

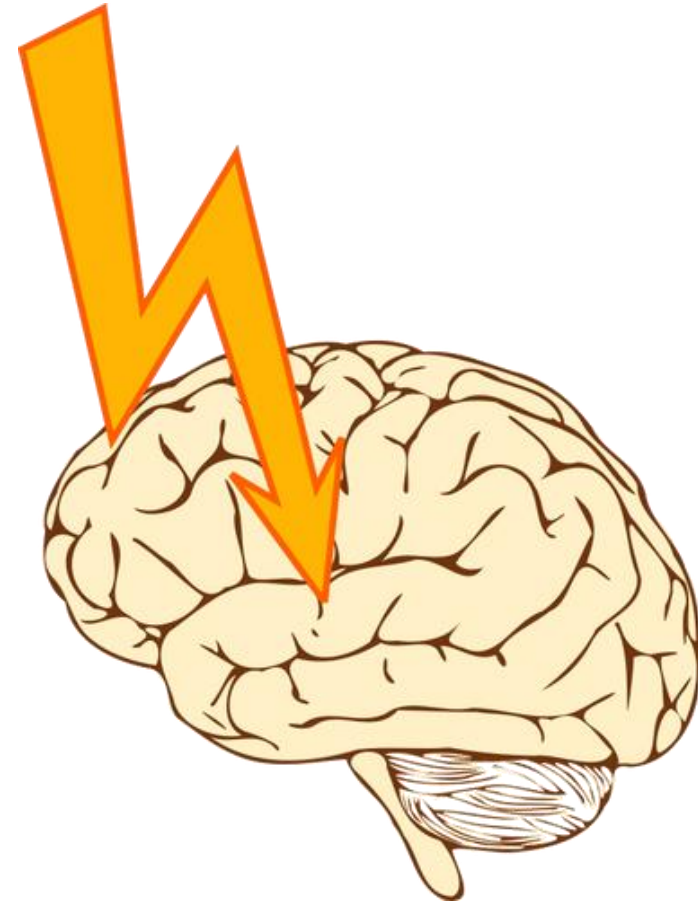
Stroke I

Jason Ryan, MD, MPH



Stroke

- Brain attack
- Patient appears “struck” down
- Sudden loss of neurological function
- Symptoms vary based on anatomy
- TIA: symptoms resolve < 24 hours
 - Transient ischemic attack
- Stroke: resolve \geq 24 hrs or persist



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Stroke

Risk Factors

- **Hypertension** (strongest risk factor)
- Diabetes
- Hyperlipidemia
- Smoking
- Same as risk factors for CAD



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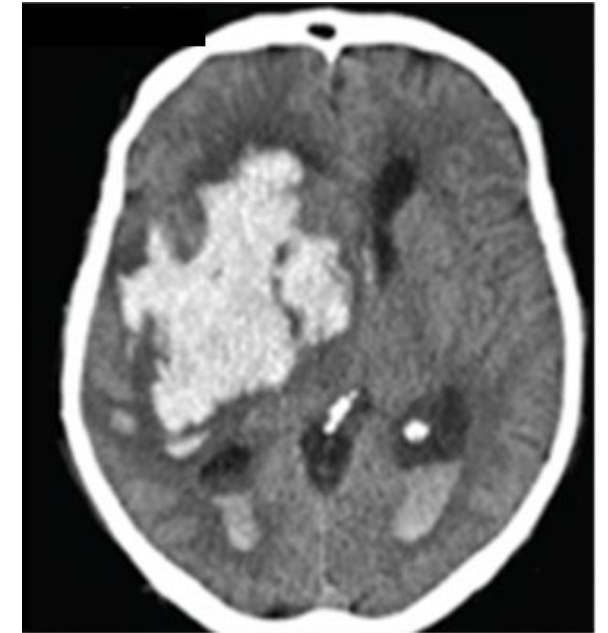
TIA and Stroke

Etiology

- Ischemic (~80%)
 - Insufficient blood flow
 - Thrombosis, embolism, hypoperfusion
- Hemorrhagic (~20%)
 - Brain bleeding
 - Sudden onset
 - Symptoms increase gradually
 - Over minutes or hours



**Ischemic Stroke
(dark/hypodense)**

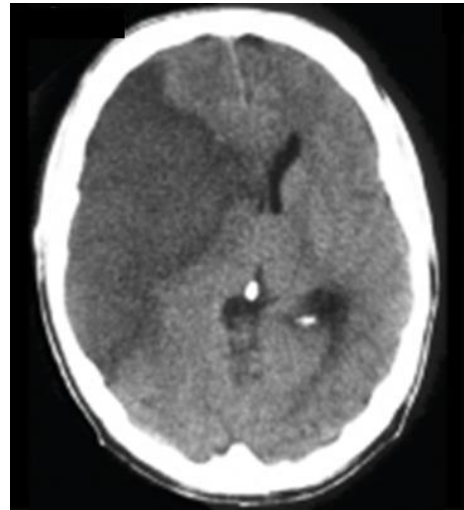


**Hemorrhagic Stroke
(bright/hyperdense)**

TIA and Stroke

Ischemic Etiologies

- Thrombotic
 - Local in situ obstruction of an artery
 - Large vessel disease: MCA, ACA, vertebral artery, basilar artery
 - Small vessel disease: lacunar stroke
 - Symptoms fluctuate: normal then abnormal, periods of improvement



TIA and Stroke

Ischemic Etiologies

- Embolic
 - Cardiac (atrial fibrillation, left ventricular thrombus)
 - Artery to artery: carotid artery
 - Multiple territories on imaging
 - Sudden onset of symptoms
 - Symptoms may wane over time
- Hypoperfusion

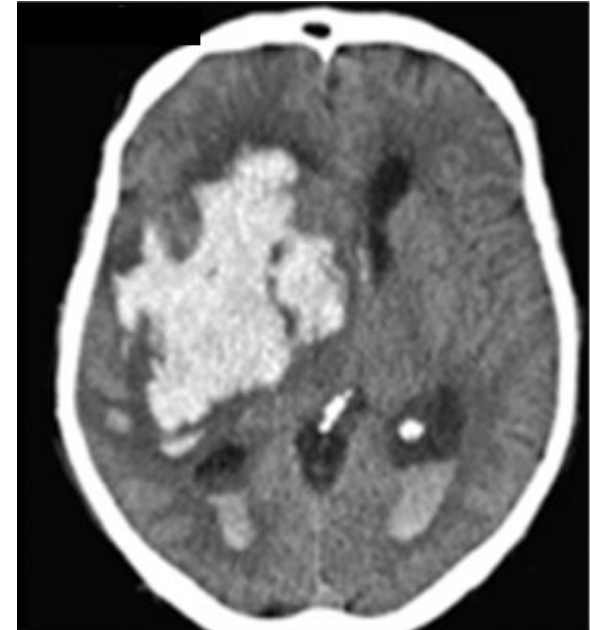


Atrial Fibrillation

TIA and Stroke

Diagnosis

- Best first test: **non-contrast CT of head**
 - Provided patient is stable
 - Evaluation for hemorrhage
- Most accurate test: **diffusion weighted MRI**
 - Higher sensitivity than CT
 - Can detect small infarcts in patients with TIA
- Diagnosis:
 - Infarct on imaging consistent with symptoms
 - Symptoms resolved < 24 hours = TIA
 - Symptoms > 24 hours or persistent = stroke



**Hemorrhagic Stroke
(bright/hyperdense)**

TIA

Stroke Risk

- Medical emergency
- **High risk of stroke**
 - ~8% risk of stroke within 30 days
 - ~10% risk of stroke within 90 days
- Stroke often within hours/days of TIA



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TIA

Management

- **Secondary prevention**
 - Aspirin
 - Statin (“strokes need statins”)
 - Blood pressure control
 - Blood sugar control
 - Smoking cessation
 - Diet, exercise
- High risk of stroke following TIA



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Stroke

Management

- **If hemorrhagic**
 - No thrombolysis: *contraindicated*
 - Reduce BP, reverse anti-coagulants, surgery
- **If non-hemorrhagic**
 - Must consider thrombolysis
- NO benefit to heparin, warfarin, anti-platelets during acute stroke
 - Some role in prevention of recurrent stroke

Thrombolysis for Ischemic Stroke

- 3 to 4.5-hour window of benefit for TPA (alteplase)
- Absolute contraindications
 - Active internal bleeding
 - Any history of intracranial hemorrhage
 - Ischemic stroke or head trauma past 3 months
 - BP > 185/110
 - Platelets < 100k
 - INR > 1.7
 - PTT > 40s



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Ischemic Stroke

Blood Pressure Management

- Over 60% of ischemic stroke patients present with elevated BP
- If thrombolysis administered
 - Goal $\leq 185/110$ mmHg
- If thrombolysis NOT administered
 - Goal $\leq 220/120$
- Intravenous medications
 - Labetalol
 - Nicardipine
 - Clevidipine

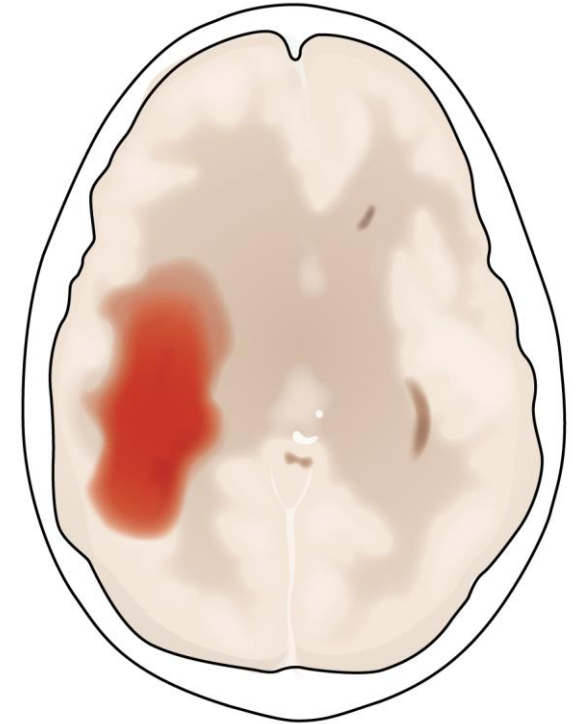


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Hemorrhagic Stroke

Intraparenchymal Bleed

- Sudden-onset neurologic impairment
- Can cause elevated intracranial pressure
 - Headache
 - Vomiting
- Numerous mechanisms
 - Ischemic stroke followed by reperfusion
 - Hypertensive vasculopathy (rupture of small penetrating arteries)
 - Cerebral amyloid angiopathy
 - Vascular malformations

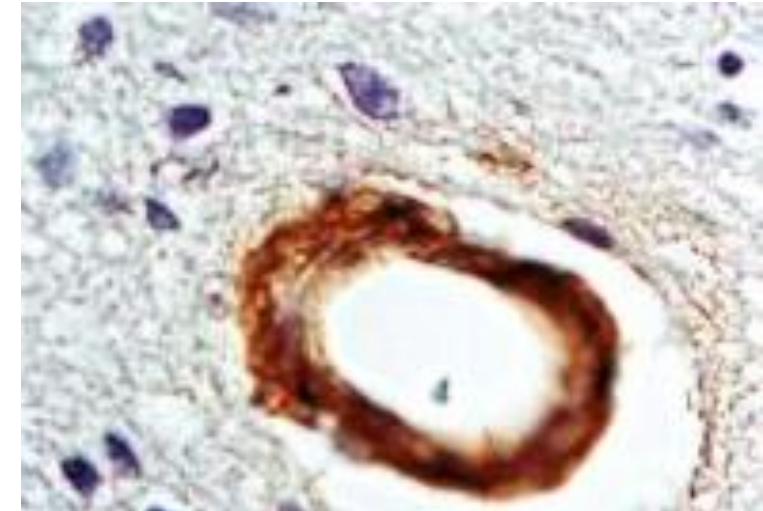


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Cerebral Amyloid Angiopathy

- Recurrent hemorrhagic strokes in elderly (>60)
- **Beta-amyloid deposits in artery walls**
 - Weak, prone to rupture
- Typically spontaneous lobar hemorrhages
 - Frontal, parietal, occipital
 - Usually smaller strokes
 - Contrast with HTN: Basal ganglia
- Diagnosis: imaging with multiple hemorrhages
 - Definitive diagnosis requires tissue
- Treatment: avoid anticoagulants

Staining for B-amyloid



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Hemorrhagic Stroke

Intraparenchymal Bleed

- Diagnosis: **non-contrast CT or MRI**
- Treatment:
 - Stop antiplatelet or anticoagulant drugs
 - Blood pressure control (target MAP 110)
 - Treat elevated intracranial pressure if present
- Can occur from **hemorrhagic transformation**
 - Initial ischemic stroke
 - Worsening symptoms hours-days later
 - Must obtain repeat CT scan



Post-Stroke and TIA

Testing

- **EKG**
 - Atrial fibrillation
 - Atrial fibrillation plus stroke = anticoagulation
 - Ambulatory EKG for long term monitoring
- **Echocardiogram**
 - Left ventricular thrombus: anticoagulation
 - Patent foramen ovale: possible closure
- **Carotid ultrasound**
 - Carotid stenosis
 - Surgery considered if >70% stenosis
 - No benefit to treatment during acute stroke

Atrial Fibrillation



Stroke in Young Patients

Age < 50

- **Hypercoagulable state**
 - Factor V Leiden mutation
 - Protein C or S deficiency
 - Antiphospholipid syndrome
- Vasculitis
- Patent foramen ovale
- Endocarditis
- Cocaine use

Post-Stroke Management

Medical Therapy

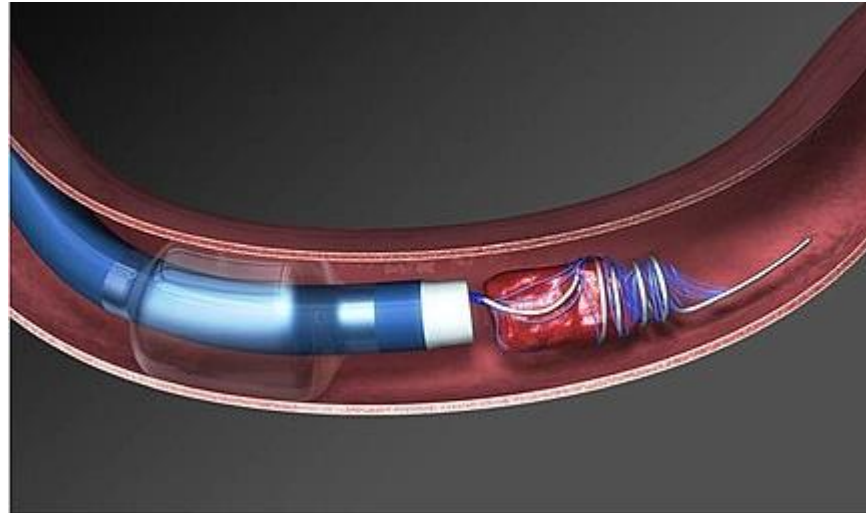
- Aspirin
 - If allergic: clopidogrel
 - Start within 48 hours of stroke onset
 - Wait at least 24 hours after thrombolysis
- Statin
- Blood pressure control
- Blood sugar control
- Smoking cessation
- Diet, exercise



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Mechanical Thrombectomy

- Catheter insertion into large intracranial artery
- Thrombus removed mechanically
- Used in ischemic stroke within **6 to 24 hours of onset**

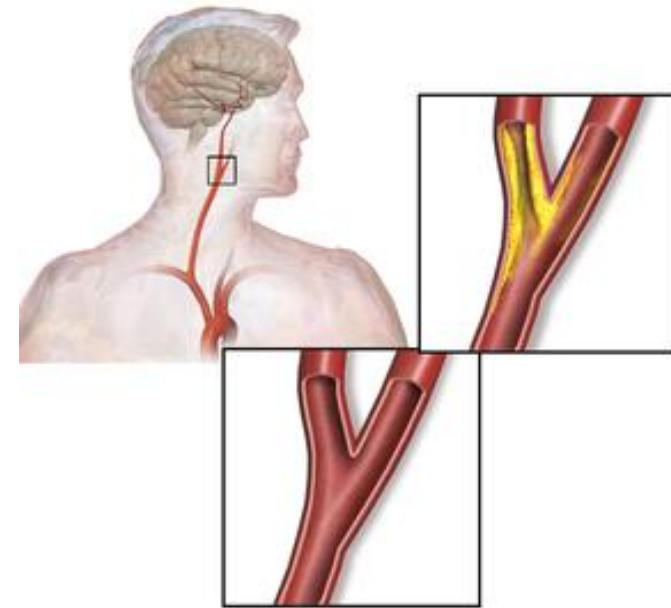


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Carotid Artery Disease

Management

- “Symptomatic” if embolization within past 6 months
- 100% stenosis: medical management
- 70-99%: carotid endarterectomy or stenting
- Men 50-69%: carotid endarterectomy or stenting
- All others: medical management



Stroke II

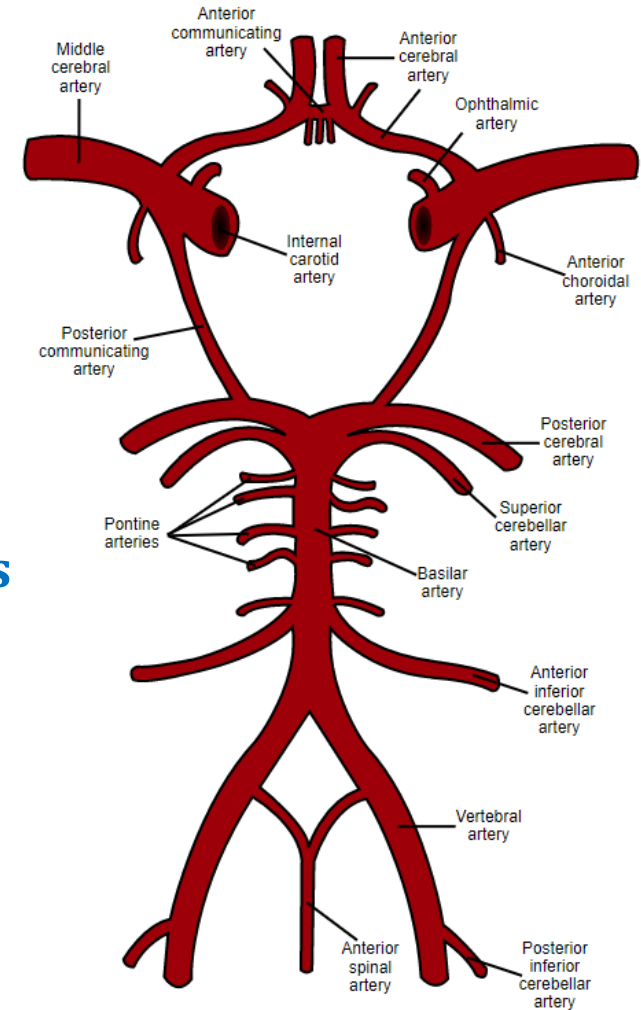
Jason Ryan, MD, MPH



Stroke Localization

Terminology

- “Anterior circulation”
 - Arises from **internal carotid artery**
 - Supplies cerebral cortex except posterior region
 - Anterior cerebral artery (ACA)
 - Middle cerebral artery (MCA)
- “Posterior circulation”
 - **Branches of posterior cerebral, basilar, and vertebral arteries**
 - Supplies posterior cortex, midbrain, and brainstem



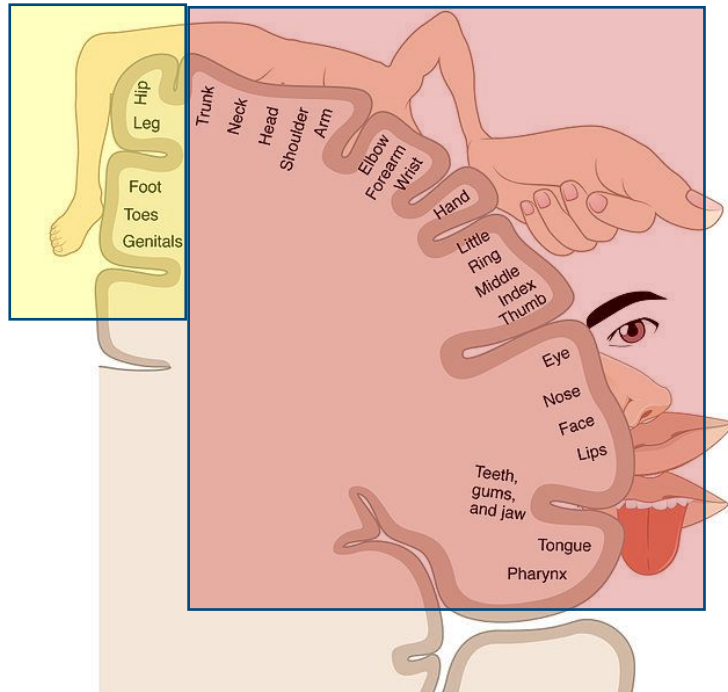
Stroke Localization

Cortical versus Subcortical Signs

- Cortex blood supply:
 - Anterior cerebral artery
 - Middle cerebral artery
 - Posterior cerebral artery
- Cortical: ischemia of cortex
 - Preferential involvement of motor areas
 - Face > leg
 - Leg > arms
- Subcortical: ischemia of subcortex/brainstem
 - Equal involvement face, legs, arms



Homunculus

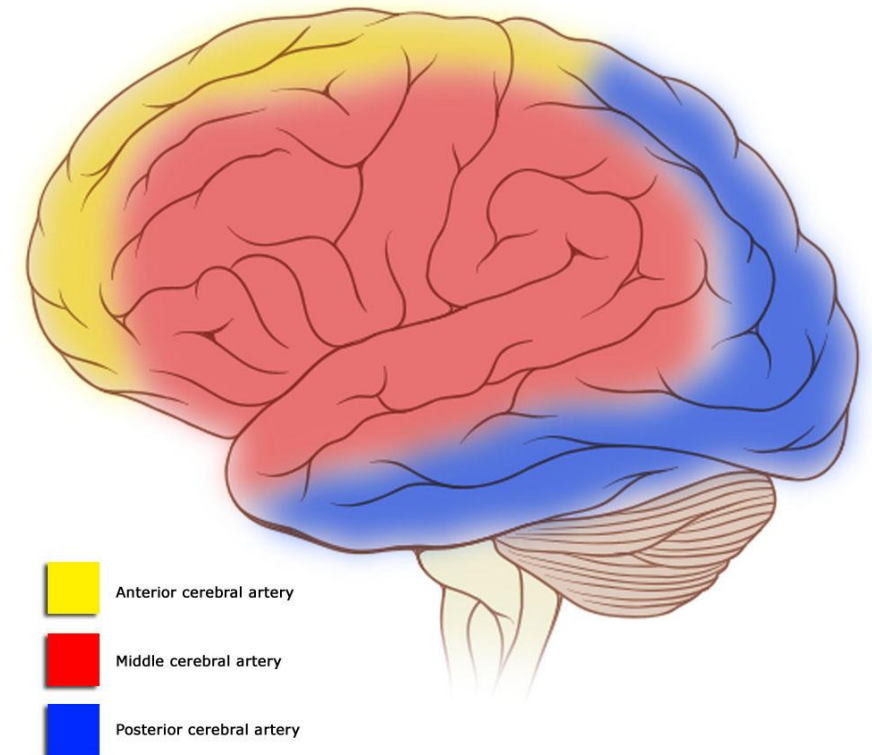


ACA: Lower limb

MCA: Upper limb, face

PCA: Vision

Cortical vascular territories

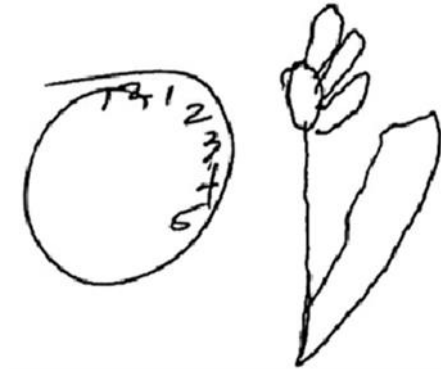


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Stroke Localization

Cortical Signs

- Aphasia: left middle cerebral artery
 - Speech center is left sided most patients
- Hemineglect: right middle cerebral artery
- Homonymous hemiansopsia



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Middle Cerebral Artery Stroke

- Most common territory of stroke
- Frontal, parietal and temporal lobes
- Contralateral motor/sensory deficit
- Arm and face > leg
- Spastic (UMN) paralysis
- If left (dominant) sided
 - Aphasia
- If right (nondominant) side
 - Hemineglect

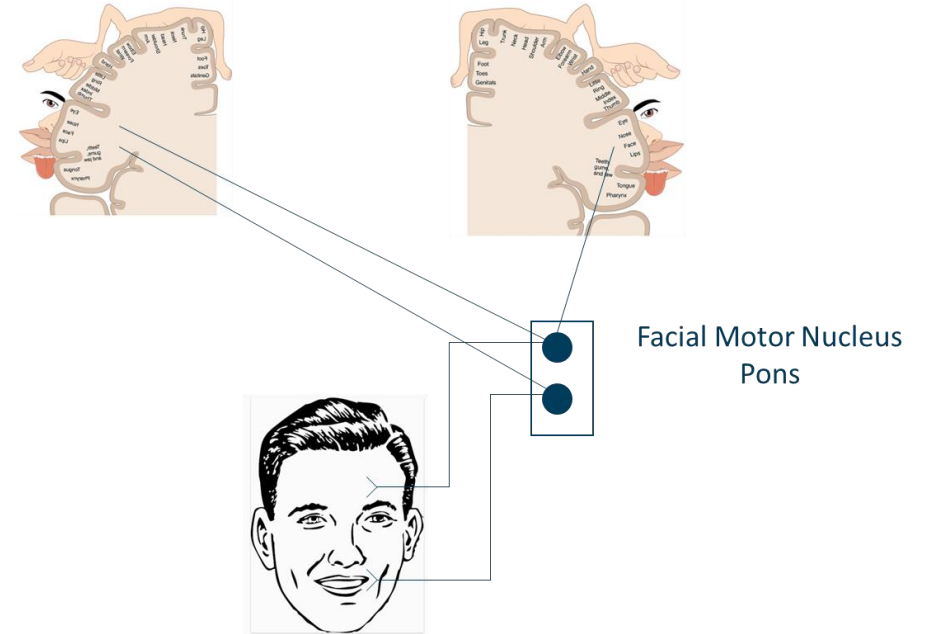


Middle Cerebral Artery Stroke

- **Homonymous hemianopsia**
- Damage to visual radiations of temporal and parietal lobes
- Eyes cannot see affected side
- Patient “looks toward side of the lesion”

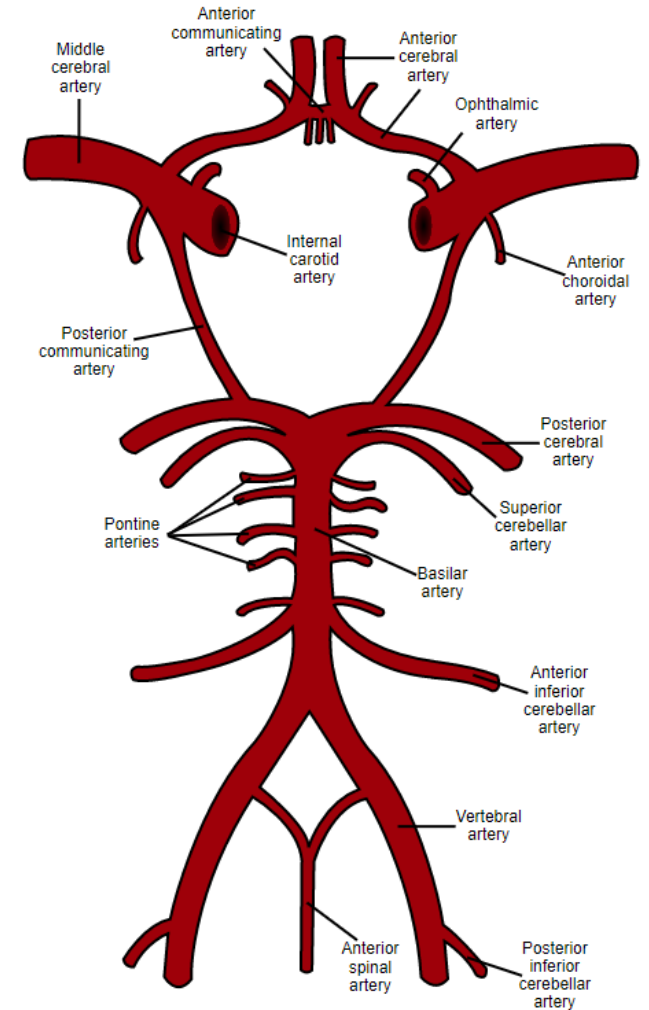
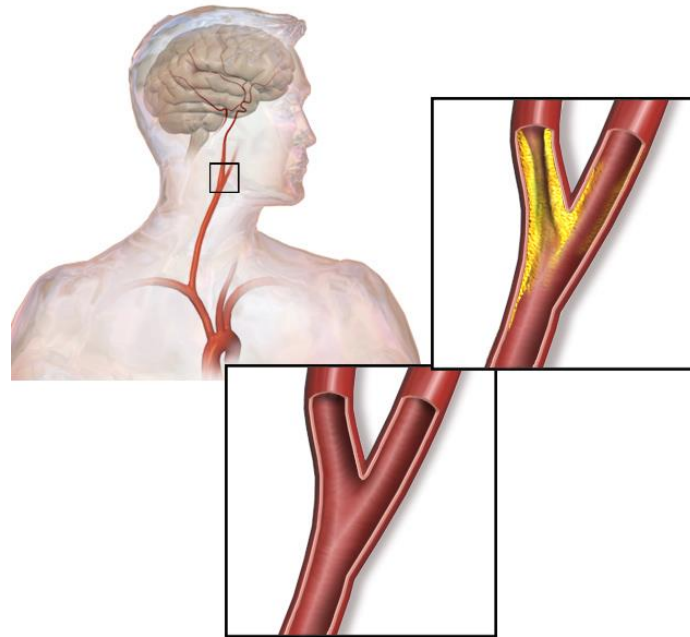
Lower Facial Droop

- Upper face: dual upper motor nerve supply
- Lower face: single upper motor nerve supply
- MCA stroke damage → lower facial droop
 - Upper face spared (dual innervation)
 - Lower face affected



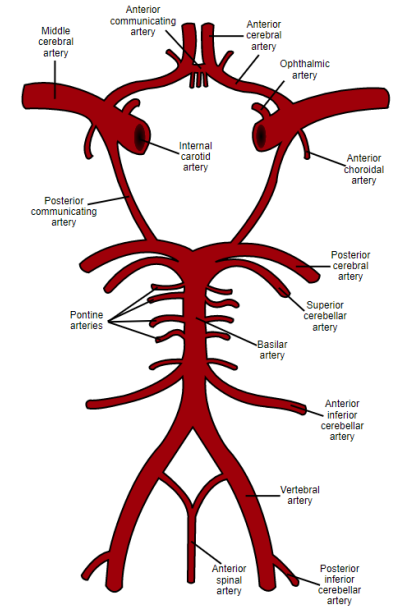
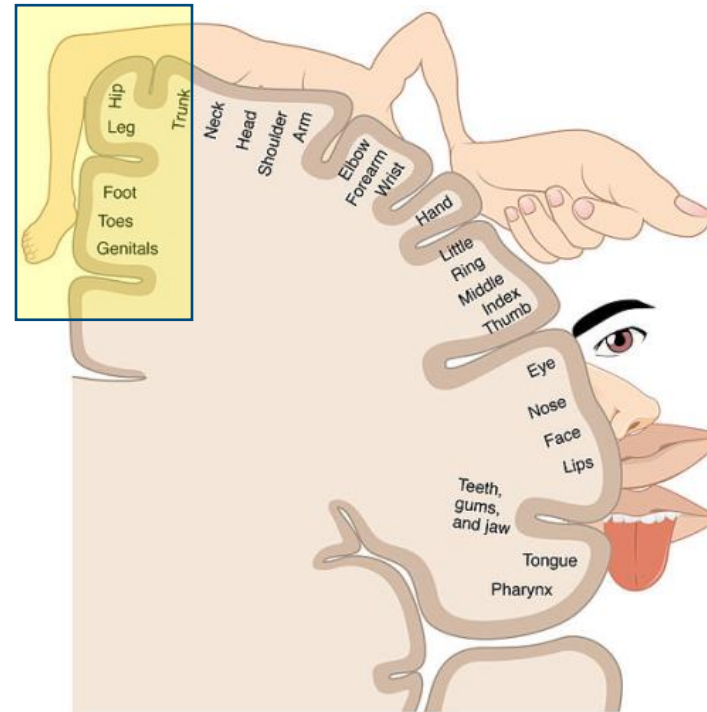
Middle Cerebral Artery Stroke

- Usually embolic
- Often due to **carotid artery disease**



Anterior Cerebral Artery Stroke

- Rare stroke territory (~2% strokes)
- Medial cortex (midline portion)
- Motor loss leg > arm
- Cognitive defects or confusion
- Urinary incontinence
- Many etiologies



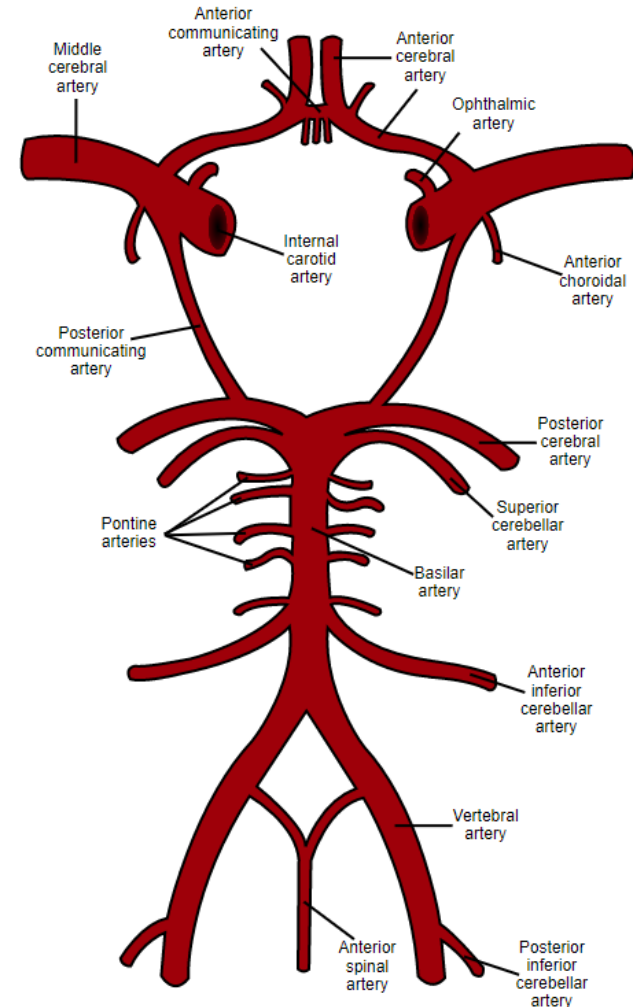
Posterior Cerebral Artery Stroke

- Posterior portion of brain
- Occipital lobe, the medial temporal lobe or the thalamus
- **Visual cortex**
- Contralateral homonymous hemianopsia
- Thalamic infarct: **contralateral sensory loss**



