These diseases are rare.
- However, the bacterial diseases are very treatable if dx and recognized in a timely fashion.
- Fatal if not recognized!
- That's why they're important.
Objectives

• Recognize and describe the **pathology** of common inflammatory and demyelinating diseases of the CNS: bacterial infections, viral infections, fungal infections, HIV and infections associated with HIV, multiple sclerosis and central pontine myelinolysis

• Describe the **pathophysiology** of the common inflammatory and demyelinating diseases of the CNS

-This lecture will focus on the Pathology
-We will get details on the organisms in micro lectures.
When evaluating a patient with inflammation and a possible infection of the CNS, it is important to consider the following:

- **Anatomic compartment**: Is it in the scalp, skull, epidural space, subdural space, arachnoid and/or cerebrum?

- **Duration of symptoms**: Acute onset and rapidly progressive? Indolent: developing and progressing over months?

- **Age of patient**: Neonate? Child? Young adult? Elderly?

- **Biological state of patient**: Normal healthy adult? HIV/AIDS? Immunocompromised?

These factors will help you ID the most likely organism.
MENINGITIS

- Inflammation of the meninges (arachnoid and pia).
- Clinical presentation is with
  - Headache, vomiting, fever and stiff neck.
  - Seizures are common in children.
  - Symptoms are caused by inflammation of the meninges and the subarachnoid space. CSF fills this space. so need to examine CSF for pathogen
MENINGITIS

- CSF abnormalities are present which vary with the organism.
  - **Bacteria** cause a neutrophilic reaction, ↑protein, ↓glucose
  - **Encapsulated organisms** cause a granulomatous reaction, ↑↑protein, normal or ↓glucose
  - **Viruses** cause a lymphocytic reaction, ↑protein, normal glucose
  - **Syphilis** cases a plasmacellular reaction.
NEUTROPHILIC (BACTERIAL) MENINGITIS

Neonates - E. coli and Group B Streptococcus

Baby's brain. Died of E. Coli infection.
-Exudate in meninges. Not as much exudate as you'd see in adults. Why?
1. in neonates, immune system not totally developed and need less pathogen to cause severe morbidity/death.
2. Cannot put out as many inflammatory cells
Case History

- 3 year male with a history of multiple middle ear infections developed fever and left ear pain. He was treated with Omnicef but developed vomiting and was unable to take his medication. He began IM injections. Fever and ear pain continued, his physician noted swelling and tenderness behind the ear and torticollis. CT demonstrated mastoiditis and an epidural abscess. MRI revealed a brain abscess. The abscess was drained and culture grew *Streptococcus pneumoniae*.
NEUTROPHILIC (BACTERIAL) MENINGITIS
MIDDLE EAR

How middle ear infection leads to meningitis.

Blood flow through bone, bacteria in ear can get into CNS. (she didn’t elaborate beyond that)

inner ear. semicircular canals

middle ear

Pneumatic cells

Pericarotid plexus

Facial nerve. enveloped by meninges
NEUTROPHILIC (BACTERIAL) MENINGITIS

*Streptococcus pneumoniae*

- Patient who died of strep pneumo meningitis.
- Compared to neonate in other slide:
  1. A lot more pus on the surface.
  2. More vascular congestion
  3. More exuberant inflammatory response

pus (white stuff)
1. acute inflammatory cells (neutrophils) but also chronic element (mononuclear cells) bc going on for a while
CEREBRITIS

If not treated, progresses to cerebritis: florid bacteria infection of the brain.

Child maintained on cardiorespiratory support for a while, so progressed to a point where you virtually have necrosis of entire cerebrum.
NEUTROPHILIC (BACTERIAL) MENINGITIS

*Neisseria meningitidis*

causes epidemic meningitis, particularly in young adults in close quarters (dorms, army)
- very contagious.
- very aggressive
- milky white inflammatory infiltrate in meninges
It is very important to note that marked individual variation occurs.

The examples cited here are guidelines only.

Remember this!
-N. meningitis could also occur in elderly, not just young adults.
-Strep pneumo can be seen in everybody, not just young child.

