Diseases of the Nervous System

Central nervous system
- Brain is a prisoner
- Basic cellular elements
  - Neurons, location means everything
  - Neuronal reaction to injury, very limited
    - Axonal growth
    - No regeneration of lost cells
    - Accumulation of junk within the cells can be harmful.
- Glial component, supportive
  - Microglia, the police force of the CNS
  - Astrocytes, structural like fibroblasts elsewhere
    - Gemistocytes are reactive astrocytes
  - Oligodendrocytes, make myelin (the insulation)
- Meninges
Cerebral Edema
- Compartmentalization can cause problems
- Injury to brain
  - Tumor
  - Rubor
- Swelling can't go anywhere
- Compression of vital structures
- Herniation
  - Sublax
  - Transtentorial
  - Cerebellar tonsils

Brainstem Hemorrhages

CSF Flow
- Made in the ventricles
- Flows down aqueduct
- Into 4th ventricle
- Out into the subarachnoid space
- Up to the arachnoid granulations
- Back into the blood
- Obstructions in movement will lead to hydrocephalus

Hydrocephalus
- Obstruction to flow of CSF
- Over production of CSF
- Inability of arachnoid granulations to restore water of CSF back into circulation
Hydrocephalus

- Noncommunicating: Can’t get out of ventricles
- Communicating: CSF can’t get to arachnoid granulations

Communicating hydrocephalus

- Cerebrospinal fluid (CSF) circulation pathways are competent through the ventricles.
- Classically it was thought to arise when the arachnoid villi became obstructed.
- Recent work by several pediatric neurosurgeons have suggested that there may be several causes for communicating hydrocephalus.
  - Altered or compromised blood circulation within the brain.
  - The skull or
  - Within the chest.
- For now though the treatment for this condition is some form of a shunt.

Shunt for Hydrocephalus

- V-P Shunt
- V-A Shunt

Trauma

- Birth trauma
- Hemorrhage
- Permanent loss

Trauma

- Closed head
  - Coup
  - Contra-coup
- Penetrating
- Hemorrhage
- Contusion
- Laceration
Contusions
- Coup
- Impact surface
- Contra-coup
- Opposite side
- Frontal impact
- Cortical blindness

Diffuse Axonal Injury (DAI)
- Rotatory injury
- Auto accidents
- Boxers
- Shears off axons
- Hard to see changes on CT

DAI

Epidural Hemorrhage
- Trauma with skull fx
- Middle meningeal a.
- Hemorrhage compresses brain

Subdural Hemorrhage
- Rotational injury tears little veins
- Slow venous bleeding
Subdural Hematoma

Subarachnoid Hemorrhage
- Not as commonly due to trauma, but maybe.
- Arterial bleeding
- Typically from Circle of Willis
- Blood in subarachnoid space
- May bleed 1-2 weeks after traumatic event.

Vascular Disease
- Hypoxic
  - TIA
  - Stroke
    - Infarction
- Hemorrhagic
  - Vascular blowout
  - Trauma

Pop tarts

Ischemic Infarcts
Chronic Ischemia
- Chronic vascular insufficiency
- Atherosclerosis
- Marked cerebral atrophy

Hypertensive Hemorrhage

Hypertensive Hemorrhage
- Hypertensive vascular disease
- "Watershed" infarcts, areas of poor anastomosis

Lacunar Infarcts
- Hypertensive vascular disease
- "Watershed" infarcts, areas of poor anastomosis

Berry Aneurysm
- Berry aneurysm
- Subarachnoid
- Parenchymal
Berry Aneurysm

- Very painful
- Fatal
- Overtly bloody CSF

Subarachnoid Hemorrhage

Intracerebral Bleed

- Bleed at any time
- Children
- Parenchymal malformations too

AV Malformations
Infections

- Brain proper
- Meninges
- Bug
  - Bacteria
  - Virus
  - Spirochetes
  - Parasites
  - Prions

Bacterial Meningitis

- Exudate over cerebral hemispheres
- Bacteria grow in CSF
- CSF
  - Cell count
  - Glucose
  - Protein
- Age of patient
- Complications
  - Scarring
  - Epilepsy
  - Abscess

