Infections of the Central Nervous System:

-The natural defense mechanisms of CNS:
  -The blood-brain barrier.
  -Local immune responses of CNS.

-Neurotropism and microbial virulence.

-Definitions.

-Meningitis:
  -Causes.
  -Port of Microbial Entry.
  -Pathogenesis.
  -Mechanism of tissue destruction.

-Diagnosis of Meningitis.
Natural defense mechanism of CNS:

The Blood-Brain barrier:
Is a separation of circulating blood from the brain extracellular fluid by the intercellular tight Junctions.
(Endothelial cells that line brain capillaries, astrocytic end-feet, and thick basement membrane).
Blood-Brain barriers prevent the passage of microbes and its toxic substances into the brain and CSF.

**However, the blood-brain barrier also:**

1. Prevents the passage of humoral immune components (complement and antibodies) to the site of infection.
2. Prevents the cellular infiltration of WBCs to the site of infection.
3. Reduces the penetration of many antimicrobial drugs.
Local Immune Responses of CNS:

The CNS has an intrinsic immunological surveillance mechanism that depends on:

1- Presence of specific antigen presenting cell;  
   (the Microglial cells).

2- Virchow-Robin spaces (the perivascular sheaths surrounding the blood vessels) contain lymph-like system of macrophages and lymphocytes.
Neurotropism and microbial virulence:

- **Neurotropism**: is the susceptibility of nervous system cells to some pathogenic microbes due to presence of specific virulence factors.

**Examples:**

1. **Polivirus** infects the motor neurons of the spinal cord and medulla. **Mumps virus** invades ependymal cells lining the ventricles in the fetal brain due to specific epitope-receptor interaction.
2-Encapsulated bacterium has anti-phagocytic capacity. The encapsulated bacterium can also resist complement-mediated lysis.

3-Some strains of *Escherichia coli* and *Group B Streptococcus* have K1 antigen (a capsular polysaccharide rich in Sialic acid); this will increase the bacterial adherence ability to the meninges.
Definitions:

- Infection of brain parenchyma results in **Encephalitis** or **Brain abscess**.
- Infection of meninges causes **Meningitis**.
- Infection of spinal cord tissue leads to **Myelitis**.
- **Meningoencephalitis** is a combination of two sites of infection.
- **Acute disseminated encephalomyelitis**, ADEM: a postinfectious viral encephalitis that is mediated by cross-reactivity-immune response against brain tissue myelin.
# Meningitis:

## Classified according to clinical presentation:

1. Acute.  
2. Subacute.  
3. Chronic.

## Classified according to Etiology:

1. Bacterial.  
2. Viral (aseptic meningitis).  
3. Fungal.  
4. Protozoal.

-Acute meningitis is usually **bacterial** or **viral** in etiology.  
-In all cases of suspected bacterial meningitis, antibiotic therapy must be administrated immediately.
Causes of Acute bacterial meningitis:

-The etiology of acute bacterial meningitis varies with the age of the patients:

1-In Neonates (28 days old) and infants younger than 3 months of age; Meningitis is caused by Group B Streptococci (50%), E. coli (20%), and Listeria monocytogenes and others (up to 10%).

2-In infants older than 3 months, children, and adults: Streptococcus pneumonia, Neisseria meningitides, and Haemophilus influenzae type b.
Acute bacterial meningitis:
Port of Entry to CNS: Hematogenous Route.

Pathogenesis:
Upper or lower respiratory tract infection:
*Neisseria meningitides*, *Streptococcus pneumonia*, & *Haemophilus influenzae* type b.
- Sore throat and epiglottitis, bronchitis, pneumonia or carriage state.
- **Bacteremia**; capsule resist humoral mediated destruction
- In **Choroid plexus**, due to **lack of tight junctions** between endothelial cells (loss of blood-brain barrier); Invasion of **ependymal cells**; infection of **ventricles**, Periventricular tissue.
Neurologic damage and mechanism of destruction:

- The CSF Glucose, protein, and oxygen content supports bacterial multiplication (in Pia arachnoid and CSF).
- Infiltration and proliferation of microglial cells.
- Chemotaxis of Lymphocytes from choroid plexus and Virchow-Robin space.
- Bacterial toxicity; the LPS Endotoxin; Cytokines produced.

- Increased CSF Secretion, defect in CSF reabsorption;
  
  Increased ICP (Intracranial pressure):
  1- Breakdown of blood-brain barrier; Intracranial hematoma.
  2- Cerebral edema; thrombosis; ischemia; neuronal injury.
- Diffuse cerebral edema; general cerebral cortical dysfunction.

