Objectives:

1. Compare inflammation with infection.

2. Describe routes of CNS and meningeal infection.

3. Define pachymeningitis, ependymitis, myelitis, radiculitis, neuritis

4. Define each of the following. Then describe the pathogenesis; etiologic agents; cellular reaction; type and location of pathologic changes; signs and symptoms (where applicable); population affected; CSF findings; and sequelae:

- **Empyema**
- **Meningitis (leptomeningitis)**
- **Encephalitis, Encephalomyelitis**
- **Intracerebral abscess**
- **CNS syphilis**
- **HIV-associated CNS disorders**
- **Progressive multifocal leukoencephalopathy (PML)**
- **Subacute sclerosing panencephalitis (SSPE)**

I. General principles

A. **Inflammation vs Infection:**
Inflammation is not synonymous with infection.The body responds to an insult with inflammation; if an infectious agent is present, inflammation is accompanied by infection. The subject of this unit is the response of the nervous system to infectious agents.

B. **Routes of Infection**:
Although the brain is well protected by coverings (meninges) and the blood brain barrier, these are not absolute barriers. Routes of infection include:

- **Hematogenous Spread: blood-borne spread from a primary source of infection, often the lung**
- **Direct Implantation: infection as the result of trauma or surgery**
- **Local extension: infection from nearby site of suppuration**
- **Spread of viruses from PNS along nerves: A few viruses can spread along peripheral nerves to reach the central nervous system**

C. **Locations and Definitions**:

Infections tend to be confined by the meninges. Terminology for infections in various compartments of the nervous system are listed below:

- **Epidural Abscess or Empyema: accumulation of pus in the space between dura and skull (periosteum)**
- **Pachymeningitis: inflammation of the dura (rare)**
- **Subdural Abscess or Empyema: accumulation of pus in the space between the dura and arachnoid**
- **Meningitis/Leptomeningitis: inflammation of the pia and arachnoid, in the subarachnoid space (e.g. meningococcal meningitis)**
- **Encephalitis: generalized inflammation of the brain parenchyma**
- **Abscess or Granuloma: localized inflammation in the brain or spinal cord parenchyma**
- **Myelitis: generalized inflammation of the spinal cord parenchyma (e.g. poliomyelitis)**
- **Radiculitis: inflammation of the nerve roots**
- **Neuritis: inflammation of a peripheral nerve**
- **Encephalomyelitis: generalized inflammation of the brain and spinal cord**
- **Ependymitis: inflammation of the ventricles and ventricular lin**

Note: the terms neuritis and myelitis are synonymous with neuropathy and myelopathy and can indicate a non-inflammatory process.

D. **Pathogenesis of neural tissue damage:**
Tissue damage may be the consequence of direct injury to cells by the organism, microbial toxins, the effects of the inflammatory response, or immune-mediated injury.
E. **Cerebrospinal Fluid:**

- Detection of **Meningitis**: The cerebrospinal fluid (CSF) is a sensitive indicator of a leptomeningeal infection, as will be noted later.
- Detection of **Reactive Meningitis**: CSF analysis can detect an inflammatory response in the leptomeninges due to infection in other locations. For example, an infection may be localized to the epidural or subdural spaces, or within the brain or spinal cord parenchyma. However, some inflammatory reaction, termed reactive leptomeningitis will be present in the leptomeninges and subarachnoid space, and will be detectable in the CSF. In this condition, organisms are NOT recovered from the CSF even though the cell count, protein concentration and pressure may be elevated.

F. **Cellular Reaction**:
The cellular reaction to infection depends on many factors. These include the kind of infectious agent, the age of the host, the location of the lesion and the presence of other diseases. In the fetus, cellular reaction may be minimal although massive destruction of the central nervous system may occur.

- **Bacterial agents usually cause purulent reactions with polymorphonuclear leukocytes and necrosis.**
- **Fungal agents cause granulomatous inflammation.**
- **Viral agents provoke a lymphocytic response and, rarely, may precede poorly understood allergic phenomena to myelin protein characterized by demyelination.**

G. **Sequelae & Complications**: Sequelae of a CNS infection depend on the pathogenesis and location of lesions. Examples include:

- **Hydrocephalus after obstruction of CSF flow in leptomeningitis**
- **Permanent damage to cranial nerves**
- **Focal and generalized signs due to neuronal destruction, e.g. seizures, movement disorders, mental retardation**
- **Thrombosis due to vasculitis**
- **Consequences of increased intracranial pressure due to edema or expanding mass lesions**

II.Epidural & subdural empyema

Abscesses are localized collections of pus. Pyogenic organisms are the infectious agent involved with abscess formation. Empyema describes the accumulation of pus within a space or cavity, again, typically secondary to pyogenic organism infection. Epidural and subdural infections can be called either abscess or empyema. Pathogenesis involves direct inoculation or spread from nearby infections. Etiologic agents are usually bacteria; streptococcus and staphylococcus are the most common.

