Meningitis and Encephalitis

Routes of Bacterial Entry
- Bloodstream
- Middle ear infection
- Sinusitis
- Direct
- CSF
- Extension
- Mouth/nose droplets

Causative Agents
- Bacteria
  - Hemophilus influenza
  - Decreased incidence over the years
  - Neisseria meningitides (meningococcal meningitis)
  - Streptococcus pneumoniae
  - Listeria
  - pneumococcal
- Viruses
- Fungus

Microorganisms
- Most common cause neonates
  - Group B streptococcus
- Most common children, teen and young adults
  - Neisseria meningitides
- Most common adult is Pneumococcus
  - Decreasing though due to the multivalent pneumococcal vaccine
  - Highest case fatality 20%

Meningococcal Meningitis
- Incubation period 2-10 days
- 3-4 days most common
- Transmission: Droplet/contact
- Not aerosolized
- Meningococcal vaccine for high risk
Bacterial Meningitis

- Infection involves pia and arachnoid layer (subarachnoid space)
- Inflammation of brain tissue occurs as well
- Accumulates exudate
- Obstruct reabsorption CSF in arachnoid villi
- Hydrocephalus
- Combination of toxins and release inflammatory mediators lead to cerebral edema
  - Cytogenic
  - Vasogenic

Signs & Symptoms

- Triad:
  - Headache
  - Fever
  - Nuchal rigidity
- Other symptoms:
  - Kernig’s sign
  - Brudzinski’s sign
  - Photophobia
  - Altered LOC
  - CN palsies
  - Petechiae & cutaneous hemorrhage

Diagnosis

- Obtain blood cultures
- Brain CT scan - rule out diagnosis
- CSF analysis is gold standard of diagnosis
- Obtain lumbar puncture as soon as possible
- CT prior to LP if suspicious mass lesion or increased intracranial pressure

Complications of LP

- Mild to severe
- Leak at puncture site
- Precipitate brain herniation
  - Pressure gradient
  - Risk relatively unknown

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Immunocompromised state</td>
<td>HIV infection or AIDS, immunosuppressive therapy, or after transplantation</td>
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<tr>
<td>History of CNS Disease</td>
<td>Mass lesion, stroke or focal infection</td>
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<tr>
<td>New onset seizures</td>
<td>Within 1 week of presentation or status epilepticus or within 30 minutes of a seizure</td>
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<td>Papilledema</td>
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<td>Altered LOC and focal neurological deficits</td>
<td>Including dilated nonreactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, drift</td>
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Diagnosis

- History and examination
  - Recent ear infections, sinusitis, respiratory tract infections
- CSF analysis
  - Turbid, cloudy
  - Increase WBC (1000-5000 cells mm\(^3\))
  - Elevation neutrophils
  - Increase protein (>150)
  - Decrease glucose (< 40 mg/dL)
  - Ratio CSF to glucose < 0.3 - 0.4
  - Increase lumbar puncture pressure
  - Positive gram stain and culture
  - Increase lactate levels

Culture and Gram Stain

- Culture 48 hours
- Gram stain
  - Correlates with concentration of bacteria
  - Depends upon the microorganism
  - 40% cases caused by Haemophilus Influenzae
  - 75% cases caused by Neisseria meningitidis
  - 50% cases caused by gram-negative bacilli
  - 30% cases by Listeria monocytogenes

Diagnosis: Combination of Tests

- CSF glucose < 34 mg/dL
- Ratio CSF to blood glucose < 0.23
- CSF protein > 220 mg/dL
- CSF leukocyte > 2000
- Neutrophil > 1180

Individual predictors bacteria vs. viral

Diagnosis Postoperative Neurosurgical Patients

- CSF lactate
  - Found superior to glucose ratio
  - 4 mmol/L or >
  - Positive predictive value 98%
  - Negative predictive value 94%

Diagnosis

- C-reactive protein (CRP)
  - May be helpful in gram negative stain when deciding about antimicrobial therapy
  - Normal CRP negative predictive value 99% for bacterial
- Procalcitonin
  - Elevates in bacterial meningitis
  - Useful differentiation
  - Concentration > 0.2 ng/mL in adults
  - False negatives have been reported

Diagnosis

- PCR
  - Rapid detection enteroviruses
  - More sensitive than viral culture
  - Faster
  - Decreased use of antimicrobial therapy for treatment of presumed bacterial meningitis
Treatment

- Supportive therapy
- Antibiotic therapy
  - Initiate prior to CT and LP
  - Delay increases morbidity and mortality
  - Will not significantly interfere with findings LP/Blood cultures
- Steroids:
  - Known or suspected bacterial
  - Administer 15-20 minutes prior to or with first antimicrobial dose
  - Not recommended if already received antimicrobial
  - Most effective adults with pneumococcal meningitis
  - May decrease complications if given early
  - Cerebral edema
  - Altered cerebral blood flow
  - Cerebral vasculitis
  - Decreased hearing losses (especially in children)

