea, and vomiting. On physical examination he is found to have neck stiffness and photophobia.

Meningitis: Infection of the meningeal covering of the brain and spinal cord (the pia and arachnoid membranes), structures in the subarachnoid space and the cerebral ventricles.

High-Yield

From past exams

1)

1. Acute bacterial meningitis

Etiology

Acute bacterial meningitis affects both sexes and all ages starting from infancy to elderly. The most common causative organisms are:

- **Streptococcus pneumoniae** is the most common cause of bacterial meningitis for all patients beyond the neonatal period.
- **Neisseria meningitidis**, spread by respiratory droplets, is the most common cause of meningitis in adolescents.
- **Listeria monocytogenes**
  - is more common in those with immune system defects, particularly of the cellular (T-cell) immune system and sometimes neutrophil defects.
  - These defects include: HIV, steroid use, leukemia, lymphoma, and various chemotherapeutic agents. Since neonates and the elderly have decreased T-cell immune function, Listeria is more common in them.
  - Even with immune deficits, Streptococcus pneumoniae is still the most common etiology—it is just that Listeria is more common in these patients, as compared to fully immunocompetent patients.
- **Staphylococcus aureus** is more common in those who have had any form of neurosurgery because instrumentation and damage to the skin introduce the organism into the CNS.
- **Cryptococcus** is more common in those who are HIV positive and who have profound decreases in T-cell counts to levels <100 cells.
- **Meningococcal epidemics** occur in tropical and subtropical countries among over crowded populations. Most epidemics outbreak during spring but sporadic cases appear all the year around.

Routes of infection

There are *at least three routes* through which the organisms reach and infect the meninges:

1) **Direct spread** from infected para-meningeal structures (otitis media, sinusitis, mastoiditis, and dental infections), post traumatic, post- operative and during lumbar puncture.
2) **Blood-borne infection** following bacteremia of systemic infection (endocarditis and pneumonia).
3) **Retrograde extension** through cribriform plate.
4) **Air-borne infection** in endemic areas during epidemics.

Clinical picture

- **Manifestation of meningeal irritation** Meningeal attitude, neck rigidity & head retraction, Brudzinski's and Kernig's signs.
- **Raised intracranial pressure** due to increased formation or decreased CSF absorption. The patient may complain of headache, nausea, vomiting, photophobia, impaired level of consciousness and convulsions, papilledema is uncommon and develop late in severe cases.
- **Cranial nerve affection:** including cranial nerve palsies as nerve deafness, oculomotor, facial and bulbar paralysis.
- **Meningococcal septicemia:** skin rash, shock, intravascular coagulation, renal failure, arthritis, and pericarditis.
- **Rash is associated with several types of meningitis.**

➲ **Petechial rash** is suggestive of Neisseria
➲ **Rash on the wrists and ankles with centripetal spread** toward the body is suggestive of RMSF
➲ **Facial nerve palsy** is suggestive of Lyme disease; the target-like erythema migrans rash of Lyme disease is seldom present by the time the meningitis develops.
➲ **Pulmonary symptoms** or abnormal chest x-ray suggest TB

Complications

Rapid diagnosis and appropriate treatment of acute bacterial meningitis result in almost complete recovery. Nevertheless, a few percentages of patients are subject for one or more of the following complications:

1. Obstructive hydrocephalus
2. Dural sinus thrombosis
3. Epilepsy
4. Cranial nerve palsies. E.g. deafness, optic atrophy and ophthalmoplegia
5. Mental retardation.

Investigation

1- CSF examination: The following table shows the CSF parameters in health and disease:

	Normal	Bacterial meningitis	Tuberculous meningitis	Viral infection
Pressure	80-180mmH2O	Increased	Increased	Increased
Colour	Colourless	Cloudy	Cloudy	Colourless
Cells	0-5/mm mainly mononuclear cell and absent RBCs.	1000-5000 polymorphs	50-5000 lymphocytes	10-2000 Lymphocytes
Glucose	2/3blood sugar	Decreased	Decreased	Normal
Protein	<40mg/dl	Increased	Increased	Normal or increased

2-Neuroimaging

CT scans of the head

- Best initial diagnostic test if patient has papilledema, focal motor deficits, new onset seizures, severely abnormal mental status, or immunocompromised status.
- If none of the above is present, CT scan is not needed first
- CT scan can delay the diagnosis; if LP is delayed >20–30 min while waiting for the CT scan, give an empiric dose of antibiotics.

Differential diagnosis

Acute bacterial meningitis should be differentiated from acute or subacute neurological diseases presenting by fever, headache or impaired level of consciousness.

