INFECTIONS OF THE NERVOUS SYSTEM

By: Shifaa’ Al Qa’qa’
• Infectious agents may reach the nervous system through several routes of entry:
  - Hematogenous spread---- mc
  - Direct implantation
  - Local extension
  - Peripheral nerves---- rabies, herpes zoster viruses
Meningitis

• **Meningitis** is an inflammatory process involving the leptomeninges

• **Meningoencephalitis**: infection spreads into the underlying brain
The meninges are the membranes covering the brain and spinal cord.

Meninges

Pachymeninges = dura mater

Leptomeninges = Arachnoid + pia mater
Infectious meningitis:
- acute pyogenic (usually bacterial),
- aseptic (usually viral),
- Chronic (usually tuberculous, spirochetal, or cryptococcal)

Chemical meningitis
Acute Pyogenic Meningitis (Bacterial Meningitis)

Neonates: - Escherichia coli
  - group B streptococci

Adolescents/young adults: Neisseria meningitidis

Older individuals: - Streptococcus pneumoniae
  - Listeria monocytogenes

Meningeal irritation
INFANTS
- Fever, possibly with cold hands & feet
- Refusing feeds or vomiting
- High pitched moaning cry or whimpering
- Dislike of being handled or fretful
- Neck retraction with arching of back
- Blank & staring expression
- Child is difficult to wake, lethargic
- Pale, blotchy complexion
- Floppy or stiff or jerking movements

CHILDREN/ADULTS
- Stiff neck*
- Headache
- Fever
- Vomiting
- Light sensitivity*
- Drowsiness or confusion
- Joint pain
- Fitting
• Lumbar puncture reveals an increased pressure;

• examination of the CSF shows abundant neutrophils, elevated protein, and reduced glucose. Bacteria may be seen on a smear or can be cultured
• MORPHOLOGY:
  - *exudate* is evident within the leptomeninges over the surface of the brain
  - focal cerebritis
  - Ventriculitis
  - Abscesses
  - Phlebitis, venous occlusion and hemorrhagic infarction
• Untreated pyogenic meningitis is often fatal, but with prompt diagnosis and administration of appropriate antibiotics, many patients can be saved.
Aseptic Meningitis (Viral Meningitis)

• The clinical course is less fulminant than in pyogenic meningitis

• examination of the CSF often shows lymphocytosis, moderate protein elevation, and a normal glucose level.

• self-limiting
• There are no distinctive macroscopic characteristics except for brain swelling, seen in only some instances.

• On microscopic examination, there is either no recognizable abnormality or a mild to moderate leptomeningeal lymphocytic infiltrate.
Chronic Meningitis

• Tuberculous
• Spirochetal
• Cryptococcal (fungus)

involve the brain parenchyma
Tuberculous Meningitis

- There is only a moderate increase in CSF cellularity,
- with mononuclear cells or a mixture of polymorphonuclear and mononuclear cells;
- the protein level is elevated, often strikingly so,
- and the glucose content typically is moderately reduced or normal
• Infection with Mycobacterium tuberculosis also may result in a wellcircumscribed intraparenchymal mass (tuberculoma), which may be associated with meningitis.

• Chronic tuberculous meningitis is a cause of arachnoid fibrosis, which may produce hydrocephalus.
• MORPHOLOGY:
The subarachnoid space contains a gelatinous or fibrinous **exudate**, most often at the base of the brain.

Discrete white granules scattered over the leptomeninges.

Obliterative endarteritis.

