بسم الله الرحمن الرحيم
Pathogenesis and Pathology of Meningitis

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CNS Infections

✓ An extremely common clinical problem.

✓ High mortality and morbidity.

✓ Mandates prompt diagnosis with appropriate therapy if consequences to be minimized.
CNS INFECTIONS

4 Routes:

a) **hematogenous spread**
   - most common

b) **direct implantation**
   i) most often is traumatic
   ii) iatrogenic (rare) via lumbar puncture
   iii) congenital (meningomyelocele).

c) **local extension** *(secondary to established infections)*
   - most often from mastoid and frontal sinuses, *cranial or spinal osteomyelitis*, infected tooth, etc.

d) **Transport along the peripheral nervous system** into CNS
   - viruses: - rabies
     - herpes zoster
CNS Infections

Infections cause damage to nervous tissue as consequence of:

- Direct injury of neurons or glia by the infectious agent.
- Indirectly through the elaboration of microbial toxins.
- Destructive effects of the inflammatory response.
- The result of immune-mediated mechanisms.
Meningitis
Introduction

* **Meningitis** is one of the most terrifying diseases.

* It can be **fatal** in hours.

* **Early symptoms** resemble self-limiting conditions *(flu and colds)*.
Meningitis

* A general name for inflammation of:

**a) Meninges:**
Sheaths that cover brain and spinal cord

**b) Cerebrospinal fluid:**
Fluid that circulates in the spaces in and around brain and spinal cord

* **Meningitis can be caused by:** infectious or non-infectious agents *(chemical meningitis)*

* **Infectious agents include:** bacteria, viruses, fungi, protozoa and rickettsia.
Meningitis

• Definitions:

✓ Meningitis refers to an inflammatory process of the leptomeninges and cerebrospinal fluid (CSF) within the subarachnoid space.

✓ Meningoencephalitis: Meningitis + with inflammation of the brain parenchyma. develops with spread of the infection from the meninges into the underlying brain.

✓ Encephalitis: Infections of the brain
Meningitis

Infectious meningitis is classified into:

- **Acute pyogenic meningitis** (usually bacterial).

- **Acute (a septic) lymphocytic meningitis** (usually viral).

- **Chronic meningitis** (usually tuberculous, spirochetal, or cryptococcal (fungal)).
Acute Pyogenic (Bacterial )Meningitis

Causative Microorganism varies with age of the patient:

- **In neonates**
  - *Escherichia coli*
  - The group B streptococci.

- **In infant and children**: *Haemophilus influenzae*

- **In adolescents and in young adults**
  - *Neisseria meningitides* is the most common pathogen.

- **In elderly**,
  - *Streptococcus pneumoniae* .
  - *Listeria monocytogenes* .

- **In the immunosuppressed** Klebsiella or an anaerobic organism. *Cryptococcus neoformans*.
Morphology

- **Grossly**: the meninges are congested, opaque. The subarachnoid space contains creamy exudates.

- **Microscopically**: the leptomeninges are congested and infiltrated by neutrophils, fibrin, and lymphocytes. Infection of the underlying parenchyma is rare.
Acute Pyogenic (Bacterial Meningitis)

Clinically:
- Fever and general signs of infections e.g. hemorrhagic rashes in the skin and mucous membrane.
- Symptoms of meningeal irritation: headache, photophobia, irritability, neck stiffness, clouding of consciousness.

CSF:
- Spinal tab is turbid fluids, under increased pressure.
- Increased cells up to 90,000 mainly P.N.Ls/ul.
- Increased protein level up to 300-800 mg\(^\%\)
- Decreased sugar content.
- Infectious agent may be demonstrated on the smear.
Symptoms of Meningitis

Central
- Headache
- Altered mental status

Ears
- Phonophobia

Eyes
- Photophobia

Neck
- Stiffness

Systemic
- High fever

Trunk,
mucus membranes,
extremities
(if meningococcal infection)
- Petechiae
Potential Complications