1. Tuberculous meningitis.
2. Cerebral abscess.
3. Viral encephalitis.
4. Subarachnoid or cerebral hemorrhage.
5. Intracranial neoplasm.

Treatment

An early IV dose of any of the third generation cephalosporins is effective against most of causative microorganisms.

- **Cefoperazone:** it is the drug of choice for all age groups, it acts against almost all meningitis causing pathogens. It should be given IV. The adult dose is 2-4 grams every 12-hours. Children dose is 50-200mg/kg/day given in 2 doses treatment should continue for 7 days.
- **Vancomycin** empiric therapy of bacterial meningitis in adults because of the increasing prevalence worldwide of pneumococci with decreasing sensitivity to penicillins) plus a third-generation cephalosporin such as ceftriaxone.
- **For the immunocompromised or those age >50 or ≤1 month**, add **ampicillin** to cover Listeria (Listeria is resistant to all forms of cephalosporins)
- **If hospital-acquired or post-neurosurgical procedure**, must cover Pseudomonas and MRSA: use vancomycin and cefepime, ceftazidime, or meropenem (for penicillin allergy, replace moxifloxacin for cephalosporin).
- **Lyme disease:** ceftriaxone
- **Cryptococcus:** amphotericin B and flucytosine initially, followed by fluconazole for HIV-positive patients (life-long or until patient is on HAART and is asymptomatic with CD4 count >100/µL for at least 3–6 months)
- **Special care for fluid and electrolyte balance** is needed, avoiding overhydration. Analgesics, antipyretics for headache and fever.

Prophylactic treatment: Patients with meningitis are infectious for 24 hours after initiation of therapy.

Prophylactic treatment is recommended for the following personnel:

1. Family and household members.
2. Close intimate contacts.
3. Hospital staff members who have been breathed on by the patient.

Drugs:

- **Rifampin** 600mg/12 hours for 4 doses (10mg/kg/12 hours in children).
- **Vaccine**: polysaccharide, meningococcal type A and C is commonly used in epidemic in large-scale prophylaxis.

Clinical Recall

A65-year-old man presents to the ED with fever, stiff neck, and photophobia. Which of the following is the best empiric treatment?

A. Vancomycin, ceftriaxone, ampicillin, and dexamethasone
B. Nafcillin, ceftriaxone, and ampicillin
C. Vancomycin and ceftriaxone
D. Vancomycin, cefepime, and dexamethasone
E. Vancomycin, ceftriaxone, and ampicillin

Answer: A

2. Viral meningitis

- Mild clinical manifestation
- Benign course
- No complication
- No specific treatment

3. Tuberculous meningitis

- Persistence of signs and symptoms of meningitis and failure of recovery despite of proper use of antibiotic therapy raises the suspicion of TB infection.
- TB meningitis usually affects debilitated and immune compromised subjects.
- It is characterized by sub acute or gradual onset and progressive course of meningitis.

Clinical picture

- **Prodromal phase (2-3 weeks):** lassitude, anorexia, and loss of weight, intermittent vomiting and confusional state.
- Symptoms of meningeal irritation.
- There is often photophobia, papilledema, focal neurological signs (endarteritis, cerebral infarction, and hemiplegia) may occur.
- Basal adhesion, deafness, dysphagia, and obstructive hydrocephalus may occur.

Treatment

- **TB meningitis:** same treatment as pulmonary TB but for longer duration, 9–12 months
- **For TB and bacterial (adult) meningitis**, steroids are appropriate.
  - Dexamethasone decreases morbidity, mortality, and rates of deafness
  - Benefit is greatest for pneumococcal meningitis
  - Administer 15–20 min before or concurrently with antibiotics
  - Give for 4 days if bacterial meningitis is confirmed (i.e., positive Gram stain of CSF fluid or >1000 WBCs within the CSF)
  - Discontinue if etiology is nonbacterial (viral, fungal, etc.)

Acute encephalitis

A young man is brought to the ED by his friends because of 1–2 days of confusion and strange behavior. He had originally complained of a headache and fever. On the day of admission, he became markedly worse and is now delirious. He is generally healthy. On physical examination you find a lethargic, confused man with an elevated temperature. You are unable to determine if he has focal neurologic findings or to obtain an accurate neurologic exam because his confusion makes him unable to follow commands.

Encephalitis

- is an infection of the brain parenchyma. Although any bacterial, protozoal, or rickettsial infection can cause encephalitis, **most cases are caused by viruses**.
  1. Herpes simplex (usually type I [HSV-1]) (most common)
  2. Varicella-zoster virus, CMV, enteroviruses, Eastern and Western equine encephalitis, St. Louis encephalitis, and West Nile encephalitis (less common)
- **It is characterized pathologically** inflammatory and degenerative changes with brain edema and cellular infiltration especially in gray matter (cortex, midbrain, and basal ganglia).

