CEREBRAL EDEMA, RAISED INTRACRANIAL PRESSURE/HERNIATION, HYDROCEPHALUS

**Cerebral Edema**
- **Definition**
  - Excess fluid (increased volume) within or around the brain parenchyma
- **Pathogenesis**
  - **Vasogenic Edema** – *bleeding into the brain*
    - BBB fails, increased permeability = increased fluid into interstitium
    - Absence of Lymphatics + Compact Parenchyma = decreased resorption
    - Can be *localized* (Cancer) or *generalized* (hypoperfusion)
    - May involve the optic nerve and optic papillae (*papilledema*)
  - **Cytotoxic Edema** – *cells swell and die*
    - Increased intracellular fluid secondary to endothelial, glial, or neuronal cell membrane injury (cell swelling or cell lysis) in the *grey matter*
    - Hypoxia/Ischemia is the most common cause
  - **Interstitial** – CSF gets squeezed into brain
    - Occurs in *obstructive hydrocephalus*
    - Failure of the CSF-brain barrier (like Vasogenic, but has no protein)
  - **Osmotic** - *brain sucks the water up*
    - Caused by *excess water* intake, or *hyponatremia*
    - Fluid shifts into brain parenchyma to neutralize osmotic balance
- **Morphology**
  - Gyri flatten, sulci narrow, ventricles get compressed
  - With increased pressure, herniation may result (next topic)

**Raised ICP and Herniation**
- **Definition**
  - Mean ICP of CSF > 200mmH₂O with patient recumbent, occurring when expansion of the brain parenchyma exceeds compression of veins and CSF
- **Types of Herniation**
  - **Subfalcine Herniation = Cingulate Gyrus**
    - Unilateral expansion of the *cerebral hemisphere* displaces the *cingulate gyrus* under the *falk cerebri*, compressing pericollosal arteries (arteries of corpus callosum) and anterior cerebral circulation
  - **Transtentorial Herniation = Uncal**
    - Medial Aspect of *Temporal lobe* goes through the *tentorium cerebelli*
    - Compression of the 3rd CN = ipsilateral pupil dilation and eye paralysis
    - Compression of the *posterior cerebral artery* = infarct of visual cortex
    - Compression of the *contralateral peduncle* = ipsilateral hemiparesis (relative to the herniation); called *Kernohan’s Notch*
    - Hemorrhage in midbrain and pons may result (*Duret’s Hemorrhage*)
  - **Tonsilar Herniation = Cerebellum**
    - Fatal herniation of *cerebellum through the foramen magnum*
    - Compresses brainstem, leading to death
Path CNS Robbins Outline

**Hydrocephalus**

**Definition**
- Accumulation of excessive CSF within the ventricular system

**Pathogenesis**
- Increased production, normal outflow = **cancer of choroid plexus**
- Normal production, decreased outflow = **ventricular mass / obstruction**
- Normal production, decreased resorption = **arachnoid impairment**
- ↑ CSF within ventricles = expansion of ventricles + ↑ ICP

**Morphology and Type**
- If hydrocephalus occurs **before closure** of cranial vault = Big Head, ↑ ICP
- If hydrocephalus occurs **after closure** of cranial vault = Normal Head, ↑↑ ICP
- If all ventricles enlarged = **communicating hydrocephalus**
  - Due to a functional impairment of the arachnoid granulations
  - Subarachnoid bleed, meningitis, Pacchioni’s Granulation (agenesis)
- If not all ventricles enlarged = **noncommunicating hydrocephalus**
  - Due to a functional obstruction, usually hemorrhage or tumor
  - Ventrices proximal to obstruction are enlarged, distal are shrunken
  - Common in foramen of Monroe
- ↑ Volume of CSF from loss of parenchyma = **hydrocephalus ex vacuo**
  - Basically, CSF expands to fill in the space left by surgery/degeneration
  - Seen in tumor resection, Alzheimer’s and other degenerative diseases

<table>
<thead>
<tr>
<th>HERNIATION SYNDROMES</th>
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<tbody>
<tr>
<td><strong>Herniation</strong></td>
</tr>
<tr>
<td>Subfalcine</td>
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<tr>
<td>Transtentorial</td>
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<tr>
<td>Cerebellar</td>
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</table>

<table>
<thead>
<tr>
<th>HYDROCEPHALUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hydrocephalus</strong></td>
</tr>
<tr>
<td>Communicating</td>
</tr>
<tr>
<td>Non-Communicating</td>
</tr>
<tr>
<td>Ex Vacuo</td>
</tr>
</tbody>
</table>
MALFORMATIONS AND DEVELOPMENTAL DISEASES (Big Robbins page 1353, Baby page 678)

**Neural Tube Defects**

- **Definition**
  - Failure of the neural tube portion to close or a closed region reopening, the most common CNS malformations

- **Pathogenesis**
  - Uncertain, varying widely between groups; morphology is better characterized than the pathogenesis behind it
  - Screened for by looking for elevated α-fetoprotein in maternal serum
  - Linked to folate deficiency in initial weeks of gestation

- **Type and Morphology**
  - **Anencephaly**
    - Incompatible with life, occurring around day 28 gestation
    - Anterior neural tube defect; no brain = no life
    - Face intact, only brain does not form correctly
    - Replaced by area cerebrovasculosa, a flattened remnant of brain tissue
  - **Encephalocele**
    - Protrusion of brain through a defect in the skull
    - Protruding part is destroyed by mechanical disruption or ischemia
    - Incompatible with life when large, compatible when small
  - **Spina Bifida**
    - Most common neural tube defect; failure of closure of caudal aspect
    - Usually occurring in the lumbarsacral region

<table>
<thead>
<tr>
<th>Type</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculta</td>
<td>No spine closure, Tuft of hair, Spinal cord and CSF are normal</td>
</tr>
<tr>
<td>Meningocele</td>
<td>No spine closure, Meninges attach to skin, CSF enlarged and bulges, spinal cord normal</td>
</tr>
<tr>
<td>Myelomeningocele</td>
<td>No spine closure, Meninges attach to skin, CSF enlarged and bulges, spinal cord exposed</td>
</tr>
</tbody>
</table>

**Forebrain Abnormalities**

- **Lissencephaly/Agyria**
  - Genetically produced “smooth brain”
  - Thick cortex with the absence of cortical sulci
  - Grey matter made of 3 layers instead of normal 6
  - Leads to psychomotor retardation + seizures

- **Polymicrogyria**
  - Excessive Number or small Gyri; Poly = many, Micro = small, gyria = gyri
  - Grey matter is composed of 4 layers or less → retardation + seizures
  - Can be induced by localized tissue injury during neuronal migration
  - There are both genetic (don’t bother with the genes) and environmental (infection, hypoxia)
**Path CNS Robbins Outline**

- **Mega-** (rare) and **Micro-** (common) encephaly
  - Relates to the size of the head and brain, mega = big, micro = small
  - Assoc. with fetal alcohol syndrome, chromosome abnormalities, HIV
  - Migration dependent on chemical and physical signals that can go awry altering size and structure of brain parenchyma
    - Trapped bundles of migrating neurons = neuronal heterotopias

- **Holoprosencephaly**
  - Spectrum of malformations arising from the failure of cerebral hemispheres to separate = one giant lobe
  - Associated with Diabetic Mothers, Trisomy 13, and Sonic Hedge Hog
  - Severe forms (alobar holoprosencephaly) produce one ventricle, one nostril and one eye, while less severe forms (semilobar) produce a range up from the incompatible with life alobar to near normal function
  - May be genetic, X-linked, though there are sporadic forms

- **Agenesis of the Corpus Callosum**
  - Absence of white bundle fibers (the corpus callosum) connecting the hemispheres, replaced by adipose tissue
  - Mutation of L1 cell adhesion molecule (neuronal migration)
  - Can be radiologically demonstrated as bat-wing ventricles

**Posterior Fossa**

- **Arnold-Chiari Malformation**
  - Small posterior fossa + misshapen cerebellum + vermis of cerebellum extending through foramen magnum (Herniation)
  - Associated with hydrocephalus & lumbar myelomeningocele
  - Multiple types, Type II is the most common, and described here

- **Dandy-Walker Malformation**
  - Enlarged posterior fossa + absent cerebellar vermis + midline cyst
  - Cyst is the expanded 4th ventricle that usually is restricted by vermis
  - Dysplasia of brain stem is common, pt presents with mental retardation

**Syringomyelia + Hydromyelia**

- Either an expansion of the central canal of the cord (hydromyelia) or the formation of a cleft-like cavity in the inner portion of the cord (syringomyelia)
- Usually occurring in the cervical vertebrae these compress and damage nearby nerves, essentially eating a functional hole from the inside out
- Ass. with Aronld-Chiari Malformations, Traumatic Injuries, Spinal Tumors
  - Manifests itself in 20s and 30s
- Progressive loss of ALS (pain/temperature) with the preservation of DCMLS
  - Syringomyelia/Syrinx starts on the inside, eats its way out
  - Symptoms occur in a cape-like fashion
  - Destroys the anterior spinal commissure then ascending ALS fibers
Path CNS Robbins Outline

PERINATAL INJURY (Big Robbins Page 1356, Baby Robbins Page 679)

**Generalities**
- Major source of liability and law suits for OB/GYN
- Often a result of **neonatal** or **perinatal hypoxia** or **toxic exposure**, but also trauma
- Common cause of **cerebral palsy**

**Intraparenchymal Hemorrhage**/ **Germinal Matrix Hemorrhage** *(highest yield)*
- **Germinal Matrix** is present only in the **fetal** and **neonatal brain** around the ventricles
- Hypoxia/Ischemia causes bleeding in this region
- Divided into 4 grades depending on involvement of ventricles
  - **Grade 1**: Germinal Matrix Only
  - **Grade 2**: Germinal Matrix + Ventricles without Hydrocephalus / Dilation
  - **Grade 3**: Germinal Matrix + Ventricles with Hydrocephalus
  - **Grade 4**: Germinal Matrix + Ventricles + Parenchyma

**Periventricular Leukomalacia**
- Infarcts occurring in **white matter** near to the ventricles, especially in premature babies
- Chalky yellow plaques consisting of discrete regions of white matter necrosis and mineralization (calcification)

**Multicystic Encephalopathy**
- Extensive version of Periventricular Leukomalacia involving **both gray and white matter**
- Large cystic lesions throughout both hemispheres.
- Periventricular Leukomalacia = White Matter Only, with small lesions
- Multicystic Encephalopathy = Grey and Whit Matter, large cystic lesions

**Ulegyria**
- Ischemic injury occurring in the **cerebral cortex** resulting in thinned-out gliotic gyri termed ulegyria
- “Mushroom-Shaped” Gyri

**Status Marmoratus**
- Basal Ganglia and Thalamus suffer ischemic injury and result in neuronal loss and reactive gliosis.
- Later, with myelination, aberrant and irregular myelin formation gives rise to a marble-like appearance of the deep nuclei.
Path CNS Robbins Outline

TRAUMA (Big Robbins page 1356, Baby Robbins Page 679)

Generalities
- Anatomic location (encased in skull) and inability to regenerate make trauma very significant to the brain
- Severity is dependent on location; a small lesion of the forebrain may be asymptomatic while a small lesion on the brainstem is fatal
- Types of trauma include penetrating and blunt
- Presentation can vary; extreme damage can occur without obvious overt external signs of trauma, while a bone fracture that exposes brain material may be asymptomatic

Skull Fx
- Energy of trauma usually dissipates at suture lines; diastatic fx cross suture lines
- Displaced Skull Fx = movement of skull > thickness of the skull
- Falling while awake results in occipital damage, falling while unconscious = frontal
- A basal skull fx occurs from occiput or lateral damage (falling off a ladder)
  - Symptoms = Lower CN + Cervicomedullary Defects
  - Get battle sign (swelling and discoloration of the mastoid) and raccoon eyes (periorbital ecchymosis, aka double black-eyes)