• Advanced bacterial meningitis can lead to brain damage, coma, and death
• Survivors can suffer long-term hearing loss, mental retardation, paralysis, and seizures
• Blood spread lead to (Waterhouse-Friderichsen syndrome): Septicemia with extensive hemorrhage and bilateral adrenal gland hemmorrhage
- Waterhouse-Friderichsen syndrome
  - results from meningitis-associated septicemia
    - hemorrhagic infarction of the adrenal glands
    - cutaneous petechiae
    - common with menigococcal and pneumococcal meningitis
To elicit Kernig’s sign, place the patient in a supine position. Flex her leg at the hip and knee, as shown here. Then try to extend the leg while you keep the hip flexed. If the patient experiences pain and possibly spasm in the hamstring muscle and resists further extension, you can assume that meningeal irritation has occurred.
Assessment Tip

Testing for Brudzinski’s sign

Here’s how to test for Brudzinski’s sign when you suspect meningeal irritation:

With the patient in a supine position, place your hands behind her neck and lift her head toward her chest (as shown at right).

If your patient has meningeal irritation, she’ll flex her hips and knees in response to the passive neck flexion (as shown at right).
Acute (a septic) Viral meningitis

- The causative agents are viruses, most common is the **enterovirus**
- The clinical features are similar to those of bacterial meningitis but less severe, - Is usually self-limiting,
  - Most often is treated symptomatically. And no life threatening complication seen as in bacterial meningitis.

The CSF shows:
- increased cells mainly lymphocytes.
- moderate increased of protein.
- Glucose level is normal
Aseptic Meningitis (Viral Meningitis)

- Macroscopic characteristics: brain swelling.
- On microscopic examination,
  - No recognizable abnormality or a mild to moderate infiltration of the leptomeninges with lymphocytes.
  - Some class of drugs have been implicated with a true noninfectious meningitis with lymphocytes.
• An aseptic meningitis–like picture may also develop subsequent to:
  • Rupture of an epidermoid cyst into the subarachnoid space.
  • The introduction of a chemical irritant ("chemical" meningitis).
  • In these cases the CSF is sterile, there is pleocytosis with neutrophils and an increased protein concentration, but the sugar content is usually normal.
Chronic Meningitis

- Chronic meningitis may be caused by bacteria or fungal.
- Chronic bacterial infection of the meninges and the brain may be caused by M. tuberculosis, Treponema pallidum, and Borrelia species.
Chronic Meningitis

- **Tuberculous meningitis**

- has fatal outcome and permanent sequelae, requiring rapid diagnosis and treatment

- Tuberculosis of the brain may be part of systemic disease or apparently isolated.

- It may involve the meninges or the brain, often together.

- **TBM**: Clinical features, headache, malaise, mental confusion, vomiting.
Tuberculous meningitis

- **CSF:**
  - Spinal tab is clear and may clott, under increased pressure.
  - Increased cells lymphocytes and polymorph
  - Increased protein, very high
  - Sugar content low
  - Chloride very low
Chronic Meningitis

- **Tuberculous Meningitis**:

  - **Morphology:** the meninges are opaque and thickened

  - The subarachnoid space contains a gelatinous or fibrinous exudate, most often at the base of the brain, and extending laterally to the sulci.

  - In late cases dense fibrous adhesion are present. End in hydrocephalus

  - Organisms can often be seen with acid-fast stains
Tuberculous Meningitis:

✓ **On microscopic** examination there are:

✓ reveal exudates formed of mixtures of lymphocytes, plasma cells, and macrophages.

✓ Florid cases show well-formed granulomas, often with caseous necrosis and giant cells, similar to the lesions of tuberculosis elsewhere in the body.
Tuberculous Meningitis:

- **Tuberculoma**: Another manifestation of the disease is the development of a single (or often multiple) well circumscribed intraparenchymal mass (tuberculoma), which may be associated with meningitis.

- may reach several centimeters in diameter, causing significant mass effect.

- On microscopic examination, there is usually a central core of caseous necrosis surrounded by a typical tuberculous granulomatous reaction; calcification may occur in inactive lesions.
What kind of CSF findings are expected in this patient?