III. Meningitis

A. Pathogenesis:
Hematogenous spread of organisms from primary infection in lungs or elsewhere in body; including infection by organisms in birth canal and aspiration of contaminated amniotic fluid.

Direct inoculation: secondary to trauma or iatrogenic (e.g. introduction of organism into CSF during lumbar puncture in patient with septicemia).

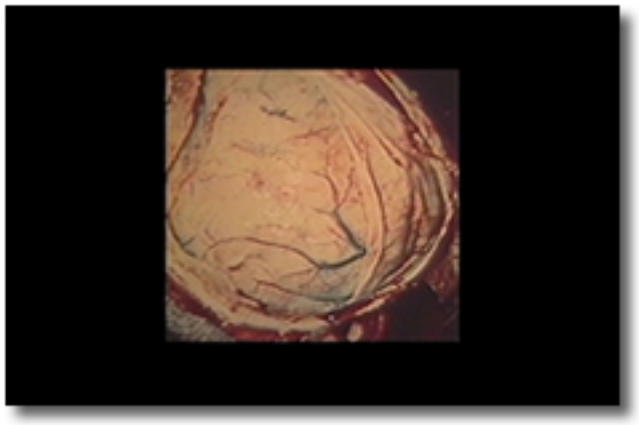
Direct spread from contiguous infection.

B. Etiologic Agents:

- **Bacteria are the most common. In general, pneumococcal and meningococcal meningitis are the most common types, but there is distinct variation by age group. In neonates, two of the most common organisms are Escherichia coli and the group B streptococci. In the elderly, Streptococcus pneumoniae and Listeria monocytogenes are common.**
- **Viruses, spirochetes, fungi, and M. tuberculosis are less common agents.**

C. Pathological changes:
1. Acute pyogenic meningitis (usually bacterial):

- **Purulent exudate in subarachnoid space and along vessels, includes neutrophils and bacteria; the severity of the exudate varies with the organism**
- **Inflammatory infiltrate in walls of arteries and veins (vasculitis); in severe cases ischemia may result from subsequent thrombosis**
- **Cellular infiltration of cranial nerves and spinal roots**
- **Edema may occur in brain tissue**



CNS 01
Dense exudate in the subarachnoid space surrounds vessels and would cause communicating hydrocephalus.

2. Acute aseptic (viral) meningitis: lymphocyte infiltrate; mild

3. Chronic meningitis - caused by fungi (e.g., candidiasis, cryptococcosis), tubercle bacillus (tuberculosis), T. pallidum (syphilis):

- **Exudate, mononuclear infiltrate with lymphocytes, mononuclear cells, small tubercles (caseous necrosis surrounded by epithelioid cells and giant cells, peripheral ring of lymphocytes)**
- **Localized over base of brain**
- **Vasculitis common**

CNS 02
Exudate concentrated at the base of the brain is seen here. The exudate may infiltrate cranial nerves.

D. Spinal fluid changes:
1. Acute pyogenic meningitis

- **Increased pressure**
- **Decreased glucose**
- **Increased protein**
- **Up to thousands (~90,000) of neutrophils**
  Appearance: cloudy

2. Aseptic (viral) meningitis

- **Normal or mildly increased pressure**
- **Normal glucose**
- **Mildly increased protein**
- **Hundreds of mononuclear cells**

3. Chronic meningitis

- **Increased pressure**
- **Sometimes decreased glucose**
- **Increased protein**
- **Hundreds of mononuclear cells**
-

E. Complications:

- **Hydrocephalus caused by obliteration of subarachnoid space, exit foramina or other sites**
- **Edema and increased intracranial pressure**
- **Cranial nerve palsies**
- **Thrombosis from inflammatory infiltrate in the walls of arteries**
- **Brain abscess or subdural abscess**
- **Seizures**