Parenchymal Injuries
- Concussion
  - Clinical syndrome of altered mental status following a change in the momentum of the head (abrupt stop against a brick wall, for example)
  - Transient neurologic dysfunction with complete recovery
    - Loss of Consciousness, Loss of Reflexes, and a Persistent Amnesia
  - May or may not occur with actual parenchymal injuries; this is a syndrome, not a physical finding, in fact there are NO physical findings

Direct Parenchymal Injury
- Definition
  - Contusion or Laceration
  - Contusion is the transfer of kinetic energy resulting in a “brain bruise”
  - Laceration is the penetration of an object into the tissue
- Pathogenesis
  - Damage leads to edema; the crests of the gyri (distant blood supply) at greatest risk, particularly of the temporal and frontal lobes
  - Head is still and is struck = coup injury (on the same side as impact)
  - Head is moving and is struck = coup + contracoup injuries (on both sides to the impact; contracoup is diametrically opposite to coup injury).
  - If the head were moving in one direction, and is suddenly struck, the brain first strikes the side of the skull where the impact was, then is pole vaulted to the opposite side, where it strikes the skull again.
Path CNS Robbins Outline

- Diffuse Axonal Injury
  o Associated with Angular Acceleration even in the absence of impact (like in a car accident, where the patient doesn’t actually strike anything, but dies)
  o Diffuse Axonal swelling occurs within hours and persists
  o ↑ Microglia in related areas in cortex with subsequent degeneration of fibers
  o People die of this without contusions, lacerations, or fractures, associated with an immediate decreased level or loss of consciousness

**Traumatic Vascular Injury** medical hemorrhage comes in the next section

- Epidural
  o Dura is closely affixed to skull, representing a potential space between
  o Associated with the middle meningeal artery and temporal trauma
  o Smooth linear contour of hematoma that compresses brain
    ▪ “Lens” or “Ellipical” shape on CT scan
  o Usually a clinically lucid interval just prior to rapid progression to death

- Subdural
  o Between the dura and the arachnoid exists a real space
  o Associated with bridging veins and dural sinuses coursing through
  o Brain can move but the vessels are fixed; with trauma, brain shears the vessels and the patient bleeds
  o Superior sagital sinus of the elderly and demented are at highest risk
  o Hematoma hugs the brain matter, but does not enter subarachnoid space (isn’t between the sulci), called a crescent shaped hematoma

**Spinal Cord Trauma**
- Trauma usually involves damage or displacement of disc; lesion size and location determines symptoms
- **Above** lesion there is no deficit, though there is degeneration of ascending and descending fibers that course through the level of the lesion to the regions below
- **Below** lesion there will be upper motor neuron signs and absence of sensation
- **At the level of** lesion there is complete loss of everything
  o Hemisection (Brown-Sequard)
    ▪ DCMLS: Ipsilateral vibrational sense and proprioception lost
    ▪ ALS: Contralateral pain and temperature lost
    ▪ Motor: Ipsilateral upper motor neuron lesions

**Sequella of Brain Trauma**
- **Post Traumatic Hydrocephalus** from ventricular outflow obstruction (hemorrhage leads to compression of the ventricles)
- **Post Traumatic Dementia** comes from repeated, protracted injury showing diffuse axonal injury, thinning of corpus callosum, and positive Aβ fibers (Alzheimer’s fibers)
- **Others** include epilepsy, tumors, infections, and psychiatric disorders
  o Patients may have altered moods, personalities, and mental capacities
Path CNS Robbins Outline

CEREBROVASCULAR DISEASE (Big Robbins 1361, Baby Robbins 681)

---

Hypoxia, Ischemia + Infarction

- Generalities
  - Brain, being 1% body weight requires 15% of cardiac output and 20% of O₂
  - Autoregulation over wide range of pressures keeps flow @50ml/100g tissue
  - Highly aerobic without the capacity for storage or long-term survival
    - **Functional Hypoxia** = ↓O₂ in blood. Good perfusion, poor O₂ sats
    - **Ischemia** = ↓Flow, as in blockage or hypoperfusion, good sats, poor perfusion

- Hypotension, Hypoperfusion, and Low-Flow States = Global Cerebral Ischemia
  - **Definition**
    - Clinical outcome of a reduced blood flow below autoregulation ranges sufficient to deprive tissue of oxygenation resulting in diffuse hypoxia
  - **Pathogenesis**
    - Outcome is proportional to severity (level of perfusion and time unperfused) from mild post-ischemic perfusion to brain death
    - Hierarchy of cells (neurons die first) and regions (distal regions die first)
      - Hippocampus CA1 (Sommer’s), Purkinje of Cerebellum, and Pyramids of the cortex are most susceptible to hypoxia
    - With severe hypoperfusion there is widespread neuronal death, irrespective of location or vulnerability
      - **Coma** = + Reflexes, + Breathing, + EEG, - Consciousness
      - **Vegetative State** = + Reflexes, + Breathing, - EEG
      - **Brain Death** = - Reflexes, - Breathing, + Heartbeat
  - **Morphology** (not as important as it was in heart)

<table>
<thead>
<tr>
<th>Type</th>
<th>Time</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early Changes</td>
<td>12-24 hrs</td>
<td>Red Neurons</td>
</tr>
<tr>
<td>Subacute Changes</td>
<td>24hrs-2weeks</td>
<td>Necrosis, Macrophages, Vascular Proliferation, Gliosis</td>
</tr>
<tr>
<td>Repair</td>
<td>2weeks +</td>
<td>Removal of necrosis, gliosis completed, loss of CNS architecture</td>
</tr>
</tbody>
</table>

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Shock, Hypoperfusion, or Low-Flow State

---

Hypertensive Changes

- Lacunar Infarct
- Slit Hemorrhage
- HTN Dementia
  - ↑ Risk of Focal Ischemic

---

Thrombotic Embolic Arteritis

- Epidural
- Subdural
- Subarachnoid
- Intraparenchymal

---

Vascular Malformations

- AV Malformations
- Cavernous Hemangioma
- Telangiectasia

---

Cerebrovascular Disease

- Stroke
- Ischemic
- Hemorrhagic
- Global
- Focal
- Thrombotic Embolic Arteritis

---

Shock, Hypoperfusion, or Low-Flow State

---

Global

---

Focal

---

Thrombotic Embolic Arteritis

---

8 Owl Club Review Sheets
Path CNS Robbins Outline

- **Notes**
  - **Watershed Infarcts** are wedge-shaped infarcts @ regions distal to vascular supply, often between two areas of perfusion = “border zone”
  - This is a particular form of infarct associated with hypoperfusion (opposed to blockage or bleed)
  - Example is between the anterior and middle cerebral zones (NO collateral circulation), shown to the left, highlighted in purple

- **Infarction from Obstruction to Flow (Focal Cerebral Ischemia)**
  - **Definition**
    - Thrombotic or Embolic event that occludes the lumen to blood flow, depriving a particular region of tissue, supplied by that artery, of O₂
  - **Pathogenesis**
    - Something (See causes) causes a transient or permanent occlusion to blood flow
    - Cells can last 4-6 minutes before irreversible cell death
    - Changes in response to ischemia are the same as in all cells plus...
      - *Glutamate* activating **NMDA Channels** causing cell death from Ca²⁺ influx is unique to neurons
      - **Peripheral Grey matter** most susceptible
  - **Causes**
    - **Thrombosis**
      - Atherosclerosis (most common)
        - Majority of thrombotic events, similar pathology to an MI
        - Risk ↑ with **Hypertension** and **Diabetes**
        - Occurs at *carotid bifurcation, middle cerebral artery*, and *basilar artery*
      - Arteritis
        - Seen with infection with syphilis or TB (now rare)
        - Opportunistic infection with CMV, Aspergillus, Toxoplasmosis
        - Results in total permanent lumen occlusion by organisms
    - **Primary Angitis**
      - Inflammation + Giant Cells in small to large arteries
      - Improves with immunosuppression
      - Often diffuse focal ischemia, nonlocalized
    - **Cerebral Amyloid Angiopathy**
      - Alzheimer’s protein Aβ deposits in vessels
      - Weakens walls ↑risk of hemorrhage
      - ApoE gene has been linked to CAA and Alzheimer’s

Robbins lists literally every possible mechanism of arterial occlusion under “thrombosis” other than an embolus. I’m not sure how much of this detail is required (probably little, from the length of the block), but it was in Robbins, so it’s in here. See the end of this section, page 12, for tables of the really important stuff.
Path CNS Robbins Outline

- **Embolism**
  - Comes from the heart (MI, Endocarditis, atrial fibrillation), atheromatous emboli from plaques (carotid, aorta), paradoxical (R→Left Shunts) or from bone fractures (fat emboli during CPR)
  - Fat emboli are termed **shower emboli** because they disperse and go all over the place, resulting in multiple, diffuse infarcts
  - Emboli usually lodge at the **grey-white border**

  **Morphology**
  - There are two types of infarcts
    - **Hemorrhagic (Red)** = associated with emboli and reperfusion injury
    - **Nonhemorrhagic (white)** = associated with thrombosis or occlusion
  - Progression for gross and histology listed below (don’t memorize)

<table>
<thead>
<tr>
<th>TIME</th>
<th>CHARACTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12hrs</td>
<td>Nothing Visible</td>
</tr>
<tr>
<td>12-48hrs</td>
<td>Pale, White, Soft, Swollen, loss of difference between grey and white matter</td>
</tr>
<tr>
<td>2-10days</td>
<td>Gelatinous and Friable, Edema recedes revealing tissue survival</td>
</tr>
<tr>
<td>2-4 weeks</td>
<td>Liquification in cavity remnant, lined by a dark grey membrane</td>
</tr>
<tr>
<td>Years</td>
<td>Old cyst surrounded by gliotic scar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIME</th>
<th>CHARACTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 hrs</td>
<td>Nothing</td>
</tr>
<tr>
<td>12 hrs -48 hrs</td>
<td>Red Neurons, Cytotoxic/Vasogenic Edema, PMNSs increase</td>
</tr>
<tr>
<td>12-48 hrs</td>
<td>PMNs increase</td>
</tr>
<tr>
<td>48hrs - 3 weeks</td>
<td>Macrophages increase, PMNs decrease</td>
</tr>
<tr>
<td>Months</td>
<td>Gliotic layer lines cavity, nuclear and cytoplasmic enlargement recedes</td>
</tr>
</tbody>
</table>

- **Clinical**
  - Area fed by blood supply determines symptoms (see neuroscience)
  - Treat thrombosis with clot busters
  - Emboli (unless clots) must be physically removed
  - Treat within a 3 hr window to prevent reperfusion injury and potential for hemorrhage

**Intracranial Hemorrhage**

- **Intracerebral (Intraparenchymal) Hemorrhage**
  - **Definition**
    - Bleeding into the cerebral tissue from cerebral vasculature within the tissue. This is bleeding inside the brain
  - **Pathogenesis**
    - **Hypertension** is the most common cause of primary brain hemorrhage
      - Causes hyaline changes in arterioles, sometimes with frank necrotization of the arterioles
      - Vessel wall changes make the wall weaker and prone to rupture
Path CNS Robbins Outline