Routes of viral infection

A. **Viruses can spread from man to man** e.g., mumps, measles and varicella.
B. **Viruses acquired from infected animals** (Zoonosis) e.g., rabies.
C. **Viruses are acquired by inoculation** as result of bites of arthropodes (arboviruses)
D. **Tran placental infection** by rubella virus, cytomegalovirus, and HIV.

Clinical picture

- Disturbance level of consciousness.
- Disturbance in mental function, behavior and orientation.
- Disturbance of sleep rhythm.
- Convulsions.
- Oculogyric crisis.
- **Focal neurological signs:** cranial nerves affection, long tracts and mental symptoms.
- It is often associated with meningism, headache, fever and neck stiffness.

Differential diagnosis

1. **Viral meningitis:** characterized by marked meningeal and less neurological manifestations. Typical CSF findings are diagnostic.
2. **Cerebral abscess:** characterized by relatively slow course. Less generalized symptoms and neurological deficits point to involvement of a single brain region. Brain CT reveals a typical picture of a cystic lesion with an enhancing ring.
3. **Cerebral hemorrhage:** due to rapidly evolving picture and associated fever, massive cerebral hemorrhage may simulate acute viral infection.

Investigations

- **CSF examinations**
- **EEG recording** may show periodic slow activity arising from one or both temporal lobes.
- **Neuroimaging (CT and MRI):** localized hypodense area in the region of the temporal and basal frontal lobes with marked swelling of the affected region.
- **PCR (polymerase chain reaction)** amplification techniques, it has a 98% sensitivity and >95% specificity, making it at least equal to the biopsy. HSV PCR may be negative early on. If imaging and clinical presentation is consistent with HSV, continue acyclovir and repeat HSV PCR in 3–5 days.

Treatment

- **Antiviral drugs**
  - Unlike RNA viruses (measles, rabies and HIV), Herpes simplex virus belongs to the treatable group of the DNA viruses. The most effective drug is acyclovir, given IV at a dose of 30mg/kg/day, divided into three daily doses, each given over one hour, treatment should be continued for 10 days.
  - Although famciclovir and valacyclovir have activity against HSV, they are not available intravenously. Ganciclovir and foscarnet are active against CMV. Acyclovir-resistant herpes is treated with foscarnet.
- **Antiepileptic drugs:** as most of the cases present with generalized or focal seizures or even in status epilepticus. IV diazepam in a dose of 10 mg could abort the succession of seizures.
- **Brain diuretics:** 250ml of 25% mannitol/12 hours for 2 days reduces brain swelling resulting in improvement of the patients' consciousness.

Autoimmune Encephalitis

Autoimmune encephalitis is caused by anti-NMDA receptor antibodies. About >50% of cases are associated with ovarian teratomas.

- **Clinical Presentation**
  - Choreoathetosis
  - Psychiatric symptoms
  - Seizures
  - Autonomic instability
  - Coma
- **Diagnosis.** CSF anti- NMDA receptor antibodies.
- **Treatment** is removal of the teratoma when present; corticosteroids; rituximab; cyclophosphamide; and IVIG.

Brain Abscess

An HIV-negative man is brought to the hospital because of a seizure. When he becomes more alert, you find that he has aphasia and weakness of the right hand and leg. CT scan of the head with contrast shows enhancement of the lesion with a "ring" around the lesion.

- Brain abscess is a collection of infected material within the brain parenchyma.
- Toxoplasmosis can reactivate in those with severe HIV disease when CD4 counts are very low (<50–100/μL).
- Brain abscesses most commonly have Streptococcus in 60–70%, Bacteroides in 20–40%, Enterobacteriaceae in 25–35% and Staphylococcus in 10%.
- Because of the diversity of the organisms potentially involved, it is difficult to have a single standard therapy.

Clinical presentation

Symptoms usually develop slowly over several weeks, but they can also come on suddenly. Symptoms you should watch for are:

- Differences in mental processes, such as increased confusion, decreased responsiveness, and irritability.
- Decreased speech, sensation, or movement due to loss of muscle function.
- Changes in vision, personality, or behavior
- Vomiting, fever and chills, neck stiffness.
- In babies the fontanelle may be swollen or bulging.

Diagnosis

- **Computed tomography** is the initial test. Contrast is used to help identify the lesion, although CNS malignancy enhances with contrast as well.