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.
Spirochetal Infections

- Neurosyphilis
- Neuroborreliosis
• **Neurosyphilis:**
  - a tertiary stage of syphilis,
  - occurs in about 10% of persons with untreated Treponema pallidum infection.
• The infection can produce:

chronic meningitis (meningovascular neurosyphilis):
- usually involving the base of the brain,
- often with an obliterator endarteritis rich in plasma cells and lymphocytes.
Parenchymal involvement by spirochetes (paretic neurosyphilis):
- leading to neuronal loss and marked proliferation of rod shaped microglial cells.
- progressive loss of mental and physical functions,
- mood alterations (including delusions of grandeur),
- eventually severe dementia
Tabes dorsalis,
- resulting from damage to the sensory nerves in the dorsal roots,
- produces impaired joint position sense and ataxia (locomotor ataxia);
- loss of pain sensation, leading to skin and joint damage (Charcot joints);
- other sensory disturbances, particularly characteristic “lightning pains”;
- and the absence of deep tendon reflexes.
• **Neuroborreliosis:**
  - involvement of the nervous system by the spirochete *Borrelia burgdorferi*—Lyme disease

  - Neurologic signs and symptoms are highly variable and include:
    aseptic meningitis,
    facial nerve palsies,
    mild encephalopathy,
    polyneuropathies
## CSF Comparison In Various Infections

<table>
<thead>
<tr>
<th>Cause</th>
<th>Appearance</th>
<th>Polymorphonuclear cell</th>
<th>Lymphocyte</th>
<th>Protein</th>
<th>Glucose</th>
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<tbody>
<tr>
<td>Pyogenic bacterial meningitis</td>
<td>Yellowish, turbid</td>
<td>Markedly increased</td>
<td>Slightly increased or Normal</td>
<td>Markedly increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Viral meningitis</td>
<td>Clear fluid</td>
<td>Slightly increased or Normal</td>
<td>Markedly increased</td>
<td>Slightly increased or Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>Yellowish and viscous</td>
<td>Slightly increased or Normal</td>
<td>Markedly increased</td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Fungal meningitis</td>
<td>Yellowish and viscous</td>
<td>Slightly increased or Normal</td>
<td>Markedly increased</td>
<td>Slightly increased or Normal</td>
<td>Normal or decreased</td>
</tr>
<tr>
<td>Type</td>
<td>Appearance</td>
<td>Pressure (cm H₂O)</td>
<td>WBC/mm³ Predom type</td>
<td>Glc (mg/dL)</td>
<td>TP (mg/dL)</td>
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<tr>
<td>-----------</td>
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</tr>
<tr>
<td>Normal</td>
<td>Clear</td>
<td>9–18</td>
<td>0–5 lymphs</td>
<td>50–75</td>
<td>15–40</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Cloudy</td>
<td>18–30</td>
<td>100–10,000 polys</td>
<td>&lt;45</td>
<td>100–1000</td>
</tr>
<tr>
<td>TB</td>
<td>Cloudy</td>
<td>18–30</td>
<td>&lt;500 lymphs</td>
<td>&lt;45</td>
<td>100–200</td>
</tr>
<tr>
<td>Fungal</td>
<td>Cloudy</td>
<td>18–30</td>
<td>&lt;300 lymphs</td>
<td>&lt;45</td>
<td>40–300</td>
</tr>
<tr>
<td>Aseptic</td>
<td>Clear</td>
<td>9–18</td>
<td>&lt;300 polys → lymphs</td>
<td>50–100</td>
<td>50–100</td>
</tr>
</tbody>
</table>
Parenchymal Infections
• viral infections ----- diffuse
• Bacterial infections ----- localized
• other organisms ----- mixed patterns.

• In immunosuppressed hosts, more widespread involvement with any agent is typical.
Brain Abscesses

- Bacterial infections
- These can arise by:
  - direct implantation of organisms,
  - local extension from adjacent foci (mastoiditis)
  - hematogenous spread ---- acute bacterial
Endocarditi (septic emboli), bronchiectasis, cyanotic congenital heart disease
• progressive focal deficits
• increased intracranial pressure
• herniation

• CSF white cell count and protein levels are usually high, while the glucose content tends to be normal

• Abscess rupture can lead to ventriculitis, meningitis, and venous sinus thrombosis
• MORPHOLOGY:
Abscesses are discrete lesions with central liquefactive necrosis and a surrounding fibrous capsule.

