Student Learning Outcomes

Review anatomy of CNS, PNS, meninges, BBB

Differentiate meningitis from encephalitis including diagnosis and treatment.

Discuss mode of transmission, etiology, disease symptoms, treatment, and preventive measures of

- Bacterial meningitis caused by *H. influenzae*, *S. pneumoniae*, *N. meningitidis*, and *L. monocytogenes*
- Tetanus
- Botulism
- Leprosy
- Rabies
- Arboviral encephalitis,
- Cryptococcosis.
- African trypanosomiasis
- Prion diseases

Compare and contrast the Salk and Sabin vaccines
How do microbes enter the CNS?
The Meninges and Cerebrospinal Fluid

Fig 22.2
Bacterial Diseases of the CNS

Bacteria can grow in CSF in subarachnoid space.

The BBB prevents passage of some materials (such as antimicrobial drugs) into CNS.

Meningitis vs. encephalitis

Meningitis can be caused by viruses, bacteria, fungi, and protozoa.

**BACTERIAL MENINGITIS**: Much more serious than viral. Can cause severe disease resulting in brain damage and death.
Bacterial Meningitis

- The three major causes:
  - *Haemophilus influenzae*
  - *Neisseria meningitidis*
  - *S. pneumoniae*

- Nearly 50 species of opportunistic bacteria can cause meningitis (*L. monocytogenes, S. pyogenes, S. aureus*)

- Symptoms: Fever, headache, stiff neck, followed by nausea and vomiting ⇒ may progress to convulsions, coma, shock, and death

- Diagnosis by Gram stain or latex agglutination of CSF

- Cephalosporins before identification of pathogen!
Epidemiology of Bacterial Meningitis

Not very contagious → spreads by direct close contact with discharges from nose/throat of infected person.

Vaccines:

1988: Hib


2005: MCV4 (MenactraT®) vaccine of choice for 11 to 55 y old (old vaccine since 1982)
Spinal Tap (Lumbar Puncture)

Spinal needle is inserted, usually between the third and fourth lumbar vertebrae.
Haemophilus influenzae Meningitis (Hib)

- Gram-negative, pleomorphic coccobacilli, capsule
- Common part of normal throat microbiota
- Fastidious → needs factors in blood (genus name!). Species name is misnomer.
- Mostly in children under age 4 (especially around 6 month of age. Why?)
- Also causes pneumonia, otitis media, epiglottitis
Neisseria Meningitis: Meningococcal Meningitis

Gram-neg cocci, capsule

~ 10% of people are healthy nasopharyngeal carriers

Begins as throat infection, typical rash → death may occur within a few hours of onset.

Continuing threat in day-care centers and schools.

Mostly in children < 2 y of age.
Sporadic outbreaks among young adults.

Vaccination recommended for college students
Meningococcal Rash

About half the children or adults with meningococcal meningitis have rash that does not fade.

Exotoxins damage blood vessel walls → blood leaks into skin.

Glass test, or pressure test – septicaemic rash usually does not fade under pressure. (Not 100% reliable.)
Pneumococcal Meningitis – *S. pneumoniae*
- Gram-positive diplococci
- Typically associated with pneumonia, but may cause pneumococcal meningitis and pneumococcal septicemia.
- 70% of people are healthy nasopharyngeal carriers
- Most common in children (1 month to 4 years)
- Mortality: 30% in children, 80% in elderly
Listeriosis

- **Listeria monocytogenes**
  - Gram-positive
  - Reproduce in phagocytes.

- Acquired by ingestion of contaminated food - psychrophil!
- May be asymptomatic in healthy adults.
- Causes meningitis in newborns, immunosuppressed, pregnant women, and cancer patients.
- Can cross placenta and cause spontaneous abortion and stillbirth
Diseases in Focus: Meningitis and Encephalitis

- A worker in a day-care center in eastern North Dakota became ill with fever, rash, headache, and abdominal pain. The patient had a precipitous clinical decline and died on the first day of hospitalization. Diagnosis was confirmed by Gram staining of cerebrospinal fluid.

- Can you identify infections that could cause these symptoms?
Tetanus (Lockjaw)

- **Clostridium tetani**
- Gram-positive, endospore-forming, obligate anaerobe
- Grows in deep wounds.
- Tetanospasmin (exotoxin / neurotoxin) released from dead cells blocks relaxation pathway in muscles. [Tetanospasmin action.](#)
- Prevention by vaccination with tetanus toxoid (DTaP) and booster (dT).
- Treatment with tetanus immune globulin.
Tetanospasmin Action

Blockage of inhibitory NT release in CNS (glycine and GABA – gamma-aminobutyric acid)

Result?
Characteristic condition: **Opistothonos**

Neonatal tetanus with severe muscle contractions.  
90% fatality rate

Why characteristic backward arc?

- courtesy of CDC-
Botulism

- *Clostridium botulinum*

- Gram-positive, endospore-forming, obligate anaerobe, ubiquitous in soil and H₂O

- Intoxication (ingestion of botulinum toxin): 7 different Neurotoxins (exotoxins, A, B and E cause most human illness)

  - **Type A**
    - 60-70% fatality
    - Found in CA, WA, CO, OR, NM.

