Intoxications and Infections of the CNS

MHD Clinical Correlation – Neuroscience Block

Gregory Gruner, MD, MBA, MHPE
Visa Dean for Education, SEEM
Professor, Department of Neurology
LCHR a member of Trinity Health

Intoxications - Bacterial toxins: Tetanus

- Exotoxin of Clostridium tetani, produced anaerobically - tetanospasmin
- During hours to weeks, exotoxin binds to interneurons of brain, brain stem, spinal cord
  - Preventing release of inhibitory glycine and GABA
- Exotoxin effect is motor disinhibition
  - Painful spasms in muscles near wound
  - Generalized, arching back (opisthotonos)
  - Jaws (trismus or lock jaw), face (risus sardonicus), respiratory muscles
  - Generalized convulsive seizures
- Diagnosis is made on clinical grounds
- Treatment
  - Neuromuscular blockade, sedation, anticonvulsants
  - Tetanus immune globulin, antibiotics
### Intoxications - Bacterial toxins: Botulism

- Exotoxin of *Clostridium botulinum*, produced anaerobically
  - Eight distinct C. botulinum toxin types (A through H)
    - A, B, E, and rarely F, G, and H, cause human disease (type H first reported in 2014)
- Foodborne botulism
  - Caused by ingestion of contaminated food (Types A, B, and E)
  - Most commonly recognized as small outbreaks (fruits, vegetables, fish)
  - Adequate cooking destroys existing and it is inactivated in chlorinated water
- Infant botulism
  - Occurs when C. botulinum spores are ingested, colonize the gastrointestinal tract
  - In the U.S., ingestion of environmental dust/soil containing C. botulinum spores
  - Toxin is primarily absorbed by the stomach and small intestine (resistant to degradation by gastric acidity and human alimentary enzymes)

### Intoxications - Bacterial toxins: Botulism

- Botulinum toxin can target multiple tissues (most potent bacterial toxin known)
  - Motor and sensory neurons - block cholinergic neuromuscular innervation of striated and smooth muscles and cholinergic innervation of tear/salivary/sweat glands
  - Affect both excitatory and inhibitory synapses, but is more active on excitatory neurons
  - Inhibits release of dopamine, serotonin, somatostatin, noradrenaline, and gamma amino butyric acid
  - Large size makes it difficult to pass through the blood-brain barrier (?) Could reach CNS by axonal retrograde or anterograde transport
- Severity of paralysis depends on amount of exotoxin ingested (after 12-24 hours)
  - Ptosis, diplopia, later dysphagia, facial, limb, and respiratory weakness can occur
- Diagnosis
  - Clinical picture (especially history), EDX testing and bioassay for exotoxin
  - Treatment – Supportive, antitoxin, Guanidine (?)

### Intoxications – Environmental (examples)

- Lead poisoning
  - Workplace, environmental, food/herbal remedies and now, municipal water supply
  - Exposure is either through inhalation (e.g. painting) or ingestion
  - Clinical Presentation
    - Acute toxicity – Variable symptoms/signs (e.g. abdominal or joint pain)
    - Chronic toxicity – Typically cognitive, encephalopathy, peripheral neuropathy
  - Diagnosis and treatment guided by serum lead levels
  - Treatment – Chelating agents (DMSA, Calcium EDTA)
- Organic solvents
  - Chemical plant/hobby exposure, Substance-use disorder (‘sniffing’, ‘huffing’, ‘bagging’)
  - Effects - alcohol-like intoxication, intense euphoria, vivid hallucinations
  - Complications – pulmonary/cardiac, encephalopathy or peripheral neuropathy
  - Diagnosis is clinical
**Intoxications – Environmental (examples)**

- **Carbon monoxide (CO)**
  - Odorless gas, greater affinity for hemoglobin than oxygen
  - Sources are malfunctioning heaters, unventilated auto garages
  - Carbon monoxide poisoning is relatively common