- **Charcot-Bouchard Microanuerysms**, minute hemorrhages caused by HTN, appear in regions supplied by small penetrating arteries, especially in the basal ganglia
- Systemic Coagulation disorders (cancer, vasculitis, A/V malformations, etc.) all encourage nontraumatic hemorrhage
- Trauma can, but is unlikely to cause, intraparenchymal hemorrhage

  o **Morphology**
  - Most commonly originates in the putamen, but can occur anywhere
  - Ganglionic Hemorrhage = basal ganglia + thalamus
  - Lobar Hemorrhage = Cerebral Lobes
  - Chronically, infarcts from hemorrhage look just like infarcts from obstruction (above table)
  - Acutely, there is a central clot with compressed parenchyma on gross as well as anoxic changes with edema on micro

  o **Clinical**
  - When large, it is devastating; when small, it can be slowly progressive
  - This is an arterial bleed, so pressure increases
  - Presents with headache, nausea, projectile vomiting, and focal lesions

- **Subarachnoid Hemorrhage + Ruptured Saccular Aneurysm**

  o **Definition**
  - Bleeding into and around the brain parenchyma (between pia and arachnoid layers) from cerebral vasculature.

  o **Pathogenesis**
  - The most common cause of subarachnoid hemorrhage is rupture of a berry saccular aneurysm
  - Associated with **Autosomal Dominant Polycystic Kidney Disease**, Vascular Collagen disorders like Marfan’s or Ehlers-Danlos, and coarctation of aorta
  - **Smoking** and **Hypertension** are predisposing factors
  - While the aneurysm is not present at birth, the genetic defect in the arteriolar wall is; all berry aneurysms come from some congenital defect

  o **Morphology**
  - Small outpocketing w/i Circle of Willis, usually in the anterior circulation
  - Brownish discoloration of surrounding tissue = previous hemorrhage
  - Adventitia is continuous, media and intima are thickened in the aneurysm but absent at the neck of the aneurysm

  o **Clinical**
  - Rupture is most common in the 4th and 5th decades of life
  - Completely spontaneous or associated with strain (having an orgasm or bearing down to force stool)
  - “Worst Headache of my Life”
  - 33% Recover, 33% Recur, 33% Die
Path CNS Robbins Outline

Vascular Malformations
- Types
  - **Arteriovenous Malformation**
    - Arteries connected to veins without an intervening capillary bed
    - Gross = Resemble tangled worms with prominent, pulsatile, high-flow AV shunt
    - Cause Seizure and Hemorrhage
  - **Cavernous Hemangioma**
    - Occur most commonly in the cerebellum, pons, subcortex
    - Distended, loosely organized, low-flow vasculature with thin collagenized walls devoid of intervening nervous tissue.
    - Cause seizure and hemorrhage
  - **Capillary Telangectasias**
    - Essentially, Hemangiomas with intervening brain parenchyma
    - Occur in the pons
    - Asymptomatic
  - **Venous Angiomas**
    - Aggregates of venous channels
    - Asymptomatic

<table>
<thead>
<tr>
<th>Malformation</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV Malformations</td>
<td>High Flow, No capillaries</td>
</tr>
<tr>
<td>Cavernous Hemangioma</td>
<td>Low Flow, No Brain Parenchyma</td>
</tr>
<tr>
<td>Capillary Telangectasias</td>
<td>Low Flow, Yes Brain Parenchyma</td>
</tr>
<tr>
<td>Venous Angiomas</td>
<td>Aggregates of Veins, Asymptomatic</td>
</tr>
</tbody>
</table>

Hypertensive Vascular Disease
- **Hypertensive Cerebral Hemorrhage**
  - Discussed above, intraparenchymal or subarachnoid
- **Lacunar Infarcts** — when HTN causes occlusion
  - HTN affects the blood vessels that supply the basal ganglia and white matter developing arteriolar sclerosis that may become occluded (just like regular vessels from the CV block)
  - Unique to the CNS is the formation of Lacunae
    - Small, Multiple, Cavitary infarcts
    - Thalamus, Internal Capsule, Deep White, Caudate, and Pons
    - Caused by occlusion of small penetrating arteries
- **Slit Hemorrhage** - when HTN causes hemorrhage
  - HTN leads to rupture of small penetrating arteries and resultant hemorrhage
  - Gross = Hemorrhages resolve (resorb), leaving slit like cavities
  - Micro = Focal tissue destruction, pigment-laden macrophages, gliosis
- **Hypertensive Encephalopathy**
  - HTN causes dementia, loss of function, basically “screwy-brain”
    - Cerebral dysfunction, headache, confusion, vomiting, coma
    - Rapid intervention required as this will not resolve
  - May be a product of vascular dementia (multi-infarct dementia)
    - Atherosclerosis, Emboli/Thrombus, Arteriosclerosis from HTN starts it
    - Diffuse focal infarcts cause nonlocalizing symptoms
    - Multiple infarcts lead to dementia, gait, and some focal defects

12 Owl Club Review Sheets
### CEREBROVASCULAR DISORDERS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Types</th>
<th>Key Concepts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral Infarcts</td>
<td>Thrombotic</td>
<td>Nonhemorrhagic/White/Pale Infarct, usually atherosclerosis complication</td>
</tr>
<tr>
<td>Embolic</td>
<td>Hemorrhagic/Red infarct; from heart, atherosclerotic plaque, L-&gt;R shunt, fat; middle cerebral artery most vulnerable</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>&quot;Watershed&quot; areas and deep cortical areas most affected</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hippocampus CA1 (Sommer’s sector), Cerebellar Purkinje, Cortical Pyramids</td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>Lacunar Infarcts; Basal ganglia most common</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemorrhages</th>
<th>Epidural</th>
<th>Almost always traumatic (temporal region). Middle Meningeal Artery ruptures. Lucid interval before loss of consciousness and death. Bleeds between dura and skull. Lens Shaped lesion on CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subdural</td>
<td>Usually traumatic. Rupture of bridging veins. Bleeds between dura and arachnoid. ↑ Risk with ↑ Age and ↑ Brain Atrophy Crescent Shaped lesion on CT</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid</td>
<td>Ruptured Berry Aneurysm, most commonly of the anterior communicating artery Associated with Marfan, Ehlers-Danlos, ADPKD, HTN, Smoking. Patient presents with the &quot;Worst headache of my life&quot;</td>
</tr>
<tr>
<td></td>
<td>Intracerebral</td>
<td>Common Causes: HTN, Trauma, Infarction. Bleeds under the Pia Most common location is the caudate or putamen a bleed of the lenticulate-striate</td>
</tr>
</tbody>
</table>

### CNS TRAUMA

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Syndrome that occurs with a change in momentum of the head (striking a rigid surface). Loss of consciousness, loss of reflexes, amnesia of event. No physical findings on the brain With recurrent events, the memory loss will get longer and longer, typical sports injury</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concussion</td>
<td>Bruising of brain from impact with the cranial vault; crests of frontal and temporal lobes most susceptible. Coup (site of injury) and contracoup (diametrically opposite) develop when the head is mobile at the time of impact. Can present with a plaque jaune (yellow lesion) indicative of an old injury</td>
</tr>
<tr>
<td>Contusion</td>
<td>Penetrating injury directly disturbs CNS tissue</td>
</tr>
<tr>
<td>Laceration</td>
<td>Injury to white matter due to angular momentum producing damage to axons at nodes of Ranvier. Poor prognosis, related to duration of coma</td>
</tr>
</tbody>
</table>

### HERNIATION SYNDROMES

<table>
<thead>
<tr>
<th>Herniation</th>
<th>Location</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subfalcine</td>
<td>Cingulate</td>
<td>Cingulate gyrus pushed under the falk cerebri and into the opposite hemisphere, compressing the anterior cerebral artery causing visual disturbances on the contralateral side</td>
</tr>
<tr>
<td>Transtentorial</td>
<td>Uncal</td>
<td>The uncus of temporal lobe displaced over the free edge of the tentorium cerebelli. In order of occurrence (severity of herniation): compression of 3rd CN causes pupillary dilation and paralysis; posterior cerebral artery causes infarcts of visual cortex; contralateral cerebral peduncle causes ipsilateral hemiparesis; shearing of the pons causes Duret’s Hemorrhage</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>Tonsilar</td>
<td>Displacement of the cerebellar tonsils down through foramen magnum. Compression of brain stem is fatal</td>
</tr>
</tbody>
</table>

Everything we’ve talked about since congenital malformations goes hand in hand, so is included here in a review. Tables taken from Kaplan’s Med Essentials with additions / editing.
INFECTION (Big Robbins 1369, Baby Robbins 684)

Routes of Spread
- Hematogenous = through the blood / sepsis
- Direct Implantation = trauma (including iatrogenically in surgery)
- Local Extension = sinusitis or osteomyelitis that spreads to brain
- PNS = extension from peripheral nerves that ascends into the CNS

Acute Meningitis
- Acute Pyogenic Meningitis = Bacterial
  - Definition
    - Inflammation of the meninges brought about by bacterial infection
  - Organisms
    - Neonates = E Coli, Group B Strep, Hib Vaccine eradicated Haemophilus
    - Adolescents = Neisseria Meningiditis with possible pandemic spread
    - Elderly = Strep Pneumo and Listeria Monocytogenes
    - Strep Pneumo most common overall
  - Clinical
    - Systemic signs of infection (fever, malaise, leukocytosis, etc)
    - Meningeal Signs = headache, photophobia, neck stiffness, confusion
    - Spinal Tap (Drummer explodes... it’s a joke, watch the movie)
      - Cloudy, purulent, increased pressure CSF with neutrophils
      - ↑↑ Protein, ↓↓ glucose
  - Morphology
    - Variable to organism + severity
    - You can see purulent exudates on the surface of the brain
    - There is a neutrophilic inflammatory infiltrate in the cerebrum, blood vessels or meninges

- Acute Aseptic Meningitis = Viral
  - Definition
    - A misnomer, “aseptic” is a clinical term for + meningeal signs without the ability to demonstrate causative organisms
  - Clinical
    - Lymphocytes instead of PMNs
    - Normal sugar, ↑ Protein, no purulence in CSF
    - Usually self-limiting with resolution is the norm
    - Usually an enterovirus: Echovirus, Coxsackievirus, Nonparalytic Polio
  - Morphology
    - No distinctive macroscopic or microscopic findings
  - Notes
    - True noninfectious meningitis exists and has been associated with NSAIDs and antibiotics, drug-induced aseptic meningitis
Path CNS Robbins Outline

Acute Focal Suppurative Infections

Brain Abscess
- Endocarditis, Infected Lungs (Bronchiectasis), and R→L shunts
- Discrete lesions with central liquifactive necrosis surrounded by a fibrous capsule found within brain parenchyma
- Presents as expanding intraparenchymal mass
- Causes focal symptoms depending on the area infected and necrosed + general symptoms of infection (headache, nausea, vomiting, seizures)
- Strep and Staph are the most common cause

- Subdural Empyema
  - Emergent collection of pus between dura and arachnoid
  - Infections of bone or hair spread to the dural space; arachnoid is spared
  - May produce a mass effect (compression) or spread into veins causing occlusion and infarction
  - With treatment, recovery is the rule, though mortality can be high

Epidural Abscess (also called Extradural)
- Slow growing infection between dura and skull
- Associated with osteomyelitis from another source (sinusitis or surgery)
- Neurosurgical emergency = drainage and antibiotics
- Pott’s Puffy Tumor = sinusitis that leads to osteomyelitis (board point)

Chronic Bacterial Meningocephalitis (chronic, atypical bacterial infections that affect the CNS)

- Tuberculosis
  - Found at the base of the brain
  - May cause a mass effect from the tuberculoma
  - May cause obliterative endarteritis leading to infarction
  - May cause arachnoid fibrosis leading to hydrocephalus
  - AIDS= same thing with ↓ host reaction and possible infection with MAC

- Neurosyphilis
  - Infection with Treponema Pallidum that goes untreated into its tertiary phase
  - Meningovascular Neurosyphilis= obliterative endarteritis usually occurring at the base of the brain or the spinal cord
  - Paretic Neurosyphilis = dementia from damage to the frontal lobe by treponema organisms (glial proliferation, gliosis, iron deposition)
  - Tabes Dorsalis = demyelination of the DCMLS, loss of proprioception, vibratory sense, and a complete ataxia