  - **Type B**
    - 25% fatality
    - Europe and eastern United States

  - **Type E**
    - Found in marine and lake sediments
Botulinum Toxin: Most Potent Toxin on Earth

- **Mechanism of action**: Irreversible inhibition of ACh release from motor neuron

- **Treatment**: ?

- **Prevention**
  - Proper canning
  - Nitrites prevent endospore germination in sausages
3 Forms of Botulism

1. **Foodborne botulism**: Intoxication not infection! Endospores survive improper canning procedures.

2. **Wound botulism**: ~ symptoms as above, start ~ 4 days after wound infection

3. **Infant botulism**: due to ingestion of endospores $\Rightarrow$ *C. botulinum* growing in intestines.

In animals: limberneck
Botulinum Toxin: Killer and Healer

**Botox**® (Botulinum toxin type A)

Medical uses: blephrospasms, strabismus, torticollis . . . . . etc.

Under investigation: migraine headaches, hyperhidrosis

Cosmetic purposes
Blepharospasm is a focal dystonia characterized by increased blinking and involuntary closing of the eyes.
Leprosy or Hansen’s Disease
- *Mycobacterium leprae* (acid-fast rod)

- Grows best at 30°C ⇒ cooler body regions (peripheral nerves and skin cells)

- Transmission requires prolonged contact with an infected person. Mostly via nasal secretions of lepromatous leprosy patients

Incubation time: Months to 10 years

*Two forms depending on immune response*

1. **Tuberculoid** (neural) form: Loss of sensation in skin areas; positive lepromin test

2. **Lepromatous** (progressive) form: in case of cell mediated IS failure) Disfiguring nodules over body; negative lepromin test
Tuberculoid leprosy in a 24-year-old Samoan woman with seven-month history of expanding plaque on cheek. Note the thickened accessory nerve coursing over the sternomastoid muscle.
Patient with active, neglected nodulous lepromatous leprosy. With treatment, all nodules could be reversed. ©WHO/TDR/McDougall
Deformity due to nerve damage with its consequent ulcers and resorption of bone. Such deformities can be worsened by careless use of the hands. © WHO/TDR
VIRAL MENINGITIS: Usually mild. Clears up within a week or two without specific treatment. Also called aseptic meningitis.

Poliomyelitis
Rabies
Viral meningitis
Viral encephalitis
Poliomyelitis – Infantile Paralysis

Poliovirus (Enteroviruses of picornaviridae)

Transmitted by ingestion. 3 strains of polio virus (1,2,3)

90% of cases asymptomatic

Initial symptoms: Sore throat and nausea

Viremia may occur; if persistent, virus can enter the CNS; Selective destruction of motor neurons and paralysis occurs in <1% of cases.

Prevention: vaccination (enhanced IPV)

Post-polio syndrome 30 y later: Crippling deterioration of originally affected muscles due to aging process of “replacement neurons”.
Worldwide Annual Incidence of Poliomyelitis

Fig 22.11
Prevention and Treatment

- 1955: Salk vaccine (Inactivated – IPV)
- OPV has caused all the polio cases in the US between 1980 and 1999
- 2000: CDC recommends new IPV (E_IPV) for routine immunization

FDR, *President from 1932 to 1945*
Rabies Virus (of \textit{Rhabdoviridae})

- **Zoonosis** – Transmission from saliva of rabid animal
- Virus multiplies in skeletal muscles, then retrograde axonal transport to CNS (encephalitis), then back out to periphery (salivary glands etc.)
- Initial symptoms may include muscle spasms of the mouth and pharynx and hydrophobia.

- **Furious rabies**: Animals restless then highly excitable.
- **Paralytic rabies**: Animals unaware of surroundings.
Pathology of Rabies Infection

1. Virus enters tissue from saliva of biting animal.
2. Virus replicates in muscle near bite.
3. Virus moves up peripheral nervous system to CNS.
4. Virus ascends spinal cord.
5. Virus reaches brain and causes fatal encephalitis.
6. Virus enters salivary glands and other organs of victim.
Treatment and Prevention

- Highly fatal – only handful of people survived

**Preexposure prophylaxis:** Human diploid cells vaccine (HDCV) applied *i.m.*

**Postexposure prophylaxis (PEP):**
- Vaccine (HDCV, applied *i.m.* on days 0, 3, 7, 14, and 28)
- Human rabies immune globulin (RIG)

- Rodents and rabbits seldom get rabies. Dogs, cats, cattle, skunks, raccoons, bats, etc. do ➞ Vaccination of pets! If necessary vaccination of wild populations
genetically engineered, vaccinia-rabies glycoprotein (V-RG) virus has proven to be orally effective in raccoons.
Reported Cases of Rabies in Animals