Posterior Cerebral Artery Stroke

- Many etiologies
- Atherosclerosis of **vertebral or basilar arteries**



Lacunar Strokes

- **Subcortical strokes (no cortical signs)**
 - Occur in small branches of large vessels
 - Involve basal ganglia, subcortical neurons or pons
- Strongly associated with **hypertension**



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Lacunar Strokes

- Diagnosis: CT or MRI
 - Small *non-cortical* area of ischemia
- Same treatment as other ischemic strokes
 - Thrombolysis in appropriate patients
- Caused by **lipohyalinosis**



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Lacunar Strokes

Subtype	Symptoms	Other Details
Pure Motor	Paralysis of face, arm and leg on one side	Posterior limb internal capsule
Pure Sensory	Complete sensory loss one side of body: Face, arm, and leg	Thalamus
Ataxic Hemiparesis	Weakness/ataxia	Internal capsule Base pons
Dysarthria-Clumsy Hand Syndrome	Dysarthria and clumsiness (weakness) of the hand	Internal capsule Base pons

*Over 20 subtypes described

Classic Lacunar Stroke

- Patient with **uncontrolled hypertension**
- Symptoms consistent with a lacunar subtype
 - Pure motor most common
- Often negative initial head CT
- **MRI** more sensitive for lacunar strokes

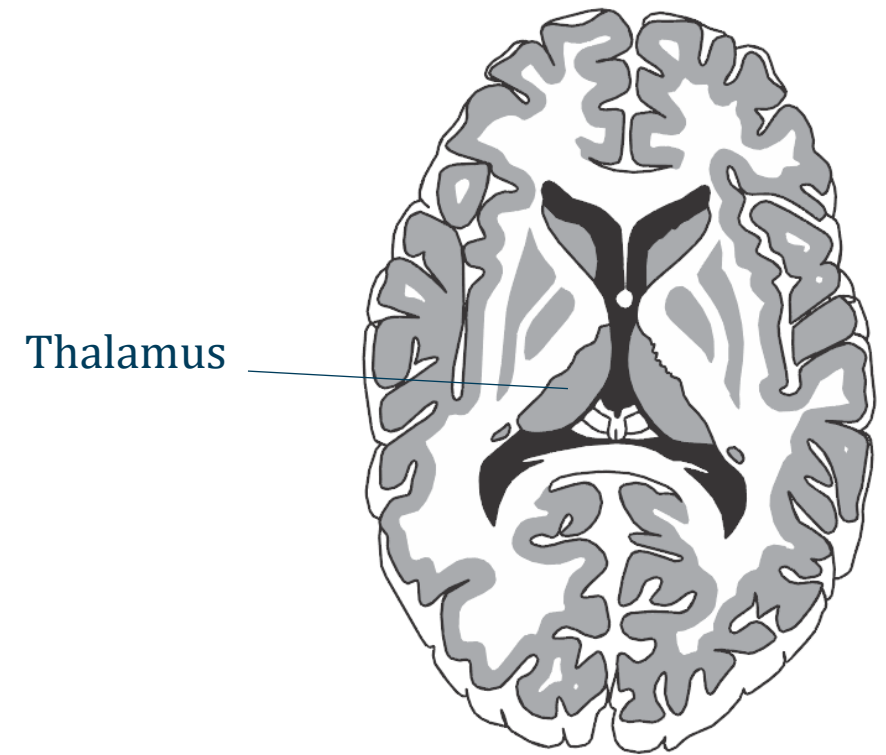


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Thalamic Pain Syndrome

Dejerine-Roussy syndrome

- Caused by thalamic lacunar infarcts
- Sensory deficits improve
- Chronic burning pain contralateral side remains
- Develops weeks to months later



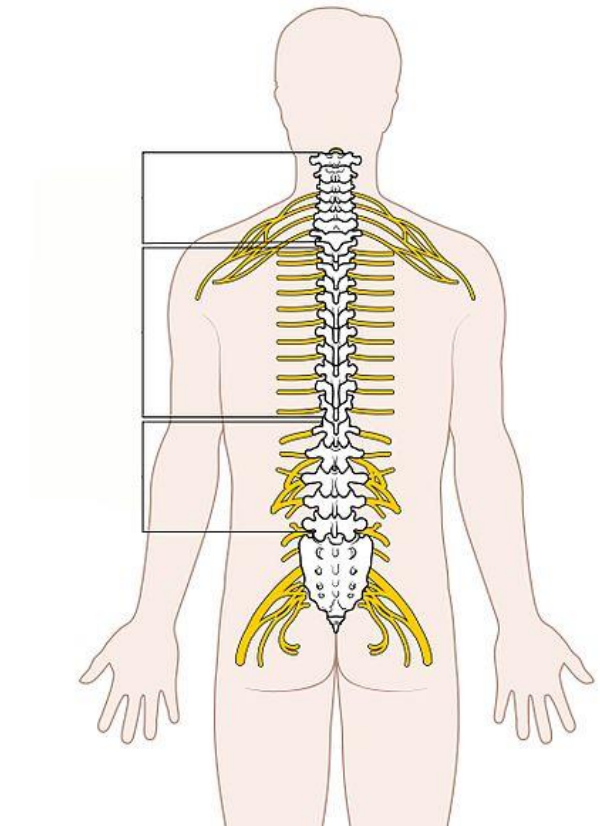
Brainstem Strokes

- Ipsilateral cranial nerve lesions
- Contralateral weakness
- Diagnosis: CT or MRI
 - Small non-cortical area of ischemia
- Same treatment as other ischemic strokes
 - Thrombolysis in appropriate patients



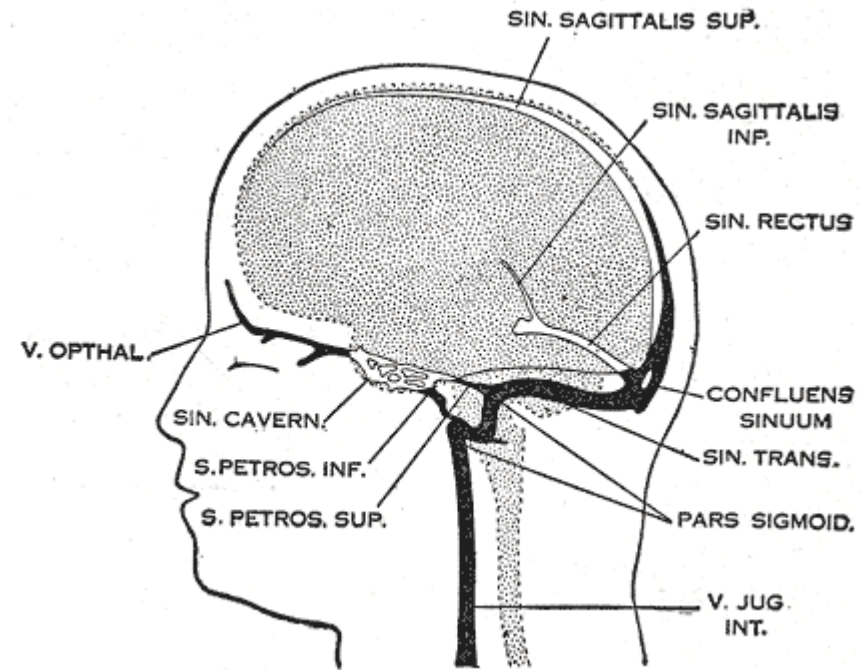
Spinal Cord Strokes

- Rare form of infarction
- Most commonly anterior spinal artery
- Sudden onset paralysis
- Loss of pain and temperature sensation below lesion level
- Position and vibratory sensation spared



Venous Sinus Thrombosis

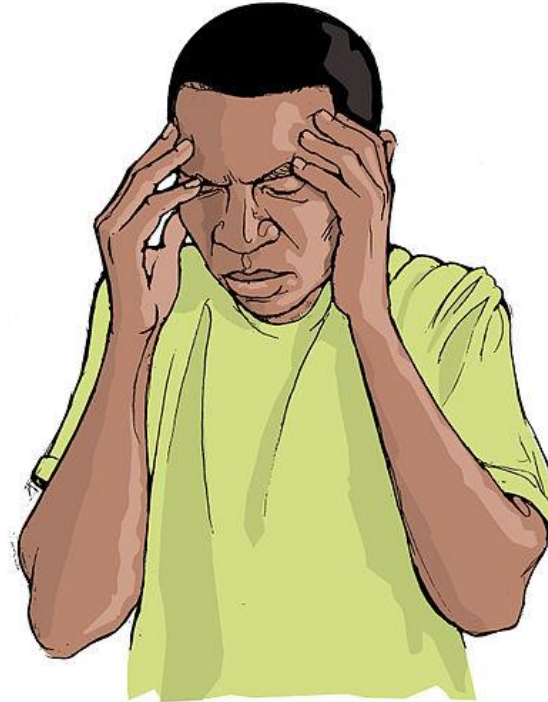
- Subtype of stroke
- Blood clot in **dural venous sinus**
 - Drains CNS blood to internal jugular vein
- Occurs in hypercoagulable states
 - Surgery
 - Infection
 - Malignancy
 - Inherited disorders



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Venous Sinus Thrombosis

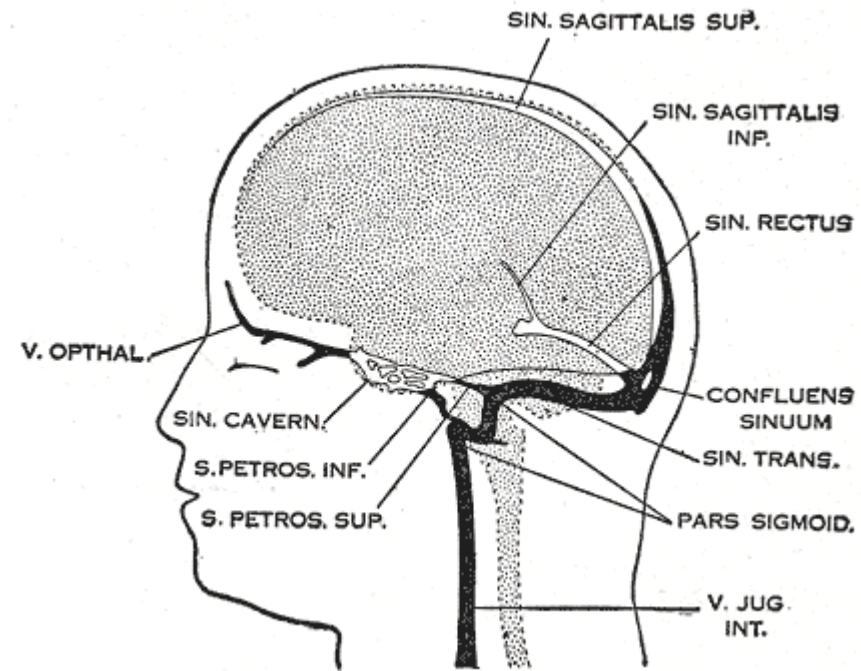
- Highly variable presentation
- Most common symptom: **headache**
 - Usually gradual onset over days
 - Rarely “thunderclap” headache
- Signs of increased ICP may be present
 - Vomiting
 - Papilledema



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Venous Sinus Thrombosis

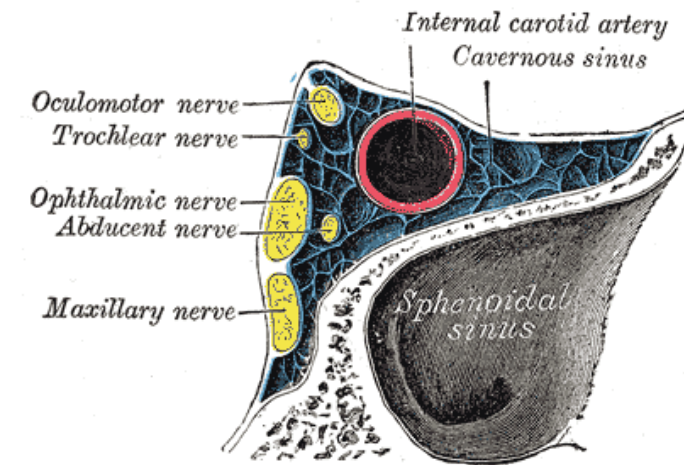
- Head CT may show edema
 - Often normal or nonspecific
- Diagnosis: **CT or MR venography**
 - Dye in venous system
 - “Filling defects” from thrombus
- Treatment: heparin



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Cavernous Sinus

- Large collection veins
- Between temporal/sphenoid bones
- Collects blood from eye and cortex
- Drains into internal jugular vein
- Many nerves:
 - CN III, IV, V1, V2 , VI, sympathetic fibers
 - All traveling to orbit
- Also portion of internal carotid artery



Cavernous Sinus Thrombosis

- Subtype of cerebral venous thrombosis
- Headache (\uparrow ICP)
- **Prominent ocular signs**
 - Orbital pain
 - Proptosis (protrusion)
 - Chemosis (swelling)
 - Oculomotor palsies
- Loss of facial sensation V1/V2 dermatomes
 - Forehead
 - Nose

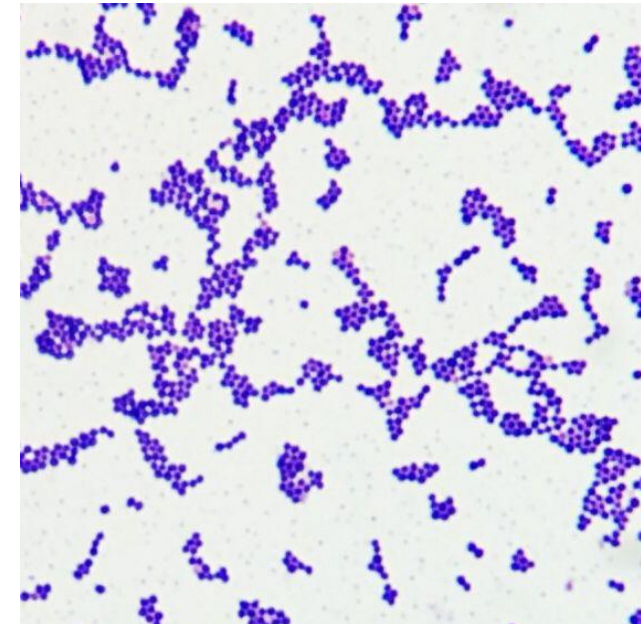


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Cavernous Sinus Thrombosis

- Often associated with **infection (septic thrombosis)**
- Follows facial infections
 - Abscess
 - Cellulitis
 - Sinusitis
 - Dental infections
- ***Staphylococcus aureus*** two-thirds of cases
 - May be methicillin resistant
- Treatment: heparin, antibiotics, surgical drainage

S. Aureus



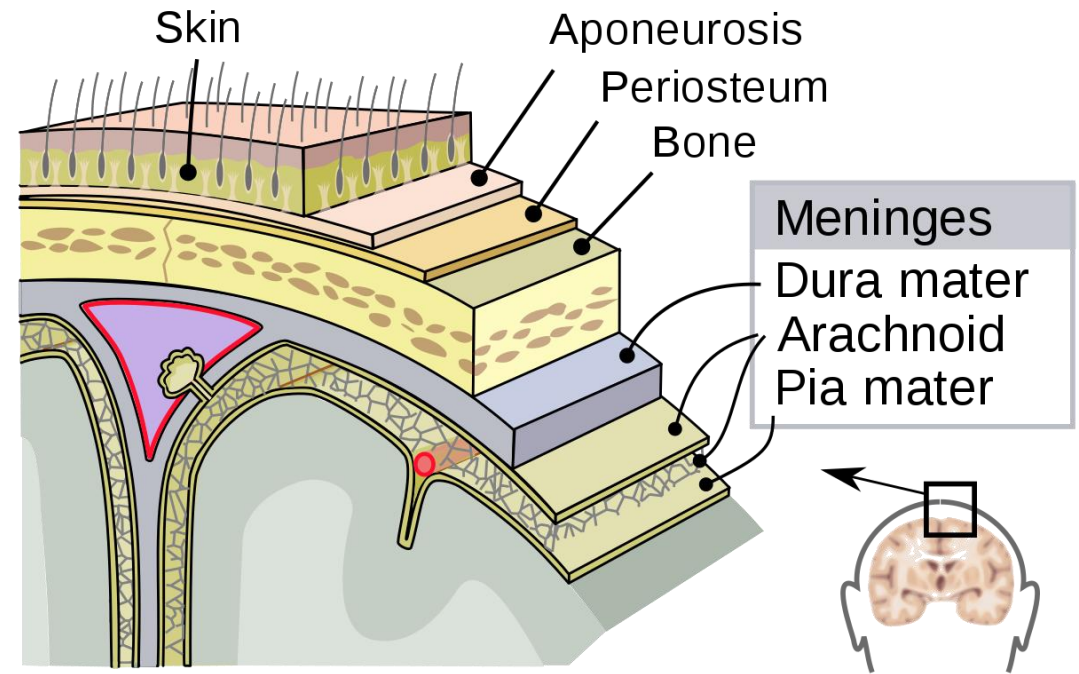
Intracranial Bleeding

Jason Ryan, MD, MPH



Intracranial Bleeding

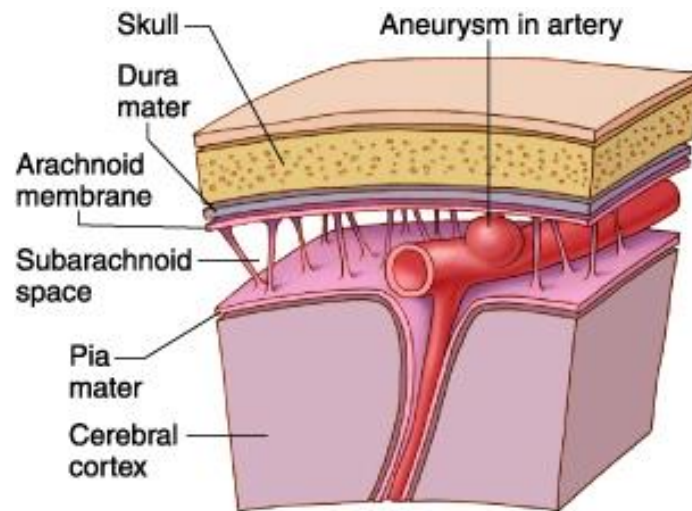
- Hemorrhagic stroke
- Subarachnoid hemorrhage
- Subdural hematoma
- Epidural hematoma



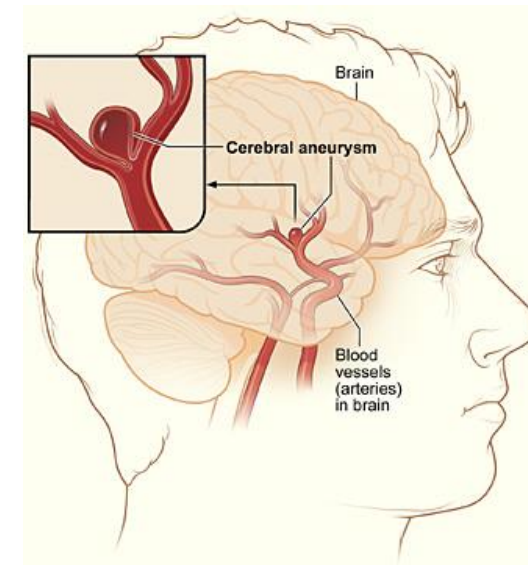
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Subarachnoid Hemorrhage

- Bleeding into space between arachnoid and pia mater
- Usually from **ruptured berry aneurysms**
 - Weak vessel wall
 - Abnormal dilation



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Subarachnoid Hemorrhage

- Sudden onset symptoms
- “Worst headache of my life”
- Fever
- Nuchal rigidity
- Focal deficits rare
- Loss of consciousness in 40% patients
 - From sudden increase ICP



James Heilman, MD

Subarachnoid Hemorrhage

- **Noncontrast CT scan usually diagnostic (95% cases)**
- Highest sensitivity **first six hours**

Subarachnoid Hemorrhage



James Heilman, MD

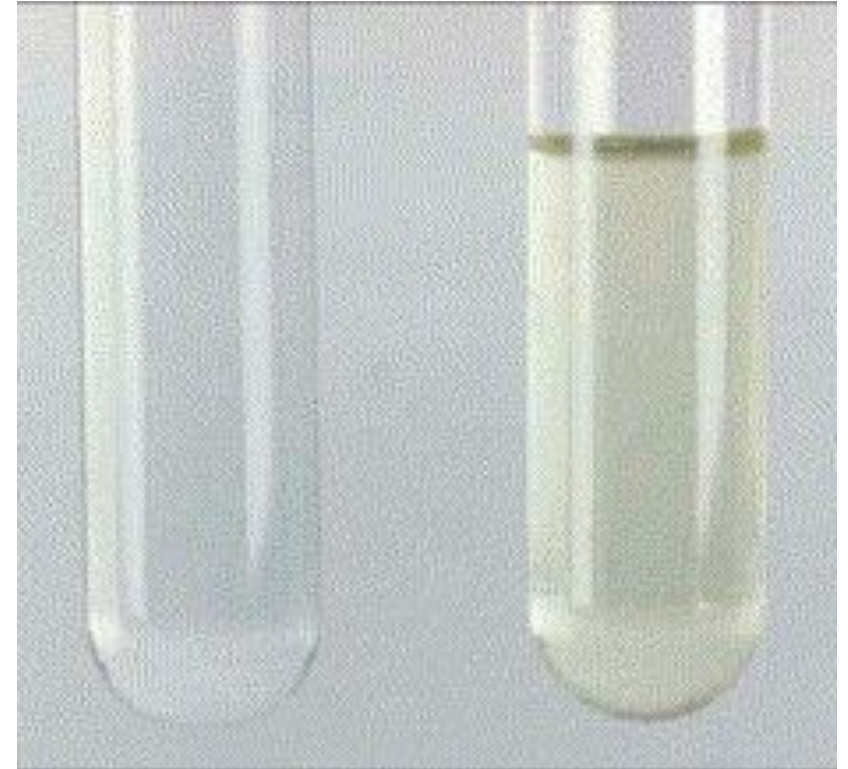
Normal



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Subarachnoid Hemorrhage

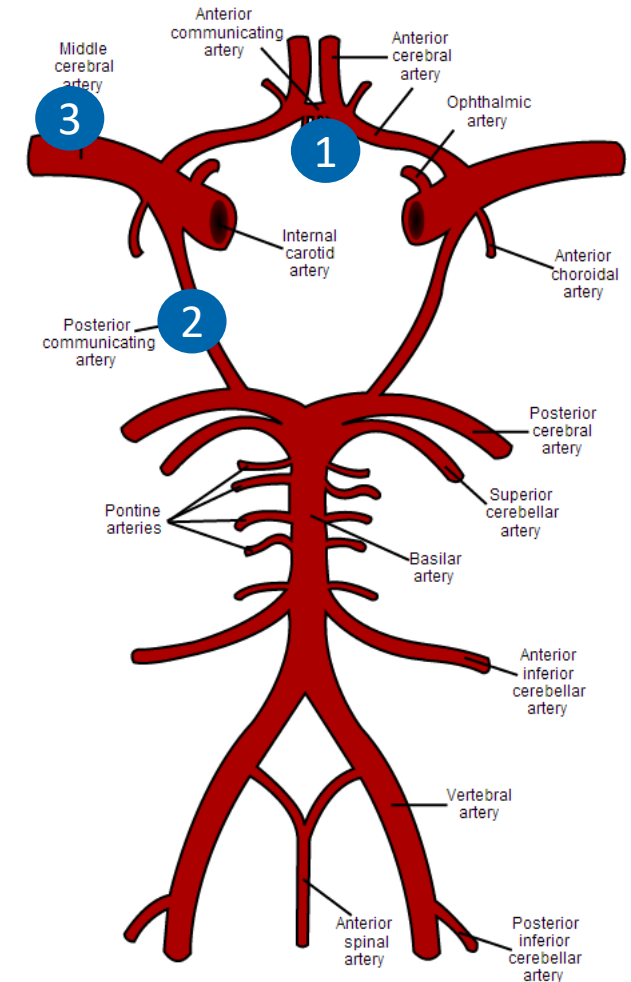
- Most accurate test: **lumbar puncture**
 - Identifies xanthochromia in CSF
 - Yellow color from RBC breakdown
 - Identifies 5% cases missed by CT
- High suspicion/negative CT: lumbar puncture
- May also show ↑ WBCs and RBCs
 - Normal ratio (1:1000) WBC to RBC
 - If increased ratio: meningitis



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Berry Aneurysms

- Usually asymptomatic
- Most common presentation: subarachnoid hemorrhage
- Rarely enlarge to cause neurologic impairment
- 85% occur in Circle of Willis
 - Most commonly anterior communicating artery
 - Posterior communicating artery
 - Middle cerebral artery



Berry Aneurysm Associations

- **Polycystic kidney disease**
- Ehlers-Danlos syndrome
- Marfan syndrome
- Hypertension
- Smoking

Polycystic Kidneys



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Anterior Communicating Artery Aneurysm

- Headache
- Visual field defects



Bitemporal Hemianopsia
Optic Chiasm Compression
Pituitary Tumor/Aneurysm

Posterior Communicating Artery Aneurysm

- Unilateral headache, eye pain
- CN III palsy
 - Eye: “down and out”
 - Ptosis
 - Pupil dilation – nonreactive to light



Pupil Sparing

- Is pupil normal (not dilated)? Are pupils equal?
- If yes, pupil is spared → lesion NOT aneurysm
- Pupillary constrictors easily compressed in subarachnoid space
- If pupil is “spared”
 - Ischemic neuropathy of CN III (small vessel disease)
 - Palsy often associated with diabetes
 - Sometimes painful
 - Spontaneously resolves
- “Rule of the pupil”



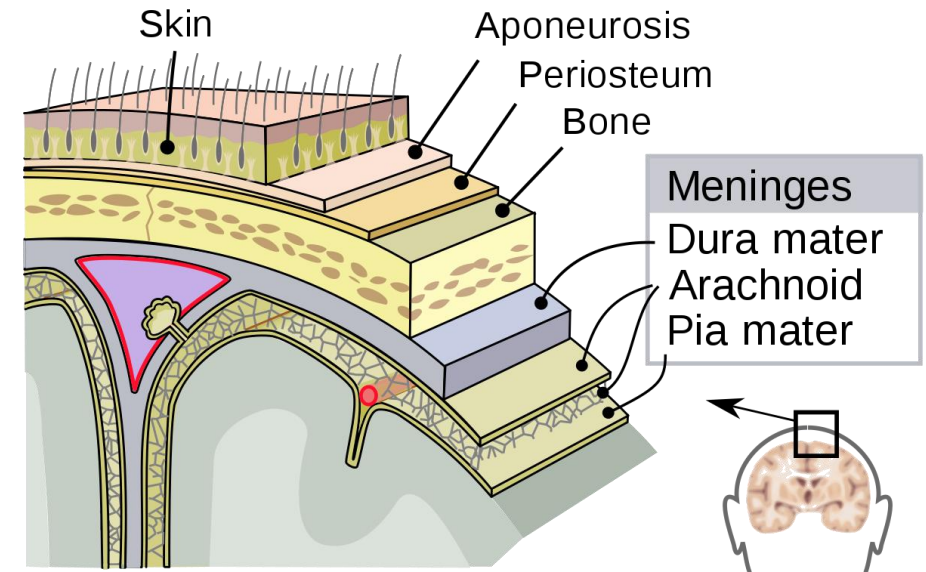
Subarachnoid Hemorrhage

Treatment

- Treat with endovascular coiling or clipping
- Rebleeding common
- **Vasospasm**
 - Triggered by blood
 - Worsening neuro symptoms
 - Days after initial bleed
- **Nimodipine (calcium-channel blocker)**
 - Improves outcome
 - Unclear mechanism
 - May prevent vasospasm

Subdural Hematoma

- Bleeding between dura and arachnoid
- Usually traumatic
- Usually caused by rupture of bridging veins
- SLOW bleeding due to low pressure veins



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Subdural Hematoma

- Risk factors
 - Old age
 - Alcohol use
 - Blood thinners
- Brain atrophy with age increases space veins must cross
 - More vulnerable to rupture
- May occur in shaken baby syndrome



Dr. Ryan's Grandmother

Subdural Hematoma

- Rarely presents acutely
 - Severe neurologic impairment
 - Coma
- Often presents slowly over days/weeks
 - “Chronic subdural hematoma”
 - Headache
 - Neurologic impairment
 - Somnolence
- Diagnosis: **CT scan**
 - Crescent shaped bleed



James Heilman, MD

Subdural Hematoma

Treatment

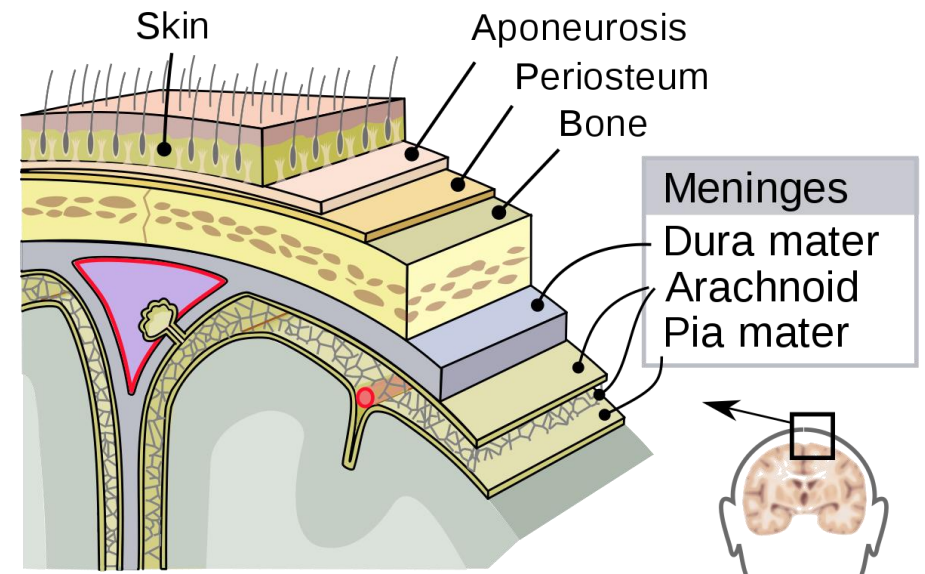
- Surgery versus observation
 - Depending on size, symptoms



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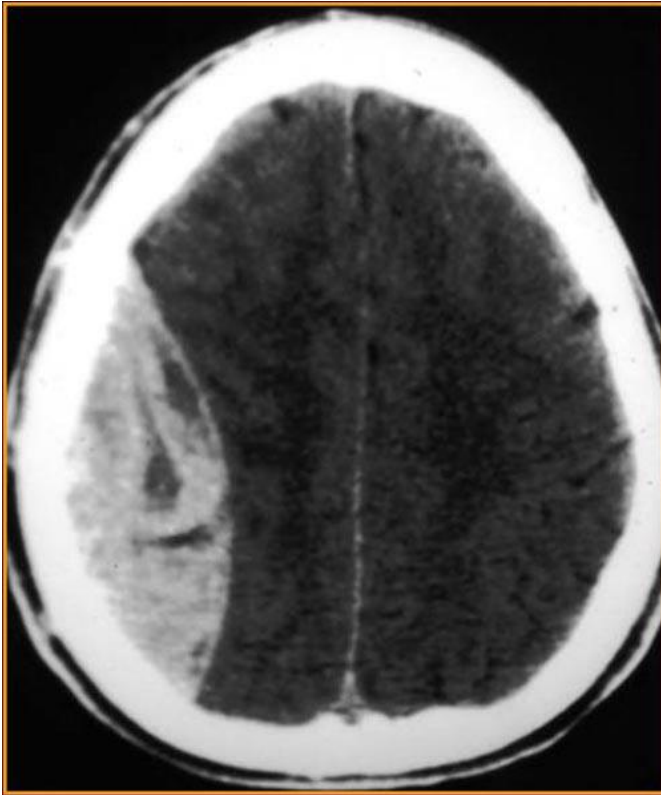
Epidural Hematoma

- Bleeding between skull and dura
- Traumatic:
 - Often fracture of temporal bone
- Usually rupture of middle meningeal artery
- Diagnosis: CT scan
 - Convex shape
- Treatment: urgent surgery



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Epidural Hematoma



Dryphi



James Heilman, MD

Epidural Hematoma

Symptoms

- General symptoms:
 - Headache, drowsiness, loss of consciousness
- **Lucid interval**
 - Loss of consciousness due to initial brain trauma
 - Recovery
 - Deterioration due to accumulating blood
 - Gradual loss of consciousness again

Intracranial Hypertension

Jason Ryan, MD, MPH



Intracranial Hypertension

- Normal ICP ≤ 15 mmHg
- Intracranial hypertension = **ICP ≥ 20 mmHg**
- Elevated ICP \rightarrow **decreased cerebral perfusion**
 - Cerebral perfusion pressure varies with MAP and ICP
- Elevated ICP may lead to **herniation**
 - Skull volume constant
 - Brain has limited compliance to shrink
 - Shifting of CNS contents within skull

$$\text{CPP} = \text{MAP} - \text{ICP}$$

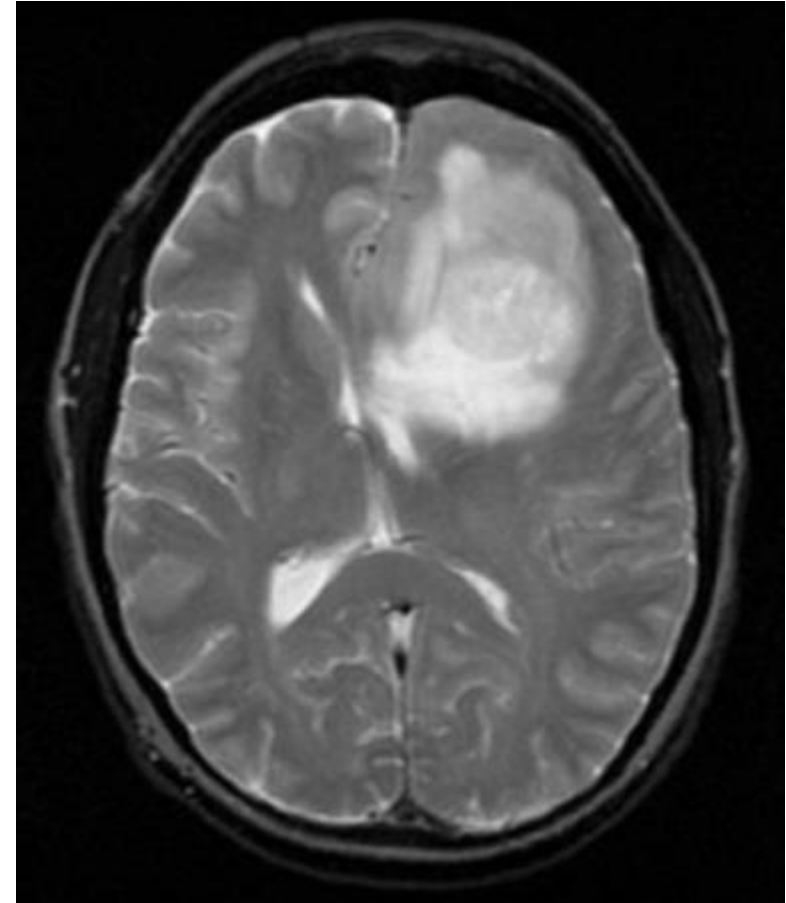
(Brain + CSF + Blood) volume = Constant

Intracranial Hypertension

Causes

- Cerebral edema
- Mass/tumor
- Trauma/bleeding
- Hydrocephalus
 - Increased CSF production
 - Decreased CSF absorption
- Idiopathic intracranial hypertension
 - Pseudotumor cerebri