Follow up LP evaluate sterilization of CSF after antimicrobials NOT recommended if responded appropriately to treatment

- If not appropriate response within 48 hours, recommend follow up LP

Surgical management
- Drain subdural empyema
- Treat hydrocephalus with shunt placement

Greater amount antigens
Larger number microorganisms in CSF samples
Delayed CSF sterilization after 24 h of antimicrobial therapy

Complications

- May extend into veins & cause vasculitis
- Secondary venous sinus thrombosis
- Fibrotic changes occur arterial wall
- May affect optic and acoustic cranial nerves
  - Hearing losses and visual changes
- Encephalitis or abscess
- Chronic hydrocephalus
- Postmeningitis sequelae

Poor Prognosis

- Also called “acute aseptic meningitis” or “benign lymphocytic meningitis”
- CSF analysis:
  - Increased WBC w/ increase lymphocytes
  - Normal glucose
  - Increased protein (less than bacterial)
  - Negative gram stain
  - Turbid
  - No elevation lactate levels

Viral meningitis
Treatment & Complications

- Supportive therapy
- No specific drug therapy
- Complications:
  - Paralysis
  - Arachnoiditis

Etiologies Encephalitis

- Herpes simplex virus
- West Nile virus
- Enterovirus
- Polio
- St. Louis encephalitis
- Cytomegalovirus
- Rabies

Identify Potential Etiology

- Clinical clues
- Recent history of infection
- Travel history
- Local risks
- Occupational or recreational exposure
- Animal contact
- Vaccination status or recent history

Herpes Simplex Encephalitis

- Worldwide
- Humans sole reservoir
- About 70-95% of humans are seropositive for Herpes Simplex virus by adulthood
- Most common cause sporadic fatal encephalitis
- Affects temporal lobe most commonly
Pathophysiology: HSV

- Questionable whether primary or recurrent infections
- Virus does lie dormant in neurons and ganglia
- But different strains have been found skin HSV and encephalitis HSV
- No triggering factors identified
- Immunosuppression does not predispose but may worsen outcomes

West Nile Virus

- Single stranded NA virus of the Flavivirus family
- Transmission by mosquito with birds as amplifying host
- About 10% mortality
- Incidence increases as age increases
- Higher incidence immunosuppressed patients

Symptoms: Viral Encephalitis

- Change in personality
- Altered mentation
- Decreased level of consciousness
- Fever
- Focal neurological findings
- Headache
- Papilledema
- Nausea and vomiting

Symptoms: More Specific WNV

- Seizures – 48% incidence WNV
- Nonconvulsive
- Overall limb weakness
- New onset movement disorders
- Due to involvement of basal ganglia

Diagnosis

- Blood culture
  - Positive culture may indicate systemic infection caused the encephalitis
- Specific clinical findings direct other culture sites
- Scrape or biopsy skin lesions

Diagnosis

- CSF analysis
  - Opening pressures often normal
  - RBC normal to elevated
  - HSV > incidence elevated RBC & xanthochromia
  - Protein elevated in 50% of patients
  - Mild to moderate
  - Elevate WBCs
  - Predominantly lymphocyte elevation
  - Mild mononuclear pleocytosis
  - Glucose typically normal
  - Rarely reduced
  - Normal gram stain
  - Elevated IgM - WNV
Diagnosis:
- EEG
  - Nonspecific
  - Spiked and slow activity
- CT
  - Uncommon finding on CT scans
  - Hypodensities in temporal or frontal lobe - HSV
- MRI
  - Show abnormalities in > 90% of patients
  - Hyperintensities in T2 and enhancements
  - Temporal lobe most common HSV
  - Periventricular - WNV

Diagnosis
- Polymerase chain reaction (PCR) for HSV
  - Highly specific and sensitive (99% and 96%)
  - First 24 hours may be negative
  - Repeat CSF samples for confirmation
- Brain biopsy
  - “gold standard” 100% specificity and 99% sensitivity
  - Not recommended/infrequently performed

Treatment
- Herpes encephalopathy
  - Acyclovir
    - Higher doses and longer duration may prevent relapses
    - Started empirically suspected encephalitis until specific results obtained
- WNV encephalopathy
  - Supportive
  - Mechanical ventilation may be required if flaccid paralysis

CNS Abscess
- Brain abscesses encapsulated mass with varying stages of infection
  - Thin walled abscess can rupture, spreading infection throughout CNS
  - Occurs in the:
    - Intraparenchymal
    - Subdural
    - Epidural