Question: Since CSF drains into spinal canal, would you also get infection/equal inflammation in the spinal cord?
YES, YES, YES! Always when you have meningitis. That's where we get CSF fluid to test for infection-spinal tab in lumbar region (cauda equina region)
ACUTE FOCAL SUPPURATIVE INFECTIONS

• Brain Abscess
  – Clinical presentation is with focal neurological signs and raised intracranial pressure.
  – ↑CSF pressure, WBC and protein & Glucose normal
• Subdural empyema
• Extradural abscess
  – Osteomyelitis infection of the bone
  – Surgical complication these are both reasons you could get an extradural abscess
CEREBRAL ABSCESS

circumsized, necrotic lesion

-surface of the brain is intact.
-if progresses, could rupture into subarachnoid space (then wouldn’t be called an abscess)

daughter abscess
ACUTE ASEPTIC (VIRAL) MENINGITIS

• Usually a benign illness of children and young adults.
• There is CSF lymphocytosis, moderate ↑protein
• Most common viruses
  – Coxsackie virus
  – Echo virus
  – Nonparalytic polio virus

usually resolve with symptomatic treatment and support.
CHRONIC BACTERIAL MENINGITIS
Mycobacterium tuberculosis

- Organisms gain access to the CNS via blood stream.
- Caseating granulomas form in the basal meninges.
- Parenchymal spread of infection results in a "tuberculoma" which may be mistaken for a tumor.
- The infection is indolent but fatal in 4 - 6 weeks if it is untreated.
CHRONIC BACTERIAL MENINGITIS

Mycobacterium tuberculosis
CHRONIC BACTERIAL MENINGITIS

*Mycobacterium tuberculosis*

“Tuberculoma”
CHRONIC BACTERIAL MENINGITIS

*Mycobacterium tuberculosis*

Caseating granuloma

same as ones you'd see in the lung with TB infection, these are just in the brain!

caseating necrosis in the center

rim of lymphoid cells and giant cells
POTT’S DISEASE

(TB of the spine)

Mycobacterium tuberculosis

Before good tx for TB, this was a fairly common complication of TB. Not so much anymore bc we have effective tx available.
Neurosyphilis is the tertiary stage of syphilis and occurs in about 10% of patients with untreated infection. Three types of neurosyphilis may occur.

- **Meningovascular neurosyphilis**
  - Chronic meningitis

- **Paretic neurosyphilis**
  - Invasion of the brain causing dementia and other symptoms.

- **Tabes dorsalis**
  - Inflammation of the Dorsal Roots causes impaired joint position sense and loss of pain sensation which leads to joint damage (Charcot joints)

This was common back in the 19th century, not so much any more with penicillin.
Which of the following statements about meningitis is/are true?

A. May be acquired via the blood stream
B. May be acquired by direct implantation (surgery or trauma)
C. May be acquired by local extension of an abscess
D. May be rapidly fatal if not diagnosed and treated
E. All of the above
VIRAL MENINGOENCEPHALITIS

- Most commonly caused by Arboviridiae.
  - Eastern and Western equine, Venezuelan, St. Louis and La Crosse most common in US
- Virus is transmitted by mosquitoes and ticks.
- Clinical features vary with the virus and the immunocompetence of the host.
- Pathology varies from mild meningitis to severe encephalitis.
- Perivascular and parenchymal mononuclear infiltrate and microglial nodules.
VIRAL ENCEPHALITIS

INCLUSION FORMING VIRUSES

• These diseases are generally less common but they are important diagnostic considerations.

• Herpes viruses
  – Herpes simplex
  – Herpes zoster
  – Cytomegalovirus

• Rabies
  – Rhabdovirus, Negri bodies

• JC virus
  – Progressive multifocal leucoencephalopathy

• Measles virus
  – Subacute sclerosing panencephalitis

you can take nice pictures of them so they show up on tests

path feature associated with Rhabdovirus infection

in AIDS population

very rare, rare, rare complication of measles
VIRAL ENCEPHALITIS
Herpes Viruses

• HSV-1 causes “cold sores”.
  – Virus resides latent in the trigeminal ganglion.
  – Reactivation may cause Herpes encephalitis which is necrotizing and localized to the temporal lobes.

• HSV-2 infects infants via birth canal.
  – It also causes a necrotizing encephalitis.

• Herpes zoster (Shingles) affects older adults.
  – Reactivation of chickenpox (Varicella) infection.
  – Causes a radiculopathy.

• Cytomegalovirus
  – Causes encephalitis in fetuses infected in utero and in immunocompromised adults, especially AIDS patients.
VIRAL ENCEPHALITIS

*Herpes simplex*

necrotizing reaction localized to the temporal lobes
VIRAL ENCEPHALITIS

Herpes simplex

microglial inflammatory reaction

DNA virus so virus within nucleus of these neurons
VIRAL ENCEPHALITIS

Cytomegalovirus
VIRAL ENCEPHALITIS

Rabies

- Rhabdovirus
  - Enveloped ssRNA
- Transmitted from saliva
  - Dogs, wolves, skunks, foxes are animal reservoir.
  - Exposure to bats without a bite may result in disease.
  - Latent period is 10 - 90 days.
- Virus travels via peripheral nerve → spinal cord → brain.
- Destruction of brain stem neurons causes “hydrophobia”.
- Negri bodies are pathognomonic cytoplasmic eosinophilic inclusions in pyramidal neurons.