Brain Tumor

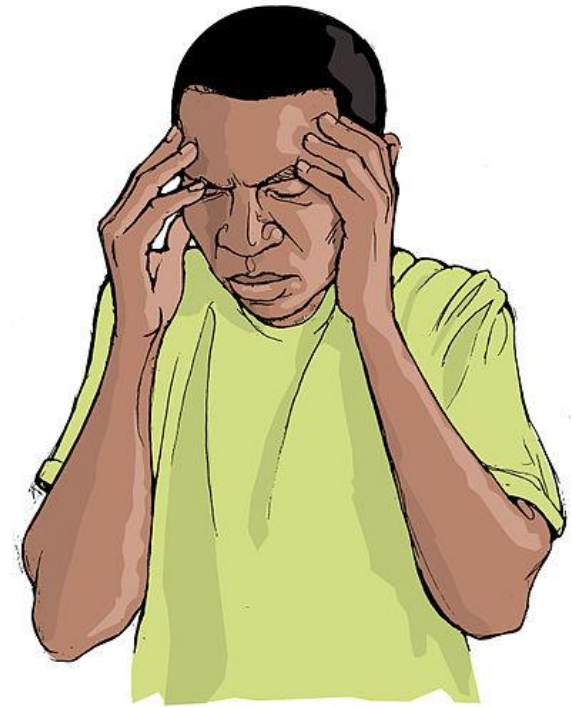


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Intracranial Hypertension

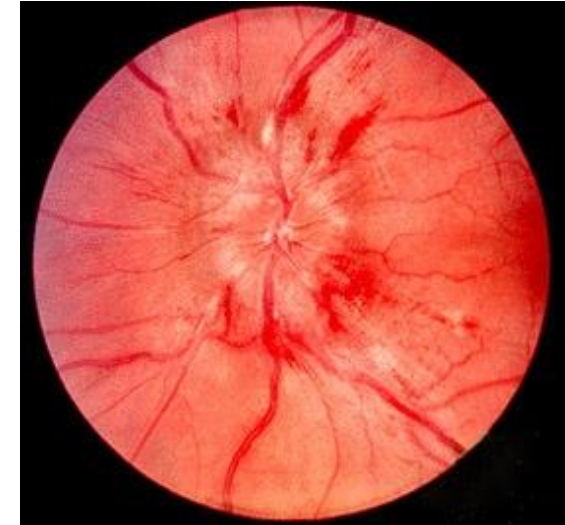
Clinical Features

- Headache
 - Pain fibers CN V in dura
 - Classically worse with maneuvers that change ICP
 - Lying down, bending over, coughing, or Valsalva
- Vomiting
- **Symptoms often change with position**

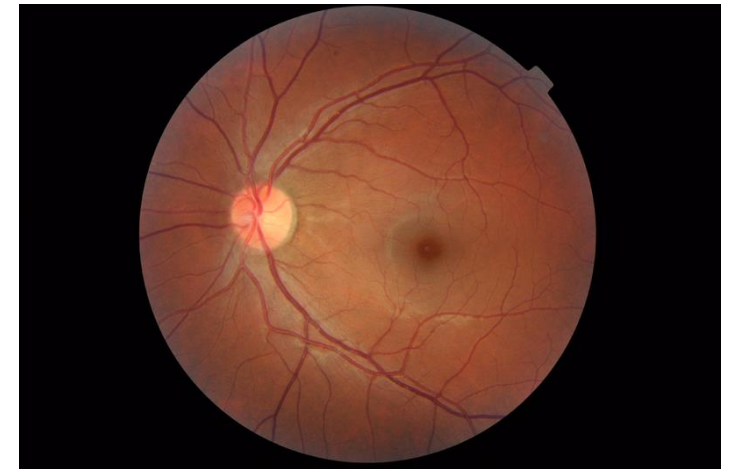


Papilledema

- Optic disc swelling
- Due to \uparrow ICP
- Also seen in severe hypertension
- Usually bilateral
- Blurred margins optic disc on fundoscopy
- **Episodic, brief vision loss with positional changes**



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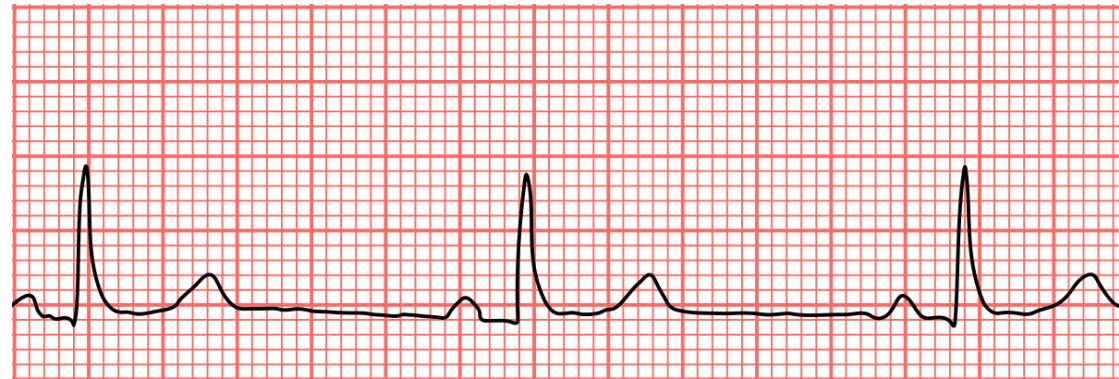


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Cushing's Triad

- CNS response to raised intracranial pressure
- Often indicates imminent herniation
- Hypertension
- Bradycardia
- Irregular respiration

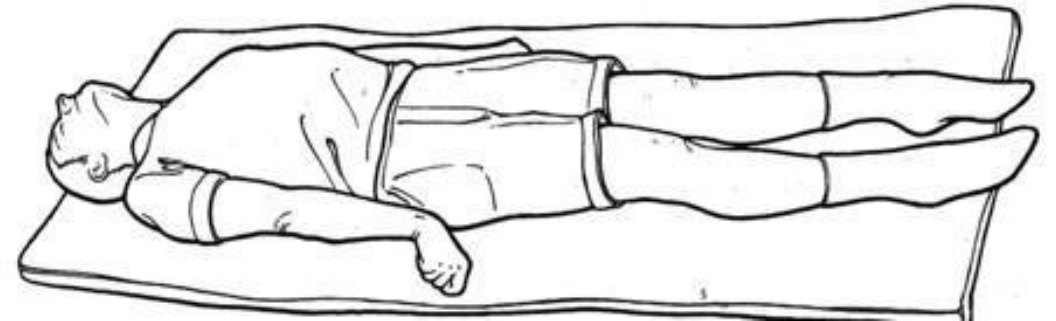
Sinus Bradycardia



Posturing



Decorticate (arms flexed)
Cerebral Hemisphere Damage
Often occurs first



Decerebrate (arms extended)
Brainstem Damage
Often occurs late as herniation progresses

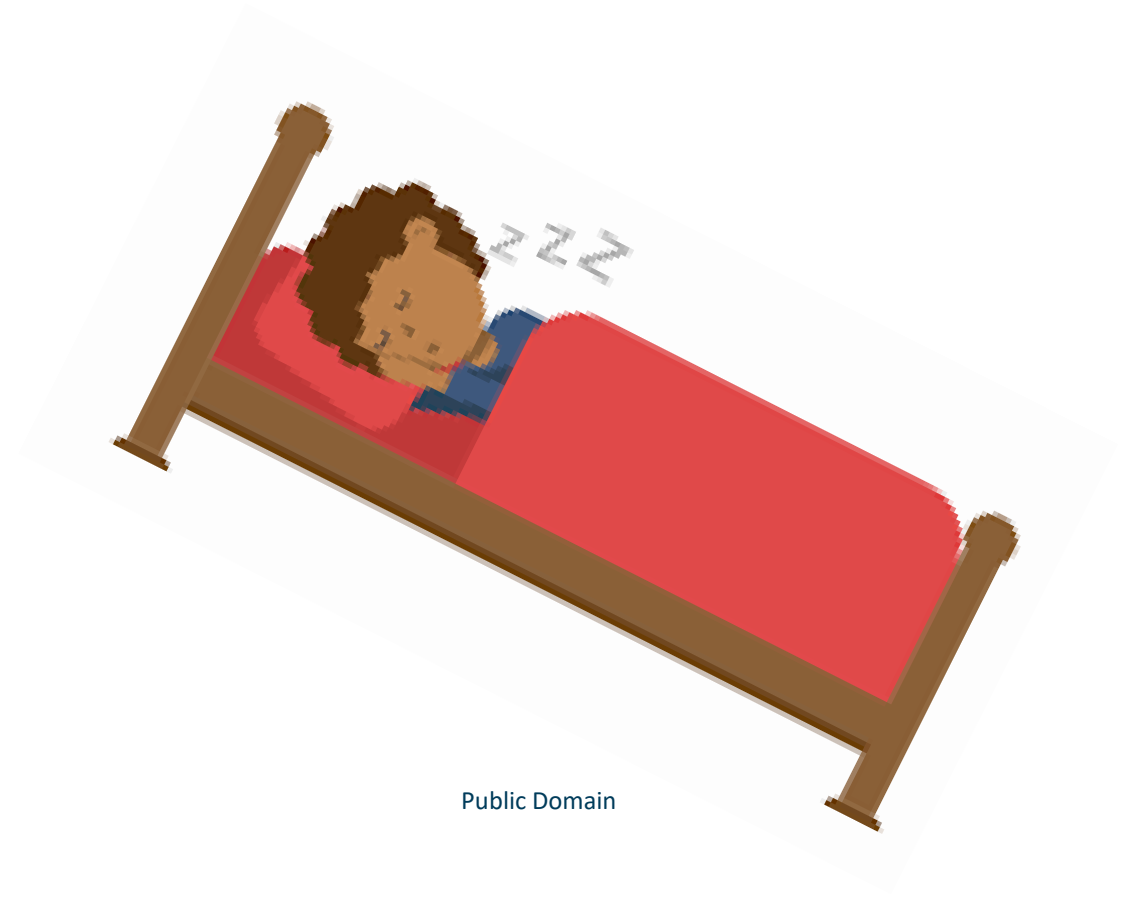
Glasgow Coma Scale

- Three tests: eye, verbal and motor
- GCS score: 3 to 15
- Eye (1-4 points)
 - Does not open, opens to painful stimuli, opens to voice, opens spontaneously
- Verbal (1-5 points)
 - No sound, incomprehensible sounds, inappropriate words, confused, oriented
- Motor (1-6 points)
 - No movements, decerebrate posturing, decorticate posturing, withdrawal to pain, localizes to pain, obeys commands

Intracranial Hypertension

Management

- **Head elevation**
 - Maximized venous drainage
- **Mannitol**
 - Increases plasma osmolarity
 - Draws fluid from tissues
- **Hyperventilation**
 - $\downarrow \text{CO}_2 \rightarrow \downarrow$ cerebral perfusion



Public Domain

Intracranial Hypertension

Management

- Sedation
 - Reduces metabolic demand
- Blood pressure regulation
 - Maintain CPP > 60 mmHg
 - $CPP = MAP - ICP$
- Fever control
 - Reduces metabolic demand
- **Most patients don't need fluids**



Freestockphotos.biza

Intracranial Pressure Monitoring

- Direct pressure measurement of ICP
- Four main anatomic sites:
 - Intraventricular
 - Intraparenchymal
 - Subarachnoid
 - Epidural
- **Allows control of CPP**

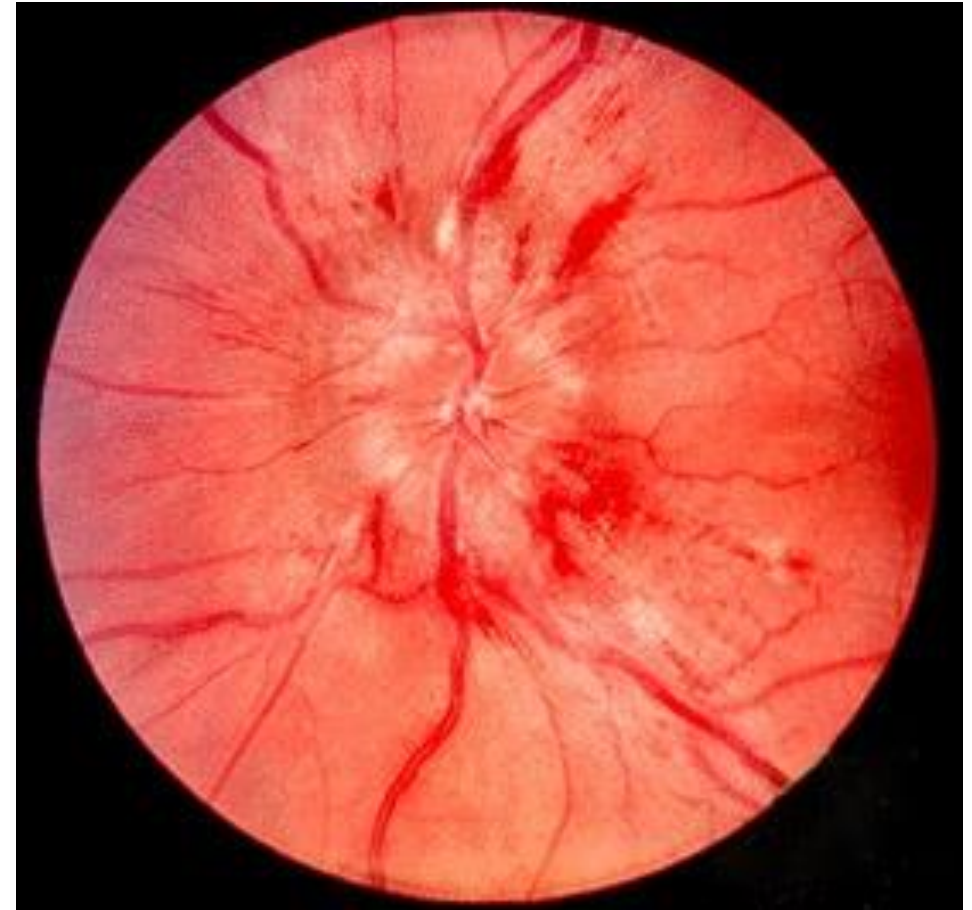
$$\text{CPP} = \text{MAP} - \text{ICP}$$



Pseudotumor Cerebri

Idiopathic intracranial hypertension

- ↑ ICP in absence of tumor or other cause
- **Intractable, disabling headaches**
- Papilledema



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Pseudotumor Cerebri

Idiopathic intracranial hypertension

- **CNVI (abducens) nerve palsy**
 - Lateral rectus muscle weakness
 - Affected eye cannot abduct
 - Diplopia
- **Pulsatile tinnitus**
 - Rushing water or wind sound
 - Transmission of vascular pulsations



Pseudotumor Cerebri

Idiopathic intracranial hypertension

- Common in **women of childbearing age (younger women)**
- Associated with **obesity**
- Case reports of onset after receiving tetracyclines
- Diagnosis:
 - MRI to exclude other causes
 - Lumbar puncture to measure pressure
- Medical treatment: **acetazolamide**
 - Decreases CSF formation
 - Alternative: topiramate

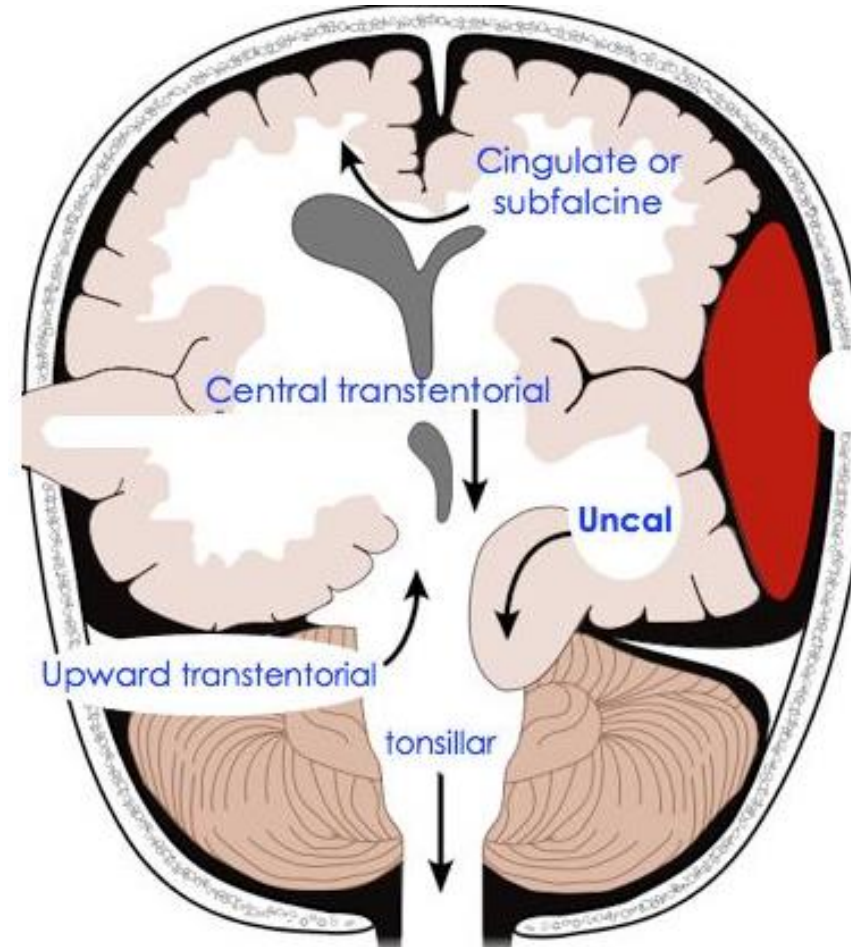


David Holt/Flickr/Public Domain

Herniation

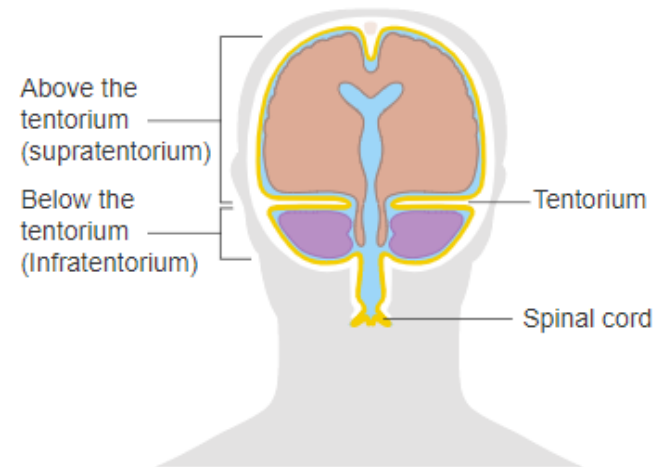
- Expanding volume: blood, tumor
- Forces brain through skull openings
- Four major herniation syndromes
 - Uncal
 - Central
 - Tonsillar
 - Subfalcine

(Brain + CSF + Blood) volume = Constant



Tentorium

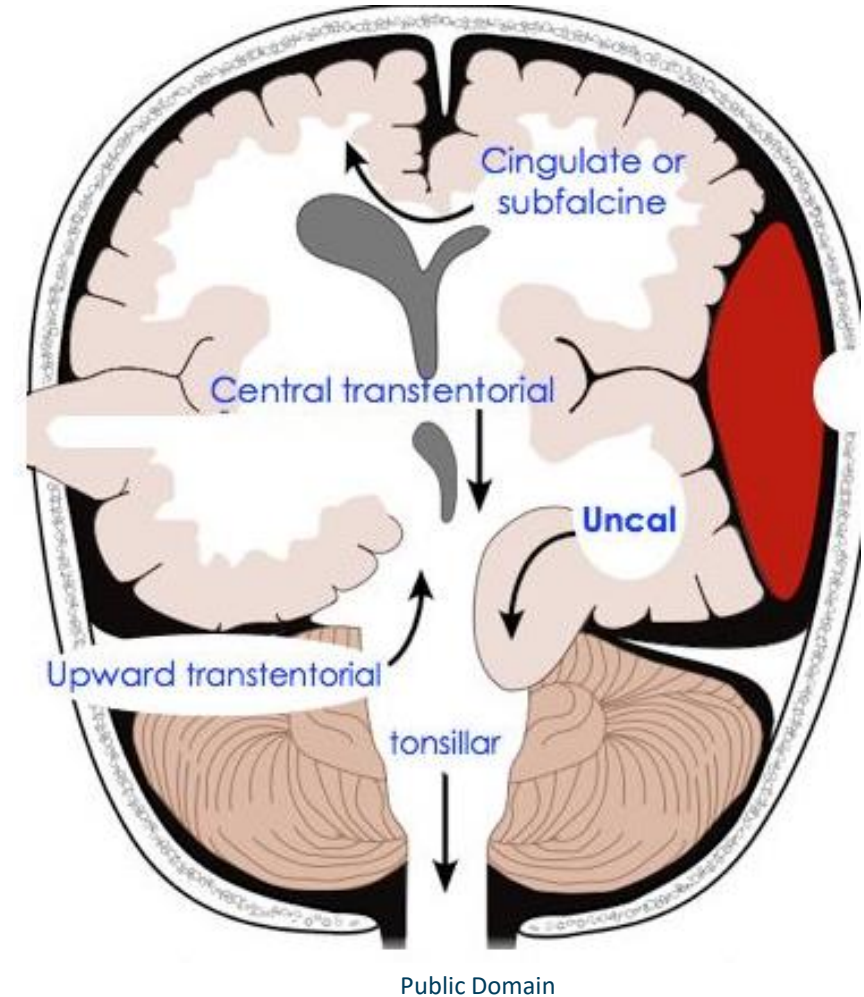
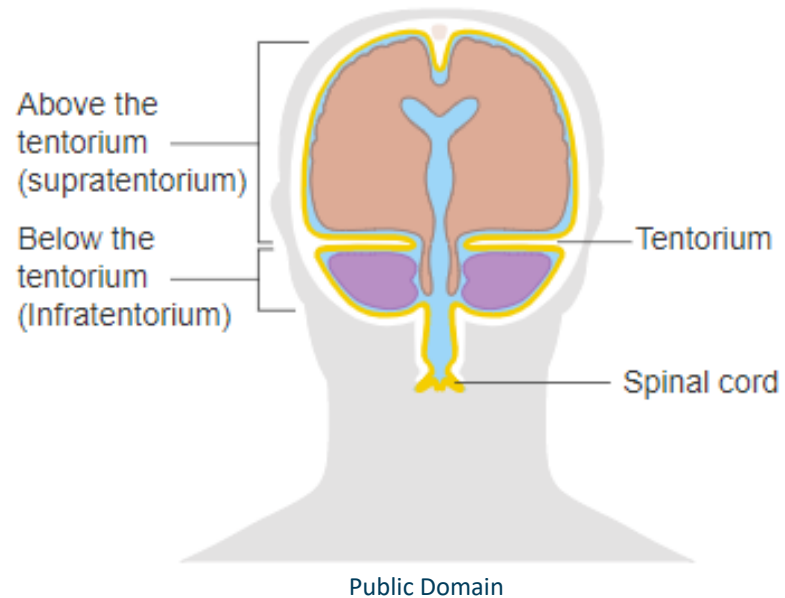
- Tentorium cerebelli
- Portion of the dura
- Covers posterior cranial fossa
- Separates occipital and temporal lobes from cerebellum and brainstem



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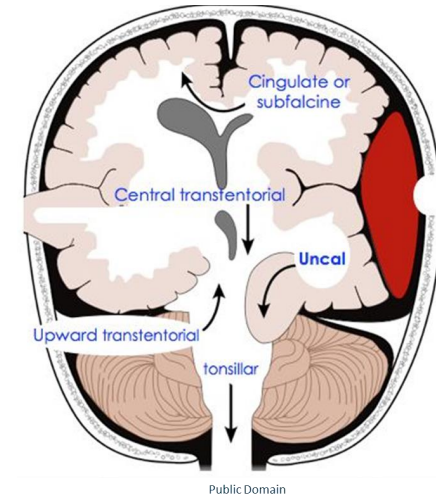
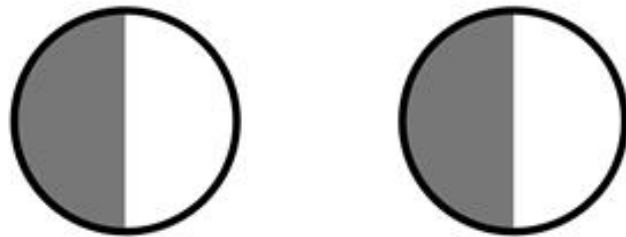
Uncal herniation

- Uncus = medial temporal lobe
- Herniates across tentorium
 - “Trans tentorial herniation”
- **Midbrain compression**



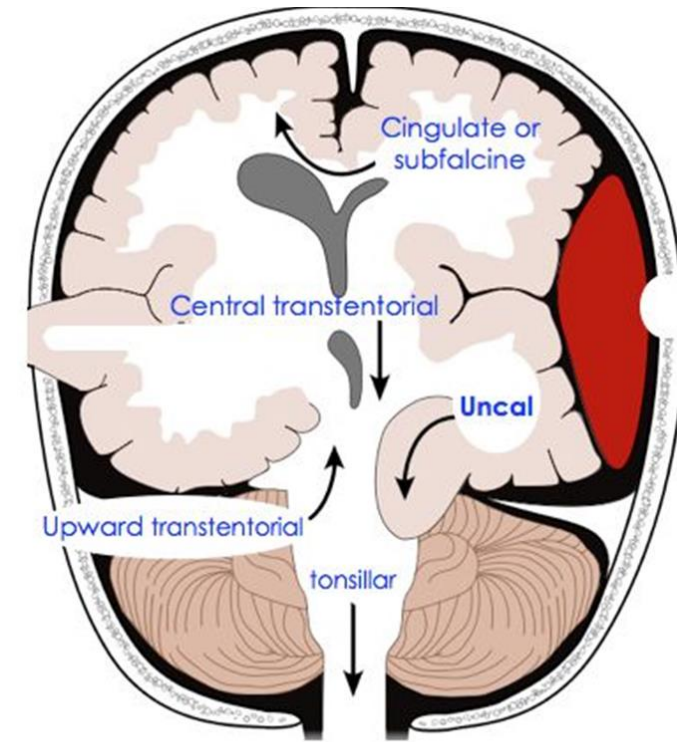
Uncal herniation

- **Ipsilateral CNIII compression**
 - First sign of uncal herniation
 - **Dilated (“blown”) pupil**
 - Lack of pupillary constriction to light
 - Eye down/out
- **Visual loss**
 - Collapses ipsilateral posterior cerebral artery
 - Homonymous hemianopsia



Uncal herniation

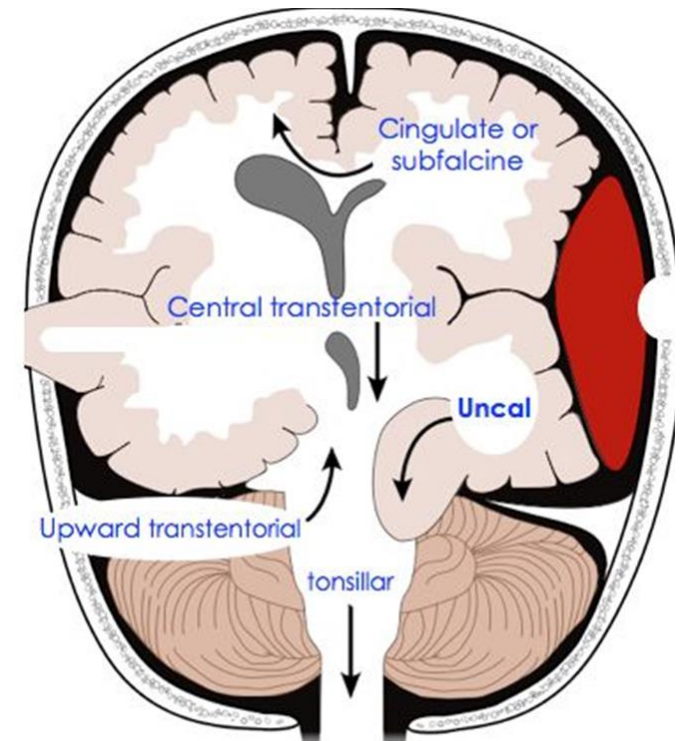
- **Paralysis**
 - Can be on side of lesion
 - Can also be on opposite side
 - Kernohan's notch
- Duret hemorrhage of pons and midbrain
 - Basilar artery rupture
 - Seen on brainstem imaging



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Central Herniation

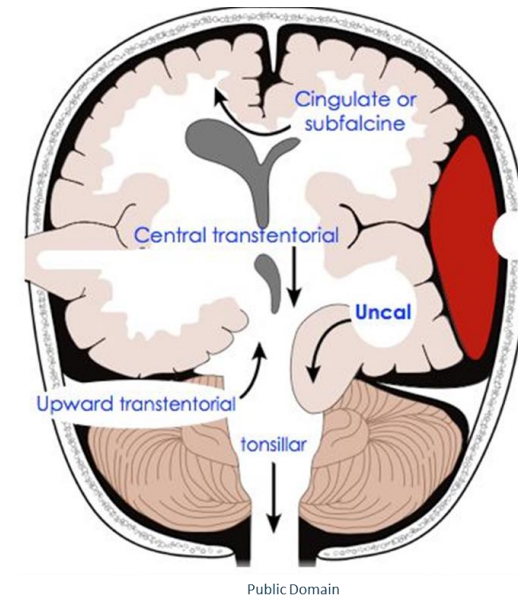
- Thalamus, hypothalamus
- Medial temporal lobes forced through tentorium cerebelli
- **Somnolence, loss of consciousness**
- Posturing
- Often fatal



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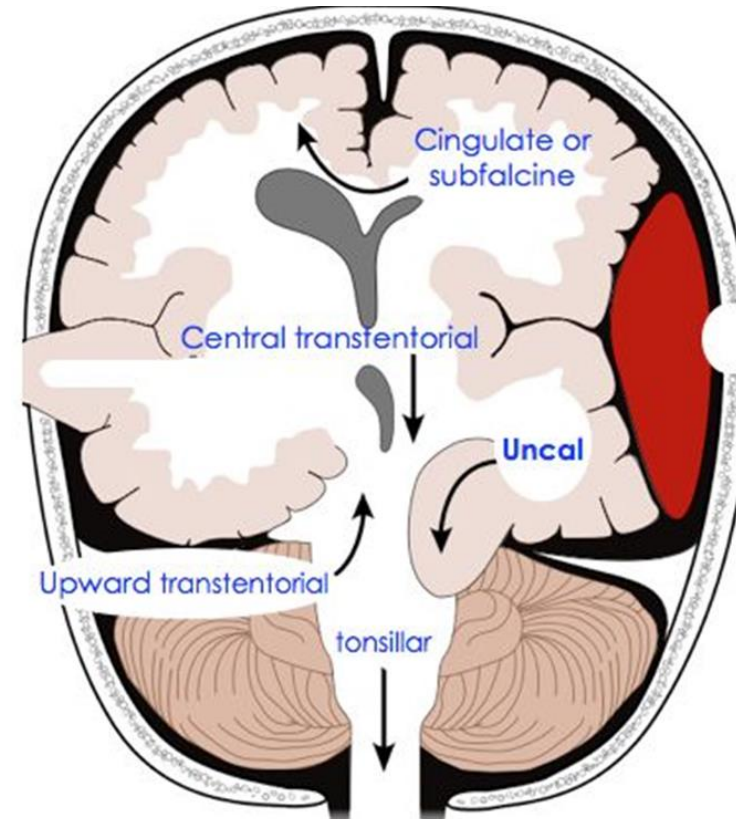
Tonsillar Herniation

- Cerebellar tonsils herniate downward through the foramen magnum
- Commonly caused by a **posterior fossa mass lesion**
- Compression of medulla
- Depression of respiration and cardiac rhythm control
- Cardiorespiratory failure



Subfalcine Herniation

- Cingulate gyrus
- Extends under falx cerebri (dura)
- Compression ipsilateral ACA
- **Contralateral leg paresis**



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Traumatic Brain Injury

Jason Ryan, MD, MPH



Traumatic Brain Injury

- Sudden-onset damage to brain tissue
- Major cause of permanent disability



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Traumatic Brain Injury

Types of Injuries

- Concussion
- Contusion
- Diffuse axonal injury
- Hemorrhage
 - Subdural
 - Epidural

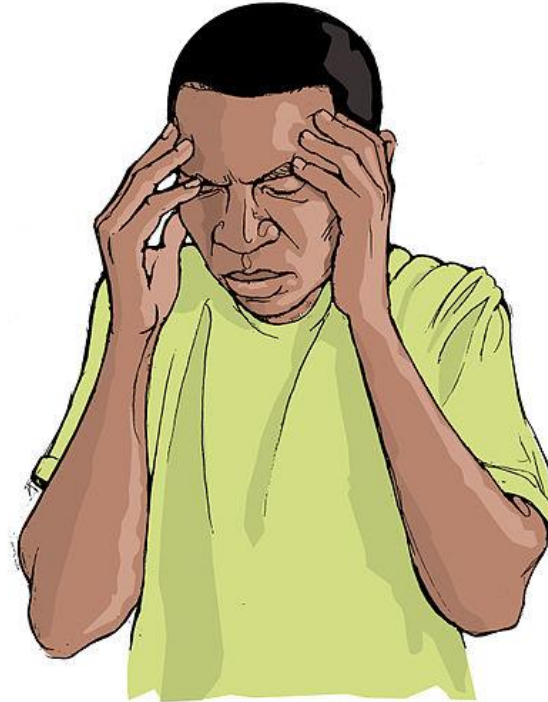


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Mild TBI

Concussion

- GCS 13 to 15
- Usually normal head imaging (if performed)
- No focal deficits
- Headache
- Dizziness
- Loss of balance
- Inability to concentrate
- Confusion
- Amnesia surrounding event