- Lyme Disease
  - Transmitted by Borellia Burgdorfi, can have neuro involvement
  - Facial Nerve Palsy, aseptic meningitis, mild encephalopathy

Viral Meningocephalitis (viral infections that affect the CNS)
- Each virus has its own tropism, but response and morphology is often similar. There is a mononuclear inflammatory infiltrate, perivascular involvement, and neurophagia (single neuron degeneration and death)
Path CNS Robbins Outline

- Arthropod Borne
  - Western/Eastern Equine, St Louis, La Crosse, West Nile
  - CSF is clear, ↑ protein, - Glucose, + Lymphocytes
  - Different prognosis dependent on organism

- Herpes Simplex 1 and 2
  - Affects infants (type II Herpes from vaginal exposure) and immunocompromised young adults (type I Herpes)
  - Alterations in mood, memory, and behavior
  - Affects the temporal lobe and orbital gyri with necrotizing hemorrhage
  - Cowdry Type A intranuclear inclusions, perinuclear halo, and nuclear molding

- Varicella Zoster
  - Childhood chicken pox have no CNS involvement
  - Virus hides in the dorsal root ganglion and descends, reactivated as shingles
  - Shingles = painfully sensitive rash that occupies one dermatome and does not cross the midline.
  - May cause encephalitis with numerous sharply confined lesions characterized by demyelination and necrosis

- CMV
  - Affects fetuses (resulting in microcephaly and calcified brains) and is the most common agent in the immunosuppressed/HIV
  - Intranuclear inclusions with a perinuclear halo inside singular enormous cells
  - Severe, necrotizing hemorrhage of ventricles and choroid plexus

- Polio
  - Usually causes a gastroenteritis; only sometimes does it invade the CNS and in still fewer cases does it cause paralysis associated with polio
  - Affects and destroys (neurophagia) the motor neurons of the ventral horn resulting in paralysis and atrophy, usually of the lower extremities
  - Only rarely does the paralysis occur; unlucky patients die of diaphragm paralysis

Rabies
- Severe encephalitis transmitted by the bite of an infected animal
- Bite introduces virus to the peripheral nerve, whereby the virus ascends to the CNS over 1-3 months. It colonizes the cerebellum and hippocampus
- First you get hypersensitivity to pain, then contracture with the inability to swallow (foaming at the mouth), and finally coma + death
- Negri bodies are pathognomonic for rabies; eosinophilic cytoplasmic inclusions in the pyramidal cells

- Progressive Multifocal Leukoencephalopathy (PML)
  - Associated with the JC virus in the presence of immunocompromise
  - Infests oligodendrocytes and leads to a progressive demyelination as the virus replaces the nucleus with a viral inclusion
  - Death results from diaphragmatic paralysis
Path CNS Robbins Outline

- **Subacute Sclerosing Panencephalitis**
  - Sequella of infection with **untreated measles**, usually in kids
  - Cognitive decline, spasticity of the limbs, seizures
  - Oligodendrocytic viral inclusions, demyelination, neurofibrillary tangles

**Fungal Infections**

- Seen only in the immunocompromised
- Involves **vasculitis** with **hemorrhagic infarcts** (Mucor + Aspergillus) or **Parenchymal Invasion** with **microabscesses** (Candida and Cryptococcus)
- Local Pandemics may also invade brain (Blastomycosis, Histoplasmosis, Coccidioides)
- **Mucor is associated with DKA** and is usually lethal once infection starts

<table>
<thead>
<tr>
<th>Organisms Brain</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthropod Borne</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Herpes</td>
<td>Meningitis and Encephalitis</td>
</tr>
<tr>
<td>Varicella Zoster</td>
<td>Descends from brain</td>
</tr>
<tr>
<td>HIV</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Poliovirus</td>
<td>Encephalitis and</td>
</tr>
<tr>
<td>Rabies</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>CMV</td>
<td>Encephalitis Microcephaly</td>
</tr>
<tr>
<td>JC Virus</td>
<td>Demyelination</td>
</tr>
<tr>
<td>Measles</td>
<td>SSPE</td>
</tr>
</tbody>
</table>

**MENINGITIS PRESENTATION**

<table>
<thead>
<tr>
<th>Meningitis</th>
<th>Cells</th>
<th>Glucose (mg/L)</th>
<th>Proteins (mg/dL)</th>
<th>Pressure (mmH₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>“None”</td>
<td>50-80</td>
<td>15-45</td>
<td>70-180</td>
</tr>
<tr>
<td>Bacterial</td>
<td>↑↑ Neutrophils</td>
<td>↓ (&lt;45)</td>
<td>↑ (&gt;50)</td>
<td>↑↑↑↑</td>
</tr>
<tr>
<td>Viral</td>
<td>↑ Lymphocytes</td>
<td>Normal</td>
<td>↑ (&gt;50)</td>
<td>↑↑</td>
</tr>
<tr>
<td>Fungal and Mycobacterial</td>
<td>↑ Lymphocytes</td>
<td>↓ (&lt;45)</td>
<td>↑ (&gt;50)</td>
<td>↑↑↑</td>
</tr>
</tbody>
</table>

Viral vs Fungal = Look at the Glucose, Bacterial vs Everything Else = Look at the Cells
# Path CNS Robbins Outline

## BACTERIAL INFECTIONS OF CNS

<table>
<thead>
<tr>
<th>Organism</th>
<th>Age Bracket</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group B Strep</strong></td>
<td>Neonates</td>
<td>Gram positive coccus, forms chains</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most common cause of neonatal meningitis</td>
</tr>
<tr>
<td><strong>E. Coli</strong></td>
<td>Neonates</td>
<td>Gram negative rod</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Second most common cause of neonatal meningitis</td>
</tr>
<tr>
<td><strong>Haemophilus</strong></td>
<td>Infants / kids</td>
<td>With the HiB Vaccine this has essentially been eradicated</td>
</tr>
<tr>
<td><strong>Listeria Monocytogenes</strong></td>
<td>Neonates and Elderly</td>
<td>Gram-positive rod with tumbling motility Found in cheese and hot dogs</td>
</tr>
<tr>
<td><strong>Strep Pneumoniae</strong></td>
<td>Elderly</td>
<td>Gram positive diplococcus colonizes the cerebral convexities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most common in elderly, most common in general</td>
</tr>
<tr>
<td><strong>Neisseria Meningiditis</strong></td>
<td>College Kids</td>
<td>Gram negative diplococcus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most common cause of meningitis in years 1 to 18</td>
</tr>
<tr>
<td><strong>Mycobacterium Tuberculosis</strong></td>
<td>Any Age with AIDS</td>
<td>Product of secondary TB causing tuberculoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May cause obliterative endarteritis, infarction, arachnoid fibrosis, and hydrocephalus, colonizing base of brain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AIDS patients have a decreased host reaction (no mass effect)</td>
</tr>
<tr>
<td><strong>Treponema Pallidum</strong></td>
<td>Any Sexually active age range</td>
<td>Spirochete that causes three types of overlapping infection Meningovascular = obliterative endarteritis Paretic = frontal lobe, dementia, &quot;crazy syphilis&quot; Tabes Dorsals = demyelination of DCMLS, loss of proprioception</td>
</tr>
</tbody>
</table>

## FUNGAL INFECTIONS OF CNS

<table>
<thead>
<tr>
<th>Organism</th>
<th>Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cryptococcus</strong></td>
<td>Parenchymal Invasion and microabscess</td>
<td>Occurs in immunocompromised host</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most common fungal meningitis in AIDS patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Budding yeast visible with India Ink</td>
</tr>
<tr>
<td><strong>Candida</strong></td>
<td>Parenchymal Invasion and microabscess</td>
<td></td>
</tr>
<tr>
<td><strong>Mucor</strong></td>
<td>Vasculitis and Hemorrhagic</td>
<td>Occurs in Diabetic Ketoacidosis</td>
</tr>
<tr>
<td><strong>Aspergillus</strong></td>
<td>Vasculitis and Hemorrhagic</td>
<td>Will show multiple hemorrhagic lesions</td>
</tr>
<tr>
<td><strong>Toxoplasmosis</strong></td>
<td></td>
<td>Pregnant women and patients with AIDS get this transmitted by cats through their feces (cat litter) Cerebral Abscess with ring enhancing lesions</td>
</tr>
</tbody>
</table>
Path CNS Robbins Outline

PRIONS (Big Robbins 1380, Baby Robbins 689)

**Transmissible Spongiform Encephalopathy** (Prion Disease)

- **Definition**
  - Transmissible spongiform encephalopathies that share a common etiology to abnormal forms of the prion protein (PrP) normally present in neurons

- **Pathogenesis**
  - PrP is the normal, stable form of the protein
  - A sporadic (slow rate), inherited (high rate), or infectious (highest rate) conformational change in the PrP α-helix to the β-Sheet “activates” protein.
  - “Activated” PrP, termed PrPsc, resists digestion and cooking, and, more importantly, facilitates cooperative conversion of normal PrP to PrPsc
    - SC is named for scraps, the disease in sheep where prions were found
  - There is a genetic link, on chromosome 20, PRNP gene, which ↑ risk of PrPsc formation, particularly in familial prion diseases; Met → Val @ codon 129
  - Accumulation of PrP causes pathology; how is uncertain

**Morphology**

- Macro = few findings, except atrophy in long-standing cases
- Micro = spongiform transformation (pathognomonic) of grey matter in the cerebral cortex, sometimes found in deep grey structures (caudate/putamen)
  - No inflammatory infiltrate
  - Unevenly distributed, varied in size, large, vacuoles in neuropil
  - Neuronal loss, reactive gliosis, cyst-like vacuoles in advanced cases
- Immuno = PrPsc Proteins

**Types and Clinical**

- Creutzfeldt-Jakob Disease (CJD; Kaplan says know only this one for Boards)
  - Mostly sporadic formation in mid 7th decade of life, though familial forms exist and iatrogenic transmission from corneal implants reported
  - Rapidly progressive dementia with death within 7 months
  - Subtle changes in memory and behavior precede the dementia (all cortical lesions) often with involuntary jerks (basal ganglia)
  - Pathogenesis described above is classic for CJD
- Variant Creutzfeldt-Jakob Disease (vCJD; Mad Cow Disease)
  - Met/Met Homozygous patients; no mutation in PRNP gene
  - Younger patients affected with a slower progression and clinical course
  - Symptoms are the same, autopsy findings are the same
  - Pandemic limited to UK, thought to be ingestion of infected meat
- Gerstmann-Strassler-Scheinker (GSS)
  - Slower progressive (like vCJD) but with a PNRP mutation (like CJD)
  - Spongiform + PrPsc plaques and neurofibrillary tangles
  - Death occurs in years, not months
- Fatal Familial Insomnia (FFI)
  - Prion disease with varying clinical course and symptoms
  - Initial stages = insomnia, followed by ataxia, stupor, coma, and death
  - Inherited, though mutation is not listed in Robbins
  - No spongiform, No cortical Lesions, instead, neuronal loss in thalamus

**Left/Blue = FFI; effects Thalamus**

**Right/Red = CJD; effects Cortex and Basal Ganglia**

Owl Club Review Sheets
DEMELINATING DISEASES (Big Robbins 1382, Baby Robbins 690)

**Multiple Sclerosis (Autoimmune)**
- **Definition**
  - An autoimmune demyelinating disorder characterized by distinct neurologic deficits separated by time, caused by white matter lesions separated in space