bit on toe=longer latent period than if bit on arm
spelunkers. transmitted in secretions without bite

what they’re looking for if you had your dog sacrificed to look for rabies...
spasm of laryngeal muscles so cannot swallow so get foaming of mouth
VIRAL ENCEPHALITIS

Rabies

Cerebellum with meningoencephalitis
VIRAL ENCEPHALITIS

Rabies

Negri bodies

negri bodies (cytoplasmic eosinophilic inclusions)
PROGRESSIVE MULTIFOCAL LEUOCENCEPHALOPATHY

• Polyoma virus (JC virus unrelated to CJD).
• Occurs in immunocompromised hosts.
• Clinical presentation is with dementia, weakness and ataxia.
• Death ensues within 6 months.
• Virus infects oligodendroglia and causes demyelination.

increasing in frequency bc of the HIV/AIDS population, although it seems to be less common in people on ARV tx
PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

Polyoma virus

- Plaques in white matter
- Cortex
- White matter
- Luxol fast blue stain (myelin is blue)
PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

Polyoma virus
PROGRESSIVE MULTIFOCCAL LEUCOENCEPHALOPATHY

Polyoma virus

Electromicroscopy
(no elaboration or explanation)
**VIRAL ENCEPHALITIS**

*Measles Virus*

Subacute Sclerosing Panencephalitis (SSPE)

- Persistent measles virus infection.
- The disease has largely disappeared due to vaccination programs.
- However, it is a rare complication in live vaccine recipients.
- Elevated measles virus antibody titer is found in the CSF.
SUBACUTE SCLEROSING PANENCEPHALITIS

Measles

sclerosing (scar) area homogenous, amorphous appearance to the white matter

subacute=slowly progressing
sclerosing=scar
panencephalitis=entire brain
SUBACUTE SCLEROSING PANENCEPHALITIS

Measles

[Image: Histological section showing measles virus inclusions]
POLIOMYELITIS

Poliovirus

• Disease is caused by a ssRNA virus which is a member of the picorna group of enteroviruses.
• Virus is spread by the fecal-oral route.
  – Causes a mild gastroenteritis in most people.
  – In a few people, it invades the CNS.
• Viral binding site is present on lower motor neurons.
• Clinical presentation is with fever, malaise, headache, meningitis and subsequent paralysis.
• Death results from respiratory failure with a mortality of 5-25%.
• Lower motor neurons show chromatolysis and neuronophagia.
• Vaccines have largely eliminated the disease.
Motor neurons infected by Polio virus

Neurons infected:
1. UMN of precentral gyrus
2. Corticobulbar motor fibers
3. LMNs of spinal cord

Result:
paralysis of skeletal muscle and motor cranial nerves
POLIOMYELITIS
Spinal cord anterior horn cells infected by virus

all of these cells are infected by polio

wind-blown appearance of the cells

microglial reaction
Which of the following statements about viral encephalitis is false?

A. It destroys neurons and is always rapidly fatal.
B. Herpes simplex virus preferentially affects the temporal lobes.
C. Polio virus affects the spinal cord.
D. Progressive Multifocal Leuкоencephalopathy is uncommon.
E. Symptoms vary with the host and the virus.
• 60% of AIDS patients develop neurologic dysfunction.
• Neuropathology is seen in 80-90% of AIDS patients.
  – The neuropathologic changes include direct effects of HIV-1 infection and indirect effects - opportunistic infection and CNS lymphoma.
• Direct effect of HIV-1 infection
  – HIV-1 Meningoencephalitis.
  – Vacuolar myelopathy. degeneration of the long tracts in the spinal cord. no specific histological findings
  – AIDS-associated myopathy and peripheral neuropathy. also no specific histological findings
HIV-1
Meningoencephalitis

• Manifest clinically with dementia referred to as “AIDS-related cognitive-motor complex”.
• Neuropathologic findings include:
  – Multinucleated giant cells due directly to viral infection
  – Microglial nodules due directly to viral infection
  – Myelin pallor secondary
HIV-1 Meningoencephalitis

Multinucleated giant cells
HIV (AIDS)

Indirect effects  Opportunistic Infections

Bacteria

• Bacterial infections of the CNS in AIDS are uncommon but do occur.
• Caustive organisms include:
  – Mycobacterium avium intracellulare
  – Mycobacterium tuberculosis
  – Treponema pallidum
    • rare
HIV (AIDS)  
Indirect effects Opportunistic Infections

Viruses

• Viral infections of the CNS are very common
  – Cytomegalovirus
  – Polyoma virus
    • Causes Progressive multifocal leucoencephalopathy (PML)
  – Herpes simplex
  – Herpes zoster
    • Causes radiculopathy
  – Epstein Barr virus
    • Causes B cell lymphoma