On microscopic examination, the necrotic center is surrounded by edema and granulation tissue, often with exuberant vascularization. Outside the fibrous capsule is a zone of reactive gliosis.
Viral Encephalitis

- better termed **meningoencephalitis** (almost invariably associated with meningeal inflammation)

- **Encephalitis:**
  
  Patients develop generalized neurologic symptoms, such as seizures, confusion, delirium, and stupor or coma, as well as focal signs, such as reflex asymmetry and ocular palsies
The most characteristic histologic features are:
- perivascular and parenchymal mononuclear cell infiltrates
- microglial nodules
- neuronophagia
• In addition to direct infection of the nervous system, the CNS also can be injured by immune mechanisms after systemic viral infections.
- **Arboviruses**:  
  - arthropod-borne viruses  
  - epidemic encephalitis ---- tropical regions  
  - Eastern and Western equine encephalitis  
  - West Nile virus infection  

- capable of causing serious morbidity and high mortality.  

- In severe cases there may be a necrotizing vasculitis with associated focal hemorrhages.  

- CSF????  
- Symptoms???
• Herpesviruses:
  HSV-1
  HSV-2
  Varicella-zoster virus (VZV)
• HSV-1 encephalitis:
  - may occur in any age group but is most common in children and young adults
  - It typically manifests with alterations in mood, memory, and behavior, reflecting involvement of the **frontal and temporal lobes**.

- MORPHOLOGY:
  - starts in, and most severely involves, the inferior and medial regions of the temporal lobes and the orbital gyri of the frontal lobes.
  - The infection is necrotizing and often **hemorrhagic** in the most severely affected regions.
  - large eosinophilic intranuclear **viral inclusions** (Cowdry type A bodies) can be found in both neurons and glial cells.
• HSV-2:
  - also affects the nervous system, usually in the form of meningitis in adults.
  - Disseminated severe encephalitis occurs in many neonates born by vaginal delivery to women with active primary HSV genital infections.
- **Varicella-zoster virus (VZV):**
  - Causes chickenpox during primary infection, usually without any evidence of neurologic involvement.
  - The virus establishes latent infection in neurons of **dorsal root ganglia**
  - Reactivation in adults manifests as a painful, vesicular skin eruption in the distribution of one or a few dermatomes (**shingles**).
  - This usually is a self-limited process, but there may be a persistent pain syndrome in the affected region (**postherpetic neuralgia**).
  - In immunosuppressed patients, acute herpes zoster encephalitis can occur. Inclusion bodies can be found in glial cells and neurons.
• **Cytomegalovirus:**
  - CMV infects the nervous system in fetuses and immunosuppressed persons
  - Intrauterine infection causes *periventricular necrosis*, followed later by *microcephaly* with *periventricular calcification*.
  - Adults: CMV produces a subacute encephalitis, again often most severe in the *periventricular* region.

  - Lesions can be hemorrhagic and contain typical *viral inclusion*–bearing cells---neurons, glial cells, ependyma, and endothelium
• **Poliovirus:**
  - Enterovirus --- subclinical or mild gastroenteritis
  - in a small fraction of cases, it secondarily invades the nervous system and damages **motor neurons** in the spinal cord and brain stem (paralytic poliomyelitis)
  - loss of motor neurons-----flaccid paralysis, muscle wasting and hyporeflexia in the corresponding region of the body
• In the acute disease, death can occur from paralysis of respiratory muscles.

• Long after the infection has resolved, typically 25 to 35 years after the initial illness, a postpolio syndrome of progressive weakness associated with decreased muscle bulk and pain can appear. The cause of this syndrome is unclear.
How Polio presents

- Initial symptoms of polio include fever, fatigue, headache, vomiting, stiffness in the neck, and pain in the limbs. In a small proportion of cases, the disease causes paralysis, which is often permanent. Polio can only be prevented by immunization.
What is Bulbar Polio?