Basilar meningitis
Granuloma with AFB stain

tuberculoma
Tuberculous Meningitis:

- The most serious complications of chronic tuberculous meningitis are:
  - Arachnoid fibrosis producing hydrocephalus,
  - Obliterative endarteritis producing arterial occlusion.
  - Infarction of underlying brain
Chronic Meningitis

- **Neurosyphilis**: A tertiary stage of syphilis. Only about 10% of untreated infection.
- Manifestations are:
  - 1- *Meningovascular neurosyphilis.*
  - 2- *Paretic Neurosyphilis.*
  - 3- *Tabes dorsalis*
Neurosyphilis (Manifestations) :

1- Meningovascular Neurosyphilis

Morphology :

Is a chronic meningitis involving the base of the brain, the cerebral convexities and the spinal leptomeninges.

✓ Associated with obliterative endarteritis, with a distinctive perivascular inflammatory reaction rich in plasma cells and lymphocytes.

✓ Cerebral gummas (mass lesions rich in plasma cells) may also occur in relation to meninges and extend into the brain.
Neurosyphilis (Manifestations):

- **2-Paretic Neurosyphilis**
  - is caused by invasion of the brain by *Treponema pallidum*
  - Manifests as insidious but progressive loss of mental and physical functions with mood alterations (including delusions of grandeur),
  - Terminating in severe dementia
  - **Morphology**: there is parenchymal damage particularly in the frontal lobe, characterized by loss of neurons with proliferation of microglia (rod cells) and gliosis
Neurosyphilis (Manifestations) :

3- *Tabes dorsalis*

- resulting from damage to the sensory nerves in the dorsal roots producing:
  - impaired joint position sense and resultant ataxia (locomotor ataxia).
  - loss of pain sensation, leading to skin and joint damage (Charcot joints);
  - "lightning pains".
  - absence of deep tendon reflexes

- **Morphology**
- loss of both axons and myelin in the dorsal roots, with pallor and atrophy in the dorsal columns of the spinal cord
LABORATORY DIAGNOSIS OF MENINGITIS

- Examination of the CSF.
- If diagnosis of meningitis is strongly considered, promptly perform a lumbar puncture.
- Measure the opening pressure and send the fluid for cell count (and differential count), chemistry (ie, CSF glucose and protein), and microbiology (ie, Gram stain and cultures).
- CT scan, MRI of the brain
Meningococcal Disease Laboratory Diagnosis

Specimen:

- Cerebrospinal fluid (CSF)
  . Fluid usually collected from arachnoid space.
  . A sterile needle is inserted between 4th and 5th lumbar vertebrae and the CSF is allowed to drip into a dry sterile container

- Blood
LP
<table>
<thead>
<tr>
<th>Agent</th>
<th>Opening pressure</th>
<th>WBC/µL</th>
<th>Glucose(mg/dl)</th>
<th>Protein(mg/dl)</th>
<th>Microbiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>200-300</td>
<td>&gt;80% PMNs</td>
<td>&lt; 40</td>
<td>&gt;100</td>
<td>Specific pathogen demonstrated in 60% of Gram stains and 80% of cultures</td>
</tr>
<tr>
<td>Viral</td>
<td>90-200</td>
<td>10-300 lymphocytes</td>
<td>Normal</td>
<td>Normal but may be slightly elevated</td>
<td>Viral isolation, PCR assays</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>180-300</td>
<td>100-500 lymphocytes</td>
<td>Reduced, &lt;40</td>
<td>Elevated, &gt;100</td>
<td>Acid-fast bacillus stain, culture, PCR</td>
</tr>
<tr>
<td>Cryptococcal</td>
<td>180-300</td>
<td>10-200 lymphocytes</td>
<td>Reduced</td>
<td>50-200</td>
<td>India ink, cryptococcal antigen, culture</td>
</tr>
<tr>
<td>Aseptic</td>
<td>90-200</td>
<td>10-300 lymphocytes</td>
<td>Normal</td>
<td>Normal but may be slightly elevated</td>
<td>Negative findings</td>
</tr>
<tr>
<td>Normal</td>
<td>80-200</td>
<td>0-5 lymphocytes</td>
<td>50-75</td>
<td>15-40</td>
<td>Negative findings</td>
</tr>
</tbody>
</table>
TREATMENT/PREVENTION

• Supportive
• Antibiotics
• Antiviral
• Surgery
• Vaccination: A, C, Y, or W135 serogroups
THE END