Bacterial Meningitis

CSF Changes

- Protein
- Glucose
- Cell Count

Cerebral Abscess

- Septic endocarditis
- Blood borne pathogens
- Must surgically drain

Abscess
Viral Encephalitis
- Infection of brain substance
- Herpes
- Absent temporal lobes
- Sporadic
- Immune suppressed
- HIV

Herpes Encephalitis

Cryptocccocal Meningitis

HIV Encephalopathy
- Meningitis
- Neuronal
- Both cognitive motor
- Diffuse cortical atrophy
- Microglia at site of dead neurons
- GP120 protein is directly toxic

Tertiary Syphilis
- Years after initial infection
- Obliterative end arteritis
- Meningitis
- Brain proper
- Tabes dorsalis

Toxoplasmosis gondii
- HIV
- Immune suppressed
- Children
- Fetal
Prion Disease

- No nucleic acid
- Sporadic or genetic
- Accumulation of abnormally folded protein
- Variety of conformations of the diseased protein
- Spongiform encephalopathy
- Kuru

Creutzfeld-Jakob

BSE

Demyelinating Disorders

- White matter
- Disease of oligodendrocytes
- Autoimmune most times
Multiple Sclerosis

- Lesions dispersed in space and time
- Come and goes
- Symptoms
  - Optic nerve
  - Urination
  - Heat makes worse
  - Weakness
- Degeneration of white matter
- Plaques

Multiple Sclerosis

- Areas of demyelination
  - Plaques
  - Active repair
  - Quiescent

Multiple Sclerosis

Degenerative Diseases, Overview

- Not just aging changes
- Neuronal Death
- Gray matter
  - White matter changes are secondary
- Selective or generalized loss
- Atrophy (local or global)
- Histological features
  - Neurofibrillary tangles
  - Intracellular or intranuclear inclusions

Alzheimer’s Disease

- Progressive loss
  - Memory
  - Cognitive
- 5-15 years
- Eventually loss of language
- Higher functions
- Parkinson’s in a few
- Pneumonia is often cause of death
Alzheimer’s Disease

- True dementia
- Marked atrophy
- Protein alterations
  - Tau protein
  - Amyloid related protein
  - Senile plaques
  - Amyloid angiopathy

Alzheimer’s Disease

- Senile plaques
- Vascular amyloid changes
Alzheimer Genes

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Mutations/Phenotypes</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Amyloid precursor protein (AP)</td>
<td></td>
<td>Early onset (64) Drug induced Ab production</td>
</tr>
</tbody>
</table>
| 14         | Presenilin-1 (PS1) | Double membrane insertion, 
                        | Early onset (64) Drug induced Ab production                                           |
| 11          | Presenilin-2 (PS2) | Early onset (64)               | Early onset (64) Drug induced Ab production                                           |
| 1           |  | Very late onset               | Current research                                                                 |
| 19          | Amyloid precursor (A) (APP) | Late onset               | Suggested link to development of AD Drug-induced in aged at 70                           |

*AlzheimersBeta (64) Familial Alzheimer disease

Pick's Disease

- Degenerative
- About 1/10th as common as Alzheimer's
- Frontal lobes
- Otherwise similar to Alzheimer's

Parkinson’s Disease

- Parkinsonism, collection of symptoms
  - R rigidity, stooped posture, gait disturbances, pill rolling, face
  - Drug induced
  - Parkinson's Disease

Parkinson Disease

- Degeneration of dopaminergic neurons leads to Parkinson's

- Degeneration of dopaminergic neurons
Parkinson Disease
- Flattened affect
- Stooped shoulders
- Pilling rolling
- Cogwheel rigidity

Cogwheel Rigidity

Huntington Disease
- Hereditary
- Progressive
- Extrapyramidal motor
- Choreaform movements
- Huntington gene
  - Trinucleotide repeats
  - CAG
  - Normal 6-34 copies
  - HD has 50-70 repeats
- Caudate nucleus atrophy
- Suicide and infections