- **Pathogenesis**
  - There is a **genetic predisposition** linked to the **DR2 HLA haplotype**; the older model of geographic location is bunk
  - It is an **autoimmune response** against myelin antigens; much is unknown
  - **CD4 T_41s** start the process (IFN-y); Macrophages/CD8s do most of the damage
  - Demyelination occurs as a result of **macrophages**, though partial regeneration of function indicates **sparing of neurons/axons**
  - Loss of function stems from the **loss of axonal transmission**, not loss of axon

- **Morphology**
  - Gross = Sparing of grey matter, **yellow-tan plaques** that look like grey matter are Periventricular and scattered randomly throughout the white matter
  - Micro = **Active Plaques** (inflammatory cells + myelin degradation) and **inactive plaques** (no myelin and no inflammatory cells) share the preservation of axons together with astrocyte proliferation
  - **Shadow Plaques** are poorly circumscribed areas, thought to be either incomplete demyelination or **surviving oligodendrocytes remyelinating axons**
  - Most plaques do not remyelinate, though the absence of active inflammation permits partial recovery of function

- **Clinical**
  - Relatively common (1:1000); females twice as likely, onset between 20-50
  - **Relapsing and Remitting** disease with gradual partial recovery of neurologic function with a gradual loss of function
  - Symptoms are **highly variable**, though the optic nerve, spinal cord, and MLF are classically affected in full MS (**vision disturbances, extremity weakness**)
  - ↑ **Gamma Globulin in the CSF** (pathognomonic) from B cell proliferation

**Notes (variants)**
- Neuromyelitis Optica = Asians, Bilateral optic neuritis, relentlessly destructive
- Marburg MS = younger patients, fulminant in months, fatal in a year

**Guillain-Barre Syndrome** (Autoimmune)
- **Ascending Paralysis** begins in the lower limbs and distal extremities (toes and fingers first) that finishes with death from paralysis of the diaphragm
- Usually follows a **respiratory** or **GI illness** 1-3 weeks prior (anti GM1-gangliosides for C. Jejuni, Anti-GM2 Ganglioside for CMV infection)
- Axonal damage and nerve death result, though **recovery is possible** from live neurons being remyelinated (some pts have residual weakness)
Path CNS Robbins Outline

Acute Demyelinating Diseases (Virus Induced)
- Acute Disseminated Encephalomyelitis (ADEM)
  o Follows a viral infection, or rarely a viral immunization
  o Symptoms begin 1-2 weeks after infection, are global, resemble meningitis
  o 20% die, most fully recover
- Acute Necrotizing Hemorrhagic Encephalomyelitis (ANHE)
  o Follows an upper respiratory tract infection in kids and adolescents
  o Fatal in many patients; some live without permanent complications
  o Macro = Grayish discoloration of white matter; multiple global lesions that may be so large as to become confluent
  o Micro = destruction of blood vessels, perivenular demyelination, inflammatory infiltrate and hemorrhage
  o Represents a hyperacute variant of ADEM

Metabolic Induced Demyelination
- Central Pontine Myelinosis
  o Loss of myelin, preservation of axons, bilaterally symmetrical in basis pontis
  o Causes rapidly evolving quadriplegia
  o Seen with rapid correction of Hypo Na, though EtOH, electrolytes, and osmolar imbalances have been implicated
- Subacute Combined Degeneration (B12 deficiency)
  o Seen commonly in long-term strict vegans or those with autoantibodies to intrinsic factor (pernicious anemia)
  o Requires decades to deplete B12 stores; B12 comes from animal products
  o Initial loss of vibration and Proprioception ending in spastic paraplegia, ataxia and impairment of sensory modalities
  o Usually targets the Dorsal Columns Medial Lemniscus System and Cortico-Spinal Tract in the thoracic and cervical region, evidenced by distention then degeneration of myelin sheaths and loss of axons

DYSMYELINATING DISEASES (Xiong’s classification, found in “Degenerative Diseases” in Robbins)

Metachromatic Leukodystrophy
- Pathogenesis
  o Autosomal Recessive deficiency in Arylsulfatase
  o Accumulation of the myelin lipid “sulfatide” kills oligodendrocytes and Schwann cells, causing loss of myelin.
- Clinical
  o Childhood disease that is asymptomatic until age 1 or 2
  o Progressive peripheral neuropathy, blindness, retardation, adult dementia
- Morphology
  o Acid Cresyl Violet stains Sulfatide Brown (this the name metachromatic)
  o Diffuse loss of myelin in white matter, sparing of subcortical areas
  o Accumulation of sulfatide in oligodendrocytes

Dr. Xiong did not differentiate between the two types, though Robbins did. ANHE is just a worse version of ADEM

This image, where you can see “3 layers” a yellow-tan, an obvious white, and a brown is Tulane’s image for this disease. Know this one

21 Owl Club Review Sheets
Path CNS Robbins Outline

**Adrenoleukodystrophy**
- **Pathogenesis**
  - X-linked mutation in the peroxisome protein ALD, a mitochondrial disease
  - Without ALD, VLCFA cannot be transported into peroxisome and accumulates
  - VLCFA causes myelin breakdown, and adrenal atrophy
- **Clinical**
  - Adrenal insufficiency first, followed by neurologic symptoms
  - Death occurs in a few years from onset of neurologic symptoms
- **Morphology**
  - Diffuse Myelin Loss with Lipid-laden Macrophages
  - EM shows trilamellar membranes with VLCFA cholesterol esters in Schwann cells and adrenal cortical cells

**Krabbe’s Disease**
- **Pathogenesis**
  - Autosomal Recessive deficiency of lysosomal beta-galactocerebrosidase
  - Accumulation of the toxic psychosine, a side metabolite of galactosylsphingosine which is normally not produced
  - Psychosine is toxic to neurons and myelin
- **Clinical**
  - Children = seizures, feeding problems, vision problems, death
  - Adult = limb weakness, spastic parapersis, vision problems, dementia
- **Morphology**
  - Cerebral Atrophy with gray discoloration of white matter
  - There is a symmetrical and confluent loss of myelin
  - Globoid Cell Leukodystrophy = globoid cell proliferation staining Sudan +

---

**Diseases of Myelin**

- **Demyelinating**
  - Autoimmune
    - Multiple Sclerosis
    - Guillan-Barre
  - Viral
    - ADEM
    - ANHE
  - Metabolism
    - Central Pontine Myelinosisis
    - Subacute Combined Degeneration

- **Dysmelinating**
  - Metachromatic Leukodystrophy
  - Adrenoleukodystrophy
  - Krabbe’s Disease
<table>
<thead>
<tr>
<th>Disease</th>
<th>Type</th>
<th>Symptoms</th>
<th>Morphology</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>Autoimmune</td>
<td>Separated in space and time. Vision loss (optic neuritis). Internuclear</td>
<td>Well-circumscribed demyelinated plaques – active, inactive, and shadow</td>
<td>Common (1:1000)</td>
</tr>
<tr>
<td></td>
<td>Demyelinating</td>
<td>Ophthalmoplegia (MLF) Motor and Sensory Defects</td>
<td>Periventricular Graying can be seen. Large demyelinated plaques appear near</td>
<td>Women twice as likely than men Onset in 30s and 40s</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the ventricles so that white matter looks like grey matter (autopsy)</td>
<td>Relapsing-Remitting Course</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increased IgG in CSF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Guillian Barre</td>
<td>Autoimmune</td>
<td>Ascending Paralysis following an infection, with potential recovery and</td>
<td>Anti-GM1 or GM2 ganglioside on IF, diffuse myelin thinning or loss.</td>
<td>2/3rds had a respiratory infection prior. Elevated CSF protein with</td>
</tr>
<tr>
<td></td>
<td>Demyelinating</td>
<td>potential fatality and potential fatality</td>
<td></td>
<td>normal glucose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ADEM) Acute Disseminating</td>
<td>Post-viral</td>
<td>Headache, Lethargy, Coma</td>
<td>Greyish discoloration without hemorrhage</td>
<td>Follows viral infection beginning 1-2 weeks after. 20% die, most fully</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>Demyelinating</td>
<td></td>
<td></td>
<td>recover</td>
</tr>
<tr>
<td>Acute Necrotizing Hemorrhage</td>
<td>Post-Viral</td>
<td>Fulminant version of ADEM</td>
<td>Greyish discoloration with damaged blood vessels and hemorrhage</td>
<td>Is usually fatal. Represents the nastier version of ADEM. Occurs in</td>
</tr>
<tr>
<td>Encephalomyelitis</td>
<td>Demyelinating</td>
<td></td>
<td></td>
<td>kids and adolescents</td>
</tr>
<tr>
<td>Central Pontine Myelinolysis</td>
<td>Metabolic</td>
<td>Spastic Quadraparesis Mental changes, may produce the “locked-in”</td>
<td>Bilateral, symmetrical demyelination of white matter in the basis ponti</td>
<td>Seen in alcoholics, hyperosmolar states, or electrolyte imbalances.</td>
</tr>
<tr>
<td></td>
<td>Demyelinating</td>
<td>syndrome; Often Fatal</td>
<td></td>
<td>Probably induced by aggressive correction of hyponatremia (Na)</td>
</tr>
<tr>
<td>Subacute Combined Degeneration</td>
<td>Metabolic</td>
<td>Loss of vibrational sense and Proprioception followed by spastic</td>
<td>Degeneration of the myelin in the DCMLS. Severe cases may involve entire</td>
<td>Strict Vegans and pernicious anemia; requires decades to deplete B12</td>
</tr>
<tr>
<td></td>
<td>Demyelinating</td>
<td>paralysis. Irreversible</td>
<td>cord circumference</td>
<td>stores.</td>
</tr>
<tr>
<td>Metachromatic Leukodystrophy</td>
<td>In-born</td>
<td>Progressive peripheral neuropathy, blindness, retardation, childhood</td>
<td>Diffuse loss of myelin in white matter, accumulation of sulfatide in</td>
<td>Autosomal recessive disease caused by arylsulfatase deficiency</td>
</tr>
<tr>
<td></td>
<td>Dysmyelinating</td>
<td>onset, adult dementia</td>
<td>oligodendrocytes giving a “marbled” appearance to the parenchyma</td>
<td></td>
</tr>
<tr>
<td>Adreno-leukodystrophy</td>
<td>In-Born</td>
<td>Adrenal Insufficiency begins in childhood Neurologic manifestations</td>
<td>Diffuse myelin loss with lipid-laden histiocytes. White matter atrophy.</td>
<td>X-linked mutation for the peroxisome protein ALD. Without ALD, VLCFA</td>
</tr>
<tr>
<td></td>
<td>Dysmyelinating</td>
<td>(behavior, vision, spasticity, ataxia) occur later. Death within a few</td>
<td>EM shows trilamellar membranes with VLCFA-cholesterol esters</td>
<td>accumulates and is toxic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>years of neurologic symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Krabbe’s Disease</td>
<td>In-Born</td>
<td>Childhood form = seizures, retardation, vision problems and death. Adult</td>
<td>Cerebral atrophy, gray discoloration of white matter and peripheral</td>
<td>Autosomal Recessive deficiency of Beta-Galactosidase causing</td>
</tr>
<tr>
<td></td>
<td>Dysmyelinating</td>
<td>form = limb weakness, visual problems, dementia</td>
<td>nerves, globoid cell proliferation that is sudan positive</td>
<td>accumulation of psychine</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
DEGENERATIVE DISEASES (Big Robbins 1385, Baby Robbins 691)