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Mild TBI

Management

- Monitor for 24 hours
- CT scan if worsening symptoms
- Slow return to sports once free of symptoms
- Usually at least 1 week of no sports



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Postconcussion Syndrome

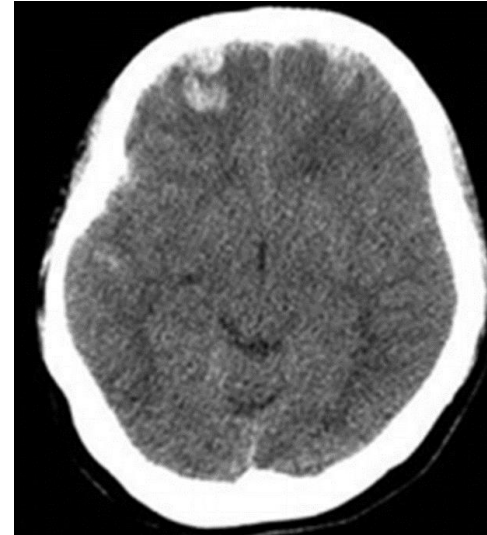
- Headache
- Dizziness
- Memory impairment
- Inability to concentrate
- Neuropsychiatric changes
 - Irritability
 - Anxiety
 - Depression
- Insomnia
- Symptoms maximal 7 to 10 days
- Usually resolve 1 month



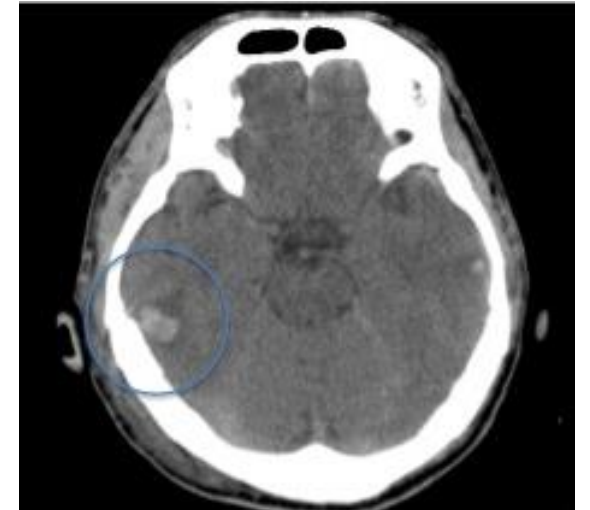
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Contusion

- Brain bruise
- Most common TBI lesions
- Often on frontal and temporal lobes



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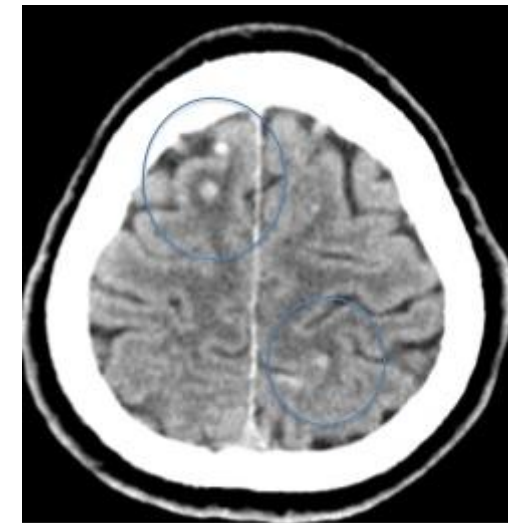
Rathachai Kaewlai/Slideshare

Diffuse Axonal Injury

- Shearing-type injury
- Affects white matter tracts
- Multiple small white lesions
- Often presents with coma
- Poor outcome



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Rathachai Kaewlai/Slideshare

Traumatic Brain Injury

Diagnosis

- Clinical exam
- Non-contrast head CT
 - Skull fractures
 - Contusions
 - DAI
 - Hematomas



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Glasgow Coma Scale

- Three tests: eye, verbal and motor
- GCS score: 3 to 15
- Eye (1-4 points)
 - Does not open, opens to painful stimuli, opens to voice, opens spontaneously
- Verbal (1-5 points)
 - No sound, incomprehensible sounds, inappropriate words, confused, oriented
- Motor (1-6 points)
 - No movements, decerebrate posturing, decorticate posturing, withdrawal to pain, localizes to pain, obeys commands

Glasgow Coma Scale

Classification of Severity

GCS	TBI Class
13-15	Mild
9-12	Moderate
≤ 8	Severe

} Need CT Scan

CT Scan Indications

Canadian CT Head Injury Rule

- For patients with minor head injuries
- GCS 13-15 plus one 1 of following:
 - Loss of consciousness
 - Amnesia to injury
 - Witnessed disorientation
- Exclusion criteria (usually need CT)
 - Neurologic deficit
 - Blood thinners
 - Seizure after injury

High Risk Criteria

GCS < 15 at 2hrs post injury

Open or depressed skull fracture

Basilar skull fracture

Age \geq 65 years

\geq 2 Episode of vomiting

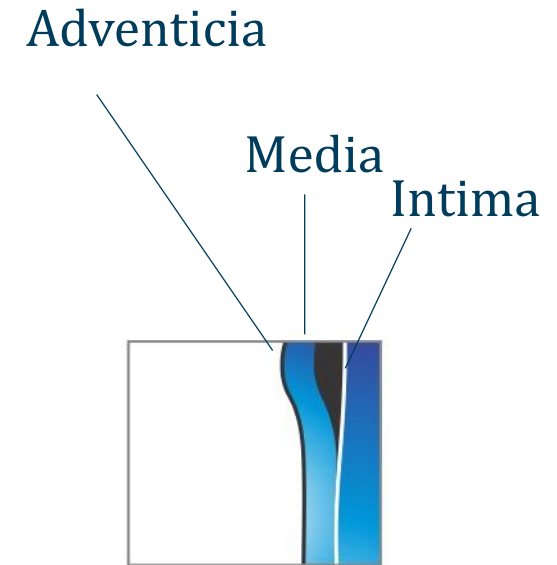
Medium Risk Criteria

Retrograde amnesia to event
 \geq 30 minutes

“Dangerous” mechanism

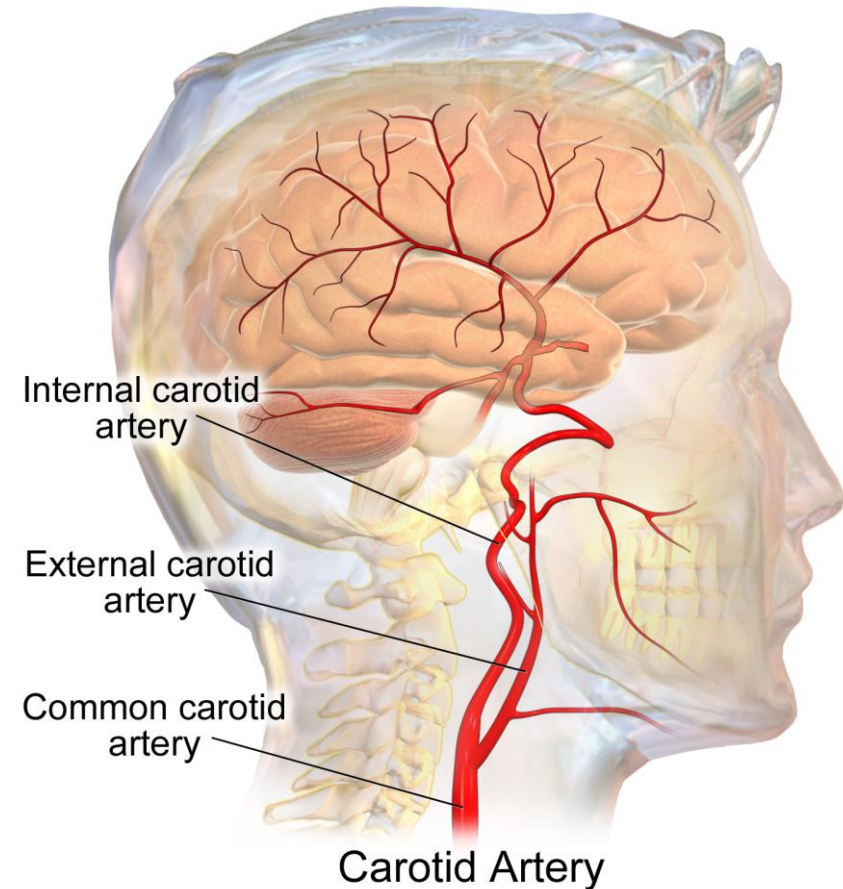
Arterial Dissections

- Occur in carotid and vertebral arteries
- Tear in intimal layer of arterial wall
- Creation of false lumen
 - Blood between intima and media
- Blood flow compromised → **ischemia**
- Thrombus may form
- Spontaneous
 - Rare cause of stroke
 - Marfan syndrome, Ehlers-Danlos
- Traumatic



Carotid Artery Dissection

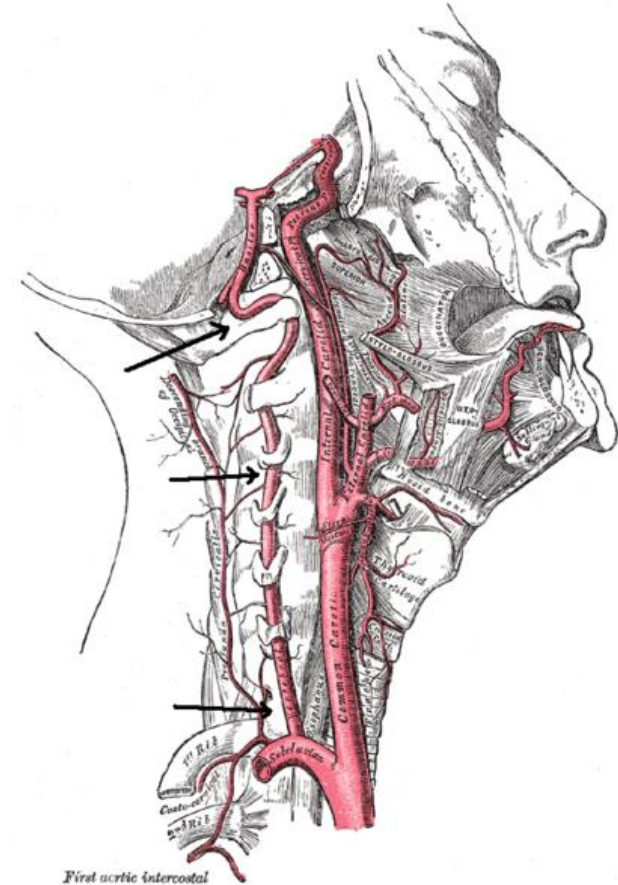
- Unilateral neck pain
- Possible carotid bruit
- TIA/Stroke symptoms
 - Anterior circulation (MCA or ACA)
- Diagnosis:
 - CTA/MRA
 - Carotid ultrasound
- Treatment:
 - Aspirin
 - Anticoagulation
 - Endovascular stenting



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Vertebral Artery Dissection

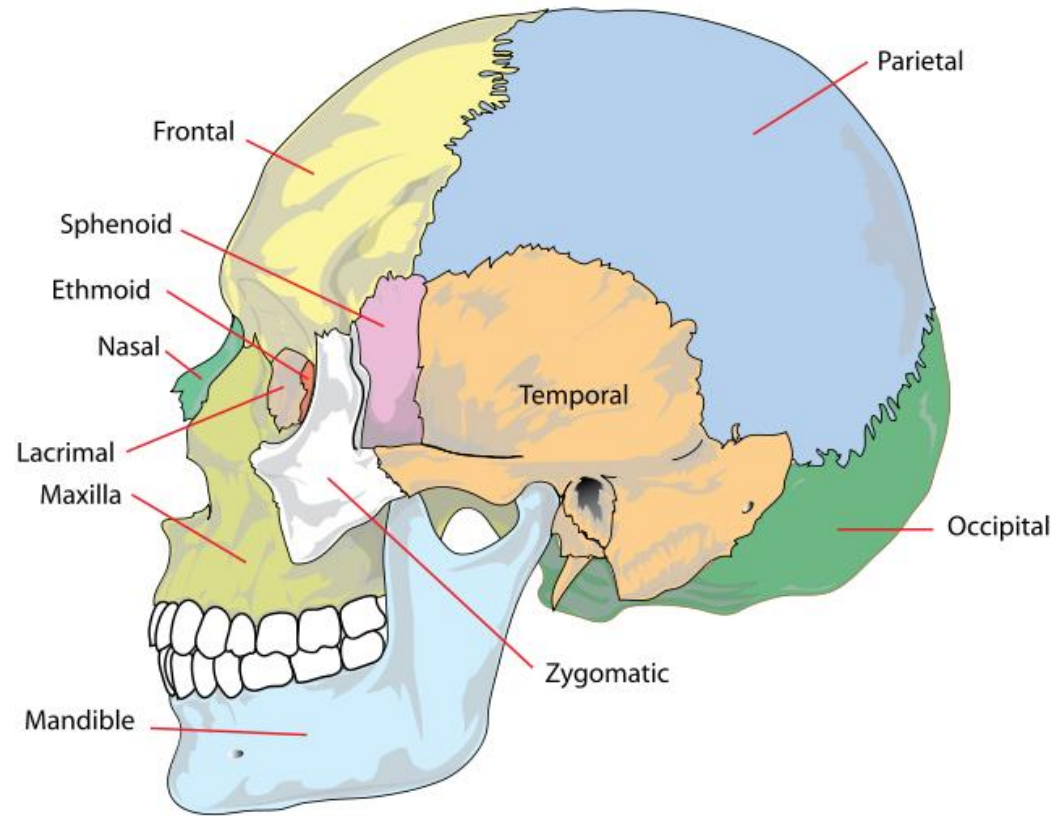
- Unilateral neck pain
- Headache – cervical or occipital area
- Neck bruit
- Brainstem and cerebellar ischemia
 - Lateral medullary syndromes (Wallenberg Syndrome)
 - Cerebellar infarctions
- Diagnosis: CTA/MRA
- Similar treatment carotid dissections



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Skull Fractures

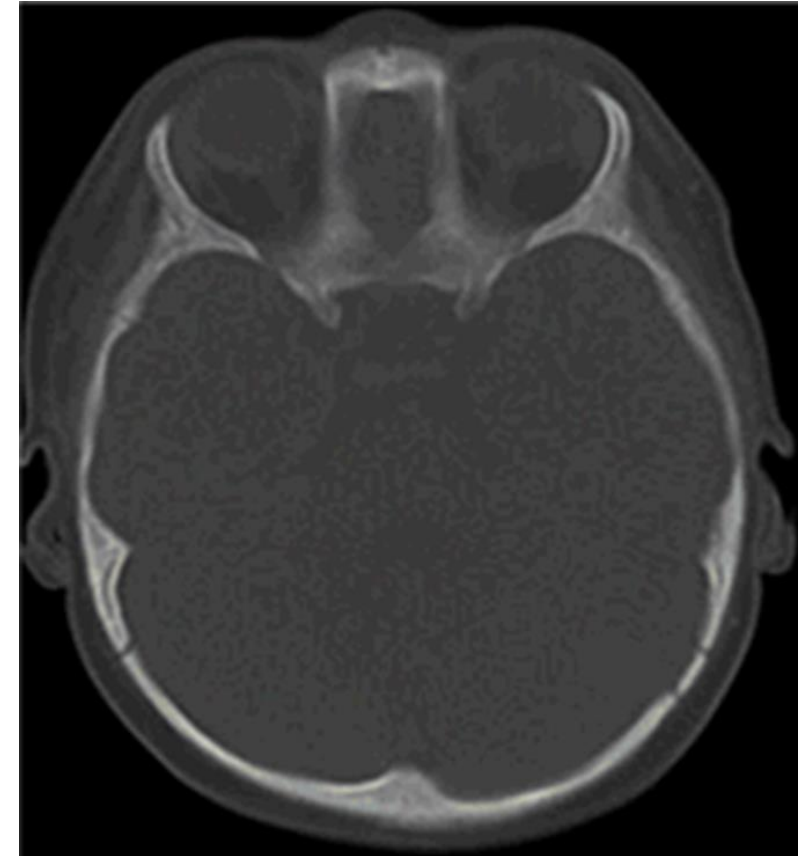
- Break in one of 8 skull bones
- Can cause intracranial bleeding
- Can lead to CNS infection
- Key subtypes:
 - Linear
 - Depressed
 - Basilar



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Linear Skull Fracture

- Often carry no clinical significance



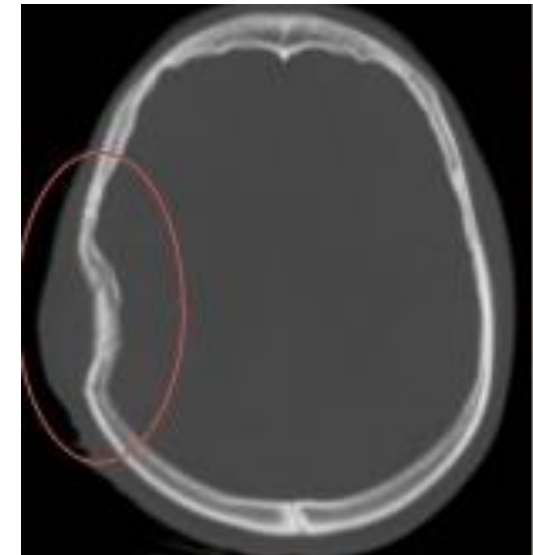
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Depressed Skull Fracture

- Depression in skull
- Often associated with brain injury
- Bone fragments can tear dura
- Portal of bacterial entry into CSF → infection



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Rathachai Kaewlai/Slideshare

Basilar Skull Fracture

- Fracture in one of five bones in skull base
 - Ethmoid
 - Frontal
 - Temporal
 - Sphenoid
 - Occipital
- Often cause epidural hematomas
- Characteristic physical exam findings



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Basilar Skull Fracture

- “Battle sign”: retroauricular or mastoid ecchymosis
- “Raccoon eyes”: periorbital ecchymosis
- Hemotympanum: blood behind tympanic membrane
- Clear rhinorrhea or otorrhea



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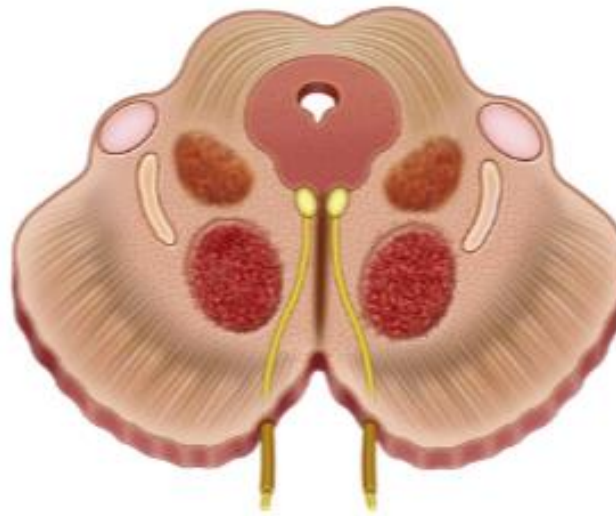
Parkinson's Disease

Jason Ryan, MD, MPH



Parkinson's Disease

- Movement disorder
- Loss of dopamine-containing neurons
- Substantia nigra of the basal ganglia (midbrain)
- Reduced excitatory input to motor cortex



Midbrain

Parkinson's Disease

Risk Factors

- Older age
- Family history of Parkinson's disease
- Smoking lowers risk (protective)



Parkinson's Disease

Diagnosis

- Clinical diagnosis
- Classic features: bradykinesia, tremor and rigidity
- Absence of alternative diagnoses
- Response to therapy

Feature	Description
Bradykinesia	Difficulty initiating movements
Tremor	Often initial feature; Resting “pill-rolling” tremor, improves with movement; worse with distractibility
Cogwheel rigidity	Resistance to passive movement

Bradykinesia

- Generalized slowness of movement
- Occurs in 80% of patients
- Difficulty buttoning clothes or tying shoes
- Dragging the legs
- Short, shuffling steps
- Feelings of unsteadiness



Parkinson's Disease

Other features

- Masked facial expression
 - Lack of movement in facial expression
- Shuffling gait
 - Narrow-based
 - Short steps
 - Freezing
- Dementia (late)



Ramanan Chandrasekaran/Slideshare

Neurogenic Orthostatic Hypotension

- Loss of autonomic nervous system function
- Supine hypertension
- Orthostatic hypotension
- Occurs in 20 to 60% of Parkinson's patients
- More common with levodopa treatment



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Parkinson's Treatments

- Goals: increase dopamine activity or block ACh activity
- Carbidopa-Levodopa
- Monoamine oxidase type-B inhibitors
- COMT Inhibitors
- Dopamine agonists



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Dopamine Drugs

Side Effects

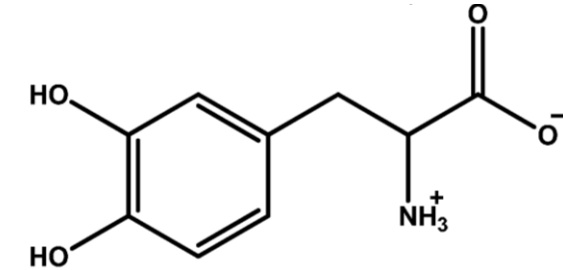
- Nausea and vomiting
- Orthostatic hypotension
- Excessive sleepiness
- Dyskinesia (involuntary movement)
- Confusion and hallucinations



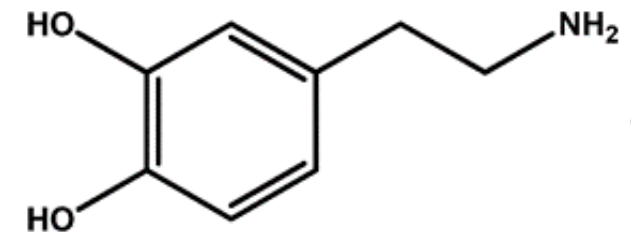
Carbidopa-Levodopa

Sinemet

- Levodopa (L-dopa) crosses blood-brain barrier
- Converted to dopamine in CNS
 - Enzyme: dopa decarboxylase
- Peripheral decarboxylase breaks down L-dopa
 - Limits benefit
 - ↑ peripheral dopamine → cardiovascular side effects
- Carbidopa inhibits peripheral decarboxylase
- Given together: Carbidopa-Levodopa



Levodopa



Dopamine

Carbidopa-Levodopa

Adverse Effects

- **“On-Off” phenomenon**
- Depletion of natural dopamine occurs over long term
- Levodopa: short half-life (~90 minutes)
- Increased response to levodopa
- Loss of response between doses



On-Off Phenomenon

Carbidopa-Levodopa

- **Off symptoms**
 - “Wearing off”
 - Symptoms return 3-4 hours after each dose
 - Freezing of gait
- **On symptoms**
 - Dyskinesia
 - Abnormal, involuntary movements



Carbidopa-Levodopa

Other Adverse Effects

- **Four common side effects:**
 - Headache
 - Nausea
 - Sleepiness
 - Dizziness
- Side effects in older patients:
 - Confusion, hallucinations, delusions (dopamine excess)



Entacapone and Tolcapone

COMT Inhibitors

- **Inhibit catechol-O-methyltransferase (COMT)**
- Enzyme that breaks down levodopa
- **Only used in combination with levodopa**
 - Boosts levodopa effects to prevent off-periods
- Entacapone: peripheral COMT inhibition
- Tolcapone: peripheral and central COMT inhibition
- Adverse effects: stimulation (excessive dopamine activity)
- Tolcapone associated with hepatotoxicity
- Urine turns orange (harmless)



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Selegiline and Rasagiline

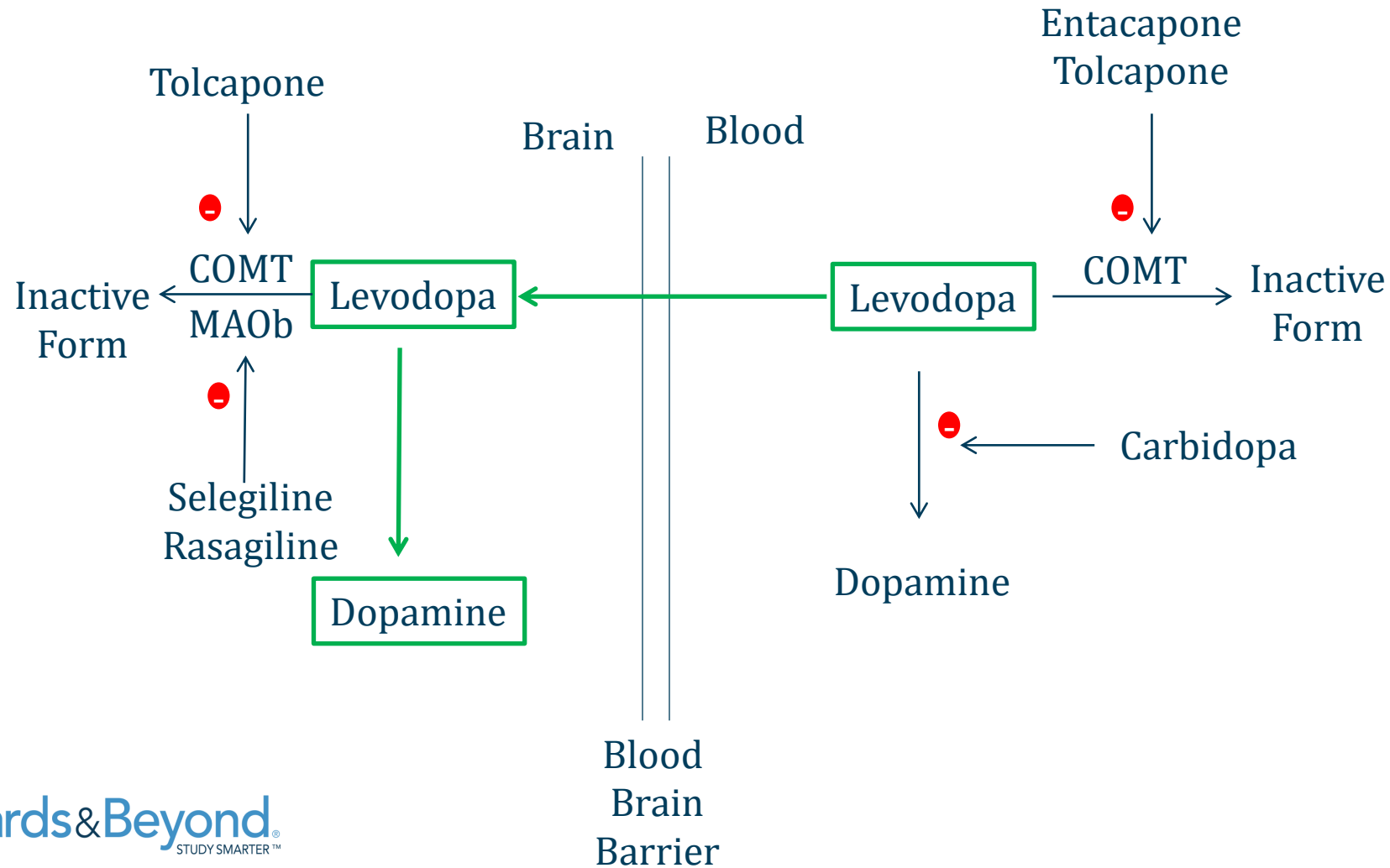
MAO-B Inhibitors

- **Inhibit monoamine oxidase type B (MAO-B)**
 - Central dopamine breakdown enzyme
 - Breaks down dopamine more than 5HT
- Increases central dopamine levels
- Used alone or added to carbidopa-levodopa
- Side effects:
 - Nausea, vomiting
 - Hypotension
 - Excessive daytime sleepiness
 - Serotonin syndrome (rare)



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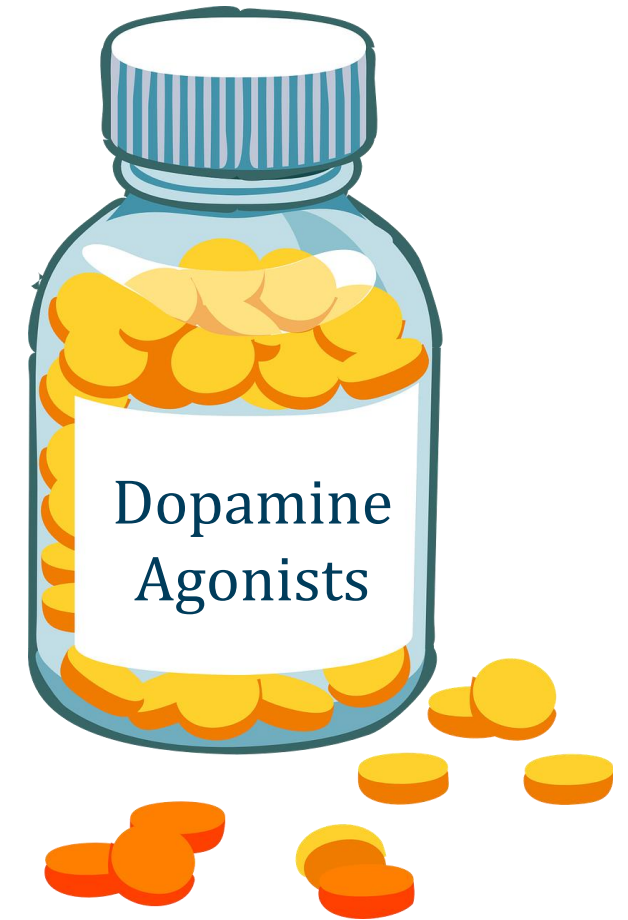
Parkinson's Drugs



Dopamine Agonists

Pramipexole, Ropinirole, Rotigotine

- Used as monotherapy in early disease
- Oral: pramipexole and ropinirole
- Transdermal patch: rotigotine
- Adverse effects similar to levodopa
 - Nausea/vomiting
 - Sleepiness
 - Orthostatic hypotension
 - Confusion
 - Hallucinations



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Tremor-Dominant Parkinson's

- Symptomatic tremor
- No significant bradykinesia or gait problems
- Better prognosis than other forms of Parkinson's
- **Trihexyphenidyl and benztropine**
 - M1 muscarinic acetylcholine receptor antagonists
 - Side effects: sedation, dry mouth
- **Amantadine**
 - Antiviral drug
 - Dopamine agonist, anticholinergic
 - Can also be used in mild Parkinson's disease



Parkinson's Treatments

Drug	Mechanism
Carbidopa-Levodopa	Converted to dopamine in CNS
Entacapone and Tolcapone	COMT inhibitors; prevent levodopa breakdown
Selegiline and Rasagiline	MAO-B inhibitors; prevent levodopa breakdown
Pramipexole and Ropinirole	Dopamine agonists
Trihexyphenidyl and Benztropine	Muscarinic antagonists
Amantadine	Dopamine agonist, anticholinergic (also an antiviral)

Parkinson's Disease

Drugs to Avoid

- Metoclopramide
- Prochlorperazine
- Antipsychotics
 - Least movement side effects: **quetiapine**
 - “Quetiapine is quiet”



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Surgical Therapy Parkinson's

- Young patients often develop toxicity from long term use of drugs
- Prior surgeries used:
 - Pallidotomy (partial ablation of globus pallidus)
 - Thalamotomy (partial ablation of thalamus)
- Modern option: **deep brain stimulation**
 - Subthalamic nucleus
 - Internal globus pallidus
 - High frequency DBS suppresses neural activation
 - Reversible – no destruction of tissue



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Lewy Body Dementia

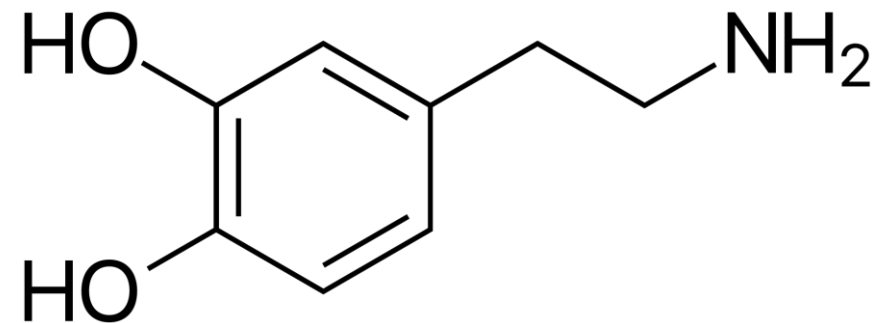
- Lewy body: protein collections in neurons
- Seen in Parkinson's disease and Lewy body dementia
- Parkinson's disease with dementia
 - Dementia develops after movement symptoms
- Lewy body dementia
 - Dementia develops *before or at the same time* as movement symptoms
- Both diseases probably a continuum of same disorder



Charles E. Driscoll, MD

Parkinsonism

- Symptoms of tremor, bradykinesia, rigidity and postural instability
- May occur in **neurodegenerative disorders**
 - Multisystem atrophy, progressive supranuclear palsy, corticobasal degeneration
 - “Parkinson-plus syndromes”
 - **Poor response to levodopa**
- May occur secondary to **drugs that block dopamine activity**
 - Antipsychotic agents
 - Metoclopramide