Amyotrophic Lateral Sclerosis (ALS)
- Sporadic loss of motor neurons
- Spinal
- Bulbar
- Poor swallowing
- Pneumonia

Toxic and Vitamin Deficiencies
Thiamine Deficiency

- Beriberi
- Alcohol abuse
- Abrupt psychotic changes
- Wernicke's encephalopathy
  - Hemorrhages in mamillary bodies
  - Confusion
  - Paralysis of extracelullar muscles
  - Ataxia
- Korsakoff's
  - Inability to form new memories
  - Confabulation

B12 Deficiency

- Inability to maintain myelin
- Posterior column degeneration
- Subacute combined degeneration

Ethanol

- Acutely, neural depressant
  - Inhibitions go first
  - Loss of depth perception
- Chronic
  - Degeneration of granular cell layer of cerebellum
  - Loss of Purkinje cells
  - Bergman's gliosis
  - Fetal alcohol syndrome
  - Microcephaly
  - Growth retardation
  - Facial abnormalities
  - Mental retardation
    - Abnormal migration of neurons during development

Fetal Alcohol Syndrome

Alcoholic Cerebellar Degeneration

Krabbe's Disease

- Inherited metabolic defect
- Galactocerbroside B-galactosidase
  - Cannot breakdown galactocerbroside
  - Alternate breakdown leads to buildup of fatty acids
  - Oligodendrocyte injury
Krabbe’s Globoid Cells

CNS Tumors
- Primary vs. metastatic
- Benign vs. malignant
- Focal vs. diffuse
- Above or below tentorum
- Not too common in adults
- About 20% of childhood malignancies
- Location is critical
- Cell type
  - None are of neuronal origin
  - Astrocytoma, most
  - Oligodendroglioma
  - Microgliomatosis
  - Ependymoma

Well Differentiated, Diffuse Astrocytoma

Astrocytoma
- Astrocytic origin
- Above tentorum most times in adults
- Multiple grades
- Compresses surrounding tissue
- Hemorrhage and necrosis
- With higher grade malignant tumors,
  - Look for vascular growth
Astrocytoma

Ependymoma

Meduloblastoma

Microgliomatosis

- Children
- Midline cerebellum
- Subarachnoid spread

- Lymphoma of brain
- Diffuse
- Perivascular
- AIDS
- EB virus?
Meningioma
- Arise from meninges
- Benign in a biological sense
- Consider where it is
- Fibroblast looking
- Cells in whirls and clusters
- Psammoma bodies

Psammoma bodies
- Little calcifications
- Microscopic
- Within the tumor
- Can spot on X-ray
- Concentric layers

Paraneoplastic Syndromes and the CNS

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Target</th>
<th>Tumor</th>
<th>Antigen</th>
<th>Potential Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary adenocarcinoma</td>
<td>Pulmonary cells</td>
<td>Bronchogenic cancer</td>
<td>Ty</td>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Larynx epidermoid, head and neck</td>
<td>Larynx</td>
<td>Squamous cell cancer</td>
<td>NC</td>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Small cell lung</td>
<td>Small cell</td>
<td>Bronchogenic cancer</td>
<td>Ty</td>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Prostate glands</td>
<td>Prostatic</td>
<td>TP</td>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Ovarian carcinoma</td>
<td>Ovarian</td>
<td>Ovarian</td>
<td>PE</td>
<td>Carbohydrates</td>
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<tr>
<td>Breast cancer</td>
<td>Breast</td>
<td>Breast</td>
<td>ER/PR</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Melanoma</td>
<td>Melanoma</td>
<td>Melanoma</td>
<td>Carbohydrates</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Myeloma</td>
<td>Myeloma</td>
<td>Myeloma</td>
<td>Carbohydrates</td>
</tr>
</tbody>
</table>

Peripheral Nerves
- Axon vs. Schwann cells
- Motor
- Sensory
- Inflammatory, autoimmune
- Toxic
- Trauma
- Vascular, especially diabetes
- Tumors

Axonal Health
PN Conduction Studies

- The integrity of the nerves are diagnosed by the following criteria:
  - Reaction time (latencies)
  - Velocities of the affected nerve
  - Amplitude of the captured waves
  - F-wave and H-reflex

  - F-wave looks at the most proximal segment of the nerve, including the root. The latencies will show if there is a delay at the spinal level of the particular nerve.
  - The Tibial H-reflex is considered to reflect the state of the S1 nerve root and its sensory component.
  - Both results are achieved by evoking the muscle/nerve through moderate stimulation.