- Reduced Cerebral perfusion pressure CPP (Blood flow pressure to the brain) due to:

  1. Increased Intracranial pressure.
  2. Reduced mean arterial pressure (MAP) secondary to shock.

This also results in: Thrombosis; Ischemia, and so Neuronal Infarction.
Clinical presentation of *Neisseria meningitides* infection:

Patients with acute *N. meningitides* infection may present clinically with:

1. Meningitis.
2. Meningitis with meningococcemia.
3. Meningococcemia without meningitis.

**General:** Headache, fever, vomiting.

**Meningitis:** Photophobia, Neck stiffness, seizures (20%), and Skin Rash (50%).

**Meningococcemia:** Purpuric skin; hemorrhagic eruption; hypotension, tachycardia.
In Meningococccemia:
1- General endothelial necrosis causes hemorrhagic eruption and purpuric skin lesions.
2- Intraluminal thrombosis causes disseminated intravascular coagulopathy (DIC); multiple organ failure.
Chronic Meningitis:

Causes:

1-Bacteria: *Mycobacterium tuberculosis*.

2-Fungi: *Cryptococcus neoformans*.

Tuberculous Meningitis:

(*Mycobacterium tuberculosis* infection):

- Lung infection; disseminated lymph nodes infection.
- Transferred to *meninges* or *brain parenchyma*; formation of small *subpial* or *subependymal foci* of metastatic lesion.
-The size of Rich foci increased; ruptures into subarachnoid space causing basilar meningitis.

-Those deeper in the brain or spinal cord parenchyma causing Tuberculoma or abscesses.

-Basilar meningitis accounts for:
  1-Cranial nerves III, VI, VII dysfunction.

  2-Obstructive hydrocephalus (enlarged ventricles).
Spinal cord involvement: (*Mycobacterium* infection):

- The earliest lesion in the lumbar vertebra due to hematogenous spread (*vertebral osteomyelitis*).

- This is frequently complicated by *Spinal epidural abscess*; rupture of abscess intra-spinally; *Spinal meningitis*.

- Involvement of the *dorsal columns* of the *spinal cord* results in *loss of position sensation* known as *tabes dorsalis* (also shown in *neurosyphilis; Treponema*).
Subdural Empyema:

Is an intracranial infection between the dura mater and arachnoid mater (usually unilateral).

In infants, and young children; it occurs as a complication of meningitis.

In adults; it occurs as a complication of paranasal sinusitis (mainly frontal and Ethmoid sinusitis; 2 weeks later), Otitis media or Mastoiditis.

(infection spreads intracranially; thrombophlebitis).
Fungal Meningitis: *Cryptococcus neoformans*:

- Melanin producing Yeast reproduces by budding.
- In tissues, it has polysaccharide capsule.
- Found in soil contaminated with bird excreted matter.
- It causes infection in immunocompetent patients (20% of cases) and children.

- **Primary infection**: lung infection; asymptomatic alveolitis.

- Resistance of phagocytosis; decreased cell-mediated immunity; carried by bloodstream.
- **Subacute or chronic meningitis**.
Amebic Meningitis or Meningoencephalitis:

- Primary amebic meningitis: *Naegleria fowleri*; the freshwater Brain-eating amoeba.
- Secondary amebic meningitis: *Entamoeba histolytica*.

**Naegleria fowleri** Meningitis:

- Classified as ameboflagellates.
- Salt, pH-sensitive microbe.
- Heat tolerant at 45.8°C.
- Exposure to river’s water (swimming) causes this rare and lethal infection within 1-2 weeks.
Pathogenesis:

- Port of entry: Neural route (olfactory nerve endings).
- Invasion of olfactory epithelium.
- Invasion of sub-mucosal nervous plexus.
- Microbial migration in the neuroepithelium through out cribriform plate of ethmoid bone to parenchymal cells of olfactory bulbs.
- Reaching Subarachnoid space; Meningitis.
- CSF supports growth by its glucose and high level of $O_2$.
- Infection of ependymal cells of ventricles; **acute ependymitis**; encephalitis.
Acute Viral Meningitis (Aseptic Meningitis):

**Aseptic meningitis** refers to the fact that the CSF of patients with the syndrome is sterile on route bacteriological culture.

**Causes:**
- Currently, more than **85% of viral meningitis** are due to **Non-Polio Enteroviruses**.

**1-Enteroviruses**: Family: Picornaviridae.
  - Echoviruses
  - Coxsackievirus A and B
  - Poliovirus.

- Coxsackievirus B accounts alone for **more than 60%** of meningitis in **children younger than 3 months**.
- Enteroviruses 70 and 71 has a strong neurotropism that results in encephalitis with polio-like paralytic syndrome associated with aseptic meningitis.

2-Mumps virus: Paramyxoviridae:
In parts of the world where vaccine is not applicable; it causes 10% of cases.

3-Arboviruses:
Arthropod-borne infection associated with 5% of cases.

4-Herpesviruses: 4% of cases.
HSV-1 and HSV-2.
5-Lymphocytic Choriomeningitis virus:
- Arenaviridae; Cerebral meningitis with lymphocytic infiltration of choroid plexuses.
- Contact with hamster, rat, mice or Excreted materials. Inhalation route, ingestion route, contaminated wound.