  **Clinical presentation**
  - Early symptoms - headache, blurred vision, dizziness, weakness, vomiting
  - Progressive symptoms - chest pain, confusion, weakness
  - “Later” symptoms - loss of consciousness, arrhythmias, seizures, death

  **Treatment**
  - Supportive, hyperbaric oxygen
  - Neurological sequela
  - Cognitive, amnesia, parkinsonism

**Intoxications – Substance-Use Disorders**

- **Diagnostic and Statistical Manual of Mental Disorders (DSM-5) does not distinguish between substance abuse and dependence**
  - Remember that substance-use disorders occur in older patients
  - Long-term substance-use can have deleterious effects with aging

  **Signs of a possible problematic Substance-Use Disorder**
  - Psychiatric (mood swings, irritability, anxiety, depression)
  - Physical (falls/injuries, malnutrition, self-neglect, confusion/disorientation)
  - Social/behavioral (withdrawal from social activities, premature prescription refills)

  **During intoxication**
  - Head trauma, intracranial hemorrhage, drug-induced seizures

  **During drug withdrawal**
  - Substance-use related syndrome
    - Cerebral infarction or hemorrhage (cocaine most common etiology)

**Intoxications – Substance-Use Disorders: Alcohol**

- **Acute intoxication**
  - Social disinhibition, impaired consciousness, cerebellar dysfunction, secondary head trauma
  - Very high levels may lead to coma, death

- **Alcohol withdrawal syndrome**
  - Early, “hyper sympathetic” stage (tremulous, sweaty, tachycardic);
  - Limited number of convulsive seizures 12 hrs-3 days after drinking stopped;
  - Later stage of delirium tremens, 3-4 days after drinking stopped, with fluctuating motor and autonomic activity, confusion, hallucinations (similar syndrome may occur with benzo diazepine and barbiturate withdrawal!)
  - Comorbid infections or trauma may prove fatal
  - Treat with benzodiazepines for sedation and seizure control, hydration and metabolic support, thiamine
Progressive stages of alcohol withdrawal syndrome after cessation of drinking.

Withdrawal seizures are generalized tonic-clonic in type. Any partial or focal seizure (or onset) suggests a focal lesion.

**Pathophysiology**
- Caused by alcohol itself, malnutrition or vitamin deficiencies, beverage contaminants or injuries when drunk
- Head trauma (subdural hematomas, cerebral hemorrhage)

**Syndromes**
- **Wernicke-Korsakoff syndrome**
  - Acute - *Wernicke encephalopathy* (nystagmus, ophthalmoplegia, gait ataxia, confusion) correctible with thiamine supplementation
  - Chronic - *Korsakoff psychosis* (amnesia, confabulation) is the chronic phase
- **Alcoholic cerebellar degeneration** (Anterior-superior vermis syndrome)
- Gait ataxia, dysmetria of lower limbs
- **Peripheral neuropathy** (rarely myopathy)
- **Dementia** (controversial)

**Inflammation from blood, foreign material or infection within the subarachnoid space**
- Symptoms and signs evolve rapidly in hours to days
  - Fever, headache, malaise, lethargy, nausea and vomiting
  - Impaired consciousness, nuchal rigidity, meningeal signs

Types of meningitis differ in regards to symptoms, rapidity of development, treatment options and outcome
- **Acute meningitis**
  - Bacterial meningitis - more severe, fulminant and may be fatal if not treated early
  - Viral meningitis – “benign”, nontoxic, untreatable but resolves spontaneously
- **Chronic meningitis**
  - “Unusual organisms” – Fungal, Tuberculosis, syphilis, parasites
  - Neoplastic
Infections of the CNS – Meningitis: Bacterial

- In bacterial meningitis, organisms may spread:
  - Through the bloodstream from a distant infection
  - Directly from an adjacent infection (otitis, sinusitis)
  - Once suspected, lumbar puncture and CSF examination is performed
- Most common bacteria involved depend on the age of the patient (*Vaccine available)