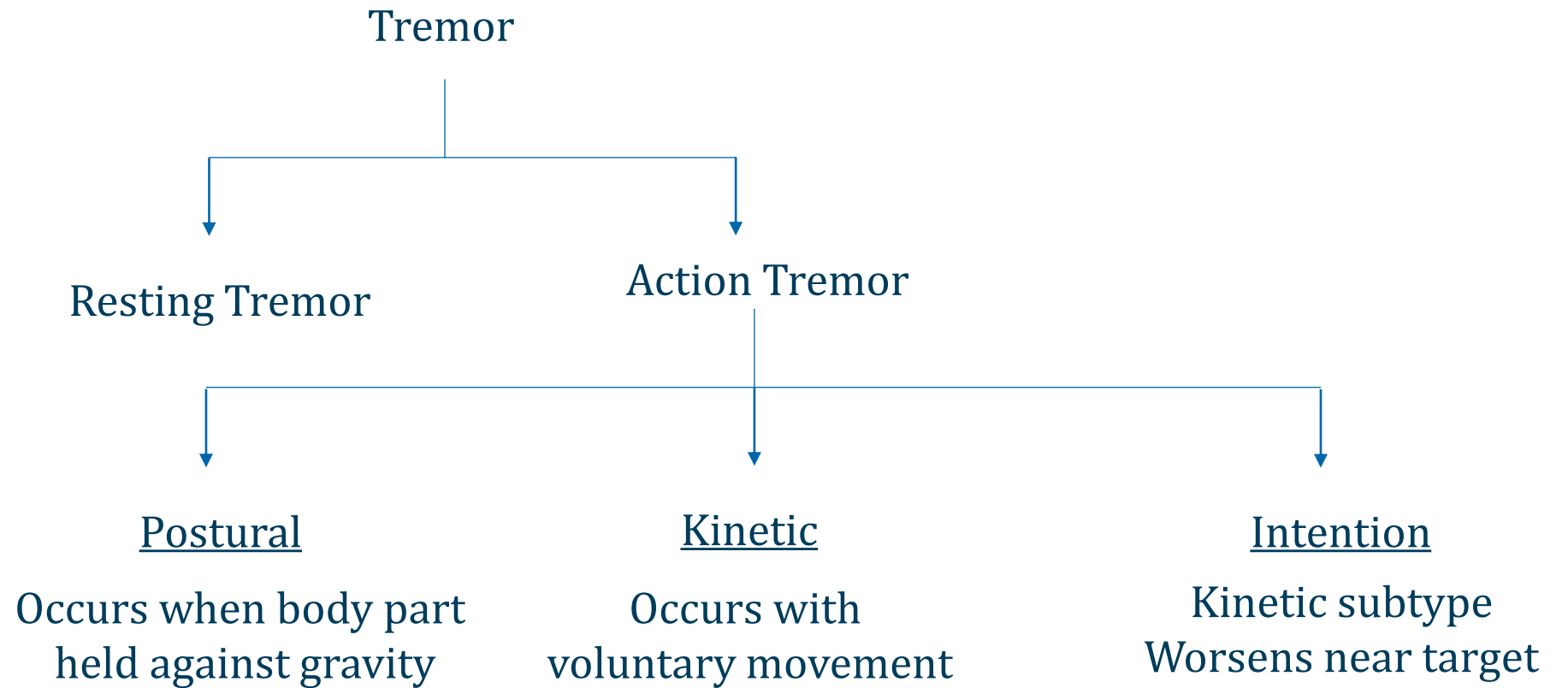
Dopamine

Movement Disorders

Jason Ryan, MD, MPH



Tremors



Resting Tremor

- Usually due to **Parkinson's disease** or variant
- “Pill-rolling” tremor
- **Improves with movement**
- Frequency: 4-6 Hz



Physiologic Tremor

- Postural tremor
- Occurs in **normal patients**
- Caused by increased **sympathetic activity**
 - Anxiety
- Frequency: 10-12 Hz



Essential Tremor

- Old name: “Benign familial tremor”
- Usually involves **arms and hands**
 - Worsened with arms outstretched
 - Significantly affects writing
- Some patients have head shaking
- Usually bilateral



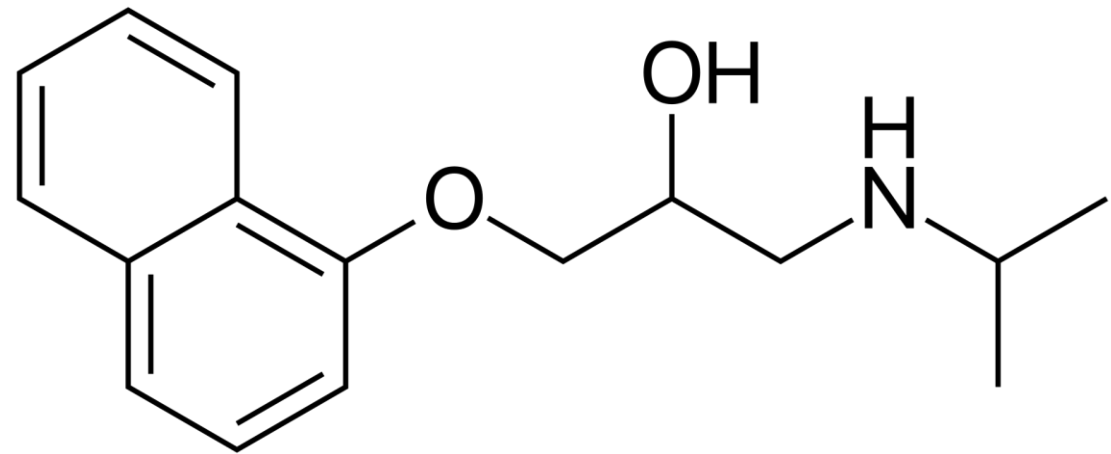
Essential Tremor

- Activated by **voluntary movements**
 - Provoked by finger to nose testing
- Frequency: 6-12 Hz (fast)
 - “Fine tremor”
- **Alcohol improves symptoms**
- Patients may self-medicate



Essential Tremor

- Genetic predisposition
- Can be confused with Parkinson's
 - ET much more common
 - ET can occur in young patients
 - Opposite effects of rest/movement
- Drug treatment
 - **Propranolol (beta blocker)**



Propranolol

Intention Tremor

- Occurs with intentional action
- Usually involves the hand
 - Usually perpendicular to movement of hand
 - **Worsens as hand approaches target**
 - Hand often over or undershoots target
- Caused by **cerebellar outflow disease**
 - Stroke
 - Multiple sclerosis
- Often unilateral
- Frequency: 2 - 4 Hz (slow)
 - “Coarse tremor”



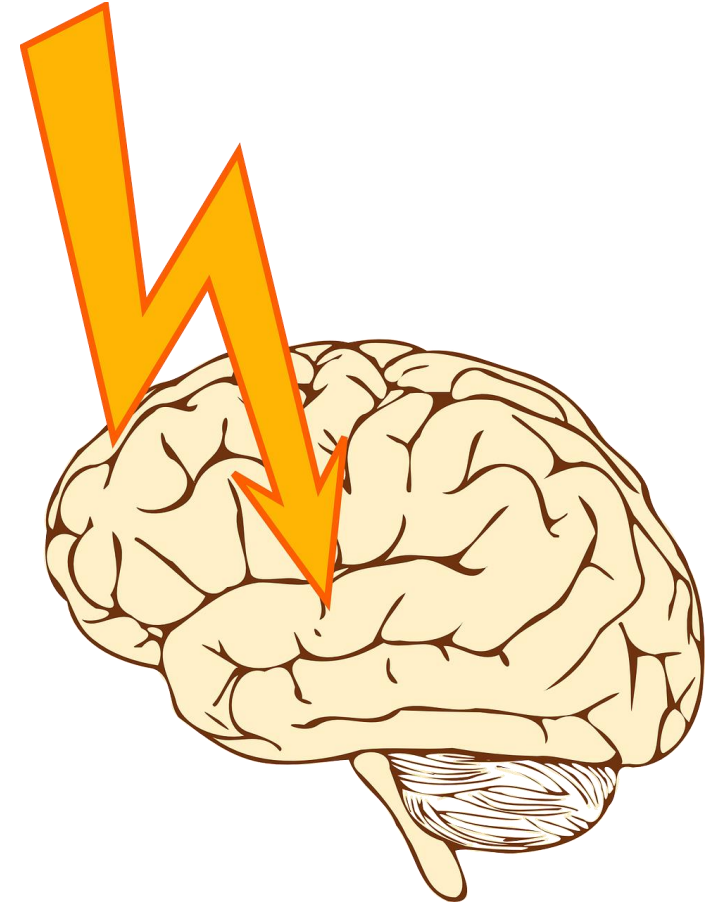
Functional Tremor

- Type of functional movement disorder
- Abnormal involuntary movement
- No evidence of known neurologic cause
- Abrupt onset
- Immediate maximal severity
- Often history of emotional or physical trauma
- **Improves with distraction**
- Varying clinical features



Myoclonus

- **Brief, shock-like, involuntary movement**
- Physiologic
 - Occurs in normal patients
 - Common with sleep
- Essential
 - Hereditary or sporadic
 - No other neurologic illness
- Epilepsy
 - Myoclonic seizures



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Fasciculations

- Small, local, involuntary muscle contraction
- Often apparent under the skin
- Usually benign
- Seen with lower motor neuron lesions
- Classic feature of **amyotrophic lateral sclerosis**

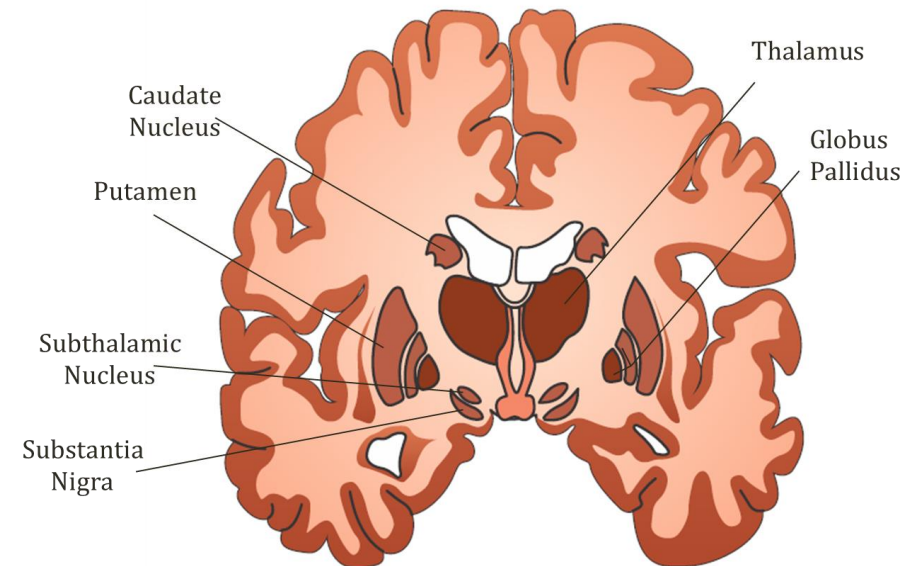
Chorea

- Involuntary brief, random, irregular contractions
- Patient appears restless
- Can be idiopathic, hereditary or part of another disorder
- Part of a spectrum of hyperkinetic movement disorders

Disorder	Features
Chorea	Involuntary brief, random, irregular contractions
Athetosis	Slow, writing, “snake-like” movements
Choreoathetosis	Chorea + Athetosis
Ballism	Large amplitude movements of arms and legs – flinging/kicking

Hemiballism

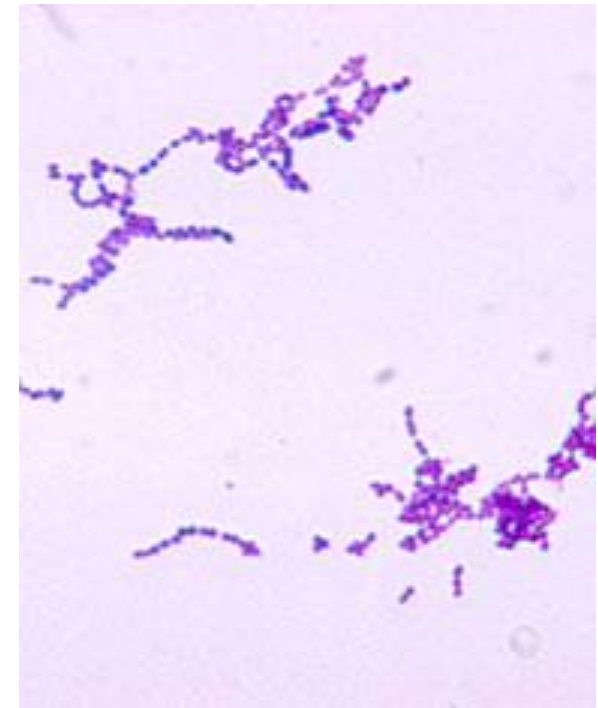
- Flinging movements of limbs on one side
- Classically attributed to lesions of the **subthalamic nucleus**
 - Part of basal ganglia
 - Damage often secondary to stroke



Sydenham's Chorea

- Occurs in children with **acute rheumatic fever**
- Consequence of **group A streptococcal infection**
- Antibodies react with neurons

Group A Streptococcus



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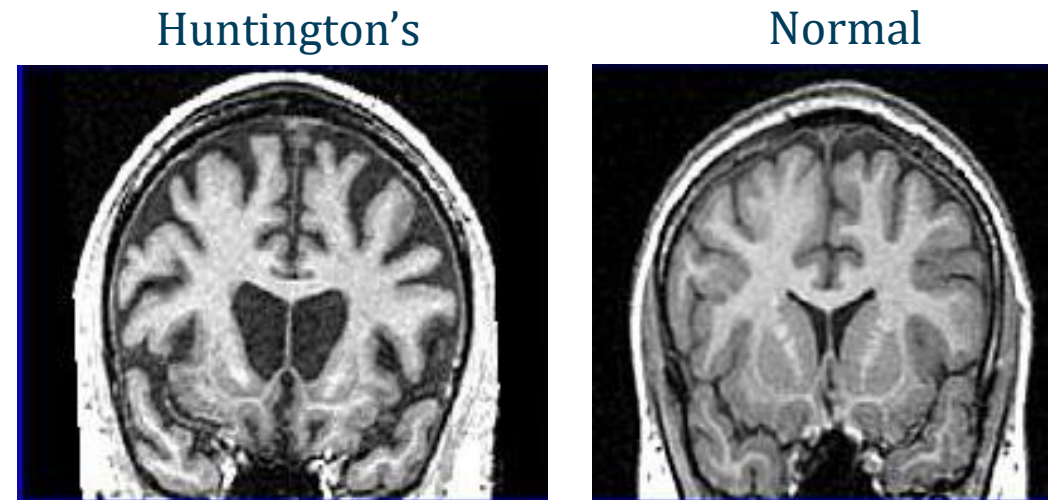
Jones Criteria

Major	Minor
Carditis	Fever
Polyarthrititis	Arthralgia
Chorea	Prior RF
Erythema marginatum	↑WBC, ESR, CRP
Subcutaneous nodules	Prolong PR interval

2 Major or 1 Major & 2 Minor
(with evidence of strep infection)

Huntington's Disease

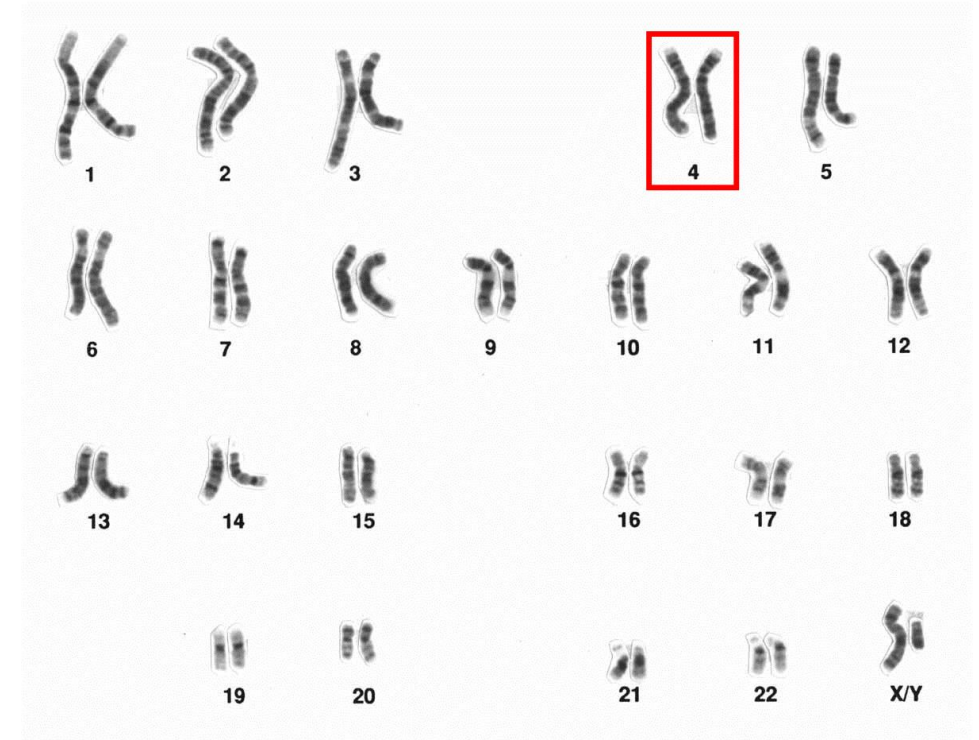
- Inherited autosomal dominant disorder
- Degeneration in **striatum**
 - Striatum = caudate + putamen
- Loss of **GABA-producing neurons**
- Brain imaging (late disease)
 - Marked caudate degeneration
 - Lateral ventricles appear large



Wikipedia/Radiopedia

Huntington's Disease

- Mutation in the **HTT gene on chromosome 4**
 - CAG repeat in gene
 - Normal 10-35 repeats
 - Huntington's 36 to 120 repeats
- Worse/earlier symptoms each generation
 - "Anticipation"
- Diagnosis: genetic testing



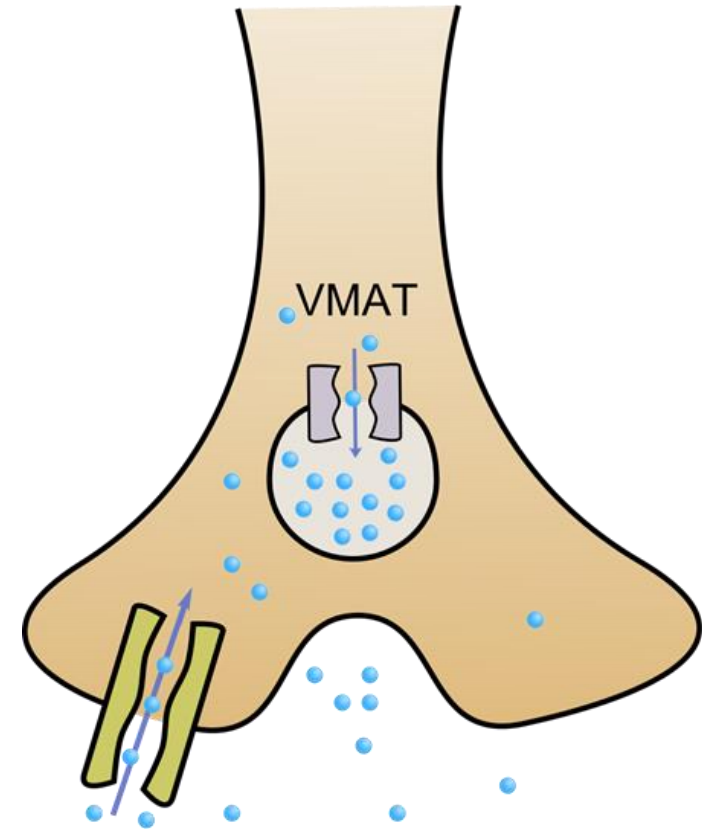
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Huntington's Disease

- Onset of symptoms 30s-40s
- Death after 10-20 years
- **Chorea**
- Aggression
- Depression
- Dementia
- Can be mistaken for substance abuse

Huntington's Chorea Treatment

- Dopamine associated with chorea
- Decreased dopamine improves chorea
- **Tetrabenazine and reserpine**
 - Inhibit vesicular monoamine transporter (VMAT)
 - Limit dopamine vesicle packaging / release
- Antipsychotic drugs
 - Dopamine receptor antagonists



Tardive Dyskinesia

- Adverse effect of long-term use of antipsychotic drugs
- **Choreoathetosis**
 - Mouth, tongue, face, limbs
- Smacking lips
- Grimacing
- **Often irreversible**
 - Stopping drug doesn't help



Needpix.com/Public Domain

Dystonia

- Involuntary muscle contractions
- **Sustained and prolonged**
 - Contrast with myoclonus (rapid, jerking)
- Focal or segmental
- Associated with overuse of muscle groups

Writer's Cramp



Common Dystonias

Dystonia	Features
Cervical (“spasmodic torticollis”)	Neck turned with head tilt
Blepharospasm	Involuntary blinking or eye closure
Spasmodic dysphonia	Voice breaks that interrupt normal speech
Oromandibular/lingual	Jaw clenching or tongue protrusion
Task specific dystonia	Writer’s cramp/musician's dystonia

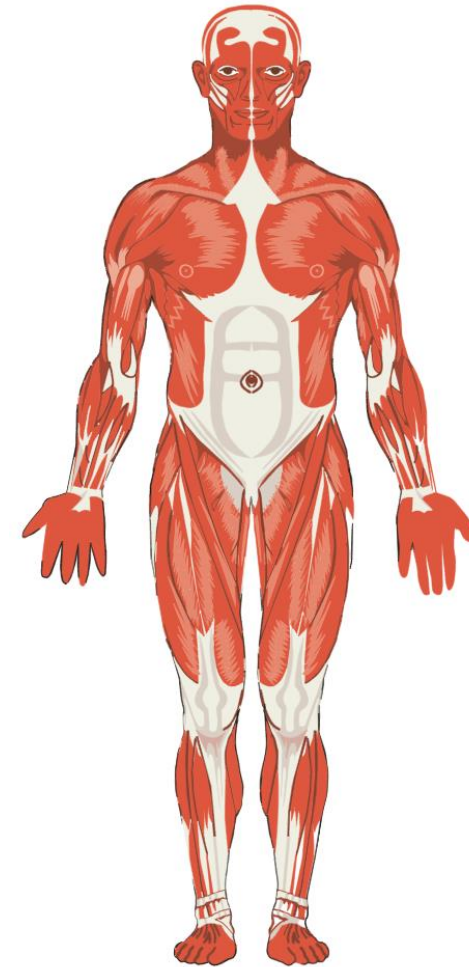
Dystonia

Treatment

- Dystonic reactions to antipsychotic medications:
 - **Benztropine (anticholinergic)**
 - **Diphenhydramine (antihistamine)**
- Levodopa-carbidopa
 - Small oral dose resolves some dystonias completely
- Botulinum toxin injection

Stiff Person Syndrome

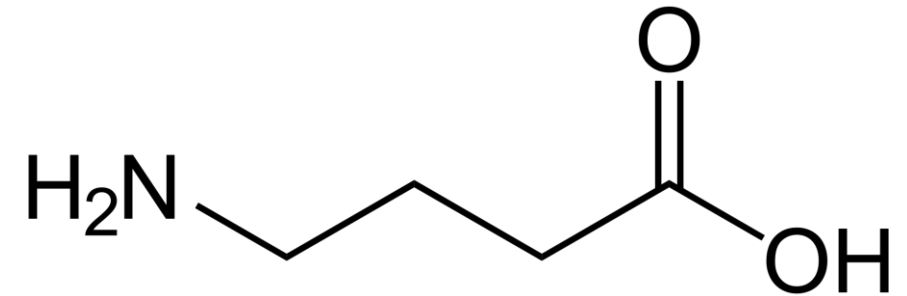
- Progressive muscle stiffness, rigidity, and spasms
- Involves **axial muscles**
 - Lumbar
 - Trunk
 - Proximal limbs
- Impairs ambulation



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Stiff Person Syndrome

- Exact cause unknown
- Likely related to **impaired GABA activity**
- Many autoimmune associations
 - Type I diabetes
 - Antibodies against GABA neural pathways
 - Anti-glutamic acid decarboxylase (GAD) antibodies



Gamma amino butyric acid
(GABA)

Stiff Person Syndrome

- Diagnosis: clinical plus supporting evidence
 - Electromyography (EMG)
 - Anti-GAD antibodies
 - Response to benzodiazepines
- First line treatment: **benzodiazepines**
 - Diazepam and clonazepam often used
 - Second line: baclofen



Wikipedia/Public Domain

Restless Leg Syndrome

- Uncomfortable urge to move legs
- Urge relieved by frequent movement
- Occurs during rest or inactivity, especially evenings
- Associated with **low serum ferritin**



Restless Leg Syndrome

- Diagnosis: clinical
- Iron replacement if ferritin low
- Behavioral treatment: exercise, reduced caffeine
- Drug treatment options:
 - Dopamine agonists: pramipexole or ropinirole
 - Neuropathic pain drugs: gabapentin and pregabalin



Cerebellar Disorders

Jason Ryan, MD, MPH

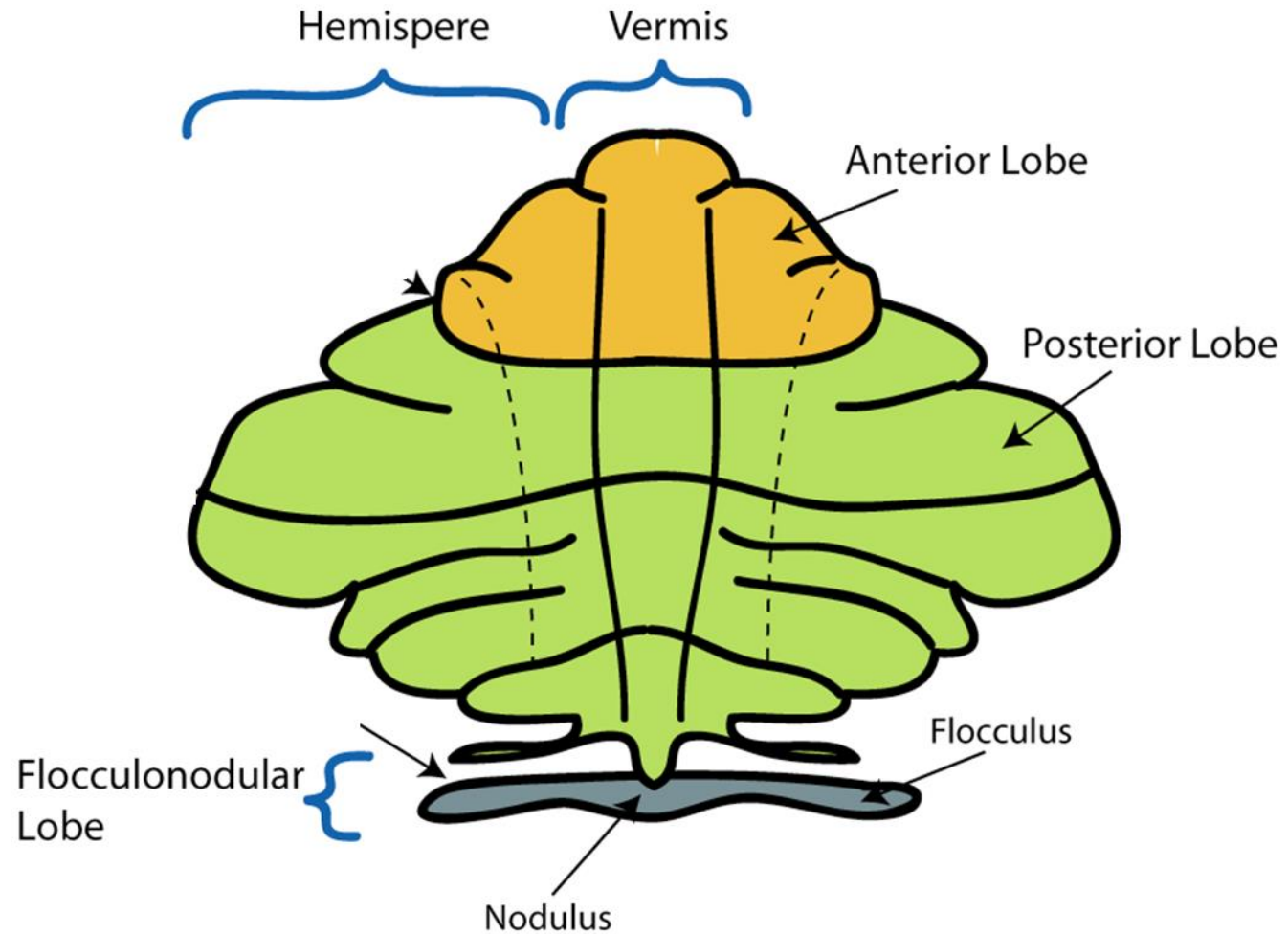


Cerebellum

- “Little brain”
- Posture/balance
- Muscle tone
- Coordinates movement



Anatomy



Cerebellar Disease Symptoms

- Dyssynergia
- Nystagmus
 - Up/down beat (vertical)
 - Gaze-evoked
- Nausea/vomiting
- Vertigo



Wikipedia/Public Domain

Dyssynergia

Loss of coordinated activity

- Dysmetria
 - Loss of movement coordination
 - Under or over-shoot intended position of hand
- Intention tremor
 - Can't get hand to target
 - Tremor worsens approaching target
- Dysdiadochokinesia
 - Can't make movements exhibiting a rapid change of motion
 - Can't flip hand in palm



Ataxia

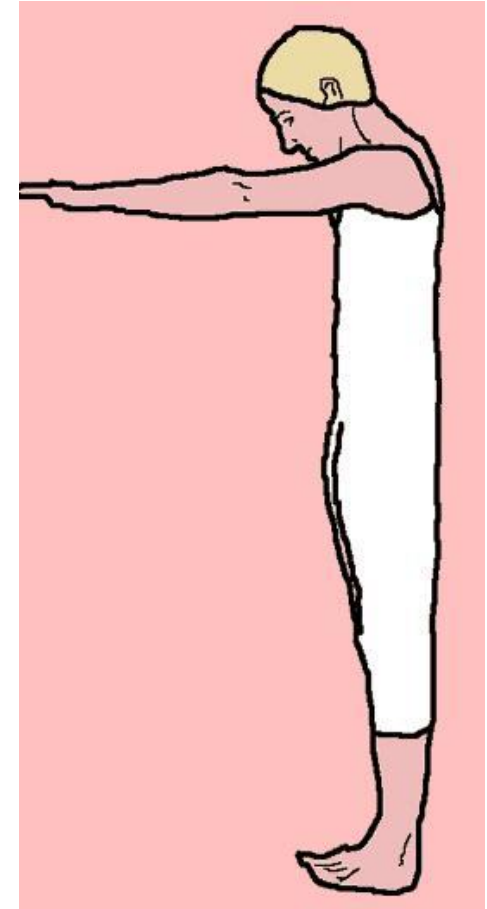
- Loss of balance
- Cerebellar ataxia
 - Due to cerebellar disease
 - **“Wide-based” gait**
- Sensory ataxia
 - Loss of proprioception
 - Damage to nerves or posterior column
 - “High-stepping” or stamping gait



medxclusive.org

Romberg Test

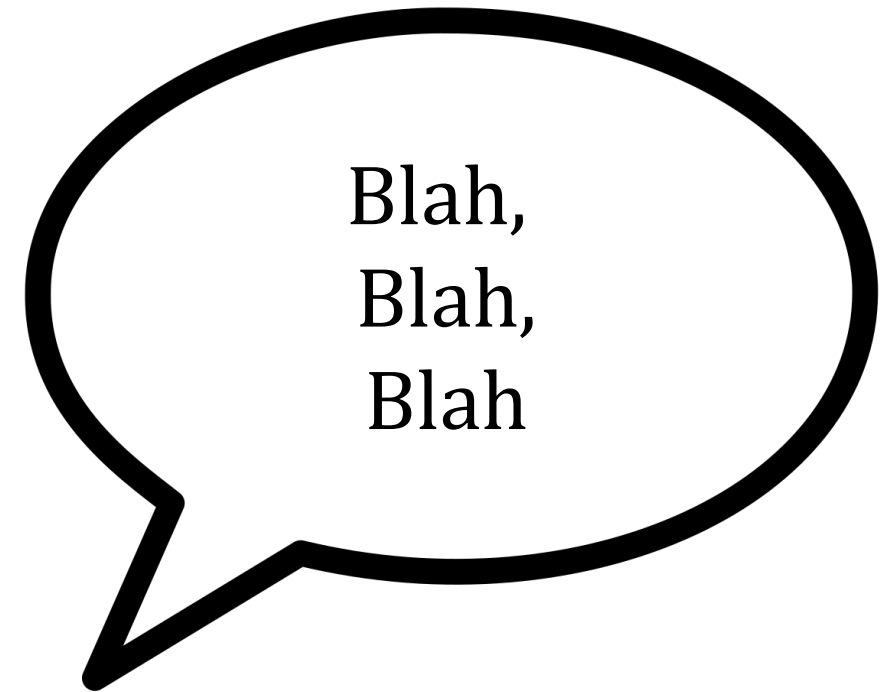
- Test to evaluate ataxia
- Loss of proprioception: compensate through vision
- Feet together, eyes closed
- Positive test: patients will lose balance or fall
- If test positive: ataxia is SENSORY
- Cerebellar ataxia occurs even with eyes open



Wikipedia/Public Domain

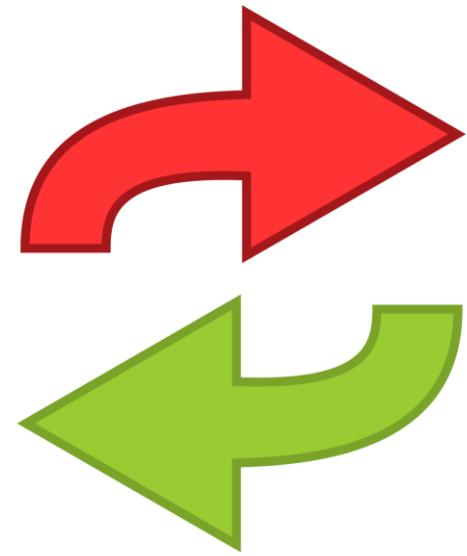
Other Cerebellar Symptoms

- Hypotonia
 - Loss of muscle resistance to passive manipulation
 - Loose-jointed, floppy joints
- Scanning speech
 - Irregular speech
 - Words broken up
 - Separated by pauses
 - Spoken with varying force
 - “How are you doing?”
 - “How...are...you...do...ing”



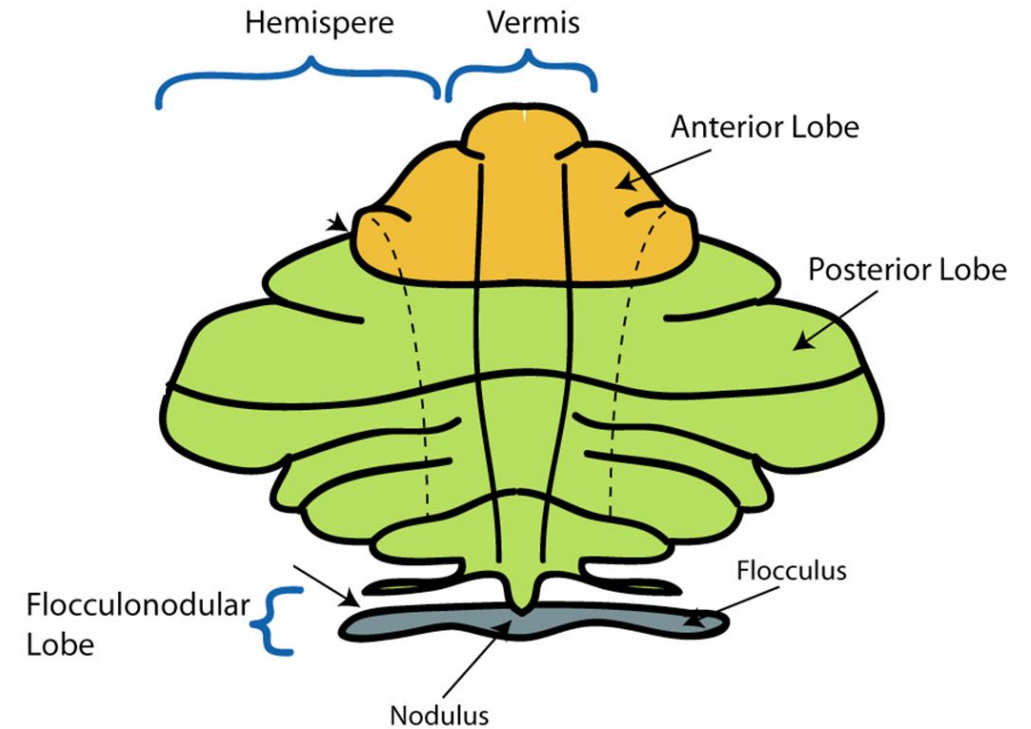
Cerebellum Control

- In general, cerebellum controls **IPSILATERAL side**
 - “Double cross”
 - Cerebellar fibers → contralateral cortex
 - Contralateral cortex → contralateral arm/leg
- Also right proprioception information → right cerebellum
- Result:
 - Left cerebellar lesion → left symptoms
 - Right cerebellar lesion → right symptoms