IV. ENCEPHALITIS

A. Pathogenesis:

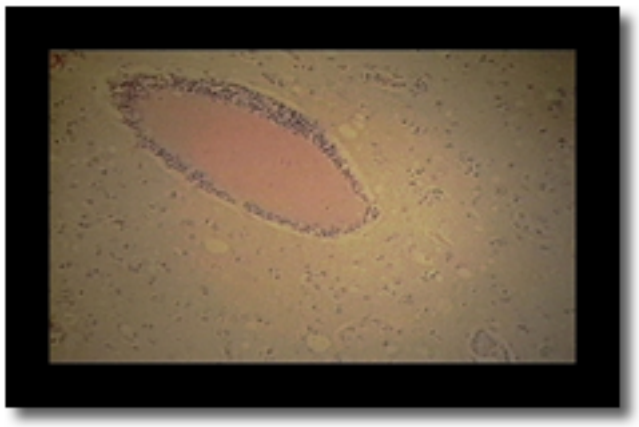
- **Hematogenous spread after viremia**
- **Spread along nerves (rabies, Herpes simplex)**

B. Etiologic Agents:

- **Usually viral: important organisms include HIV, polio, rabies, Herpes simplex, Herpes zoster, equine encephalitis and St. Louis encephalitis viruses.**
- **Rickettsia (typhus and Rocky Mountain spotted fever) and protozoa (toxoplasma) also cause a diffuse inflammatory reaction in the central nervous system.**
- **Bacterial invasion of the CNS typically results in abscess formation, not encephalitis or encephalomyelitis.**

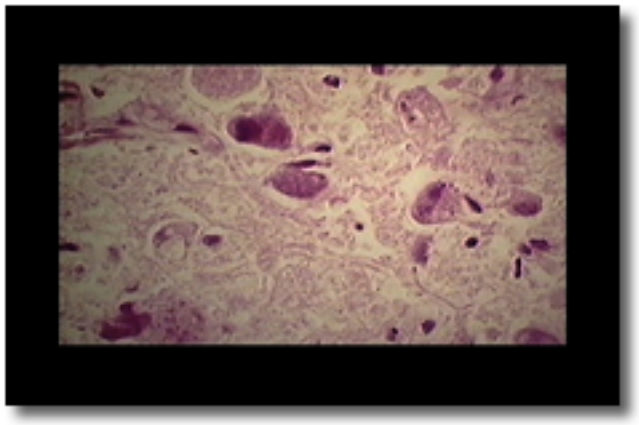
C. Pathological Changes:

1. General description: Multiple and/or widespread areas of CNS involvement occur, as opposed to localized nature of abscess formation. Specific viruses affect specific anatomic areas or subpopulations of cells, a phenomenon called "tropism". An example of this is the predilection of herpes simplex virus to produce lesions in the limbic system, and infection of lower motor neurons by poliovirus. Microscopic changes include: **perivascular cuffing** by lymphocytes and plasma cells; neuronal necrosis; **inclusion bodies**; microglial proliferation and **glial nodules**; hemorrhagic necrosis (common in Herpes simplex encephalitis). Calcification can be detected in some neonates infected in utero with encephalitis-producing agents like CMV and HIV viruses.

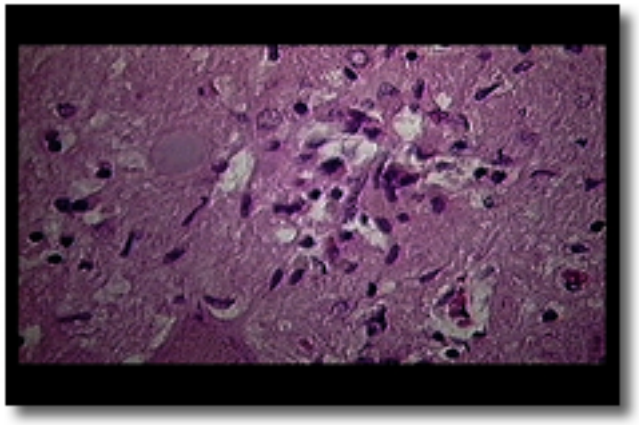


CNS 03

Perivascular cuffing is seen in this image. Mononuclear cells escape from vessels and cluster around the vessel.



CNS 04
This image illustrates inclusion bodies in neurons. There may be different types of inclusion bodies in infections caused by different viruses.



CNS 05
A glial nodule is seen. This is produced by proliferation of microglia, which engulf dead neurons and remain for long periods as a hallmark.