<table>
<thead>
<tr>
<th>Newborns</th>
<th>Group B Streptococcus</th>
<th>Streptococcus pneumonia*</th>
<th>Listeria monocytogenes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Babies and children</td>
<td>Neisseria meningitidis</td>
<td>Haemophilus influenzae type b*</td>
<td>Group B Streptococcus</td>
</tr>
<tr>
<td>Teens and young adults</td>
<td>Neisseria meningitidis</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Older adults</td>
<td>Neisseria meningitidis</td>
<td>*</td>
<td></td>
</tr>
</tbody>
</table>

Emergently give antibiotics with broad coverage
- Cefotaxime (or ceftriaxone) and Vancomycin (or rifampicin)
- Ampicillin added for possibility of Listeria (elderly or neonates)

- Change to specific antibiotics when organism identified from CSF
- Dexamethasone (corticosteroid) given before/with antibiotics lessens complications

Infections of the CNS – Meningitis: Bacterial

<table>
<thead>
<tr>
<th>Opening Pressure (50 - 200 mm H2O)</th>
<th>Normal</th>
<th>↑</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC  (10^3/mm3)</td>
<td>↑</td>
<td>100 - 1000 PMNs</td>
<td>↑</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>Ratio &lt; 0.6</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>Protein (mg%)</td>
<td>↑</td>
<td>500 - 50000</td>
<td>↑</td>
</tr>
</tbody>
</table>

Complications of bacterial meningitis
- Hydrocephalus from pus obstructing CSF pathway
- Secondary inflammation and edema of cortex (meningoencephalitis)
- Infarction from thrombosis of inflamed superficial vessels of cortex, spinal cord
- Deafness (monitor hearing in children)

Chronic Meningitis
- Evolves over weeks to months
- Variety of organisms (tuberculosis, fungus, syphilis, parasites)
  - Need special cultures (titers) of CSF
- Polymerase chain reaction (PCR) testing (e.g., TB)
- Elderly, malnourished, immunosuppressed patients most susceptible
- Subtle symptoms of mild headache or confusion, no-obvious meningeal signs
**Infections of the CNS – Abscesses**

- Staphylococcus and Streptococcus species - most frequent etiology
- Neurologic symptoms/signs related to location
- Brain MRI with DWI - most sensitive imaging test
- Early aspiration (stereotaxic) is vital to acquire the pathogen and rationalize treatment.

**Infections of the CNS – Encephalitis**

- Primary infection & inflammation of brain, usually viral
  - Viral transmission by seasonal arthropods (ticks, mosquitoes)
    - Inhalation or reactivation (Herpes simplex)
- Cerebrospinal fluid findings
  - Increased WBC (lymphocytes), normal to decreased CSF glucose
- Symptoms and signs evolve in hours to days
  - High fever, headache (as in meningitis)
  - Seizures, focal neurological deficits, changes in behavior and consciousness (more specific for encephalitis)
- May need to treat elevated intracranial pressure (IV dexamethasone, sedatives) or seizures

**Infections of the CNS – Encephalitis: Herpes simplex**

- From HSV-1 (cause of oral herpes)
- Nonepidemic and nonseasonal
- Predilection for frontal and temporal lobes
  - Aphasia, behavioral changes, memory impairment
- One of the most commonly recognized and devastating types
  - Begin acyclovir if suspected, continue if CSF PCR for HSV-1 is positive
  - Acyclovir treatment drops mortality from 40-70% to 20%
West Nile Virus
- Bird epidemic in past few summers, spread to humans by mosquitoes
- Encephalitis (fever, headache, rash)
- Weakness from affecting peripheral nerves or anterior horn cells (similar to polio)

Poliomyelitis
- Infects motor neurons in brain stem, spinal cord
- Mild regional weakness to severe generalized paralysis, even of respiratory muscles
- Survivors often have asymmetrical atrophy and weakness in one limb
- Post polio muscular atrophy (Post polio syndrome) – Late onset weakness of previously recovered muscles (“burn-out” of remaining LMNs that reinervated previously denervated muscle fibers?)
- Increasing concern over vaccine derived poliovirus infection (gradual shift to limited serotypes and deactivated virus-based vaccines)