Clinical Disease

- Lateral lesions
 - Cerebellar hemispheres
 - Affect extremities
- Midline lesions
 - Vermis
 - Affect trunk
- Flocculonodular lobe
 - Connects to vestibular nuclei
 - Vertigo
 - Nystagmus



Lateral Lesions

- Extremities
- Problems coordinating movements
- Dysmetria
- Intention tremor
- Fall toward side with lesion



Central Lesions

- Affect trunk/midline
- Central (vermis)
 - Truncal ataxia
 - Can't stand independently
 - Falls over when sitting
- Flocculonodular lobe
 - Nystagmus
 - Vertigo

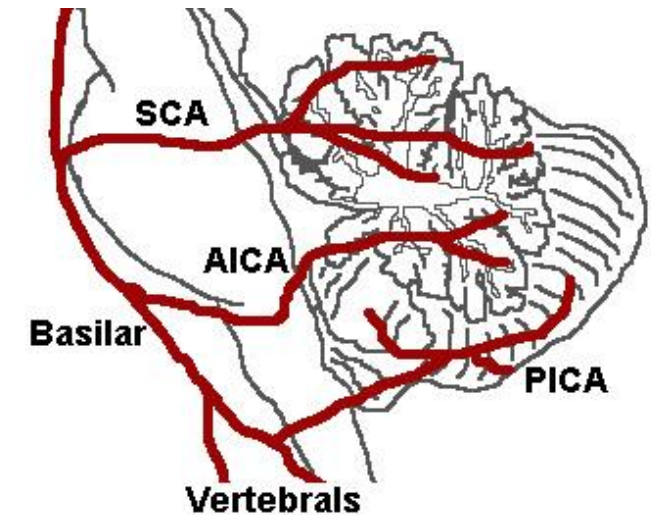
Vertigo



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Cerebellar Strokes

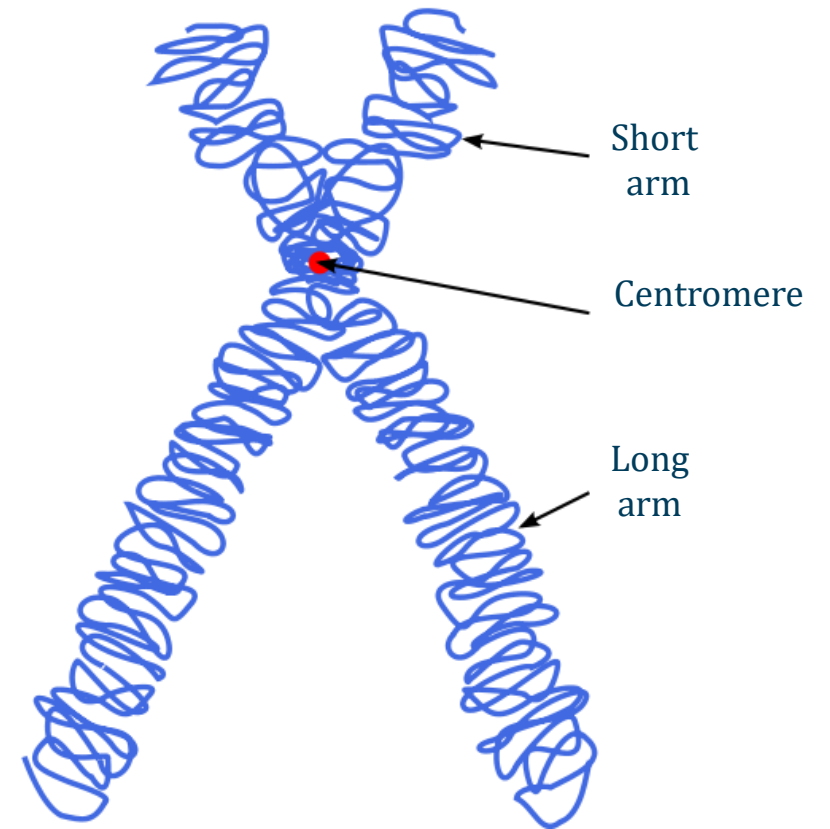
- Posterior circulation stroke syndromes
 - Branches of basilar and vertebral arteries
 - Superior cerebellar artery (SCA)
 - Anterior inferior cerebellar artery (AICA)
 - Posterior inferior cerebellar artery (PICA)
- Often has other brainstem stroke signs/symptoms



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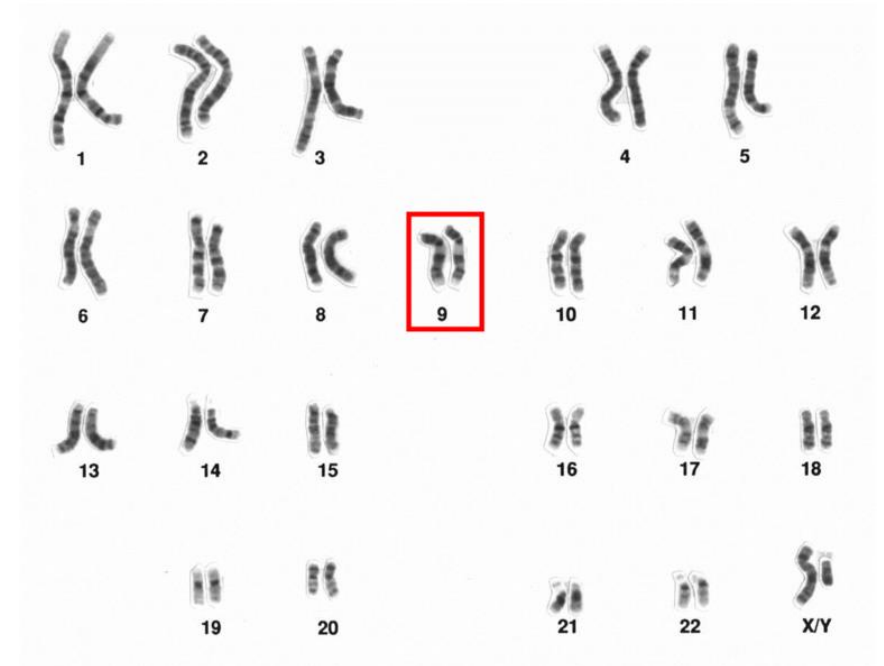
Hereditary Ataxias

- Numerous hereditary disorders
- Motor incoordination related to cerebellum
- Friedreich's Ataxia
- Ataxia Telangiectasia
- Spinocerebellar Ataxia



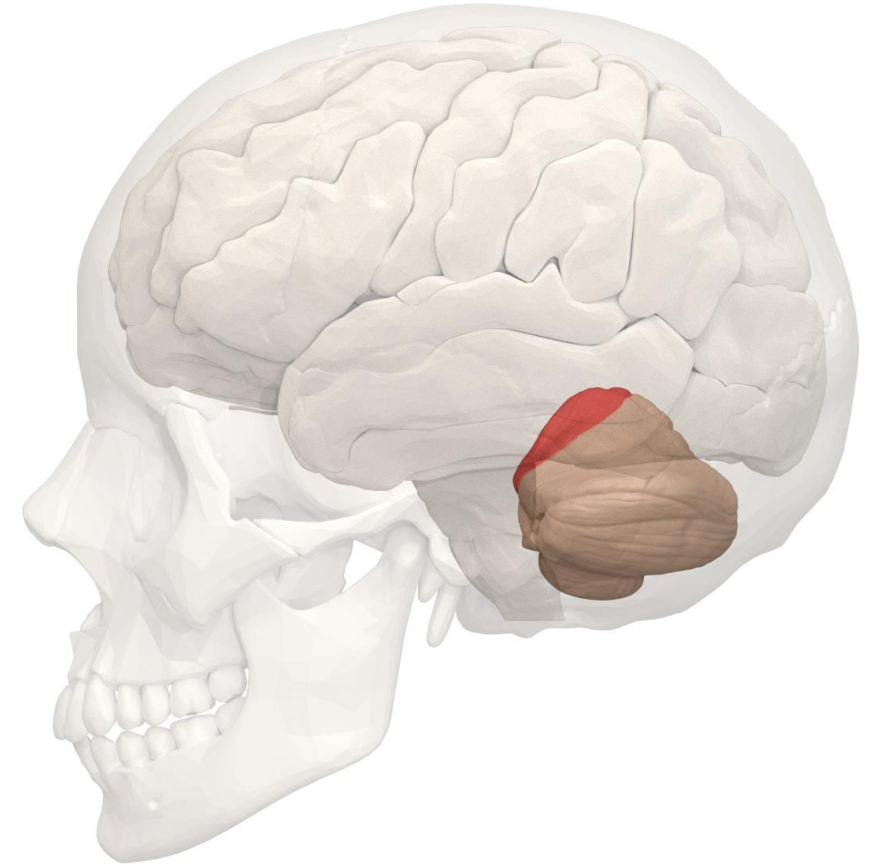
Friedreich's Ataxia

- Autosomal recessive disorder
- Mutation of frataxin gene chromosome 9
 - Needed for normal mitochondrial function
 - Increased number of trinucleotide (GAA) repeats present
 - More repeats = worse prognosis
 - Leads to decreased frataxin levels
- Frataxin: mitochondrial protein
 - High levels in brain, heart, and pancreas
 - Abnormal frataxin → mitochondrial dysfunction



Friedreich's Ataxia

- Begins in adolescence with progressive symptoms
- Cerebellar and spinal cord degeneration
- Degeneration of spinocerebellar tract
 - Ataxia, dysarthria
- Loss of spinal cord: dorsal columns
 - Position/vibration
- Loss of corticospinal tract
 - UMN weakness in lower extremity



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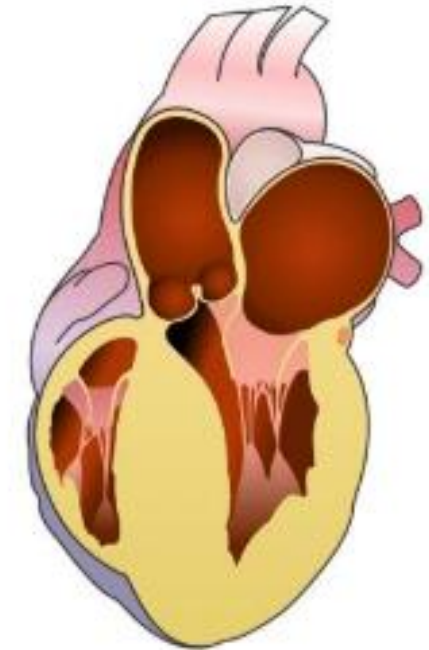
Friedreich's Ataxia

Other Features

- **Hypertrophic cardiomyopathy**
- Diabetes
 - Insulin resistance and impaired insulin release
 - Beta-cell dysfunction



Normal



Hypertrophic

Friedreich's Ataxia

Other Features

- Kyphoscoliosis
- Foot abnormalities (pes cavus)
 - High arch of foot; does not flatten with weight bearing
 - Seen in other neuromuscular diseases (Charcot-Marie-Tooth)



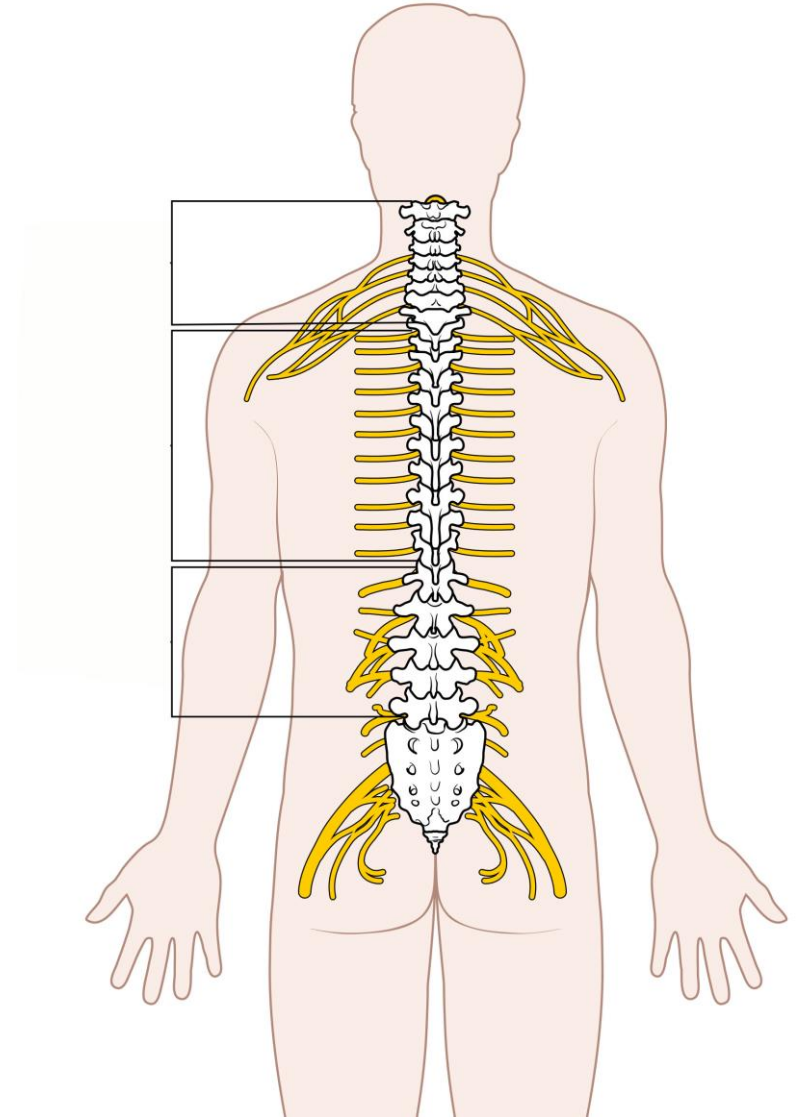
Axelrod FB, Gold-von Simson G.



Benefros/Wikipedia

Spinocerebellar Ataxia

- Group of hereditary disorders
- Degeneration of cerebellum and sometimes spinal cord
- Cerebellar ataxia
- Variable muscle symptoms based on subtype
- No effective therapies



Wikipedia/Public Domain

Alcoholic Cerebellar Degeneration

- Chronic cerebellar disease due to alcohol use (not thiamine deficiency!)
- Degeneration of Purkinje cells
- Primarily affects vermis (midline cerebellum)
- Causes wide-based gait
- Other cerebellar features may occur
 - Intention tremor, nystagmus
- Diagnosis: clinical
- Treatment:
 - Cessation of alcohol use
 - Nutritional supplementation
- Gait usually does not improve



Wikipedia/Public Domain

Acute Cerebellar Ataxia

Post-infectious Cerebellitis

- Occurs in children
- Days to weeks after trigger
 - Historically varicella or measles infections
 - Also Epstein-Barr or other viral infections
 - Seen after some immunizations
- Main feature is rapid-onset cerebellar ataxia
- Diagnosis: clinical diagnosis
 - Must exclude toxin ingestion, infection, CNS disease
- Self-limited



Wikipedia/Public Domain

Other Cerebellar Disorders

- Tumors
 - Pilocytic astrocytoma
 - Medulloblastoma
 - Ependymoma
- Congenital disease
 - Dandy-Walker malformation
 - Chiari malformations

Multiple Sclerosis

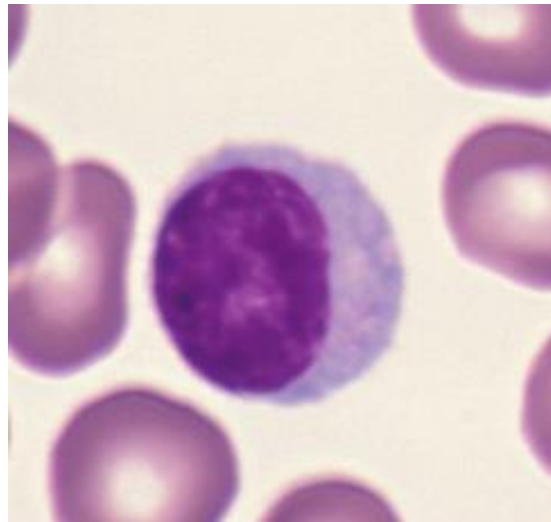
Jason Ryan, MD, MPH



Multiple Sclerosis

- **Autoimmune demyelination** of central neurons
- Affects brain and spinal cord
- Lymphocytes (T-cells) react to myelin antigens
- Loss of oligodendrocytes

Lymphocyte



Public Domain

Multiple Sclerosis

Demographics

- Women
- Aged 20 – 40
- Distance from equator
 - Prevalence increases with distance from equator
- Sunlight and vitamin D levels
 - Associated with lower risk
 - Possible explanation for geographic variation

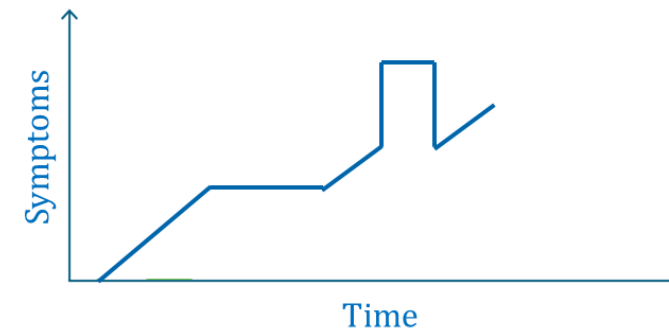
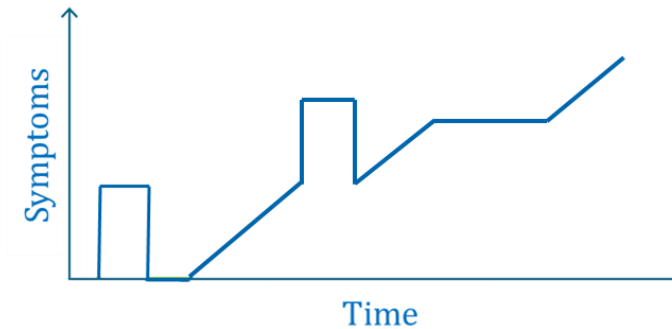
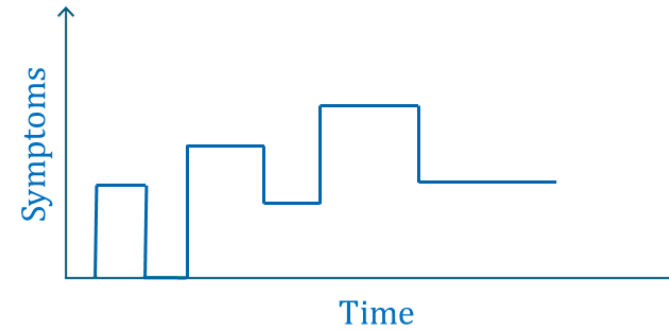


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Multiple Sclerosis

Subtypes

- **Relapsing-Remitting**
 - Most common form at onset (80-90%)
 - Episodic acute worsening of symptoms
 - Partial or complete recovery
- Secondary progressive
 - Initial relapsing-remitting course
 - Gradual worsening
- Primary progressive
 - Worsens over time
 - No early relapse or remission

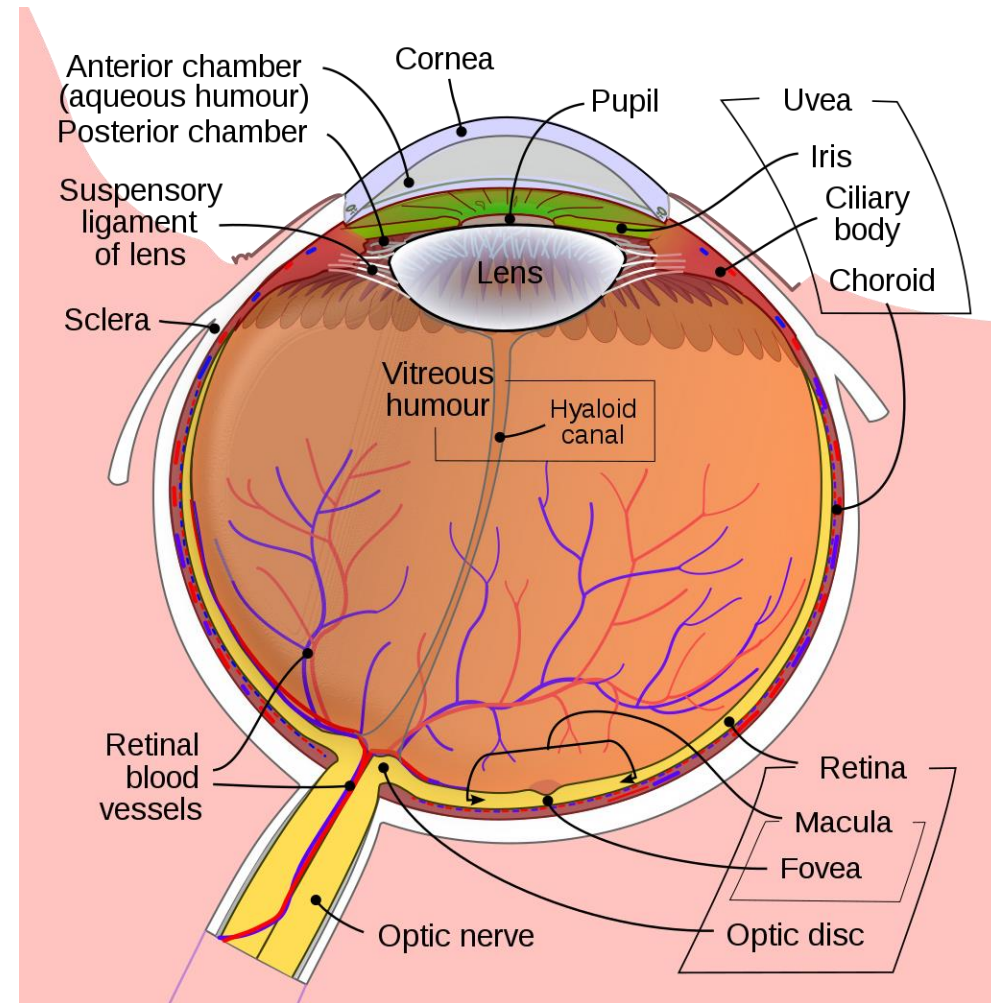


Clinically-Isolated Syndrome

- First episode of MS symptoms
- No history of prior MS symptoms
- Any neurologic symptom may occur
- Several classic presentations
 - Optic neuritis
 - Internuclear ophthalmoplegia
 - Brainstem or cerebellar syndrome
 - Partial transverse myelitis

Optic Neuritis

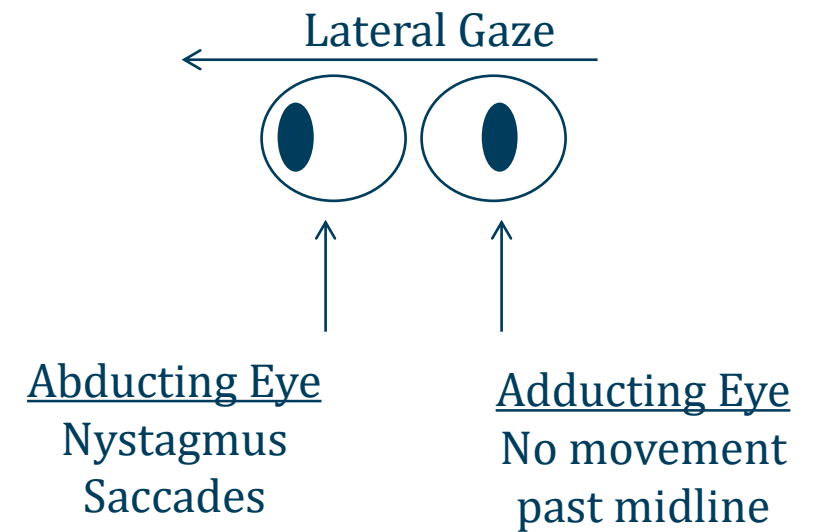
- Painful eye movements
- Affects one eye (monocular)
- Visual blurring or scotoma
- Treatment: **IV steroids**
 - May delay onset of MS
 - Protects vision
 - Oral prednisone not used



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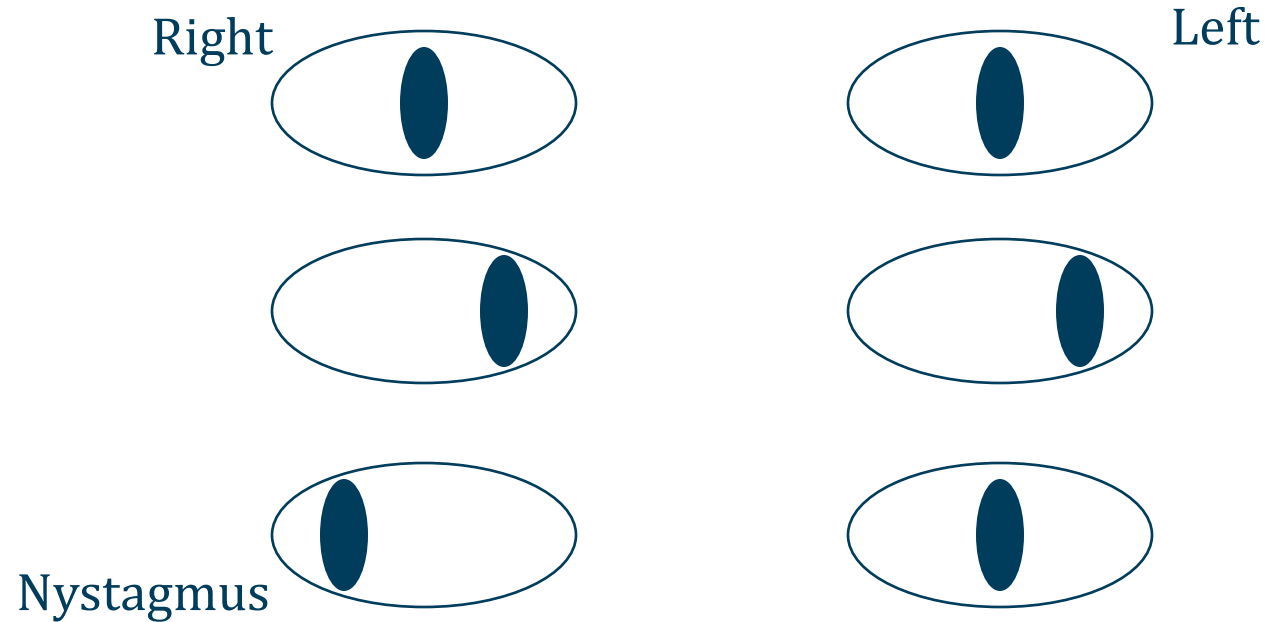
Internuclear Ophthalmoplegia

- Caused by lesion of the **medial longitudinal fasciculus**
- **Diplopia and nystagmus**
- Horizontal gaze disorder
- Weak adduction (medial movement) of one eye
- Affected eye cannot move toward nose
- Unaffected eye develops nystagmus
- Convergence is usually spared
 - Different neural pathway



Internuclear Ophthalmoplegia

Example: Left INO

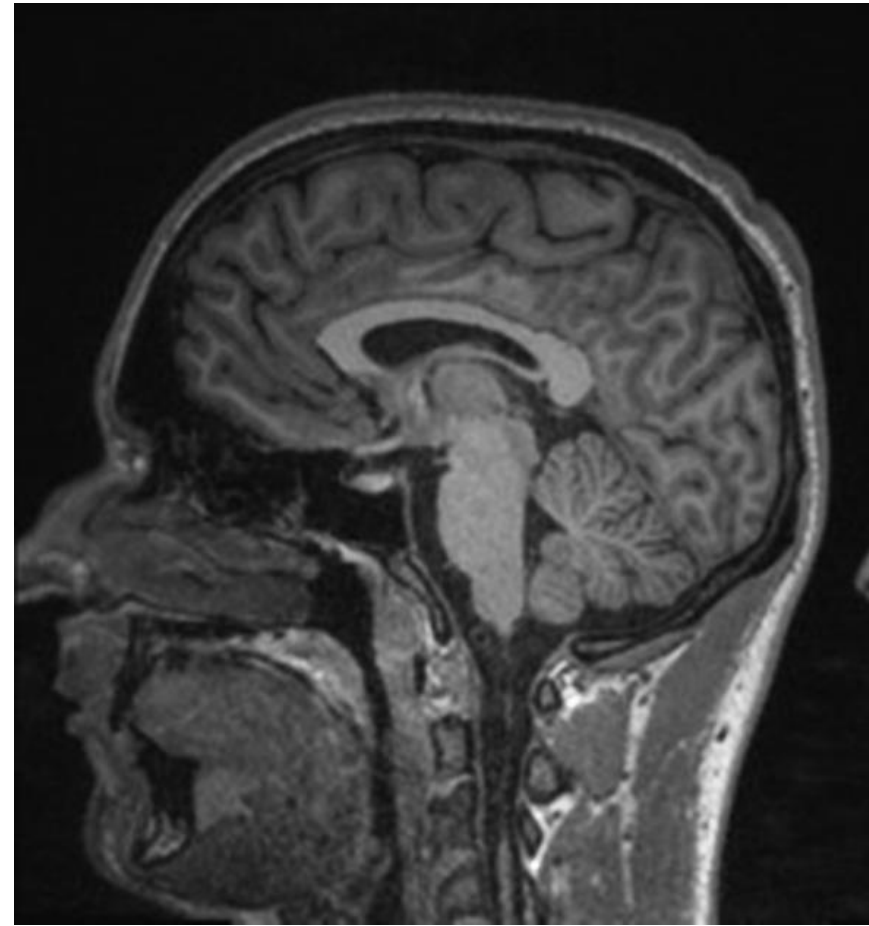


Side that cannot go medial is side with MLF lesion

Problem looking right = left MLF lesion

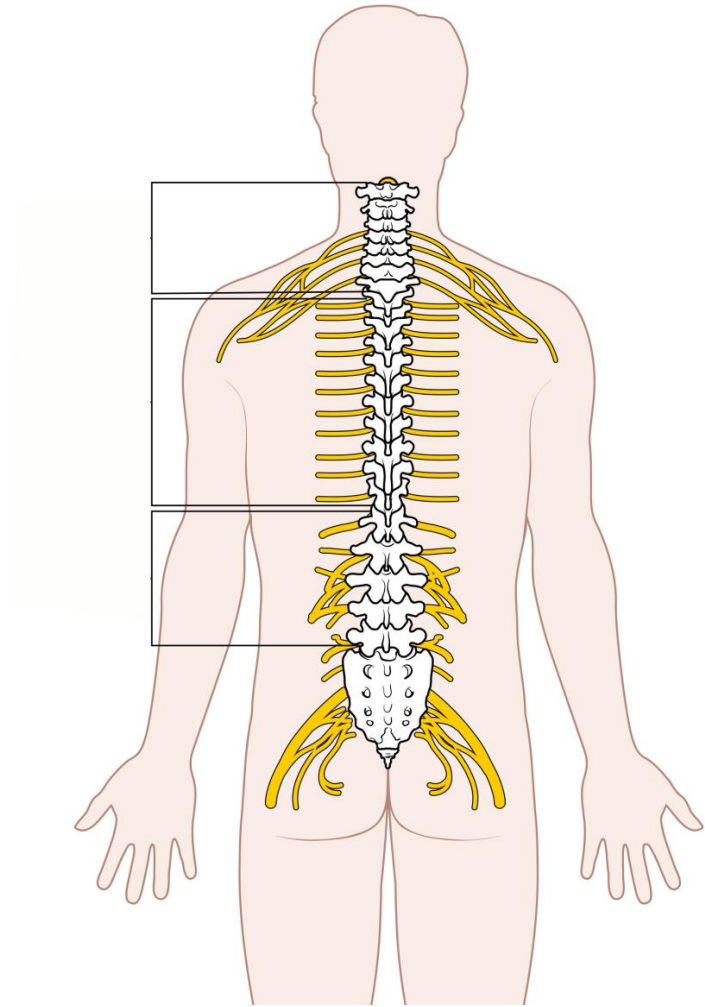
Brainstem or Cerebellar Syndrome

- Ataxia
- Vertigo
- Nystagmus
- Facial numbness
- Dysarthria
 - “Scanning speech”
 - Words broken up
 - Separated by pauses
 - Spoken with varying force



Partial Transverse Myelitis

- **Spinal cord lesions**
- Transverse = affects one level of cord
- Motor symptoms below lesion
- Sensory symptoms below level of lesion
 - Ipsilateral vibration and proprioception
 - Contralateral pain and temperature
 - Similar to Brown-Sequard syndrome
- Bowel and bladder dysfunction