6-Other viral causes:
- Adenovirus.
- HIV: in 5-10% of AIDS patients.
- Measles.
Diagnosis of Meningitis:

A-In Hematology Laboratory:

Leukocytes count and differential count:

1- Normal Leukocytes count: 0-6 cells/mm$^3$.
   - If it is > 1000/cumm: suspected Bacterial infection.
   - If it is less than 300/cumm: Viral infection.

2- Differential count:
   - If % Neutrophils is >50%: suspected bacterial infection.
   - If % of neutrophils < 50% and lymphocytes dominates: other WBCs; Viral infection.
B-In Biochemistry Laboratory:
- Decreased glucose level; suspected bacterial infection.
- Increased or normal protein level: Viral infection.
  Increased protein: bacterial infection.

C-In Microbiology Laboratory:
1-Direct Microscopy:
- CSF specimen should be concentrated by centrifugation; and the pellet will be used for:
  1-Gram’s stain: Gram’s positive or negative Cocci or Bacilli.
  2-Z.N stain: for acid-fast bacilli; *Mycobacterium tuberculosis*
  3-Capsule stain: for *Streptococcus pneumoniae*.
  4-India ink Wet-mount: for all capsulated microbes.
The Gram’s negative diplococcus (*N. meningitidis*) inside polymorpho-Nucleated neutrophils. (Gram’s stain).

*Mycobacterium* (Z.N Stain); lymphocytic Infiltration.

The Budding capsulated yeast *Cryptococcus neoformans* as shown in India ink wet mount.
2-Microbial cultivation and identification:

A-Isolation of *Streptococcus pneumoniae*:

(most common cause in adults):

- Gram positive Lancet-shaped capsulated Cocci.
- Alpha hemolytic on blood agar.
- Optochin sensitive.
B-Isolation of *Neisseria meningitidis*:
(Most common between the ages of 2-18 years).

- Gram negative diplococci inside polymorphonucleated phagocytes (in CSF).

- **Fastidious** bacterium grow best on chocolate agar (Hemin and NAD\(^+\)) and at microaerophilic conditions of 5-10 % CO\(_2\).

- Oxidase positive, and glucose and maltose fermenters.
C-Isolation of *Haemophilus influenzae*:

(Infants and young children):

- **Pleomorphic Gram’s negative Coccobacilli** to filamentous bacilli.
- **Fastidious** (Similar to *N. meningitidis*).
- **Type b capsule** can be examined by Quellung swelling test or immunofluorescent staining.
D-Isolation of Group B Streptococci:

*(Streptococcus agalactiae)*:

- The *leading cause of neonatal meningitis* and septicemia with high mortality rate.
- Found *normally* in the *vagino-cervical tracts* of female carriers.
- Transmitted during birth.

- **Gram positive cocci** in chains.
- **Beta hemolytic** activity.
- **Bacitracin resistant.**
E-Isolation of *E. coli*:

- Neonatal Meningitis.
- K1 Capsular antigen.
- Gram’s negative bacilli.
- Lactose fermenters.
- Indole positive.
- Metallic green sheen on EMB medium.
3-Detection of microbial genetic material by PCR:

PCR has a significant diagnostic value for:
1. Detection of *Mycobacterium* genes in CSF.
2. Detection of viral genetic material in CSF (RT-PCR).

4-Direct agglutination serologic methods for detection of:

A. Microbial capsule.  
B. The microbial exotoxins.
Case Study:

Ms. G., a 32-year-old, immigrated to the United States 2 months ago with her husband and three children. Four weeks following her arrival, her oldest child returned from child care with chicken pox. Two weeks later, Ms. G and the rest of her family developed the disease.

All recovered, however Ms. G developed a headache and vomited a few times (over the next week). She developed stupor 4 days later and taken to a local hospital.
On physical examination, Ms. G was noted to have impaired eye movements. A chest radiography showed right upper lobe pneumonia. A cranial computerized tomography (CT) scan showed enlarged ventricles suggestive of acute hydrocephalus. A lumbar puncture revealed an opening pressure of 310 mm H$_2$O (highly elevated), and the CSF showed 350 WBCs/mm$^3$, of which 87% were lymphocytes. The CSF protein was 168 mg/dl (increased), and the glucose was 20 mg/dl (decreased). Gram’s stain and acid-fast stain of CSF showed negative results. A positive PCR results confirmed chronic bacterial meningitis.
Ms. G was treated with isoniazid, rifampin, pyrazinamide, and streptomycin with steroids for 2 months. With resolution of her symptoms, she was discharged to receive 10 additional months of therapy with isoniazid and rifampin.

1-What is the suspected causative agents?
2-How this infection is initiated by chicken pox infection?
3-What is the explanation for Ms. G eye movement abnormalities?
4-How do the CSF finding in this case compare with other viral or bacterial meningitis?
5-Why are multiple drugs required for the treatment of Ms.G?