Alzheimer’s – degeneration of the Cerebral Cortex!!!!
- Definition
  - A progressive degenerative disease of the cerebral cortex caused by accumulation of abnormal proteins, demonstrable as plaques and tangles
- Pathogenesis
  - Amyloid Precursor Protein (APP) and Aβ
    - APP is normally present in astrocytes and glia, and has 3 sites of secretase activity (α, β, and γ)
    - Cleavage by α-secretase = normal soluble protein, Aβ = 26 amino acids
    - Cleavage by γ-secretase = separation of cytoplasmic (Carboxy-terminus) unit and Aβ unit; has no relevance to Alzheimer’s (it’s the same site in the good and the bad protein)
    - Cleavage by β-secretase = insoluble protein, Aβ42 = 42 amino acids
      - Larger, insoluble protein forms extracellular aggregates called plaques, or fibrils
      - Stains positive for Congo red
      - Are considered to be directly neurotoxic
  - Presenilin-1
    - Has γ-secretase activity
    - Aberrant activation of Presenilin-1 may also contribute to formation of Aβ42 and the generation of plaques
  - Genetic Components

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Gene</th>
<th>Mutations/Alleles</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Amyloid precursor protein (APP)</td>
<td>Single missense mutations</td>
<td>Early-onset FAD Increased Aβ production</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Double missense mutation Trisomy 21 (gene dosage effect)</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Presenilin-1 (PS1)</td>
<td>Missense mutations Splice site mutations</td>
<td>Early-onset FAD Increased Aβ production</td>
</tr>
<tr>
<td>1</td>
<td>Presenilin-2 (PS2)</td>
<td>Missense mutations</td>
<td>Early-onset FAD Increased Aβ production</td>
</tr>
<tr>
<td>19</td>
<td>Apolipoprotein E (ApoE)</td>
<td>Allele ε4 = risk</td>
<td>Increased risk of development of AD Decreased age at onset of AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allele ε3 = normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allele ε2 = protective</td>
<td></td>
</tr>
</tbody>
</table>
Path CNS Robbins Outline

- **Clinical**
  - Insidious onset, time course is approximately 10 years from onset to death
  - **Cerebral Atrophy** is seen, severity ↑ with passage of time
  - **Memory** (first short term then long-term), logic and mathematics, motor skills (incontinence, walking, fine motor) will all be lost
  - Death usually results from a secondary source (**pneumonia**)
  - Treated now with **Acetyl-Choline Agonists** though this only prolongs the inevitable, giving the patient more healthy time.

- **Morphology**
  - **Gross**
    - **Cortical Atrophy** especially in the frontal, temporal, and parietal lobes
    - **Widening of sulci** (more space between gyri)
    - Compensatory ventricular enlargement (**hydrocephalus ex vacuo**)
  - **Micro**
    - These are not specific for Alzheimer’s, though is almost always present
    - **Neuritic Plaques**
      - Most often in the hippocampus and amygdala
      - Dilated, tortuous, silver staining neuritic processes (**dystrophic neurites**) surrounding a **central Amyloid core** (**Aβ42**)
      - Stains positive for Congo Red, as all Amyloid does
    - **Neurofibrillary Tangles**
      - Found in the **cytoplasm** of cortical pyramidal neurons
      - Caused by a **hyperphosphorylated state** of a microtubule-associated protein called tau
      - Tau aggregates while microtubules fall apart; tau aggregates are insoluble, producing “ghost tangles” that persist after neuron dies, in the classic **flame shape** seen on Silver Stain and H&E
    - **Granulovacular Degeneration**
      - Just what it sounds like; there are vacuoles within the neurons in a granular pattern.
      - Everyone mentions “**Hirono Lesions**” as a classic finding, but no one defines it nor gives me a picture
    - **Diagnosis**
      - Diagnosis is made on morphological characteristics only after death; clinical symptoms are highly suggestive of the disease and therefore treatment algorithms

---

Take away is that there are 4 classic lesions: Plaques, Tangles, Granulovacular Degeneration and Hirono bodies, all found at autopsy following someone with cerebral atrophy and dementia. By the time hydrocephalus ex vacuo is noticeable, the patient is deep into their dementia, too deep to be helped.
Path CNS Robbins Outline

Cerebral Degeneration Linked with Tau Pathology

- Frontotemporal Dementia with Chromosome 17
  - Dementia accompanied by frontal and temporal cerebral atrophy
  - Specifically linked to a variety of mutations in the microtubule associated protein (MAP) stabilizing protein called tau, caused by mutations in the tau gene
  - There may be 4 repeat tau mutations (introns), or mutations within the actual microtubular association (exons)

- Pick Disease !!!!!
  - Rare, distinct, progressive dementia found in sporadic cases
  - Frontopolar Atrophy is severe, distinguishable from the general cerebral atrophy of Alzheimer’s, accompanied in particular by language involvement
  - Neuronal loss is most sever in the outer 3 layers of cortex
  - Pick Bodies, which resemble neurofibrillary tangles of Alzheimer’s, stain brilliantly with silver but not on H&E; after neuronal death they are cleared (unlike in Alzheimer’s); pick bodies differentiate Tau from Alzheimer’s

- Progressive Supranuclear Palsy (PSP)
  - No mutations in tau have been identified; an uncertain link to a specific tau haplotype does increase risk for development of disease (just like CBD, below)
  - Widespread loss of neurons in midbrain structures (globus, subththalamic nucleus, substantia nigra, cerebellum)
  - Trunchal rigidity, ocular disturbances, abnormal speech, and nuchal dystonia describe this disease that causes progressive dementia and is fatal within 5-7 years. Vignette’s classically have loss of vertical gaze and ataxia in and adult
  - Can also be considered a degeneration of basal ganglia disease (below)

- Corticobasal Degneration (CBD) (nothing in bold)
  - No mutations in tau have been identified; an uncertain link to a specific tau haplotype does increase risk for development of disease (just like PSP, above)
  - Extrapyramidal rigidity, asymmetric jerking movements (alien hand), with dementia
  - Cortical Atrophy of motor, premotor, and sensory regions, in particular
  - Tau-positive structures, astrocyte plaques, tau-positive intrneuronal inclusions, and neuronal loss are the most distinguishing characteristic for diagnosis
  - Can also be considered a degeneration of basal ganglia disease (below)

Cerebral Dementia not linked with Tau (nothing in bold)

- Vascular Dementia
  - Typically present in a stepwise degradation rather than a gradual decline
  - Are associated with strategic infarcts, which allow for significant loss of function
  - Others are caused by small infarcts (lacunar infarcts, hypoperfusion), or diffuse white matter injury (as in CADASIL)
  - Vasculitis is a particular cause of vascular dementia that causes occlusion, stroke, and dementia, though responds to therapy, unlike many of the irreversible conditions
Degenerative Disease of the Brainstem and Basal Ganglia

- **Parkinsonism** (not Parkinson’s Disease)
  - Caused by damage to the nigrostriatal dopaminergic system
  - Characterized by *diminished facial expression*, stooped posture, *slow movements*, *cog-wheel rigidity*, *pill-rolling tremor*, and *festinating gait* (progressively shortened, accelerated steps, aka “Shuffling”)

- **Parkinson’s Disease !!!!!!**
  - **Definition**
    - Presence and progression of parkinsonism without a toxic or underlying defect
  - **Pathogenesis**
    - Loss of the substantia nigra neurons projecting to striatum; the disease is *primarily attributed to the decrease or absence of dopamine in the striatum*
    - ↓ substantia nigra neurons = ↓ dopamine = ↓ movement ability
    - Some link, but not a strong one, to α-synuclein gene mutation/duplication or mutations in parkin; no causal mutation has been identified
    - You can give it to yourself by trying to make elicit drugs (MPTP toxicity)
  - **Morphology**
    - **Pallor of the substantia nigra** and locus ceruleus
    - Pallor is the result of loss of a significant portion of catecholamine neurons
    - **Lewy Bodies** are filamentous projections of the protein α-synuclein or ubiquitin, present in surviving neurons and can be found in cortex (cause dementia)
  - **Clinical**
    - Progressive disease that is diagnosed based on its clinical symptoms (parkinsonism) and at autopsy by the presence of Lewy Bodies that may be associated with dementia, especially in advancing age
    - Treated with L-DOPA, a dopamine precursor that provides the missing dopamine; with disease progression, the effectiveness of treatment decreases
    - **Deep brain stimulating electrode** into the striatum is the next treatment option
    - Finally, fetal mesenchymal tissue inserted into the substantia nigra has shown promising initial results.

- **Multiple System Atrophy (MSA)**
  - Overarching nomenclature that now includes 5 previously distinct diseases
  - All linked to α-synuclein inclusions but without mutations of α-synuclein as in parkinson’s disease
  - Degeneration of *midbrain structures* (cerebellum, pons, peduncles) and the presence of *α-synuclein inclusions* are characteristic morphological features
  - Causes both *parkinsonism* and *autonomic dysfunction* (particularly orthostatic hypotension); specific diseases, when occurring in isolation, have specific names, but most often there is a combination of symptomatology that prompts the use of the MSA heading
- **Huntingtons !!!!!**
  - **Definition**
    - This is a degenerative disease of the caudate and putamen ("Striate neurons") caused by an *autosomal dominant* inheritance of a *trinucleotide repeat* (CAG) in the **Huntington gene** (chromosome 4) which results in **chorea** and **dementia** and which demonstrates **anticipation**.
  - **Pathogenesis**
    - There is a **loss of inhibitory signal on motor output** that permits inappropriate, spastic movement realized as a jerky chorea
    - **Mechanism**
      - Subthalamic Nucleus = Final output and Inhibition of movement; Striate = inhibitory to the Globus Pallidus; GP = Inhibitory to SN
      - ↓ Striate signal = ↓ Inhibition of GP = ↑ GP signal = ↑ inhibition of SN = ↓ SN signal = ↓ inhibition of movement = ↑ motor output
    - **Chromosome 4 codes for Huntington**, for which the coding region has a **trinucleotide repeat (CAG / glutamine)**; the more repeats, the worse the disease gets and the earlier its onset
    - Huntington is a necessary protein, but what it does we aren’t sure
  - **Morphology**
    - **Caudate nucleus is dramatically atrophied**, with accompanying atrophy of the putamen, cortex, and hydrocephalus ex vacuo of the 3rd ventricle
    - Significant neuronal loss, especially of the **GABA** producing neurons of caudate
    - Direct relationship between the severity of the disease and severity of neuron loss
  - **Clinical**
    - Commonly seen in the 4th and 5th decade of life; motor problems (the characteristic **chorea**) precede dementia
    - Death in 10-15 years from symptom onset
    - Genetic screening for trinucleotide repeat (triplet) possible
    - Genetics shows **anticipation** = generation of more repeats in gametogenesis; it gets worse with each generation even without pairing with another Huntington’s carrier

**Spinocerebellar Degenerations**
- **Spinocerebellar Ataxia**
  - There are many different types of spinocerebellar ataxias based on inheritance patterns
  - All involve some degeneration of the cerebellum (**progressive ataxia**), brainstem, spinal cord, and peripheral nerves.
  - There are 20 diseases marked “SCA#” that you just do not have to know, but you must know the two particular kinds, which continue below
- Friedreich’s Ataxia

  o Pathogenesis
    - **Autosomal Recessive**, GAA trinucleotide repeat in the **FXN gene** coding for **frataxin** on chromosome 9
    - Frataxin is a mitochondrial matrix protein so shows morphological and clinical features of both degenerative diseases and metabolic encephalopathies
  
  o Morphology
    - There is a degeneration of the **DCMLS, Dorsal Roots, Cerebellar Peduncles and atrophy of peripheral nerves**
    - There is loss of **both neurons and axons** from all elements of nervous system as well as **myocytes** in the heart
  
  o Clinical
    - Effects **children** in first decade of life, **wheelchair bound by 5**
    - Loss of vibratory sense and proprioception (DCMLS) but occasional loss of pain and temp (ALS) accompanies **absent deep tendon reflex**
    - High incidence of **cardiac disease** (CHF and Arrhythmias)