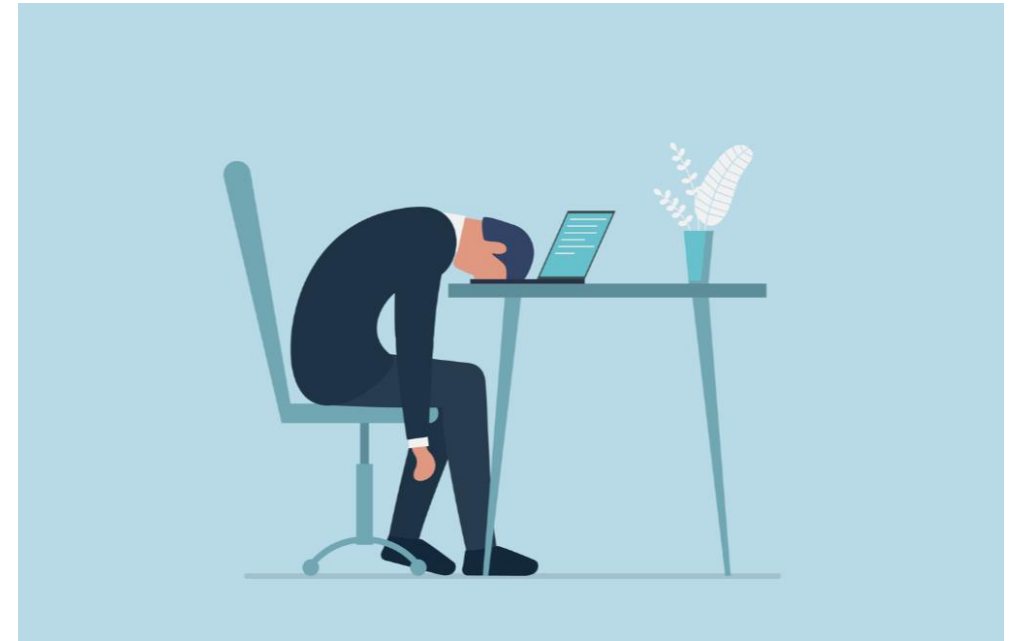


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Multiple Sclerosis

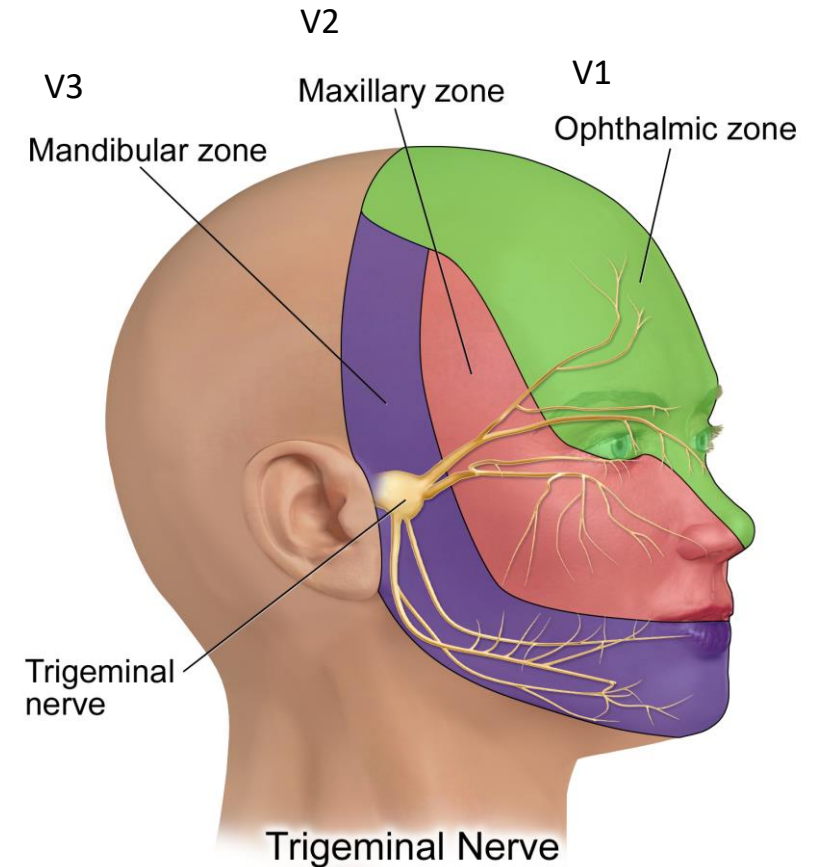
Other Clinical Features

- **Fatigue** is extremely common
- Bladder dysfunction common
 - Detrusor overactivity (overactive bladder)
 - **Urge incontinence**
 - Urgency, frequency and incontinence
 - Treatment: anticholinergic and antimuscarinic drugs
 - Oxybutynin is first-line medication



Trigeminal Neuralgia

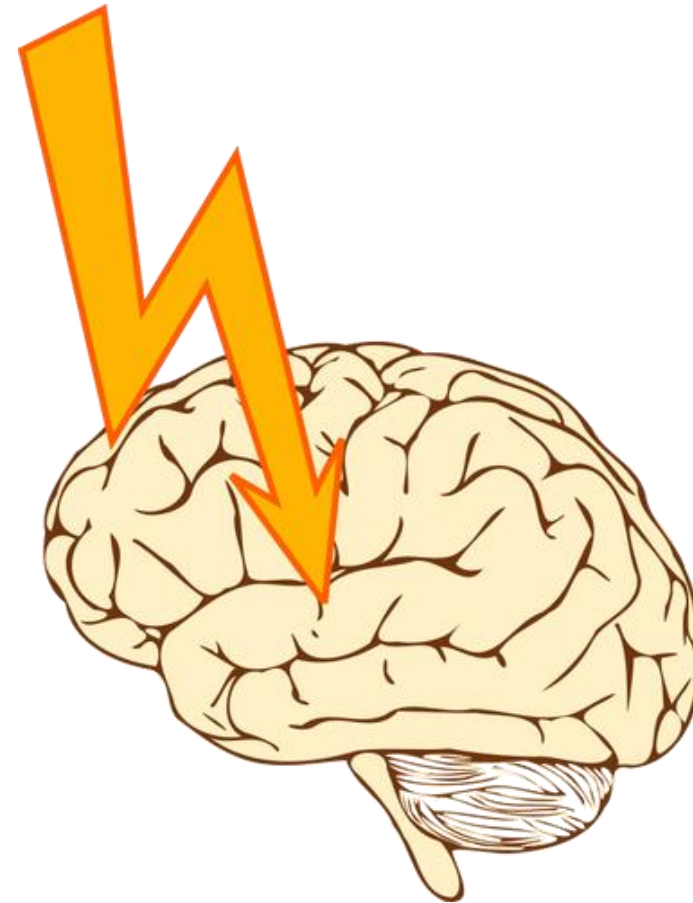
- Sudden onset facial pain
- V2-V3 branches of trigeminal nerve
- Pain triggered by touching face, chewing
- Usually caused by nerve root compression
 - Most cases due to artery or vein
- **Twenty times more common in multiple sclerosis**
- Can be **bilateral** in MS patients



Multiple Sclerosis

Other Clinical Features

- Lhermitte's sign
 - Electric shock sensation
 - Down neck and spine into limbs
- Uhthoff's sign
 - Symptoms worsen with heat
 - Decreased nerve conductivity
- Charcot's neurologic triad
 - Scanning speech
 - Intention tremor
 - Nystagmus
 - All cerebellar symptoms

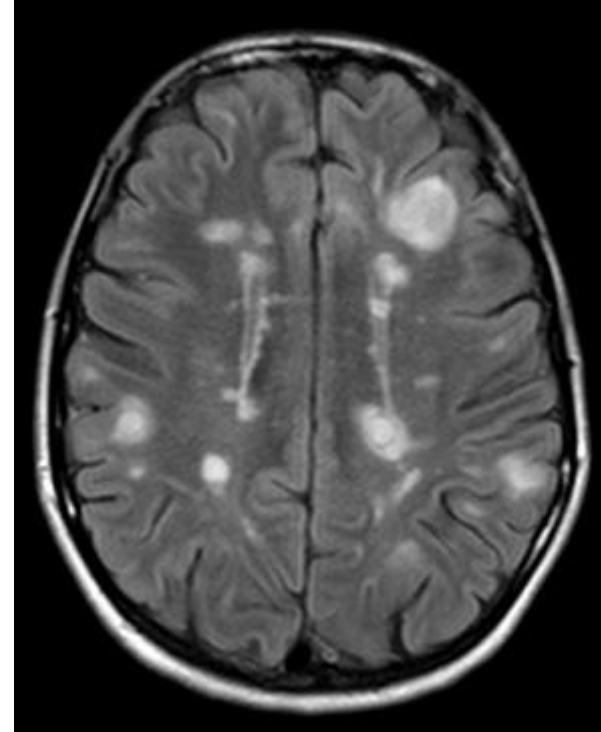


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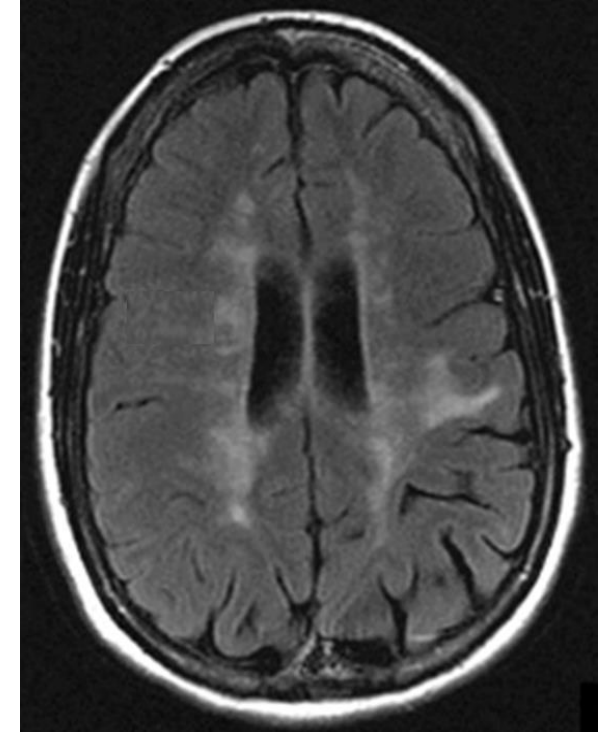
Multiple Sclerosis

Diagnosis

- **Clinical features plus MRI findings**
 - Best first test: MRI
 - Shows oval-shaped plaques
- New and old white matter lesions
 - New: white with gadolinium contrast
 - Old: dark
- Dawson's fingers
 - Plaques extending from corpus callosum
- If MRI nondiagnostic:
 - Check VEPs or CSF



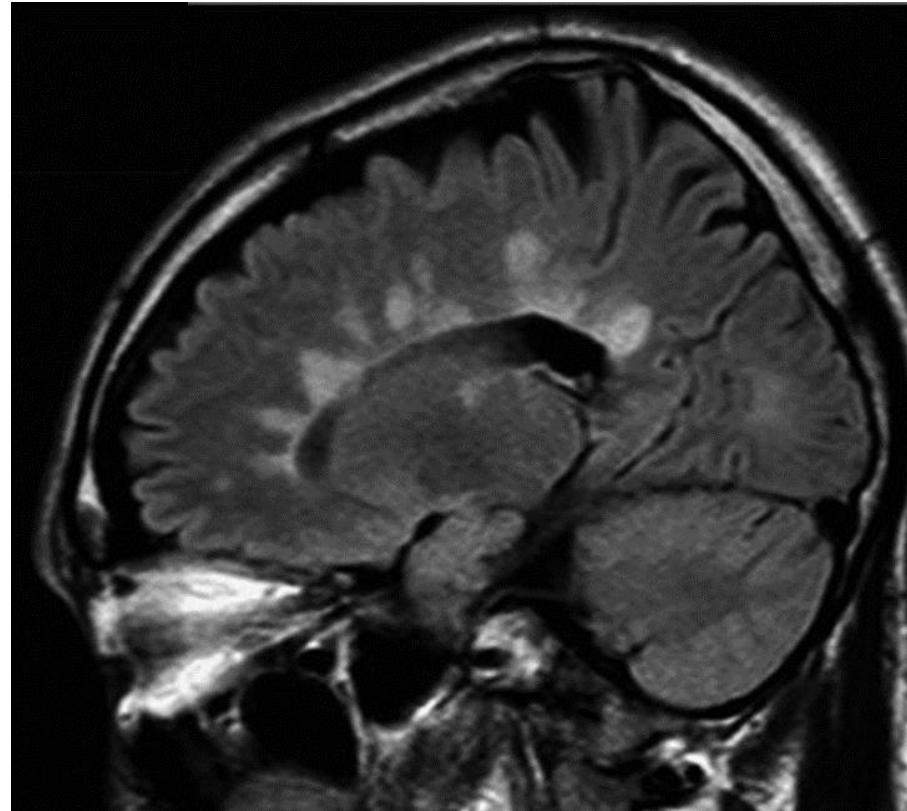
Radiopedia/Bruno DiMuzio



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Multiple Sclerosis

Dawson's Fingers

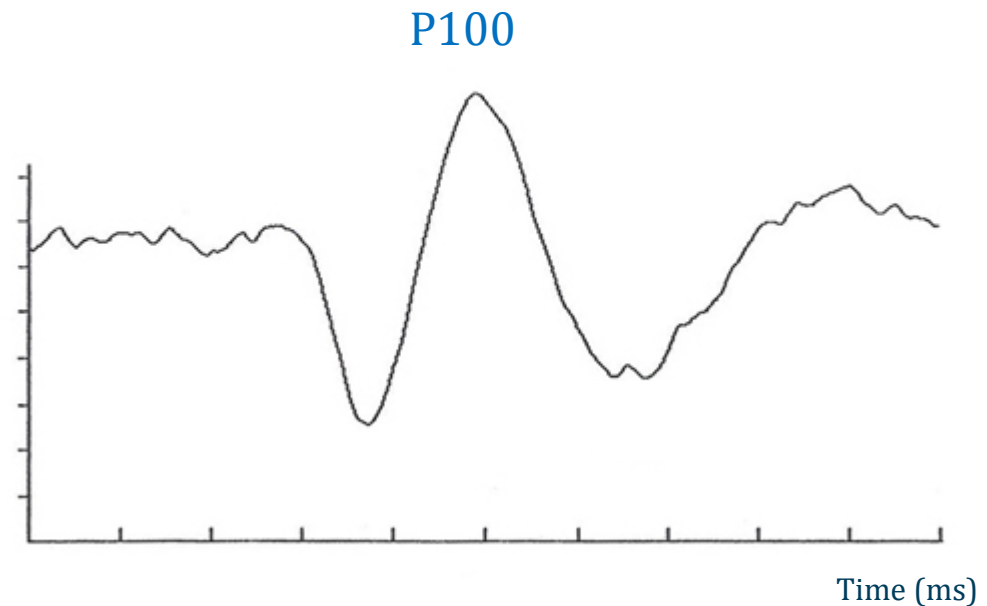


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Multiple Sclerosis

Visual evoked potentials

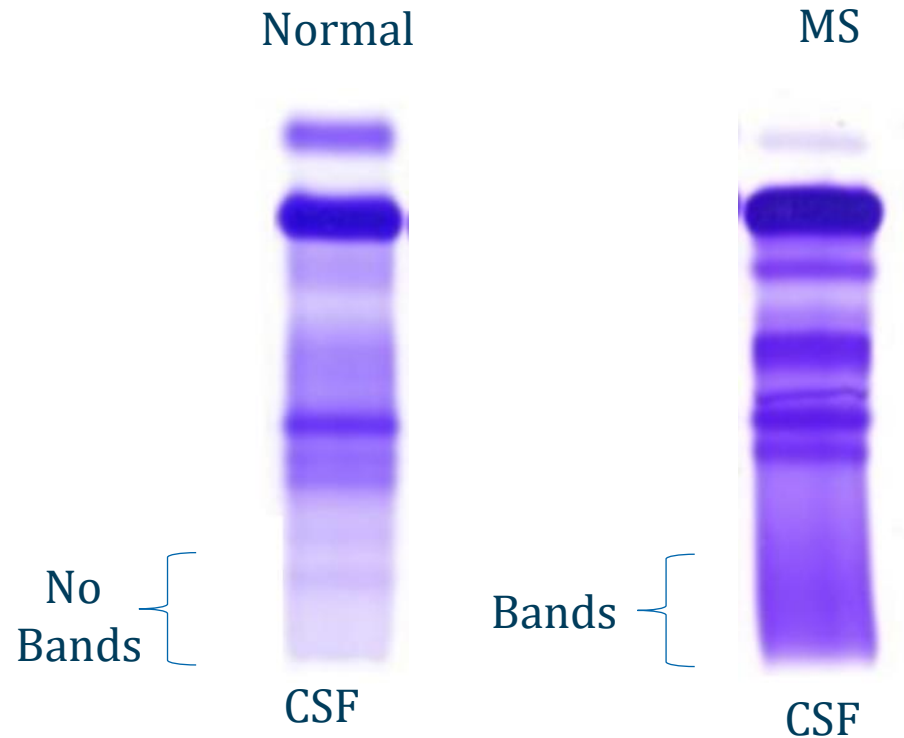
- Evaluates optic nerve conduction
- Electrodes placed on back of head
- Visual stimulus shown to patient
- Measures time for signal to reach visual cortex
- Time to **P100 peak** delayed in MS



Multiple Sclerosis

CSF Findings

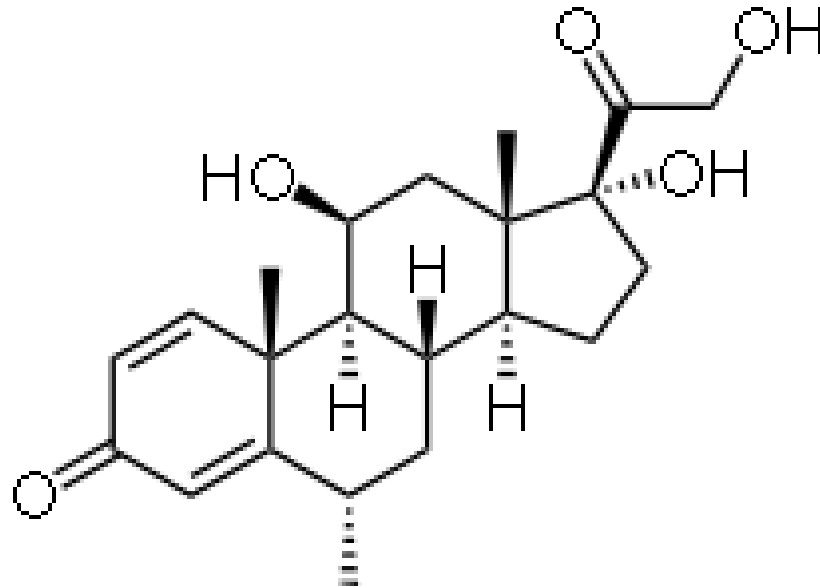
- **Oligoclonal bands**
 - Class of antibodies
 - Appear as a band on gel electrophoresis
 - Occur in about 85% patients
- Increased CSF IgG level
- “Positive CSF” in MS
 - Presence of oligoclonal bands
 - Increased IgG level



Multiple Sclerosis

Treatment

- Acute exacerbations
 - **IV corticosteroids (methylprednisolone)**
 - Speed recovery but do not alter long-term prognosis



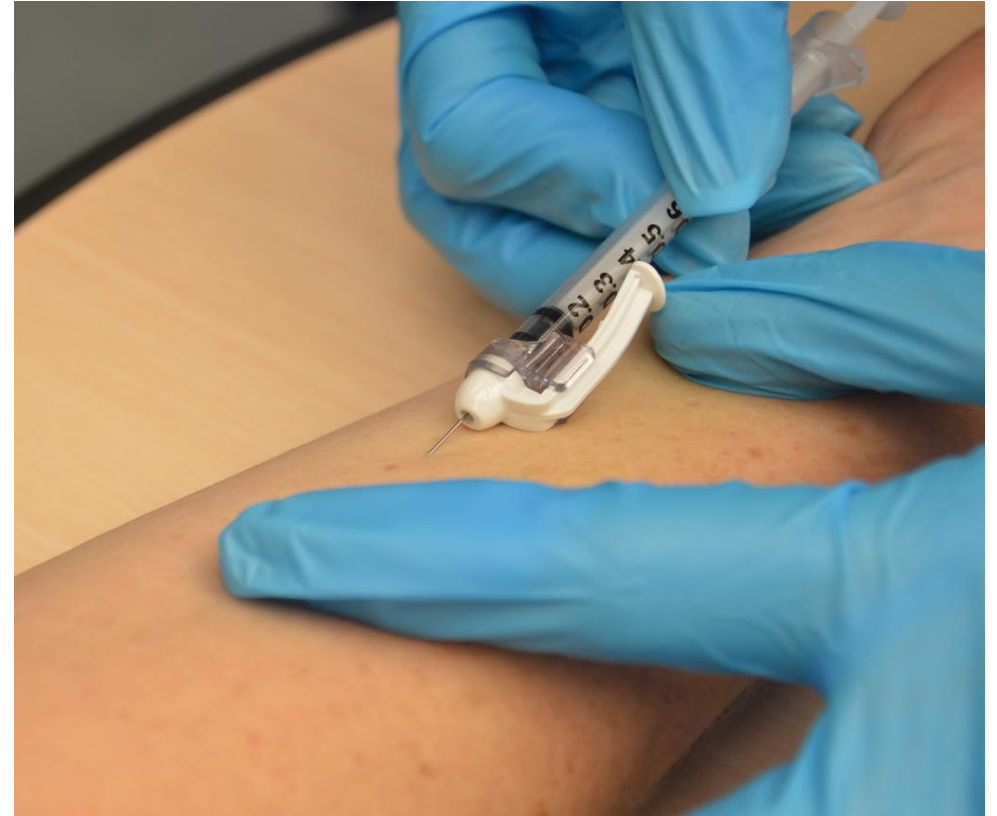
Methylprednisolone

Multiple Sclerosis

Long-term Treatments

- **Interferon β**
 - Inhibit T-cell function
 - Subcutaneous injection
 - Few major side effects
- **Glatiramer**
 - Mixture of polymers of four amino acids
 - Similar to myelin basic protein
 - T-cells bind drug instead of neuronal MBP
 - Subcutaneous injection
 - Few major side effects

Subcutaneous Injection



Wikipedia/Public Domain

Multiple Sclerosis

Long-term Treatments

- **Natalizumab**
 - Antibody against alpha-4 subunit of integrin molecules
 - Expressed by lymphocytes
 - Allows adhesion to vascular endothelium
- Administered as infusion
- Risk of **progressive multifocal leukoencephalopathy (PML)**
- Risk higher in patients with **anti-JCV antibodies**

Multiple Sclerosis

Treatment Summary

- Acute exacerbations
 - IV corticosteroids (methylprednisolone)
- Relapsing-Remitting
 - Interferon β
 - Glatiramer
 - Natalizumab
- Many other drugs
 - Used in refractory cases
 - Used in primary progressive



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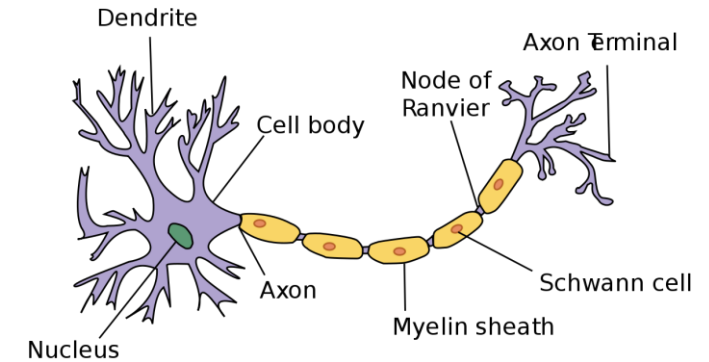
Demyelinating Disorders

Jason Ryan, MD, MPH



Demyelinating Disorders

- Central demyelinating disorders
 - Multiple Sclerosis
 - Acute disseminated encephalomyelitis (ADEM)
 - Neuromyelitis Optica
 - Progressive multifocal leukoencephalopathy (PML)
- Peripheral demyelinating disorders
 - Guillain-Barre syndrome
 - Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)



Wikipedia/Public Domain

Acute Disseminated Encephalomyelitis

Postinfectious Encephalomyelitis

- Inflammatory central demyelinating disorder
- Common in children
- Acute onset multifocal motor/sensory deficits
- Encephalopathy (confusion)
- Often rapid deterioration → hospitalization
- Rare adverse effect of **infection or vaccinations**
 - Mean 26 days after
 - Infections: varicella or measles
 - Vaccines: rabies, smallpox

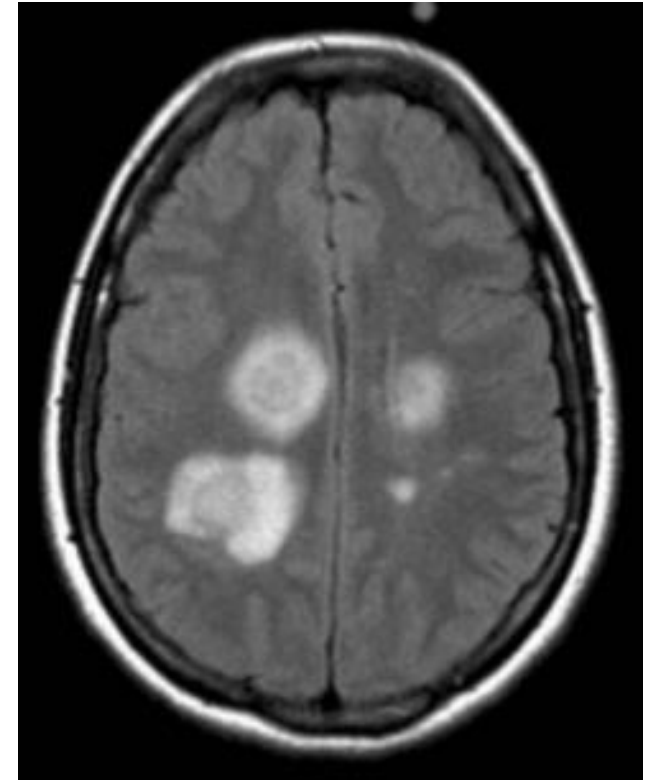


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Acute Disseminated Encephalomyelitis

Postinfectious Encephalomyelitis

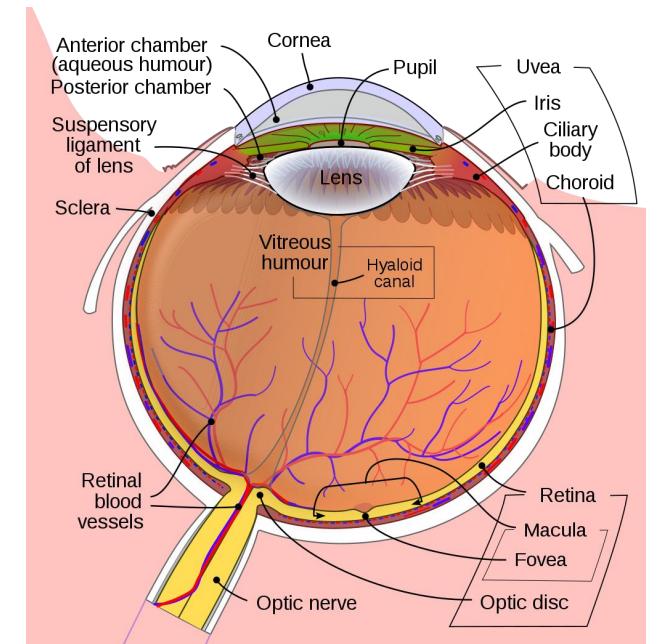
- MRI findings
 - Bilateral, asymmetric lesions
- Treatment: steroids
 - Methylprednisolone



Satyendra Raghuwanshi/Slideshare

Neuromyelitis Optica

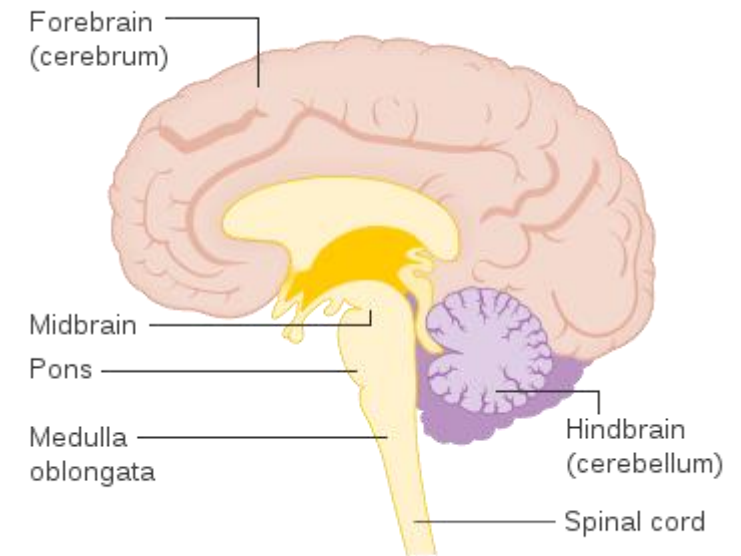
- Inflammatory central demyelinating disorder
- Involves **optic nerve and spinal cord**
- Caused by **IgG antibodies to aquaporin-4 (AQP4)**
 - Water channel protein
 - Found in spinal cord and CNS
 - Distinguishes NO from MS
- Diagnosis: MRI plus AQP4 antibody test



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Neuromyelitis Optica

- Presents as optic neuritis with additional symptoms
 - Transverse myelitis (motor and sensory loss)
 - Brainstem syndromes
- **Area postrema clinical syndrome**
 - Area of medulla
 - Chemoreceptor trigger zone
 - Intractable nausea, vomiting or hiccups
- Treatment: steroids
 - Methylprednisolone
- Recurrent attacks treated with immunosuppressants



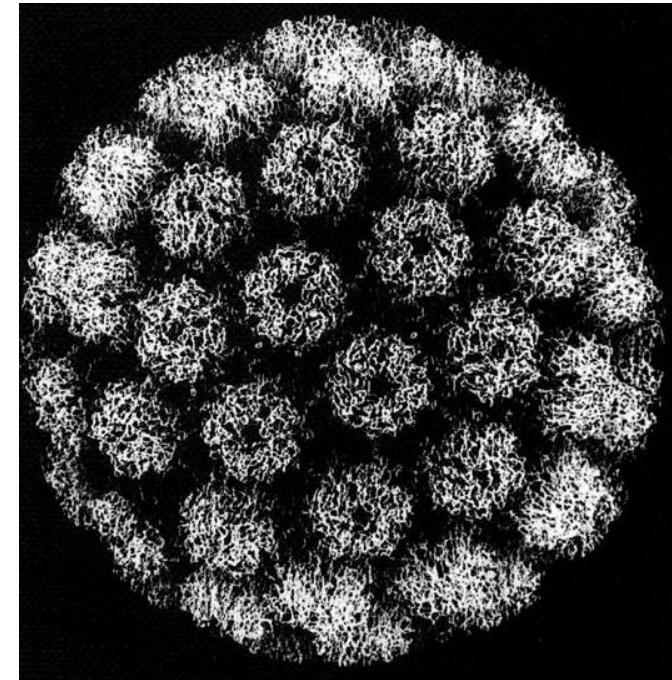
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PML

Progressive Multifocal Leukoencephalopathy

- Inflammatory central demyelinating disorder
- Reactivation of a **latent JC virus**
- Viral destruction of oligodendrocytes
- Occurs with immunosuppression
 - HIV
 - Leukemia/lymphoma
 - Natalizumab (MS antibody treatment)

JC Virus

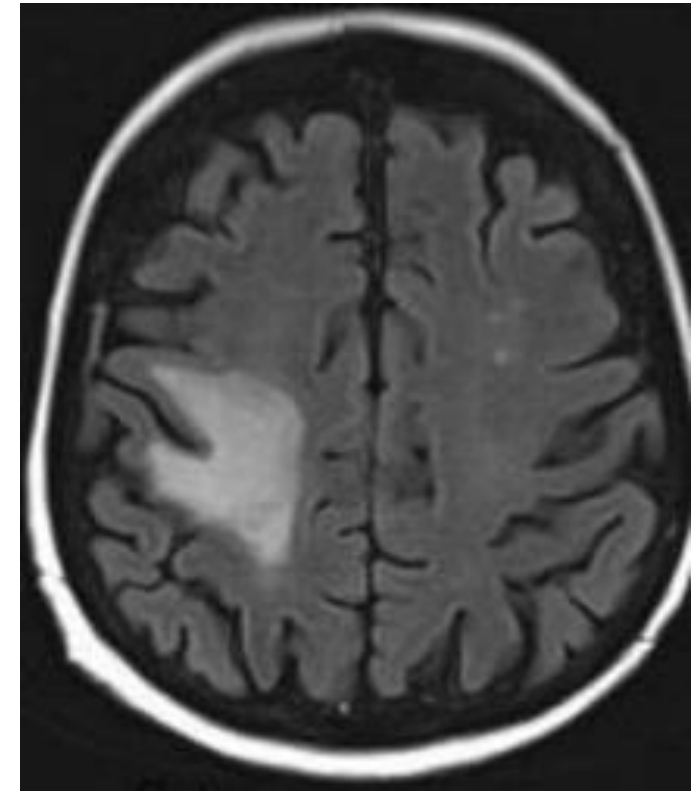


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PML

Progressive Multifocal Leukoencephalopathy

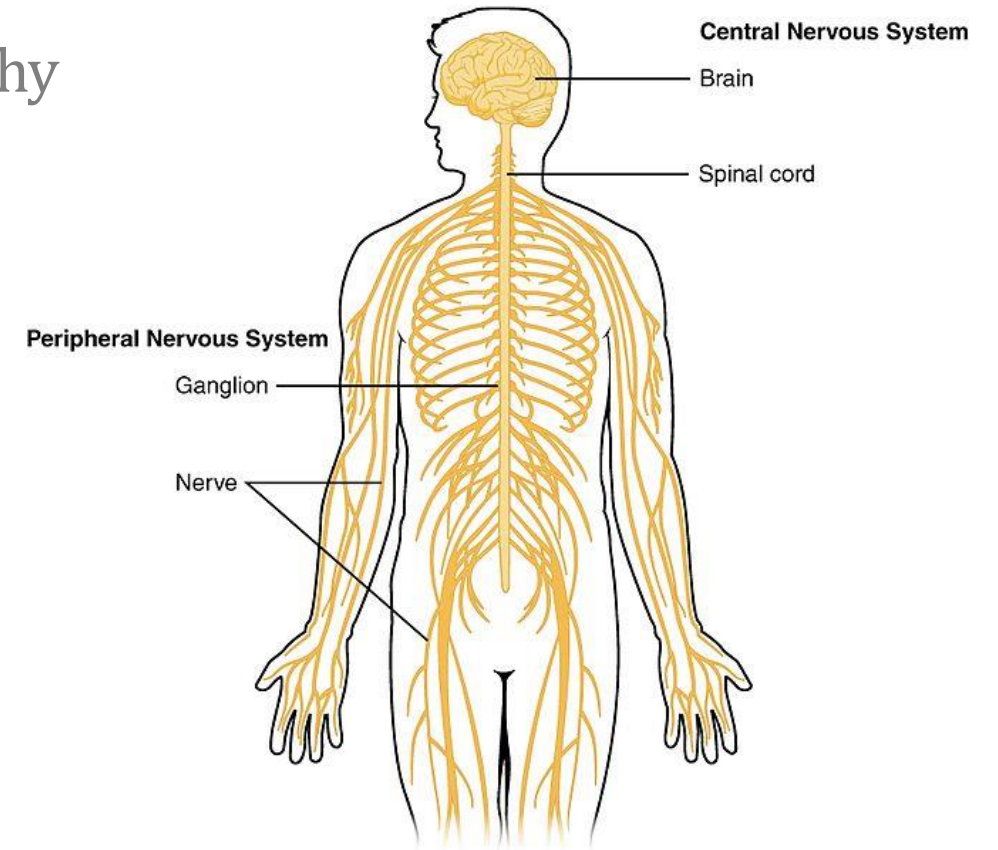
- **Subacute (slow-onset) focal neurologic deficits**
 - Motor or sensory
- Encephalopathy (confusion)
- Diagnosis:
 - MRI: multifocal lesions with no mass effect
 - CSF: JC virus IgG
 - Brain biopsy (rarely done)
- No effective therapy
- Treatment: **resolve immunosuppression**