2. Examples:

a. Arthropod-borne viral (arboviral) encephalitis is responsible for most outbreaks of epidemic viral encephalitis. Most of these viruses have animal hosts and mosquito vectors. The pathology due to different viruses is similar, although the severity and area affected (cortex or basal ganglia) varies.

b. Herpes Simplex Virus Type 1 (HSV-1) produces the most common non-epidemic form with high mortality levels. Acyclovir is an effective treatment, leading to reduction in the mortality rate. The most common presenting symptoms are alterations in mood, memory and behavior, due in part to lesions in the limbic system. Lesions involve the inferior and medial regions of the temporal lobes, and the orbital gyri of the frontal lobes. Pathological changes include necrosis and hemorrhagic regions. Perivascular inflammatory infiltrates and inclusion bodies are usually present.

c. Rabies is transmitted by the bite of a rabid animal. The virus enters the CNS by ascent along peripheral nerves. Microscopic changes include Negri bodies, pathognomonic findings that consist of inclusions in pyramidal neurons of the hippocampus.

D. Spinal Fluid Changes: Varying numbers of lymphocytes, usually some increase in protein; glucose usually normal.

E. Complications: Generalized edema, with space-occupying effects

V. BRAIN ABSCESSES

A. Etiologic Agents:
a. Usually pyogenic bacteria; streptococci and staphylococci are the most common.
b. Fungi may produce localized areas of intracerebral inflammation called granulomas; these occur most often in immunosuppressed patients. The difference between an abscess and granuloma is determined by pathological examination.

B. Pathogenesis:
Secondary to hematogenous spread, direct extension from nearby suppurative focus or direct implantation of foreign bodies (surgery, trauma). Predisposing conditions include acute bacterial endocarditis; cyanotic congenital heart disease, in which there is a right-to left shunt and loss of pulmonary filtration of organisms; and chronic pulmonary sepsis.

C. Pathological Changes: Discrete lesions with central liquefactive necrosis; surrounded by inflammatory cells and **zone of fibrous tissue,** with proliferation of small blood vessels (granulation tissue). Marked vasogenic edema is associated with the neovascularization. Fibroblasts are recruited from the vascular system. Outside the fibrous capsule is a zone of reactive gliosis.

D. Spinal Fluid Changes: Usually increased pressure, relatively few cells, mildly elevated white cell count and protein level, normal glucose (reactive meningitis)

E. Clinical presentation: Progressive focal deficits, general signs of increased intracranial pressure

F. Complications: Space occupying mass and edema with herniation; necrosis of functional tissue. Abscesses may rupture into ventricles or subarachnoid space, resulting in ependymitis and meningitis. Seizures occur in approximately 50% of cases.

VI. CENTRAL NERVOUS SYSTEM SYPHILIS

Patients with syphilis may pass through a stage of asymptomatic syphilitic meningitis with the CSF showing an increased cell count and positive serologic reaction. A minority (10-

20%) of patients will develop tertiary neurosyphilis years later. There are 3 types of tertiary neurosyphilis, which may occur alone or in combination.

A. Meningovasculitis:

1.. Pathology: Infiltration of meninges and vessels by lymphocytes and plasma cells; may cause symptoms of meningitis or vascular occlusion.

2. Clinical symptoms: similar to low grade meningitis and/or "stroke" (due to vascular occlusion)

B. Paretic Neurosyphilis (General Paresis):

1. Pathology: Atrophy, loss of cortical neurons especially in frontal lobes, gliosis, proliferation of microglial cells (rod cells), perivascular lymphocytes and plasma cells. Spirochetes present in brain tissue.

2. Clinical symptoms: mental changes, progressing to dementia; headache

C. Tabes Dorsalis:

1. Pathology: Inflammatory lesions involving meninges and vessels in subarachnoid space of dorsal nerve roots. Loss of axons and myelin in dorsal roots with Wallerian degeneration of dorsal columns. (T. pallidum absent in cord parenchyma.)

2. Clinical symptoms: lightning pains; sensory deficits, including loss of pain sensation and loss of position sense (leading to ataxia); Argyll-Robertson pupils (react to accommodation but not to light)

VII. HIV-ASSOCIATED CNS DISORDERS

CNS involvement may occur due to primary effects of HIV infection or to secondary effects of immune suppression. Between 10 and 20% of HIV-infected patients present with neurologic signs as their first clinical manifestation of infection. In some, no other signs of AIDS develop. Between 50 and 70% of all AIDS patients eventually develop some features of what is called AIDS dementia or the AIDS-related cognitive-motor complex. This term is used to describe the characteristic pattern of cognitive, motor, and behavioral dysfunction, including mood disturbances, seen in AIDS patients. At autopsy, between 60 and 90% of AIDS patients' brains show some form of pathology.