- Ataxia-Telangiectasia

  o Pathogenesis
    - **Autosomal Recessive** disease caused by mutation of **cell cycle protein ATM** on chromosome 11, which normally orchestrates responses to double-stranded DNA breaks
  
  o Morphology
    - CNS Similar to Freidrich’s with preference for the **cerebellum**
    - Telangiectasias (vessel proliferation and dilation) are present in abundance on skin of the face, arms, torso as well as within the **conjunctiva of the eye**
    - Nuclei of cells in many organs show **bizarre nuclear enlargement**
    - Lymph Nodes, Thymus, Gonads are hypoplastic
  
  o Clinical
    - Relentlessly progressive with **death in 2nd decade of life**
    - Immunocompromised from hypoplastic Thymus/Lymph Nodes
    - Many develop **lymphoid malignant disease** (Leukemia/Lymphoma)

Degenerative Diseases of Motor Neurons

- Targets and Affects
  
  o **Lower Motor Neurons** are found in the anterior/ventral horns of spinal cord. Lesions here result in **atrophy, areflexia, and weakness leading to paralysis**
  
  o **Upper Motor Neurons** are found along the length of the spinal cord and into the brain. Lesions here induce **hyprereflexia, spasticity, and babinksi**
- **Amyotrophic Lateral Sclerosis!!!! (ALS or Lou-Gehrig Disease)**
  - **Definition**
    - Autosomal dominant mutation of superoxide dismutase resulting in degeneration of both lower and upper motor neurons with NO sensory deficits.
  - **Pathogenesis**
    - Autosomal dominant mutation of superoxide dismutase; chromo 21
    - Toxic product of superoxide dismutase destroys both neurons/axons and glia/myelin
    - Degeneration of upper motor neurons and lower motor neurons results in combined defects, ultimately progressive to paralysis
    - Death is a result of diaphragmatic paralysis
  - **Morphology**
    - Degeneration and atrophy of anterior horn and gross demyelination of spinal cord corticospinal tracts
    - Atrophied Muscles of affected tracts
  - **Clinical**
    - Related to neuronal involvement, either upper or lower, all ending in lower motor symptoms, sensory systems are spared
    - Early = weakness of hands, cramping, inability to perform fine motor
    - Mid = atrophy of muscles, weakness, spasticity (upper + lower)
    - Late = complete paralysis (lower predominates)

- **Bulbospinal Atrophy (Kennedy Syndrome)**
  - X-linked Adult onset disease characterized by distal limb amyotrophy and bulbar signs such as fasciculations of the tongue.
  - Caused by an expansion of trinucleotide CAG repeat in the androgen receptor
  - Causes androgen insensitivity, gynecomastia, and testicular atrophy

**Vitamin Deficiencies**
- **Vitamin B12** (see page 20)
  - Vegans get degeneration of the sensation and possible spastic paralysis
- **Vitamin B1** (Thiamine Deficiency)
  - Long term deficiency may produce a slowly progressive beriberi
  - Commonly encountered in alcoholics
  - Some patients may develop the acute, reversible disease with psychotic symptoms termed Weirnicke’s Encephalopathy
  - If Weirnicke’s persists, the chronic, irreversible disease of memory loss and confabulation sets in, termed Korsakoff Syndrome

**Mitochondrial, Toxin, and Metabolic Diseases** of “Degenerative Diseases” were not included in our syllabus, so are not included here. Summary of critical diseases included on next page.
### Path CNS Robbins Outline

#### DEGENERATIVE DISEASE

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetics</th>
<th>Path</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pick’s</td>
<td>None given</td>
<td>Tau pathology → Pick Bodies</td>
<td>Frontotemporal Degeneration, Language Disturbance, Pick Cells/Pick Bodies pathognomonic for Pick vs Alzheimer’s</td>
</tr>
<tr>
<td>Parkinson’s</td>
<td>Parkin Gene, α-synuclein Gene</td>
<td>Lewy Bodies = inclusions of synuclein protein; loss of substantia nigra and dopaminergic “go” signal</td>
<td>Pill-rolling tremor, mask-like face, difficulty initiating movement, treated with L-Dopa and Deep Brain Stimulation</td>
</tr>
<tr>
<td>Huntington’s</td>
<td>Autosomal Dominant CAG repeats in Huntington gene; ch 4</td>
<td>Loss of inhibitor GABA neurons from Caudate and Putamen, end result = unrestrained movement</td>
<td>Chorea, memory loss, dementia. Demonstrates anticipation</td>
</tr>
<tr>
<td>Freidrich’s Ataxia</td>
<td>Autosomal Recessive GAA repeats in FXN gene coding the protein frataxin; ch 9</td>
<td>Mitochondrial matrix protein abnormalities</td>
<td>Spinal Ataxia, degeneration of spinal cord, dorsal roots, posterior column, cerebellar peduncles, begins in childhood</td>
</tr>
<tr>
<td>Ataxia-Telangiectasia</td>
<td>Unknown</td>
<td>Poorly characterized</td>
<td>Spinal Ataxia, Immunodeficiency, Vasodilation</td>
</tr>
<tr>
<td>Amyotrophic Lateral Sclerosis</td>
<td>Autosomal Dominant Superoxide Dismutase Gene; ch 21</td>
<td>Superoxide Dismutase mutation is toxic to lower and upper motor neurons</td>
<td>Upper: Hyprreflexia, babinski, spasticity Lower: Atrophy, areflexia, weakness, paralysis</td>
</tr>
<tr>
<td>B1 Deficiency</td>
<td>None, this is a deficiency of diet</td>
<td>B1 (Thiamine) Deficiency results in Beriberi. Acute, Reversible Weirnicke’s may appear, giving way to chronic, irreversible Korsakoff</td>
<td>Common in alcoholics. Weirnicke’s is a disease of psychosis and eye problems. Korsakoff is memory loss and confabulation</td>
</tr>
<tr>
<td>B12 Deficiency</td>
<td>None, this is a deficiency of diet</td>
<td>Over decades, B12 stores get depleted, neurons/myelin die</td>
<td>Common in strict vegans and in pernicious anemia. Tingling in extremities followed by loss of vibratory sense. Spastic paralysis may follow</td>
</tr>
</tbody>
</table>

#### TUMORS

**Generalities**

- **Epidemiology**
  - Half of all CNS tumors are metastatic
    - Metastatic tumors present with multiple sites of growth
    - Usually spread via hematogenous route
  - Half of all CNS tumors are primary
    - Account for 2-3% of cancer deaths each year (i.e. are rare)
    - Malignancy cannot be determined by metastasis because tumors kill the patient before they metastasize; invasion and anaplasia are used instead; Hypercalcemia is not seen because there is no chance for metastasis to bone.
    - Most common CNS tumors (and the most high-yield) are Meningiomas and Glioblastoma Multiforme (grade 4 astrocytoma)

There are a crapload more tumors listed in Robbins. If you want to familiarize yourself with them, look to Baby Robbins. These are the high-yield tumors only. Make sure you also take a look at the path CD for images of tumor, which are abundant.
Path CNS Robbins Outline

- **Clinical Manifestations**
  - A headache that is worse at night and when awakening
  - Seizures when the cortex is involved
  - Focal Neurologic Symptoms related to location of growth
  - Increased Intracranial pressure (herniation, hydrocephalus, edema)
  - Location of tumor can be predicted by age of onset
    - Kids get tumors in the posterior fossa (Cerebellum)
    - Adults get tumors in the anterior fossa (Cortex)

- **Difference between Primary and Metastatic Tumors**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly Circumscribed</td>
<td>Well Circumscribed</td>
</tr>
<tr>
<td>Usually singular</td>
<td>Often Multiple</td>
</tr>
<tr>
<td>Location varies on type</td>
<td>Located at Junction of Grey and White Matter (where vessels narrow)</td>
</tr>
</tbody>
</table>

**Astrocytomas**

- General
  - Originate from astrocytes
  - Account for 80% of Primary CNS tumors
  - Area either Fibrillary or Pilocytic

- **Fibrillary Astrocytomas**
  - Based on Nuclear Atypia, Necrosis, Mitoses, and Vascular Proliferation (VP)
  - Grade
    - Grade 1 = Pilocytic Astrocytoma: ↑ Cellularity Only
    - Grade 2 = Diffuse Astrocytoma: ↑ Cellularity + Atypia
    - Grade 3 = Anaplastic Astrocytoma: ↑ Cellularity + Atypia + Mitoses
    - Grade 4 = Glioblastoma: ↑ Cellularity + Atypia + Mitoses + VP

**Glioblastoma Multiforme (GBM)**

- Most common CNS tumor and is ring enhancing
- Has rows of anaplastic cells lined up around a region of central necrosis, called pseudopalasading necrosis
- Vascular proliferation looks like a glomerulus, so is termed glomeruloid
- Occur in white matter and frequently cross the corpus callosum “Butterfly Lesion”
- Death within 1 year, difficult to resect, unresponsive to chemo

**Pilocytic Astrocytoma**

- Benign astrocytic tumor of children and young adults
- Characteristic cystic lesion connected to a mural nodule seen on MRI
- Contain Rosenthal fibers
- Surgical resection yields good prognosis.
- Occurs in posterior fossa
Path CNS Robbins Outline

**Oligodendroglioma**
- Derived from oligodendrocytes of middle aged patients
- Lesion of white matter that does not cross corpus
- Characteristic fried-egg appearance of a central nucleus with perinuclear clearing
  - Blood vessels from a chicken wire appearance → “chicken wire + fried eggs”
- Slow-growing tumor with decent prognosis (5-10 years), though they tend to recur

**Ependymomas**
- Derived from ependymal cells lining the ventricles
- Location by age
  - Children = Posterior Fossa = 4th Ventricle
  - Adults = Anterior Fossa = Lateral ventricle (or spinal canal)
- Gross = tumors from the wall of the ventricles growing inside CSF
- Micro = ependymal rosettes (cells organizing themselves around a central lumen) and Perivascular pseudorosettes (cells organizing themselves around a central blood vessel)
- Since they are in free floating CSF, they may cause hydrocephalus, and may embolize down the spinal column

**Meningiomas**
- Derived from meningothelial cells of the arachnoid
- Tumors occur in adulthood, men more often than women
- This lesion is literally attached to the dura and does not invade
- Pathognomonic cellular whorls + psammoma bodies tip you off
- Because it does not invade, resection is curative

**Medulloblastoma**
- Derived from primordial neuroglial precursors, so is a poorly differentiated tumor
- Typically develop in children, usually in the cerebellum
- Histology shows small, blue, round cells that may break off into CSF
- May disseminated through the CSF to the cauda equina called drop metastases
- Amenable to radiation

**Schwannomas**
- Originates in the Schwann Cells of cranial or spinal nerves
- The most frequent location is the 8th cranial nerve, called acoustic neuromas
  - Presents with hearing disturbances and tinnitus
- Commonly show areas of hypercellularity (Antoni A regions) mixed with areas of hypocellularity (Antoni B regions)
- Pathognomonic for Schwannomas are Verocay Bodies and expression of S-100
- There is good prognosis with surgical resection

**Craniopharyngioma**
- Arises from the remnant of Rathke’s Pouch near the pituitary
- Usually affects children and young adults
- It is benign but tends to recur and degenerate after resection
- It is a cystic lesion that may impinge on the optic chiasm → bitemporal hemianopsia

**CNS Lymphoma**
- High grade B-cell non-hodgkins lymphoma, commonly infected with Epstein Barr Virus
- Occurs in immunocompromised such as AIDS