Bulbar Polio is a form of Paralytic Poliomyelitis in which the brainstem gets attacked by the poliovirus. This attack on the brainstem by the poliovirus results in extensive damage to the motor neurons of the brainstem...

For more information, visit www.epainassist.com
• **Rabies Virus:**
  - Rabies is a severe encephalitic infection transmitted to humans from rabid animals (dogs, bats), usually by a bite.
  
  - Virus enters the CNS by ascending along the peripheral nerves from the wound site, so the incubation period depends on the distance between the wound and the brain. usually taking a few months.
The disease manifests initially with nonspecific symptoms of malaise, headache, and fever.

As the infection advances, the patient shows extraordinary CNS excitability;
- the slightest touch is painful
- violent motor responses progressing to convulsions.
- Contracture of the pharyngeal musculature may create an aversion to swallowing even water (hydrophobia).
- Periods of mania and stupor progress to coma and eventually death, typically from respiratory failure.
Rabies

How it spreads

ANIMAL BITE: The farther away from brain, the longer virus takes to spread

VIRUS: Spreads through central nervous system

Common carriers of rabies

Infected animals: Show no fear for humans; act very agitated

- Bat
- Fox
- Cat
- Skunk

Dog: Another common rabies source

Symptoms in humans

- Fever, depression
- Agitation
- Painful spasms followed by excessive saliva
- Death within a week without vaccine

Treatment:
Hospitalization, immune globulin injections, anti-rabies vaccine

Foaming at mouth after drinking: Produced by spasms in throat
• **Human Immunodeficiency Virus:**
  - direct effects of virus on the nervous system,
  - opportunistic infections,
  - primary CNS lymphoma
- Aseptic meningitis
- HIV encephalitis (HIVE)
- HIV-associated neurocognitive disorder (HAND): cognitive dysfunction ranging from mild to fullblown dementia.

stem from HIV infection of microglial cells in the brain. This leads to activation of innate immune responses.

neuronal injury likely stems from a combination of cytokine-induced inflammation and toxic effects of HIV-derived proteins.
multinucleate giant cell microglial nodules, HIV
• Polyomavirus:
  - Progressive multifocal leukoencephalopathy (PML)
  - JC virus infects oligodendrocytes---demyelination
  - Most people show serologic evidence of exposure to JC virus during childhood----PML results from virus reactivation, as the disease is restricted to immunosuppressed persons
The lesions are patchy, irregular, ill-defined areas of **white matter destruction** that enlarge as the disease progresses. Each lesion is an area of **demyelination** in the center--- lipid-laden macrophages and a reduced number of axons. At the edges--- enlarged oligodendrocyte nuclei with glassy-appearing amphophilic **viral inclusions**.

The virus also infects astrocytes, leading to bizarre giant forms with irregular, hyperchromatic, sometimes multiple nuclei.
• Patients develop focal and progressive neurologic symptoms and signs,

• Imaging studies show extensive, often multifocal, ring-enhancing lesions in the hemispheric or cerebellar white matter.
PML: Progressive Multifocal Leukoencephalopathy

- Common presenting symptoms and signs
  - Hemiparesis
  - Gait abnormality
  - Speech disturbances
  - Cognitive dysfunction
  - Dysarthria
  - Ataxia
  - Sensory loss
  - Vertigo
  - Visual impairment
Fungal Encephalitis

• **Candida albicans:**
  - multiple microabscesses,
  - with or without granuloma formation
• **Mucormycosis:**
  - infection of the nasal cavity or sinuses of a diabetic patient.
  - spread to the brain through vascular invasion or by **direct** extension through the cribriform plate.
• **Aspergillus fumigatus:**
  widespread septic hemorrhagic infarctions because of its marked predilection for blood vessel wall invasion and subsequent thrombosis
• **Cryptococcus neoformans:** soap bubble”–like appearance, mucoid encapsulated yeasts
Other Meningoencephalitides

• Cerebral Toxoplasmosis:
  - Protozoan Toxoplasma gondii
  - Immunosuppressed
• Newborns (triad of chorioretinitis, hydrocephalus, and intracranial calcifications),
• the CNS abnormalities are most severe when the infection occurs early in gestation during critical stages of brain development.