Zika virus (ZIKV)
- Mosquito-borne flavivirus
- Asymptomatic infection in 80% of people
- Acute ZIKV infection
  - Fever (may or may not be present), rash, arthralgia, conjunctivitis
  - Most recover with no complications
  - It is a neurotrophic virus so, encephalitis, seizures, neuropathies can occur
- Congenital Zika syndrome (CZS)
  - Infants born with microcephaly, brain abnormalities, ocular findings, congenital contractures, neurologic impairment
Infections of the CNS – Viral: HIV

- Transmission by infected body fluid
- HIV infects CD4+ lymphocytes and can lead to Acquired Immunodeficiency syndrome or AIDS
- Nervous system is often involved through
  - Direct viral invasion (dementia, meningitis)
  - Indirect damage from cell lysis or inflammation
  - Complications of immunodeficient state
- Three major therapeutic revolutions since the virus was first isolated in 1983
  - Introduction of protease inhibitors (1996) and in combination with two nucleoside-analogue reverse-transcriptase inhibitors, produced highly active antiretroviral therapy (HAART) - greatly improved the prognosis
  - Use of treatment as prevention
  - Individual clinical benefit of early cART, even with a CD4 count greater than 500 cells/μL

Prior to the use of antiretroviral therapy (most common disorders)
- Opportunistic infections of the central nervous system
- CNS malignancy were common

Current neurologic complications
- Acute
  - Aseptic meningitis
  - Acute inflammatory demyelinating polyneuropathy
- Chronic
  - Neuropathies
  - Progressive multifocal leukoencephalopathy
- HIV-associated neurocognitive disorders (HAND) – severity reduced (progressive HIV-associated dementia once predominated) to a milder chronic form of potentially disabling neurocognitive impairment (need for other therapies?)
Progressive Multifocal Leukoencephalopathy (PML)

- An opportunistic infection in immunodeficient patients
- Increasingly encountered in therapeutic immune-mediated therapies (e.g., for multiple sclerosis)
- Reactivation of polyomavirus (JC virus) infection of oligodendrocytes
- Leads to patchy demyelination in the CNS and focal deficits
- Diagnosis
  - Positive PCR assay for JC virus in CSF
  - Brain biopsy
- No current effective treatments

Infections of the CNS – Prion Diseases

- "Infectious proteins" (all other infectious organisms contain nucleic acid)
- Misfolded proteins (prions) induce conformational changes in normal proteins, neuronal death occurs in absence of inflammation
- Transmitted by human graft tissue or neurosurgical instruments;
- Other prion diseases are hereditary in nature
- Cause transmissible spongiform encephalopathies in humans (and animals)
  - Creutzfeldt-Jakob Dementia (CJD) most common
    - Rapidly progressive, untreatable, fatal in weeks to months
    - Dementia with prominent myoclonus
    - Often corticospinal, extrapyramidal, cerebellar or lower motor neuron signs
    - EEG demonstrates specific abnormality (periodic sharp waves)
    - Brain biopsy shows spongiform changes
  - Bovine spongiform encephalopathy ("mad cow disease")
    - Spread to humans attributed to eating meat from infected cattle
EEG findings of asymmetric slowing and periodic lateralized discharges in Creutzfeldt-Jakob disease

Brain biopsy, left temporal lobe, H&E staining. Vacuolization in the neuropil and neuronal loss indicate spongiform degeneration.

Brain biopsy, left temporal lobe, immunohistochemical staining for PrP. Immunopositive deposits around the spongiform change may be observed (arrowhead).

Infections of the CNS – Does AD act like a “Prion” disease?

Schematic Representation of Cell-to-Cell Transmission of Tau Pathology and Cortical Spread of Alzheimer Disease–Associated Tau