Hereditary Neuropathies

- Hereditary motor and sensory
- HMSN
- Hereditary sensory with autonomic
- HSAN

Charcot-Marie-Tooth

- Hypertrophic form of HMSN 1
- Peroneal atrophy
- Partial chromosome duplication
  - Segmental trisomy
  - 17p11.2-p12
Guillian-Barré Syndrome

- Autoimmune?
- Follows
  - Infection
    - viral
    - Mycoplasma
  - Allergic reaction
- Demyelination
- Ascending paralysis
- Phrenic nerve involvement is life threatening

Guillian-Barré Syndrome

Shingles

Diabetic Neuropathy

For millions with diabetes, this feeling is all too real.
Diabetic Neuropathy
- Vascular
- Sorbitol
- Sensory

Traumatic Neuroma

Peripheral Nerve Tumors
- Actually nerve sheath tumors
  - Schwann cells
- Peripheral nerves
- Cranial nerves too
  - V & VIII

Schwannoma
- Schwann cell
- Encapsulated
- Peripheral nerves
- Unique histological pattern.
- Different from a neurofibroma

Neurofibromatosis
- Two types
- No capsule
- Type 1
  - Genetic
  - All over the body
  - Glioma of optic n. (rare)
  - Meningioma
  - Café-au-lait spots
  - Pigmented nodules of iris
Neurofibromatosis

- Like type 1, but with bilateral acoustic neuromas

Muscular Diseases

- Denervation
- Inherited
  - Enzyme deficiency
  - Structural protein
  - Mitochondria
- Inflammatory
  - Infectious
  - Drug related
  - Autoimmune
  - Motor endplate
  - Sarcomere
Muscle Fibers

<table>
<thead>
<tr>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Sustained force</td>
</tr>
<tr>
<td></td>
<td>Weight bearing</td>
</tr>
<tr>
<td>Enzyme content</td>
<td>NADH dark staining</td>
</tr>
<tr>
<td></td>
<td>ATPase pH 4.2 dark staining</td>
</tr>
<tr>
<td>Lipids</td>
<td>Abundant</td>
</tr>
<tr>
<td>Glycogen</td>
<td>Scar</td>
</tr>
<tr>
<td>Uptake</td>
<td>Myo, mitochondria</td>
</tr>
<tr>
<td>Physiologic</td>
<td>Slow twitch</td>
</tr>
<tr>
<td>Color</td>
<td>Red</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Solon (pigmen)</td>
</tr>
</tbody>
</table>

Fiber Types

- Duchenne Muscular Dystrophy

Denervation

- Atrophic changes of denervated fibers
- Hypertrophy of others

Myasthenia Gravis

- Autoimmune motor endplate disease
- Antibodies against acetylcholine receptor
- Decreased number of receptors
- Progressive weakness
- Thymic hyperplasia or tumor
- Other autoimmune diseases in 15%

Duchenne Muscular Dystrophy
Other Muscular Dystrophies

- Myotonic Dystrophy
  - Sustained contractions
  - Chromo 19
  - Botched Kinase
  - Trinucleotide repeats
    - CTG.........

Other Muscular Dystrophies

- Neural Tube Defects
  - Early in development
  - Folic acid
  - Encephalocele
  - Spina bifida
  - Anencephaly

Forebrain

- Volume
- Gyrus development
- Lissencephaly
- Microgyria
- Neuron migration
- Heterotopias
- Holoprosencephaly
- Corpus callosum

Posterior Fossa

- Dandy-Walker
  - Enlarged fossa
  - Absent vermis
  - Roofless 4th ventricle
- Arnold-Chiari
  - Small fossa
  - Downward extension of vermis
  - Hydrocephalus
Ependymal Canal Abnormalities

- Hydromyelia
- Syringomyelia