• Necrosis of periventricular lesions gives rise to secondary calcifications as well as inflammation and gliosis, which can lead to obstruction of the aqueduct of Sylvius and hydrocephalus.
• MORPHOLOGY:
Abscesses (multiple, cerebral cortex)

Edema around lesions (ring enhancing lesions on CT and MRI)

free tachyzoites and encysted bradyzoites may be found at the periphery of the necrotic foci
other

- Cysticercosis
- Amebiasis
Prion Diseases

- The agent in prion diseases is an abnormal form of a cellular protein, termed prion protein (PrP).

- PrPc (normal)---- PrPsc (Abnormal)--- protease resistant/resistant to proteolysis

- Accumulation of PrPsc in neural tissue seems to be the cause of cell injury
Figure 22-21 Pathogenesis of prion disease. α-Helical PrPC may spontaneously shift to the β-sheet PrPsc conformation, an event that occurs at a much higher rate in familial disease associated with germ line PrP mutations. PrPsc may also be from exogenous sources, such as contaminated food, medical instrumentation, or medicines. Once present, PrPsc converts additional molecules of PrPc into PrPsc through physical interaction, eventually leading to the formation of pathogenic PrPsc aggregates.
• sporadic, familial, iatrogenic, and variant forms of Creutzfeldt-Jakob disease (CJD)
• scrapie in sheep
• bovine spongiform encephalopathy in cattle (“mad cow disease”
• Creutzfeldt-Jakob Disease:
  - rapidly progressive dementing illness
  - Sporadic in approximately 85% of cases.
  - Commonly affecting persons older than 70 years of age, familial forms caused by mutations in PRNP may present in younger people
  - infectious nature of PrPsc
How Creutzfeldt-Jakob disease works

**CAUSE**
Creutzfeldt-Jakob disease is caused by abnormal proteins called prions that are not killed by standard methods for sterilizing surgical equipment.

**CONSEQUENCES**
Those affected lose the ability to think and to move properly and suffer from memory loss. It is always fatal, usually within one year of onset of illness.

As prions build up in cells, the brain slowly shrinks and the tissue fills with holes until it resembles a sponge.

**NORMAL HUMAN PROTEIN**

**DISEASE-CAUSING PRION**

**SPONGE-LIKE LESION**

SOURCES: World Health Organization, Centers for Disease Control and Prevention, National Institute of Neurological Disorders and Stroke, AP

DAVID BUTLER, CHIQUI ESTEBAN, JAVIER ZARRACINA/GLOBE STAFF
SPREADING CJD

- Not Contagious Through Casual Contact
- Can't Be Transmitted Through Breathing Or Touching
- Can be Transmitted Through Exposure To Infected Spinal Cord Fluid Or Brain Tissue
- Traditional Sterilization does not kill CJD
Creutzfeldt-Jakob Disease Symptoms

- Undergo Personality Changes
- Insomnia
- Impaired Judgment
- Memory Disorders
- Thinking
- Depression
- Visual Disturbances
• MORPHOLOGY:
The progression to death in CJD usually is so rapid that there is little, if any, macroscopic evidence of brain atrophy.

On microscopic examination, the pathognomonic finding is a spongiform transformation of the cerebral cortex and deep gray matter structures----
- microscopic vacuoles of varying sizes within the neuropil and sometimes in the perikaryon of neurons-----neuronal loss, No inflammation
Variant Creutzfeldt-Jakob Disease

- Young adults,
- behavioral disorders figured prominently in early disease stages,
- the neurologic syndrome progressed more slowly than in other forms of CJD

- is a consequence of exposure to the prion disease of cattle, called bovine spongiform encephalopathy????

- + cortical amyloid plaques