33 Owl Club Review Sheets
## PRIMARY TUMORS OF CNS

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Character</th>
<th>Unique Histo/Path</th>
</tr>
</thead>
</table>
| Glioblastoma Multiforme (Astrocytoma Grade IV) | - Most common 1° Brain Tumor  
- Highly Malignant  
- Fatal in 8-12 months | - Forms in white matter, and may cross midline through the corpus callosum, so called **butterfly glioma**.  
- Areas of necrosis surrounded by hyperchromatic nuclei is pathognomonic, called **pseudopalasading necrosis** |
| Pilocytic Astrocytoma (Astrocytoma Grade I)  | - Benign tumor of kids and young adults; therefore, usually found in posterior fossa | - **Rosenthal Fibers** are pathognomonic  
- **Cystic lesions attached to a mural nodule** on CT |
| Oligodendroglioma (Oligodendrocytes) | - Slow Growing, Tend to recur  
- Long Survival (5-10 years) | - **Fried Egg Appearance** on Histo |
| Ependymoma (Ependymal Cells)      | - Grow in CSF; 4th ventricle in kids, lateral in adults  
- Causes **hydrocephalus** | - **Rosettes** of cells circling a central lumen  
- **Pseudorosettes** of cells circling vasculature |
| Medulloblastoma (Primary Neuroectodermal) | - Highly malignant cerebellar tumor occurring in kids | - Blue, small, round cells  
- May break off and travel down into spinal cord |
| Meningioma (Meningothelial Cells) | - Second most common 1° brain tumor  
- Dural convexities, parasagittal region | - Attached to dura, **does not invade**, but does compress local tissue; **highly amendable to surgery**  
- **Psammoma Bodies** in whorls are pathognomonic |
| Schwannoma (Schwann Cells) | - 3rd Most common 1° brain tumor  
- Found at cerebellopontine angle on CN VIII called **acoustic neuroma**  
- **Hearing loss, Tinnitus** | - Areas of hypocellularity (Antoni B) and hypercellularity (Antoni A)  
- **Verocay Bodies** and S-100 pathognomonic  
- Bilateral acoustic neuromas = Neurofibromatosis II |
| Craniopharyngioma (Rathke’s Pouch) | - Derived from odontogenic tissue,  
Remnants of Rathke’s Pouch  
- Usually kids and young adults | - **Cystic Lesion** near the optic chiasma can produce bitemporal hemianopsia  
- Amendable to surgery, but may recur |
| CNS Lymphoma                      | - B cell non-Hodgkins Lymphoma                     | - Occurs in **immunocompromised /AIDS** |

## COMPARISON BY DERIVATION

<table>
<thead>
<tr>
<th>Primary</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly Circumscribed</td>
<td>Well Circumscribed</td>
</tr>
<tr>
<td>Usually singular</td>
<td>Often Multiple</td>
</tr>
<tr>
<td>Location varies on type</td>
<td>Located at Junction of Grey and White Matter (where vessels narrow)</td>
</tr>
<tr>
<td>Just Less than 50% of all CNS Tumors</td>
<td>Just greater than 50% of all CNS Tumors</td>
</tr>
<tr>
<td>Glioblastoma &gt; Meningioma &gt; Schwannoma</td>
<td>Breast &gt; Lung &gt; Skin</td>
</tr>
</tbody>
</table>

## COMPARISON BY AGE GROUP

<table>
<thead>
<tr>
<th>Childhood</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior Fossa</td>
<td>Anterior Fossa</td>
</tr>
<tr>
<td>Pilocytic Astrocytoma</td>
<td>Glioblastoma Multiforme</td>
</tr>
<tr>
<td>Medulloblastoma, Craniopharyngioma, Ependymoma</td>
<td>Oligodendrocytoma, Meningioma, Schwannoma, Ependymoma</td>
</tr>
</tbody>
</table>
Path CNS Robbins Outline

PHAKOMATOSIS (From Lecture Only)
These are congenital Neuro-cutaneous syndromes = problems with CNS + problems with skin.

**Neurofibromatosis Type 1**
- Inherited as an **autosomal dominant** mutation of Neurofibromin on chromosome 17
  - Neurofibromin is a tumor suppressor gene
- There is classically café-au-lait spots and hamartomas of the iris (Lisch Nodules)
- Risk of Schwannoma, optic nerve glioma, and Meningioma
- Kid + Café-au-lait spots + Hamartoma of the Eye = NF 1

**Neurofibromatosis Type 2**
- Inherited as an **autosomal dominant** mutation of NF2 on chromosome 22
  - NF2 codes for schwannomin, also called merlin, a tumor suppressor
- **Bilateral Acoustic Neuromas** (Schwannomas of CN VIII) = NF 2

**Tuberous Sclerosis**
- Inherited as an **autosomal dominant** mutation of Hamartin and Tuberin (ch 9 and 16)
- A child presenting with **seizures** and **mental retardation** that also demonstrates
  - Supependymal Giant Cell Astrocytomas (SEGA)
  - Cortical Hamartomas of the brain (Tubers)
  - Angiofibromas of the skin, heart, kidneys
  - Hypopigmented skin lesions “ash leaf” lesions shown by **Wood’s Lamp Test**

**Sturge-Weber Syndrome**
- A **nonhereditary** disease, though this is up for debate
- Classic Characteristics include (this is really a list you just have to memorize)
  - Nevi Flammei = “port wine stain” = Facial Cavernous Angioma
  - Choroidal Hemangioma = “tomato catsup” fundus of the eye
  - Ipsilateral hemangioma/AV malformations of the meninges
  - “Train Track” intracranial calcification

**Von Hippel-Lindau Disease**
- Inherited as an **autosomal dominant** disease of VHL gene, a tumor suppressor on ch 3
- Highly associated with
  - Cysts of the liver and pancreas
  - Pheochromocytoma = tumor of adrenal gland, hypersecretory catecholamines
  - Hemangioblastoma of cerebellum and retina

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosome / Gene</th>
<th>Character</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis 1</td>
<td>Neurofibromin, Chromosome 17</td>
<td>Café-au-lait spots + hamartomas of the eyes</td>
</tr>
<tr>
<td>Neurofibromatosis 2</td>
<td>NF2 “merlin”, Chromosome 22</td>
<td>Bilateral Acoustic Neuromas</td>
</tr>
<tr>
<td>Tuberous Sclerosis</td>
<td>Hamartin + Tuberin, 9 + 16</td>
<td>Seizures, mental retardation, Angiofibromas everywhere, Tubers of the brain, SEGA, Ash-Leaf skin lesions</td>
</tr>
<tr>
<td>Sturge-Weber</td>
<td>Non-hereditary</td>
<td>Nevus Flammeus, Choroidal Hemangioma, Calcification</td>
</tr>
<tr>
<td>Von Hippel-Lindau</td>
<td>VHL gene, chromosome 3</td>
<td>Cysts of liver and pancreas, Pheochromocytoma, Hemangioblastoma of cerebellum and retina</td>
</tr>
</tbody>
</table>
SEIZURES  (From Lecture Only)

**Generalities**
- **Epilepsy** is a disease of the brain in a patient who has had at least one seizure and a cerebral defect predisposing them for others
- **Seizure** is a clinical neurological event characterized by a change in behavior, sensation, or cognition associated with hypersynchronous cerebral discharge
- **Status Epilepticus** is one long seizure or multiple seizures back to back without regaining consciousness
- **Kindling** is a term whereby “seizures beget seizures;” having one seizure lowers the threshold to have another seizure in the same spot
- **Post-Ictal** phase is the period after a seizure where the patient is confused, has a headache, or still has altered mental state. Occurs in general and partial complex.

**Types of Seizures** *(seizure does not equal Epilepsy!)*
- **Generalized Seizure**
  - Complete Brain involvement on EEG, + loss of consciousness
  - Subtypes
    - **Tonic Clonic** = Jerking convulsions shown on TV
    - **Absence Seizure** = brief loss of consciousness (2-3 seconds) without a post ictal phase and maintenance of posture
    - **Tonic** = loss of consciousness and motor tone while standing; patients are usually kids and they have to wear helmets to protect from trauma
    - **Myoclonic** = spastic jerk of a muscle group
- **Partial Seizure**
  - Incomplete brain involvement on EEG, change, but no loss of consciousness
  - Subtypes
    - **Simple Partial** = localized to one region, no surface EEG changes, usually a change in sensorium (sound, sight, touch, smell)
    - **Complex Partial** = localized to one region, surface EEG changes, usually a change in consciousness without loss presenting with automatisms and amnesia of the event

**Types of Epilepsy** *(seizure does not equal Epilepsy!)*
- **Idiopathic**
  - “Unknown” cause, but current research leaning towards genetic
  - Focal Idiopathic usually go away by 17, generalized idiopathic mostly go away, the rest are controllable with medications
  - Usually seen in **kids**
- **Symptomatic**
  - Structural lesion causing the seizure (trauma, tumor, mass effect, infection)
  - Most common adult-onset epilepsy, occurring in the frontal lobe most commonly, then temporal, then a variety of diseases (AV malformations, cavernous hemangiomas).
  - Usually seen in **adults**
**Path CNS Robbins Outline**

**Peripheral Muscular Diseases (Self Study)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Genetics / Epi</th>
<th>Path</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Muscular Atrophy</td>
<td><strong>Autosomal Recessive</strong> mutation of Motor Neuron Survival Gene, SMN1 on chromosome 5</td>
<td>Cannot override apoptosis, spinal cord cells just kill themselves</td>
<td><strong>Progressive</strong> loss of anterior horn and cranial nerve motor neurons. Begins in first year, peaks in childhood, presents with muscular weakness (lower motor neuron)</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td><strong>X-linked recessive</strong> loss of the protein dystrophin. Carriers asymptomatic but carry ↑ risk for cardiomyopathy. Huge gene, lots of opportunity for breakage</td>
<td><strong>Dystrophin</strong> is a hemidesmosome that links Z-disks to basal lamina. Without them, muscles literally tear themselves apart</td>
<td>Begins in childhood. Muscles are replaced by fat and scarring. “Huge Calves” are typical as a result of fatty tissue. Progressive muscle weakness; in a wheelchair by 10, dead by 20.</td>
</tr>
<tr>
<td>Becker’s Muscular Dystrophy</td>
<td><strong>X-linked recessive</strong> mutation (but not loss) of the dystrophin gene, with an abnormal dystrophin protein</td>
<td>Because it dystrophin is not gone, it is simply a milder form of the diseases. Weakness results, but most function remains</td>
<td><strong>Normal Life Span</strong>, patients have a slower, more variable progression. Cardiac disease is common, but with meds and training these kids can be essentially normal</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Unknown genetic component, it is autoimmune, so females are at increased risk. Treat with Acetylcholinesterase Inhibitors</td>
<td><strong>Anti-ACh-Receptor Antibodies</strong> are made that competitively antagonize ACh-Receptors in the periphery.</td>
<td>Continued repetitive use of a muscle draws weakness as ACh in presynaptic terminal is depleted. Look for diplopia while watching TV or difficulty with repetitive motions. Often have thymic growths</td>
</tr>
<tr>
<td>Lambert-Eaton</td>
<td>Paraneoplastic syndrome of small cell carcinoma of lung</td>
<td>Antibodies against the presynaptic Calcium Channels of peripheral muscle, limiting amount of neurotransmitter released</td>
<td><strong>Proximal Muscle Weakness</strong> with autonomic dysfunction. Weakness is worst in the morning but improves with activity but not with cholinesterase inhibitors</td>
</tr>
</tbody>
</table>

Acing the Test:
- Duchenne is a worse form than Becker’s of the same disease; a mutation in dystrophin.
- Myasthenia and Lambert-Eaton are both diseases of autoimmune disease to the synaptic cleft of neuromuscular junctions. Myasthenia gets worse with use, improves with drugs, affects distal muscles. Lambert-Eaton gets better with use, no change with drugs, and affects proximal muscles