CNS Abscess
- Hematological spread
- Otitis or sinusitis
- Direct extension from meninges
- Brain trauma
- Cranial surgeries
- Congenital heart disease
- Rare cases with tongue piercing or endovascular coiling

Presentation
- Signs of original infection
- Headache
- Altered mental status
- Papilledema
- Vomiting
- Focal neurological deficits – 75%
- Fever
- Seizures – 50%
Diagnosis

- Contrast CT & MRI
- Hypodense ring (enhancement of capsule)
- Capsular ring 1-3 mm thick
- May have surrounding edema

Treatment

- Drain through burr hole or craniotomy
- CT guided biopsy/ aspiration
- Administer antibiotics

Neurocysticercosis

- Most common parasitic disease of CNS
- Approximately 2.5 million people worldwide carry the adult tapeworm
- More infected with cysticerci
- Caused by infection of larval stage of pig tapeworm (Taenia solium)
- Primary cause of epilepsy in developing countries

Neurocysticercosis

- Endemic countries (where free roaming pigs)
- More common in Mexico
- Central and South America
- Sub-Saharan Africa
- Indonesia
- China
Neurocysticercosis

- Immigration of tapeworm carriers from endemic areas bring into the US disease prevalent in states Texas, New Mexico and California
- Increasing incidence non-endemic countries due to travel to endemic countries

Routes of Entry

- Cysticerci are ingested by humans through under-cooked pork (in pig muscle)
- Tapeworms attach to the wall of small intestines by suckers and hooks and lay eggs
- Up to 250,000 eggs per day
- Eggs pass out in feces
- Human cysticercosis is acquired by fecal-oral contact with carriers of adult tapeworm
- Ingestion of contaminated food or water with eggs of Taenia solium

Scolex of Tapeworm

- Human cysticercosis occurs when eggs ingested in contaminated food or water
- Carrier can also develop cysticercosis from own feces
- Egg wall dissolves & penetrates intestinal mucosa
- Enters lymphatics & mesenteric vessels
- Eventually enters muscle, tissues and brain tissue
Incubation Period

- Symptoms can occur within 2 months to 30 years after infection

Symptoms of Neurocysticercosis

- Meningeal inflammation
- Mass effect of cysts
- Inflammatory responses
- Seizures (50%)
- Hydrocephalus (30%)
- Stroke (4-12%)
- Presence of subQ nodules
- Cystercotic encephalitis

Diagnosis

- CT scan
- MRI
- CSF analysis
  - Increased pressures
  - pleocytosis with > eosinophils
  - lymphocytes elevated
  - IgG levels
  - low glucose
- Stool samples
- Biopsy
Treatment

- Treat seizures with antiepileptics
- Antiparasitic treatments
  - Abendazole
  - Praziquantel
- Between 60% and 85% of parenchymal brain cysticerci are killed after standard courses of treatment
- Between the 2nd and 5th day of therapy there is usually exacerbation of neurological symptoms
- Caused by local inflammation due to death larvae
- Administer steroids

Prion Disease

- Transmissible spongiform encephalopathies (TSEs)
  - Known as prion diseases
  - Rare degenerative brain disorders
  - Characterized by tiny holes that give the brain a “spongy” appearance
- Prion diseases are invariably fatal brain disorders
  - Occurs both in humans and certain animals
The form BSE (bovine spongiform encephalopathy) is called “mad-cow” disease.

In humans, the best known of the prion diseases is Creutzfeldt-Jakob Disease (CJD), which affects around one person per million per year. In the United States, this translates to approximately 280-300 new cases per year. A new type of CJD, called variant CJD (vCJD), was first described in 1996 and has been found in Great Britain and several other European countries. The initial symptoms of vCJD are different from those of classic CJD, and the disorder typically occurs in younger patients.

2002, reported 119 deaths, but the number currently incubating the disease is still unclear. Results from human consumption of beef from cattle with BSE or "mad cow disease.".

Prion diseases are caused by an abnormal version of a protein called a prion. Prion is short for proteinaceous infectious particle. Prion proteins occur in both a normal form (harmless protein) found in the body's cells and an infectious form (disease causing).

Human TSEs can occur in three ways: sporadically, hereditary diseases, and transmission from infected individuals.
Sporadic Transmission

- Sporadic TSEs may develop because some of a person's normal prions spontaneously change into the infectious form of the protein and then alter the prions in other cells in a chain reaction
- Unknown cause
- Most common form (85% cases)
- Affects mainly people over age of 50
- Spontaneously converts protein into an abnormal form or prion
- Ataxia

Hereditary Transmission

- Inherited cases arise from a change or mutation in the prion protein gene that causes the prions to be shaped in an abnormal way
- Inherited mutation of protein gene which are inherited from one parent
- 50-50 chance each child inheriting the mutated gene
- Since CJD does not usually strike until later in life, people carrying the gene may not realize that they may have passed it on to their children
- Accounts 10-15% cases