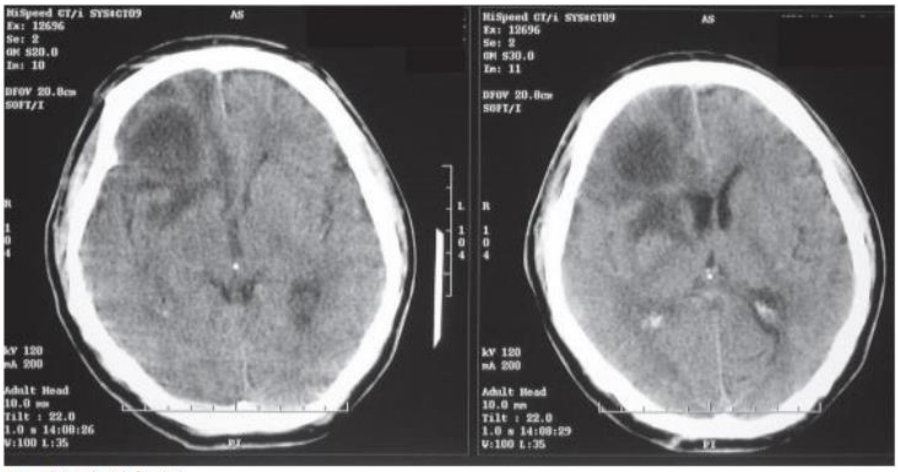

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Figure 7-1. CT Scan Demonstrating Large Cerebral Abscess

- **MRI** is more accurate than the CT scan, although no radiologic test alone can give the precise etiology. In the case of bacterial brain abscess, examination of the abscess fluid (obtained by stereotactic aspiration or surgical excision of the abscess) for Gram stain and culture is essential.

In HIV-positive patients, 90% of brain lesions will be either toxoplasmosis or lymphoma. This is the only circumstance where empiric therapy is sufficient to establish a specific diagnosis. If the lesion responds to 10–14 days of therapy with pyrimethamine and sulfadiazine, continue to administer this therapy, as it accurately predicts cerebral toxoplasmosis.

Treatment

A brain abscess is a serious medical situation.

- A stay in the hospital will be required.
- Pressure due to swelling in the brain can lead to permanent brain damage.
- If your abscess is deep inside your brain or it's 2.5 centimeters or less, it will probably be treated with **antibiotics**.
  - Antibiotic medications will also be used to treat any underlying infections that may have been the cause of the brain abscess.
  - Broad-spectrum antibiotics are the most prescribed. You may need more than one type of antibiotic.

- **Surgery**
  1. No response to antibiotics.
  2. Abscesses greater than 2.5 centimeters wide, there is a risk of rupture or containing gases produced by bacteria. The fluid that's removed is normally sent to a lab to determine the cause of the infection.

QUIZ

1) **The CSF changes of viral encephalitis include which of the following?** **(Mid-term 59)**
   A. Predominance of polymorph nuclear leukocytes
   B. Increased number of lymphocytes
   C. Glucose level is low
   D. Protein level is less than 40 mg/dl
2) **In case diagnosed with meningitis, what is the suspected finding in brain neuroimaging?** **(Mid-term 59)**
   A. Atrophic changes in frontal lobe.
   B. Brain abscess
   C. Hemorrhagic foci lesion in temporal lobe
   D. No brain focal lesion
3) **A Patient diagnosed with TB meningitis, based on which of the following pathognomonic parameters in CSF findings?** **(Final 59)**
   A. Clear aspect, normal glucose, and lymphocytes >10mm.
   B. Clear aspect, normal glucose, and lymphocytes>5mm
   C. Cloudy aspect, low glucose, and polymorphs>10mm.
   D. Cloudy aspect, low glucose, and lymphocytes >10mm.
4) **Which of the following is considered a complication of acute bacterial meningitis?** **(Final 59)**
   A. Obstructive hydrocephalus.
   B. Raised intracranial pressure.
   C. Photophobia
   D. Neck rigidity.
5) **A child is diagnosed with acute bacterial meningitis, which of the following is considered a complication of this diagnosis?** **(Final 60)**
   A. Neck rigidity
   B. Obstructive hydrocephalus.
   C. Photophobia
   D. Sleep disturbance
6) **Anti-viral drugs (Acyclovir) is given IV in a dose of 30 mg/kg/day divided into three doses/day, for 10-14 day in which presentation with viral encephalitis?** **(Final 60)**
   A. Chicken box
   B. Herpes simplex encephalitis
   C. HIV encephalitis
   D. Measles encephalitis

1	2	3	4	5	6
B	D	D	A	B	B