AIDS=no/low T cells, cannot fight off viruses
HIV (AIDS)
Indirect effects Opportunistic Infections

Fungi

• Fungal infections of the CNS are common
  – *Cryptococcus*
    • very common
  – *Aspergillus*
    • very common
  – *Coccidioides*
    • residents of the Southwest
  – *Histoplasma*
    • residents of the Mississippi valley
  – *Zygomycetes*
  – *Candida* sp.
HIV (AIDS)
Indirect effects
Opportunistic Infections

Parasites

- *Toxoplasma gondii*
  - Very common, often treated empirically.
  - The brain shows necrotizing focal infection with abscesses.

- *Acanthamoeba*
  - Rare
FUNGAL MENINGOENCEPHALITIS

*Cryptococcus neoformans*

- Cryptococcus organisms are encapsulated spheres 5 - 15 µ diameter.
- They cause an indolent infection in an immunocompromised host. 
- There may be minimal tissue reaction.
- India ink examination of the CSF is used for diagnosis
Cryptococcus neoformans

meninges, florid granulomatous inflammatory response

cerebrum
Cryptococcus neoformans

INDIA INK
CEREBRAL TOXOPLASMOSIS

• Very common in HIV infected patients
• Symptoms develop over 1-2 weeks and may be focal or diffuse
• CT and MRI show multiple ring enhancing lesion which must be distinguished from CNS lymphoma, TB and fungal infection
gross micrograph of brain with toxo

circumcised abscess in putamen

in globus pallidus
"what it looks like on imaging"
Toxoplasma gondii
Pseudocyst with bradyzoites and free tachyzoites
You see a 40 year old nurse in the ED who has a two week history of fever and sinusitis. EMS was called because she had a grand mal seizure. She had another seizure in the ambulance. After she arrives a CT scan is obtained that shows an 3 cm lesion in the frontal lobe. What is your diagnosis?

A. Brain abscess
B. Rabies
C. Poliomyelitis
D. Viral encephalitis
E. Syphillis

B-E cause a diffuse process
she has a 3 cm focal process

"this could be a brain tumor, but you don't have that as a choice"
MULTIPLE SCLEROSIS

• The onset is acute, at age 20 - 40 years.
• Symptoms are separated in space and time.
• Clinical course is quite variable with relapses and remissions.
• Risk factors
  – Living in northern latitudes.
  – Relative affluence.
  – HLA haplotype A2, B7, DW2.
• Prevalence is 1 per 1000 in US and Europe.
MULTIPLE SCLEROSIS

White matter plaques

Pattern of plaques is "willy-nilly"

Location of plaque determines symptoms:
- Temporal lobe = memory problems
- Thalamus = motor problems
- Descending corticospinal tract = motor problems

Irregular, demyelinated plaques tend to be located around ventricles.

H&E with luxol fast blue stain:
- Myelin = blue
MULTIPLE SCLEROSIS PLAQUE

LFB

GLEES

reactive astrocyte

luxol fast blue stain, myelin is blue. There's NO blue=no myelin

axons are still present
CENTRAL PONTINE MYELINOLYSIS
Clinical features

• Caused by rapid correction of hyponatremia
• Susceptible populations
  – Alcoholics
  – Debilitated patients

This could affect anyone who's hyponatremic, these are just populations that are often hyponatremic!

very rare today bc we understand what causes it and therefore how to prevent it

if patient comes in hyponatremic and you put put put them on normal saline, they could develop this.

Avoid by careful fluid management
CENTRAL PONTINE MYELINOLYSIS

Depression of central part of pons due to dissolution of the myelin

Question: What's the symptomology of this? Acute paralysis, dysphagia, dysarthria and other neurological symptoms.

- If obtunded person comes in with hyponatremia and you give too much Na, they crash "go down the tubes really quick". May also occur after too rapid correction of hypernatremia. PubMed Health
Bacterial Infections
- Meningitis
- Cerebritis
- Abscess

Viral Infections
- Meningitis
- Meningoencephalitis
- HSV, CMV, Polio, JCV, SSPE

HIV
Opportunistic infections
- Multiple Sclerosis
- Central Pontine Myelinolysis

Question: Are the symptoms of JC virus similar to MS except that it doesn't get better/relieved?
- Yes! Also, JC virus only in immunocompromised MS in otherwise healthy people

A summary
1. Meningitis: inflammation of arachnoid and pia
2. Cerebritis: inflammation of the brain itself
3. Abscess: A localized process

Meningoencephalitis: inflammation of meninges and the brain itself

HAVE A GOOD DAY!