A. Pathologic Changes due directly to HIV infection

1. The pathology associated with the AIDS-related cognitive-motor complex, sometimes called subacute encephalitis, is located mainly in subcortical areas, with relative sparing of cerebral cortex. Microscopic changes include:

- **diffuse white matter pallor**
- **perivascular infiltrates of lymphocytes and macrophages**
- **foci of necrosis, gliosis, and/or demyelination**
- **microglial nodules, macrophages and multinucleated cells**

The virus enters the brain, probablyprimarily by way of macrophages, as HIV has been localized in CNS, mainly in macrophages, microglia and multinucleated giant cells.The virus is able to reproduce in the brain.

2. Vacuolar myelopathy is sometimes seen in the spinal cord. This change consists of white matter vacuolation in posterior and lateral columns, and is mainly due to swelling within myelin sheaths.

B. Secondary Effects of Immune Suppression: Opportunistic infections. In addition to HIV infection, opportunistic viral infection of the brain is a relatively frequent complication of HIV-related immunosuppression. A variety of viruses and fungi, have been identified, primarily cytomegalovirus, cryptococcus, and toxoplasma. These infecting agents can be isolated from the brains of about 25% of AIDS patients. Other secondary effects include increased incidence of primary CNS lymphoma and progressive multifocal leukoencephalopathy (PML) –see below

VIII. PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

A. Clinical features

Onset: occurs in patients with associated immune suppression or chronic disease, e.g. lymphoma, AIDS

Clinical presentation: The major consistent symptom is intellectual deterioration and dementia. Other symptoms include cortical visual symptoms, motor disorders, abnormal movements.

Duration: death usually in 2-6 months

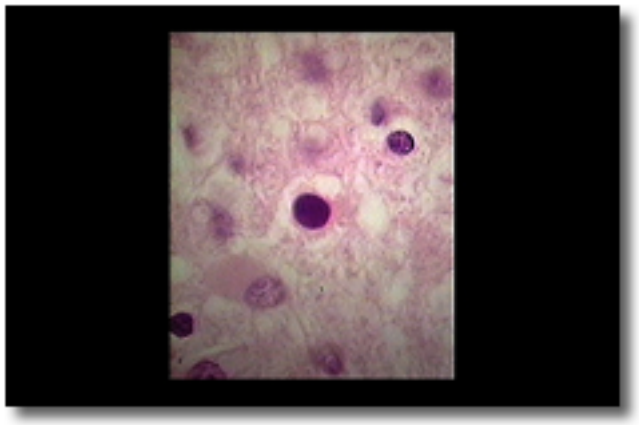
CSF findings: normal

B. Pathogenesis –viral encephalitis caused by a polyomavirus. Because the virus preferentially infects oligodendrocytes, demyelination is its principal pathologic effect.

C. Pathological changes

- **<u>Gross pathology</u>: Multiple and/or widespread areas of demyelination**
- **<u>Microscopic pathology</u>: Inclusion bodies in oligodendroglia nuclei; transformed bizarre astrocytes and gliosis; numerous areas of demyelination (due to oligodendrocyte dysfunction). Lesions are primarily in subcortical**

white matter, but also occur in brainstem and cerebellum. Ultrastructural changes include identification of papovavirus particles in the oligodendroglial nuclear inclusions.



CNS 06
This is an example of an oligodendrocyte nucleus filled with viral particles

IX. SUBACUTE SCLEROSING PANENCEPHALITIS (SSPE)

A. Clinical features

Onset: 5-20 years of age. The disease occurs in children or young adults, months or years after an initial, early-age acute infection with measles.

Clinical presentation: personality changes, intellectual deterioration; seizures, spasticity of limbs

Duration: death usually in several years

CSF changes: elevated gamma globulin; antibody titer against measles is elevated

B. Pathogenesis – persistent but nonproductive infection of the CNS by altered measles virus.

C. Pathological changes

Gross pathology: Changes are mild and are not diagnostic.

Microscopic pathology: Inclusion bodies in oligodendroglia, neurons and astrocytes; chronic inflammatory reaction (perivascular cuffing by lymphocytes and plasma cells); some neuronal loss, gliosis and demyelination. Ultrastructural changes include paramyxovirus nucleocapsid tubules characteristic of measles virus in the inclusion bodies.