Infected Individuals

- TSEs cannot be transmitted through air or most forms of casual contact
- May be transmitted through contact with infected tissue, body fluids, or contaminated medical instruments.
  - Normal sterilization procedures such as boiling or irradiating materials do not prevent transmission of TSEs.
  - The prion survives normal disinfection procedures which would destroy bacteria and viruses
  - Contracted CJD from brain surgeries/EEG depth electrodes done with instruments which were previously used on a CJD patient
  - New WHO guidelines for sterilizing instruments
  - Destroying instruments

Infected Individuals

- Transmission of CJD occurred with corneal transplants and grafts of dura mater
- Incubation time iatrogenic CJD is 19-46 months
- In December, 2003 the U.K. reported first case of suspected transmission of vCJD by blood transfusion, the donor gave blood 3.5 years prior to becoming symptomatic
  - Donor symptomatic 6.5 years after donating
  - Several since: 5-8 years after transfusion

Infected Individuals

- Transmitted human growth hormones prepared from pooled cadaver pituitary glands
  - No longer used to make hormones
  - Pituitary hormones now prepared by recombinant techniques
  - Largest iatrogenic spread has been through pituitary hormones
  - Recorded 160 deaths

Infected Individuals

- Concern potential for silent carriers that pass the lethal form along through surgeries or blood transfusions
- Prediction of scientists in UK estimate about 3800 people could test positive for prion proteins
Variant CJD

- Variant CJD Exposure to BSE contaminated meat
- Younger population (20-30 years of age)
- Course of disease longer than sporadic (about 1 year)
- Presents greater psychiatric changes before neurological changes

Chronic wasting disease (CWD)

- Affects hoofed mammals (mule deer, elk, moose)
- No strong evidence transmission to humans
  - but because of the long time between exposure and development of disease, it may be difficult to identify the risk
- Minimize handling or eating brain and spinal cord
- Do not eat if test positive CWD or if animal looks sick

Pathophysiology

- Histological triad
  - Spongiform vacuolation
  - Neuronal loss
  - Astroglial proliferation with and without amyloid plaque
- Prion reaches CNS tissue through extraneural pathways
  - except for brain surgery
- Prions reach CNS tissue
  - colonize lymphoid organs after exposure (spleen, lymph nodes, and tonsils)
  - reach CNS through autonomic nerves (SNS and PNS)

Symptoms

- personality changes
- psychiatric problems such as depression
- lack of coordination, and/or an unsteady gait (cerebral ataxia)
- involuntary jerking movements called myoclonus
- rigidity in limbs
- unusual sensations
- insomnia
- confusion
- memory problems
- hallucinations
- incontinence
- slurred speech
- difficulty with swallowing
**Symptoms**

- “Typical” sporadic CJD early symptoms:
  - depressions, mood swings, memory lapses, social withdrawal and lack of interest
  - rapid progression to dementia and obvious neurological symptoms
- Within weeks, develop unsteady gait, lack coordination and cerebellar ataxia
- Progresses to blurred vision, hallucinations, blindness, rigidity of limbs, sudden jerking movements and incontinence

**vCJD Symptoms**

- The symptoms of vCJD different from classical CJD
- Often, will be referred first to a psychiatrist
- Several weeks or months > neurological symptoms occur including:
  - Unsteadiness in walking and sudden jerky movements
  - Anxiety, depression, withdrawal and behavioral changes
  - Progressive dementia (loss of mental function, marked by symptoms such as memory loss)
  - Persistent pain and odd sensations in the face and limbs
- Death occurs approximately a year after the onset of symptoms

**Diagnosis**

- History and physical examination
- Electroencephalography (EEG)
- CSF presence of a protein released from damaged or dying nerve cells
  - Protein (14-3-3) and tau
  - detectable in over 90% of patients with typical CJD
  - not specific and can be detected in some patients with other disorders such as viral encephalitis
- MRI has recently useful radiological aid to the diagnosis of CJD
  - In about 80% of the cases, an increased signal ‘light up’ the basal ganglia unilateral or bilateral

- No tests are sensitive/specific enough to identify every case of CJD
- Brain biopsy is no longer needed or advised in the diagnostic evaluation of suspected cases of CJD
- Since the disease progresses rapidly, the patient may die before a diagnosis can be made
- Consequently, CJD may be mistaken for neurological disorders like Alzheimer's Disease, Pick's Disease, Huntington's Disease, cerebral hematomas and vascular irregularities
Definitive Diagnosis

- Frozen brain biopsy tissue examination
- vCJD distinctive “daisy” plaques upon tissue examination
- Amyloid deposits, known as plaques, are found in the brain on autopsy (about 10% sporadic cases)
- Final diagnosis can take 1 1/2 months to 2 years