Fig 22.13

KEY
- Skunk
- Raccoon
- Fox
- Fox and skunk

KEY
- Wild
- Domestic

<table>
<thead>
<tr>
<th>Animal</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Raccoons</td>
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<tr>
<td>Bats</td>
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<tr>
<td>Cattle</td>
<td>1%</td>
</tr>
<tr>
<td>Horses/mules</td>
<td>1%</td>
</tr>
</tbody>
</table>
Arboviral Encephalitis

- Arboviruses are arthropod-borne viruses that belong to several families.
- Prevention by mosquito control.
- Horses and humans affected.
- Incidence of arboviral encephalitis ↑ in summer, when mosquitoes are most numerous.
- Sentinel animals, e.g.: caged chickens
- Diagnosis based on serological tests.
- Symptoms from subclinical to coma and death
## Notifiable Arboviral Encephalitis Infections

<table>
<thead>
<tr>
<th>Encephalitis</th>
<th>Reservoir</th>
<th>Mosquito vector</th>
<th>U.S. distribution</th>
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<tbody>
<tr>
<td>Western equine</td>
<td>Birds, horses</td>
<td><em>Culex</em></td>
<td>![Map]</td>
</tr>
<tr>
<td>Eastern equine</td>
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<td><em>Aedes, Culiseta</em></td>
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<tr>
<td>St. Louis</td>
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<td>California</td>
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<tr>
<td>West Nile</td>
<td>Birds, mammals</td>
<td><em>Culex, Aedes</em></td>
<td>![Map]</td>
</tr>
</tbody>
</table>
Diseases in Focus: Types of Arboviral Encephalitis (p. 628)

- An 8-year-old girl in rural Wisconsin has chills, headache, and fever and reports having been bitten by mosquitoes.

- Which type of encephalitis is most likely?
Cryptococcus neoformans Meningitis

- Also called cryptococcosis
- Soil fungus associated with pigeon and chicken (aerosolization of dried up contaminated droppings)
- Transmitted by the respiratory route; spreads through blood to the CNS
- Mortality up to 30% – Primarily affects AIDS patients (~ .4%)
- Diagnosis: Serology to detect cryptococcal antigens in serum or CSF
- Treatment: Amphotericin B and flucytosine
Cryptococcus neoformans

Figure 22.15
Protozoan Disease of Nervous System

African Trypanosomiasis (Sleeping Sickness)

Caused by *Trypanosoma brucei*; vector: tsetse fly (day-biting)

- *T.b. gambiense* infection is chronic (2 to 4 years).
- *T.b. rhodesiense* infection is more acute (few months).

Without treatment: death

Treatment: Eflornithine blocks an enzyme necessary for the parasite
Antigenic variation allows for persistent evasion of the immune system $\Rightarrow$ Cyclic parasitemia (7-10 days)
Tsetse fly Stages

1. Tsetse fly takes a blood meal (injects metacyclic trypomastigotes)
2. Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
3. Trypomastigotes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
4. Trypomastigotes in blood
5. Tsetse fly takes a blood meal (bloodstream trypomastigotes are ingested)
7. Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
8. Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.

Human Stages

1. Tsetse fly takes a blood meal (injects metacyclic trypomastigotes)
2. Injected metacyclic trypomastigotes transform into bloodstream trypomastigotes, which are carried to other sites.
3. Trypomastigotes multiply by binary fission in various body fluids, e.g., blood, lymph, and spinal fluid.
4. Trypomastigotes in blood
5. Tsetse fly takes a blood meal (bloodstream trypomastigotes are ingested)
7. Procyclic trypomastigotes leave the midgut and transform into epimastigotes.
8. Epimastigotes multiply in salivary gland. They transform into metacyclic trypomastigotes.

\[ i = \text{Infected Stage} \]
\[ d = \text{Diagnostic Stage} \]
Nervous System Diseases Caused by Prions

Transmissible Spongiform Encephalopathies

Prions convert normal proteins into abnormal proteins

Post mortem sponge-like appearance of brain tissue
  large vacuoles in cortex and cerebellum due to loss of neurons

Chronic and fatal

Transmitted by ingestion or transplant or inherited.

- Typical diseases
  - Sheep scrapie
  - Creutzfeldt-Jakob disease
  - Kuru
  - Bovine spongiform encephalopathy
Prions

PRION PROTEIN (PrP)

PrP
alpha-helical protease sensitive

PrPRES or PrPSC
beta-pleated sheet protease resistant

Helical - Happy

Beta-pleated sheet - Bad
How can a protein be infectious?

1. PrP^c produced by cells is secreted to the cell surface.
2. PrP^Sc may be acquired or produced by an altered PrP^c gene.
3. PrP^Sc reacts with PrP^c on the cell surface.
4. PrP^Sc converts the PrP^c to PrP^Sc.
5. The new PrP^Sc converts more PrP^c.
6. The new PrP^Sc is taken in by endocytosis.
7. PrP^Sc accumulates in endosomes.
8. PrP^Sc continues to accumulate as the endosome contents are transferred to lysosomes. The result is cell death.
Surgical instruments sterilized by
- NaOH
- + extended autoclaving at 134°C