@IDBugbowl/Twitter

Guillain-Barre Syndrome

- Peripheral nerve disorder
- Acute inflammatory demyelinating radiculopathy
- Schwann cells destroyed by immune system
- Motor and sensory deficits



Wikipedia/Public Domain

Guillain-Barre Syndrome

Variants

- Acute inflammatory demyelinating polyneuropathy
 - Most common variant
- Acute motor axonal neuropathy
 - No sensory features
- Acute motor and sensory axonal neuropathy
 - More sensory features
- Miller Fisher syndrome
 - Ophthalmoplegia (inability to move eyes)
 - Ataxia
 - Areflexia

Guillain-Barre Syndrome

Acute Inflammatory Demyelinating Polyneuropathy Variant

- **Ascending muscle weakness**
 - Develops over days → weeks
 - Starts in legs
 - Spreads to other areas
 - Respiratory failure 10-30%
 - Facial muscle weakness > 50%
- **Loss of deep tendon reflexes**
- Sensory deficits occur (paresthesias) but mild
- Symptoms usually resolve over weeks to months



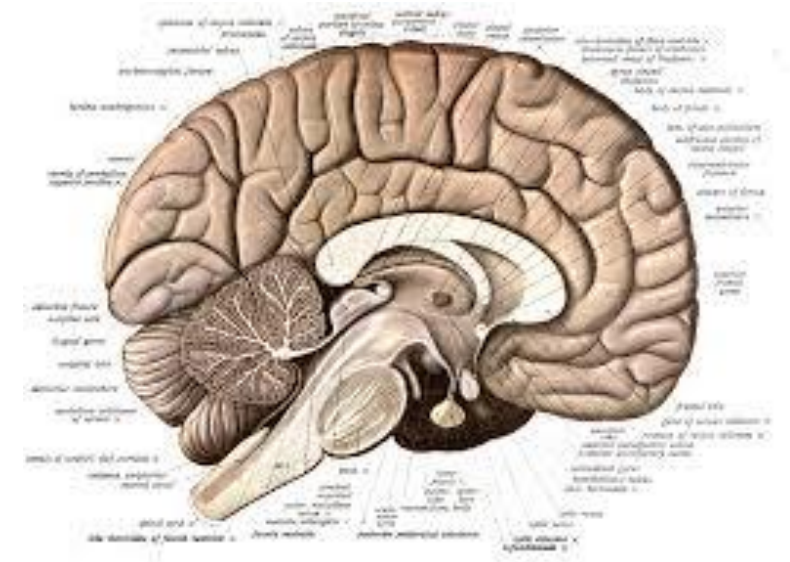
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Guillain-Barre Syndrome

Acute Inflammatory Demyelinating Polyneuropathy Variant

- **Autonomic dysfunction >70%**

- Tachycardia
- Urinary retention
- Hypertension/hypotension
- Arrhythmias
- Ileus
- Loss of sweating
- Death from:
 - Severe autonomic dysfunction
 - Respiratory failure

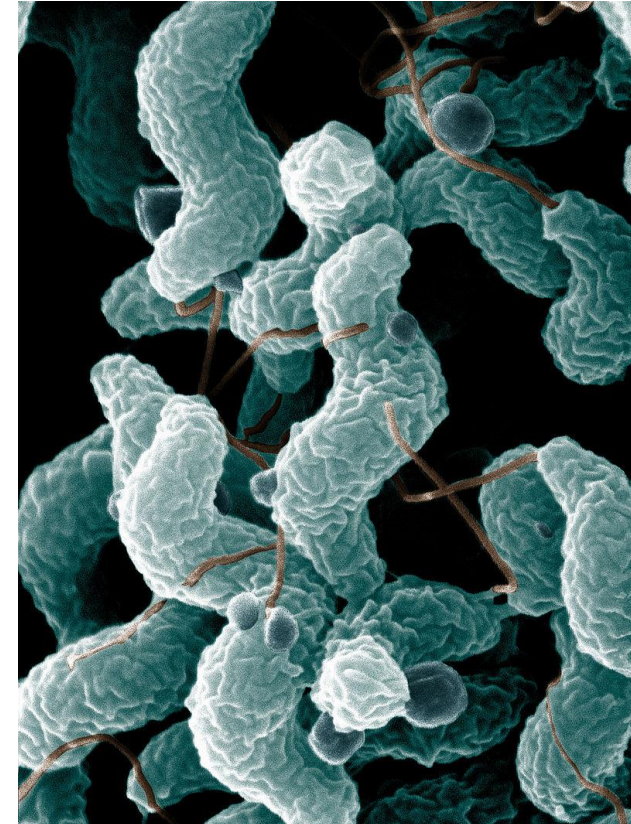


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Guillain-Barre Syndrome

- Often triggered by infection
- Classic agent: **campylobacter jejuni**
 - Bloody diarrhea
- Other agents:
 - Cytomegalovirus
 - Epstein-Barr virus
 - Human immunodeficiency virus (HIV)
- Rarely occurs after immunization

C. jejuni

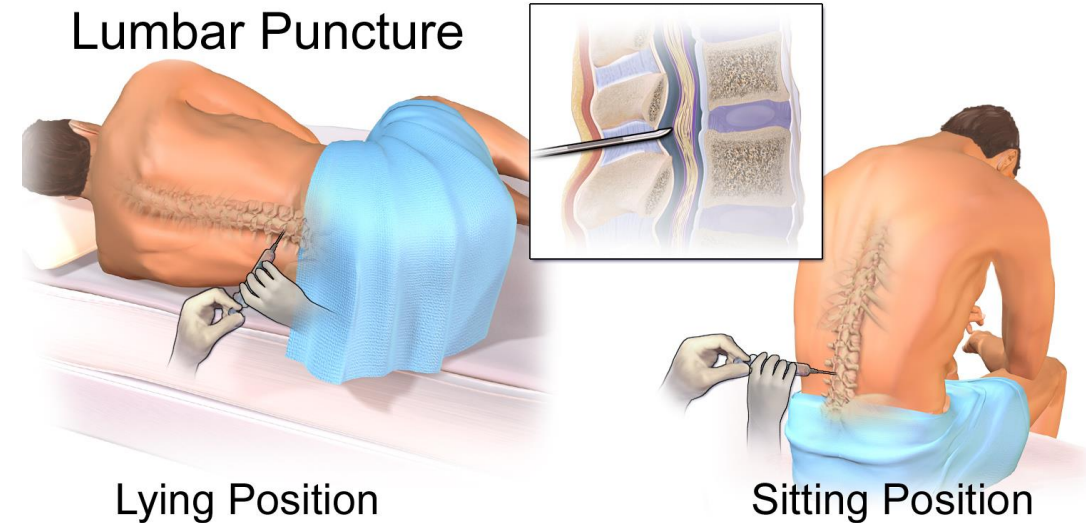


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Guillain-Barre Syndrome

Diagnosis

- Clinical diagnosis
- Supported by CSF finding:
 - Elevated protein level
 - Normal cell count
 - **“Albuminocytologic dissociation”**
- Nerve conduction studies
- Three A’s:
 - Ascending paralysis
 - Autonomic neuropathy
 - Albuminocytologic dissociation



Wikipedia/Public Domain

Guillain-Barre Syndrome

Treatment

- Respiratory monitoring and support
 - Vital capacity (spirometry)
 - Negative inspiratory force (NIF monitor)
- Plasmapheresis
- IV immune globulins
- Note: steroids not effective

Plasmapheresis



Mr Vacchi/Public Domain

CIDP

Chronic Inflammatory Demyelinating Polyneuropathy

- Peripheral nerve disorder
- Similar to AIDP variant of Guillain-Barre
 - Motor weakness
 - Loss of reflexes
 - Albuminocytologic dissociation
- Distinguished by **time course** and **steroid responsiveness**

CIDP

Chronic Inflammatory Demyelinating Polyneuropathy

- **Time course**
 - GBS: time to maximum weakness 4 weeks or less
 - CIDP: Longer than 8 weeks
- **Corticosteroids**
 - GBS: No benefit
 - CIDP: Effective

MARCH						
S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

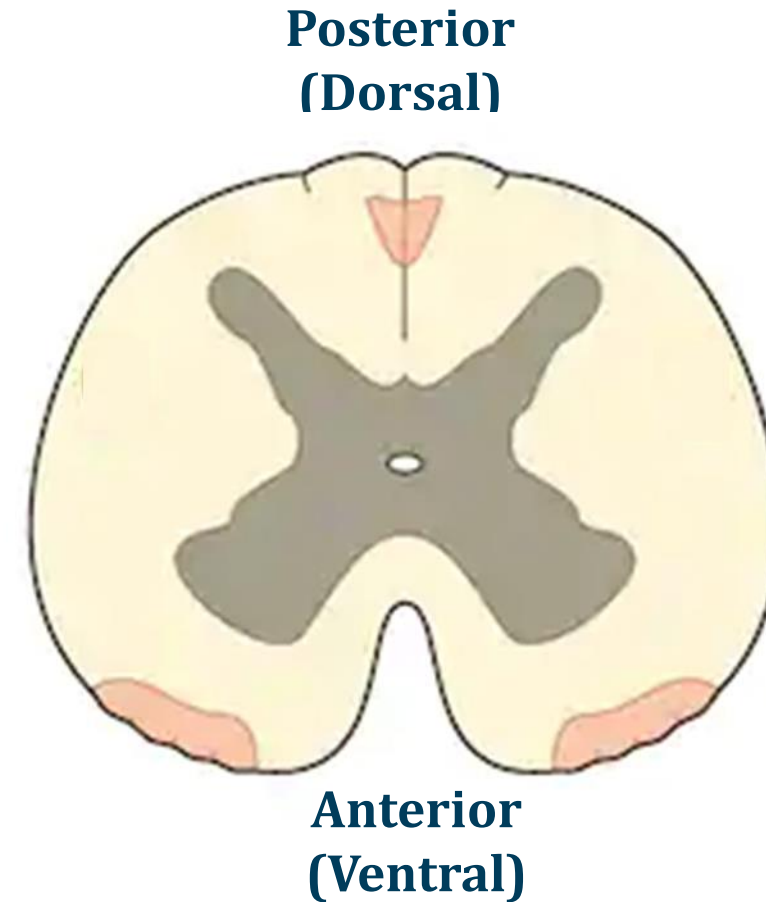
Spinal Cord Disorders

Jason Ryan, MD, MPH



Spinal Cord Tracts

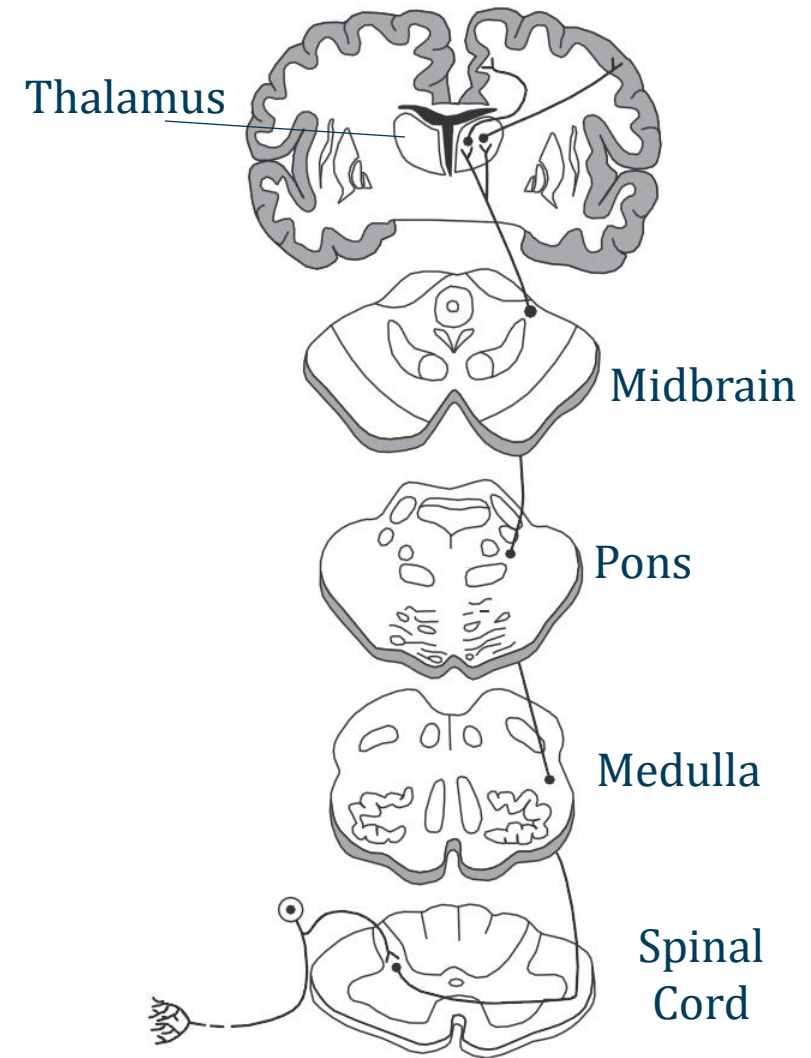
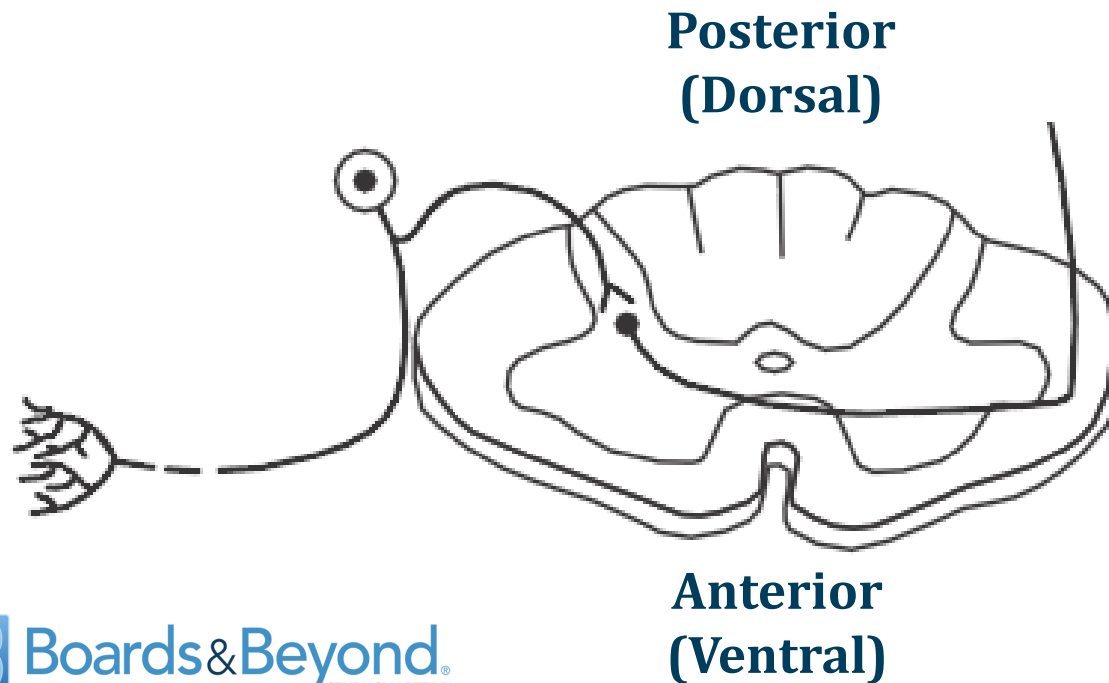
- **Sensory**
 - Spinothalamic tract
 - Posterior column
- **Motor**
 - Corticospinal tract



Spinothalamic Tract

Pain/temperature/crude touch

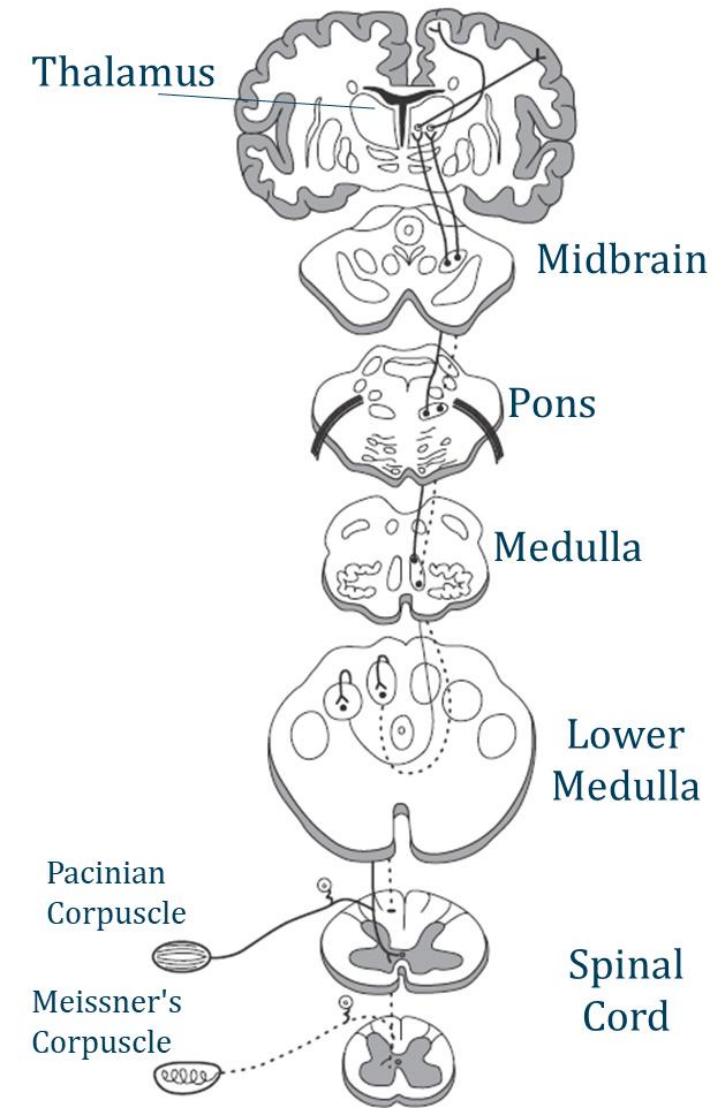
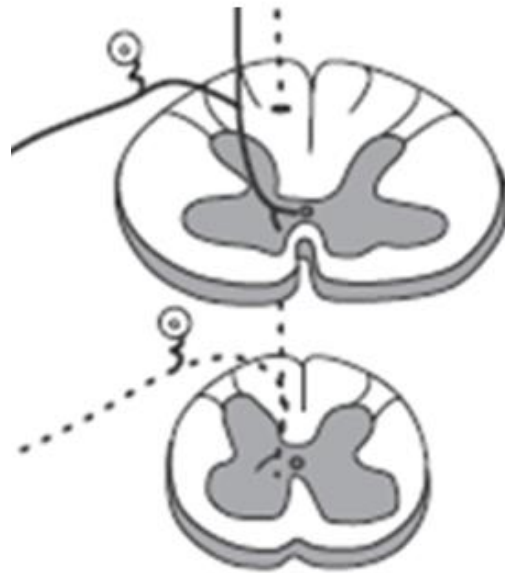
- Enters cord and crosses
- Cord carries contralateral sensory information
- Ascends to thalamus



Posterior Column

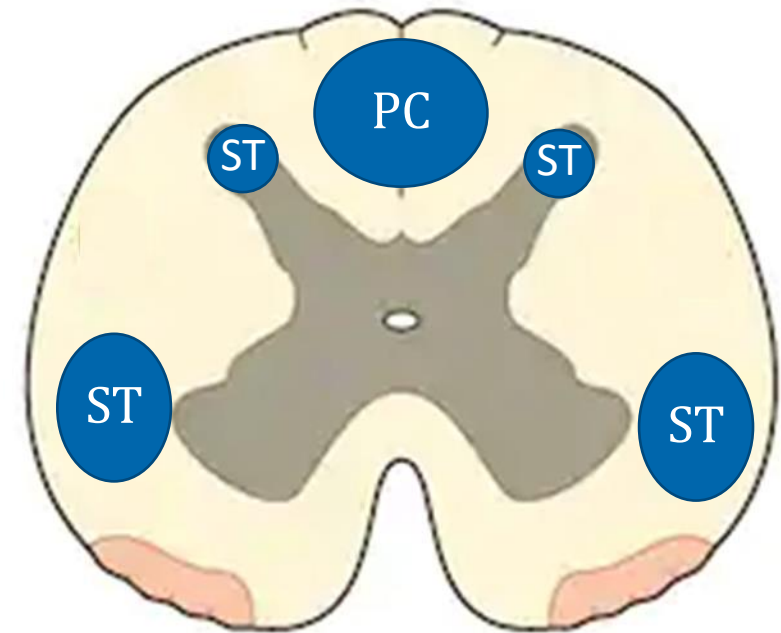
Dorsal Column-Medial Lemniscus

- Vibration/Proprioception/Fine touch
- Crosses in medulla
- Ascends on same side as sensory nerves



Sensory Information to Brain

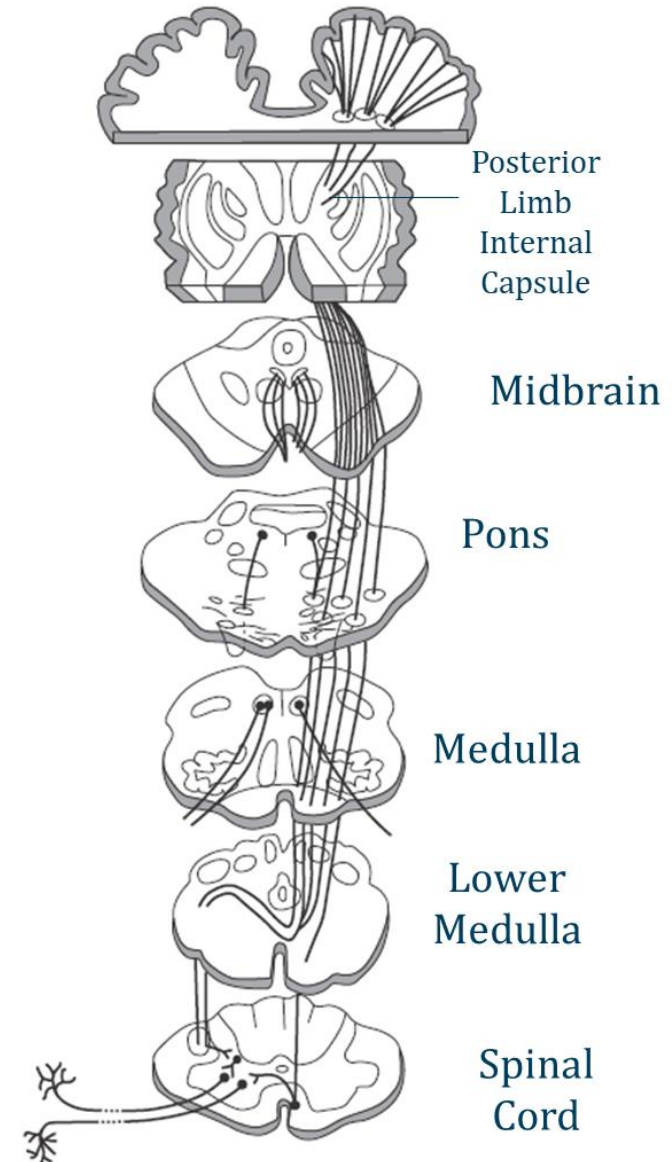
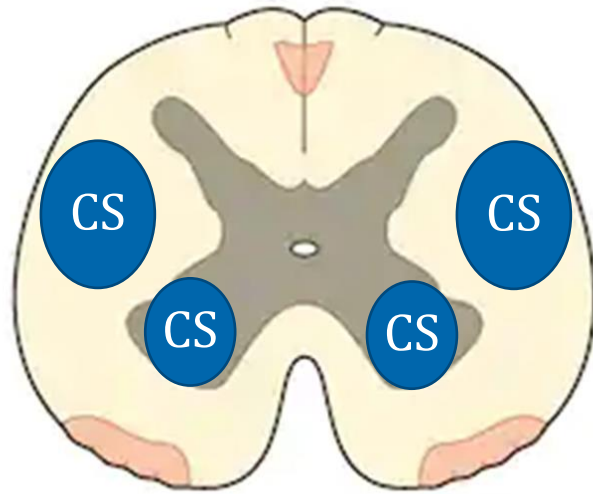
- **Spinothalamic**
 - Pain/temperature/crude touch
 - Cross cord level
- **Posterior column**
 - Vibration/proprioception/fine touch
 - Ascend in cord
 - Cross medulla
- Key point: both cross but in different places



Corticospinal Tract

Motor Innervation

- 1st Neuron: cortex to anterior horn
- 2nd Neuron: anterior horn to muscle
- Decussation in lower medulla



Motor Lesions

- **Upper motor neuron damage**
 - Spastic paralysis
 - Hyperreflexia
 - Pronator drift (arms out, palms up)
- **Lower motor neuron damage**
 - Flaccid paralysis
 - Loss of reflexes
 - Fasciculations
 - Atrophy

Reflex Grading



0 = No reflex

1+ = Diminished (LMN lesion)

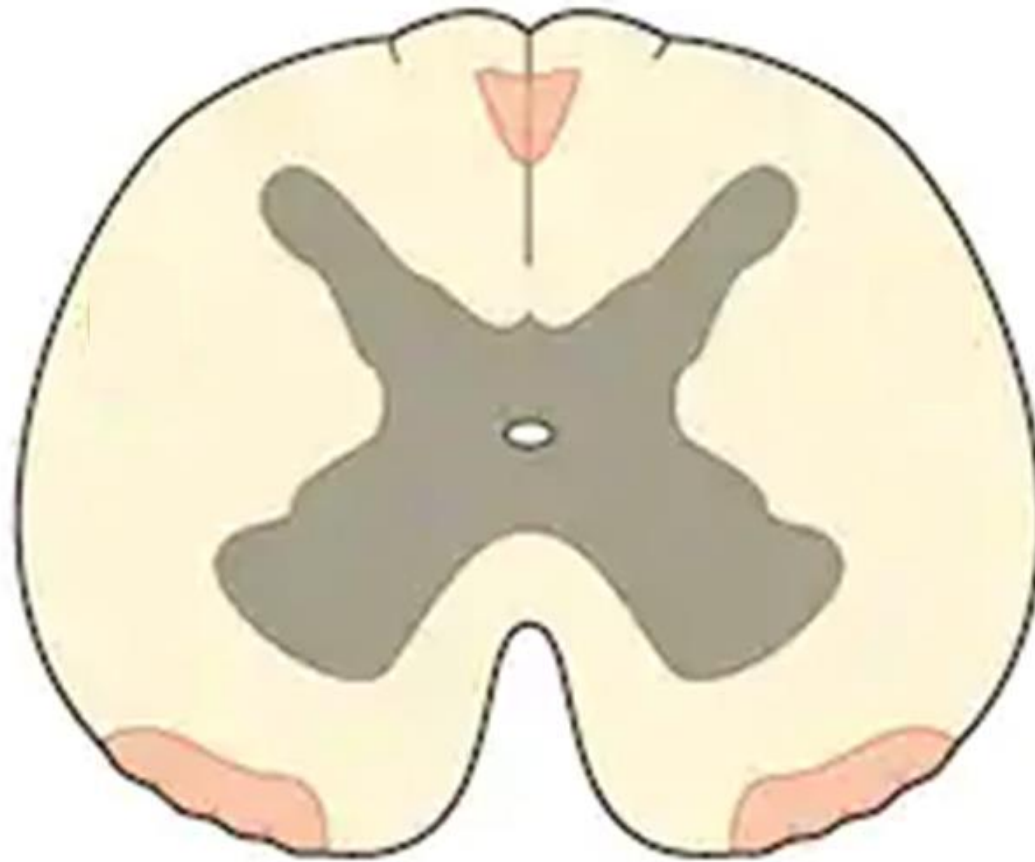
2+ = Normal

3+ = Brisk (UMN lesion)

4+ = Very brisk

5+ = Sustained clonus

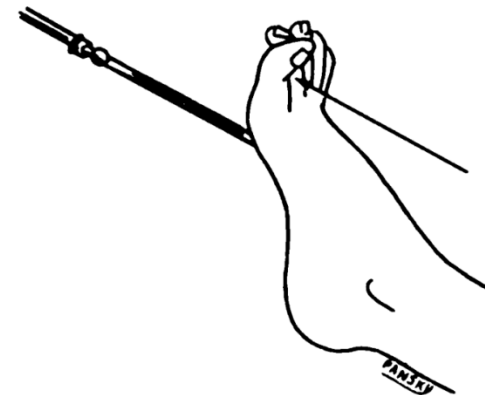
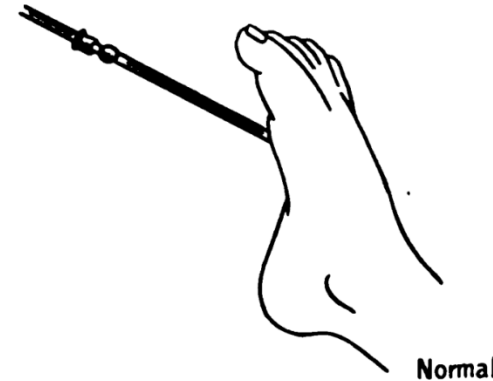
Reflexes



Babinski Sign

Plantar Reflex

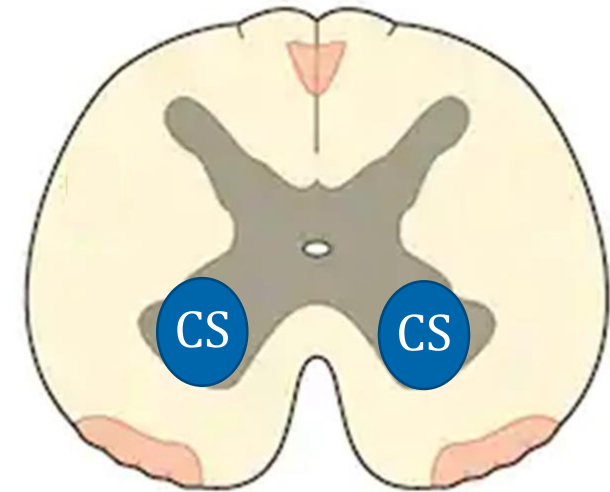
- Rub bottom foot
- Normal: downward
 - Plantarflexion
- Abnormal: upward
 - Dorsiflexion
 - UMN damage
 - UMN suppress reflex
- Upward = normal infants
 - < 12 mo
 - Incomplete myelination



Positive (+) Babinski sign
(dorsiflexion of big toe)

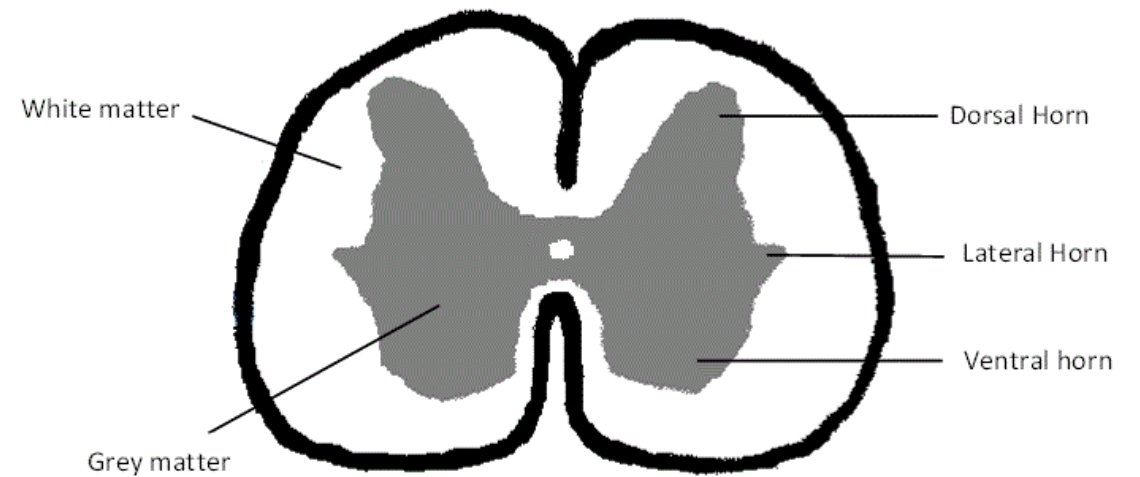
Motor Lesions

- UMN Lesions
 - Strokes
 - Brain tumors
- LMN Lesions
 - Polio virus
 - Destruction of **anterior horn**
 - Unvaccinated child
 - Febrile illness
 - Neuro symptoms 4-5 days later



Lateral Horn

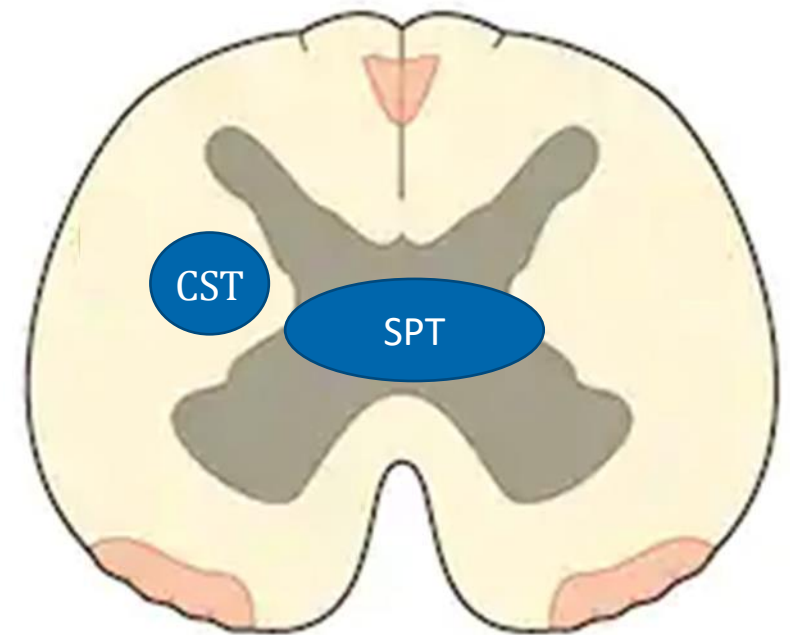
- Found in cord only from T1 to L2
- Contains sympathetic nerve cell bodies
- Damage leads to **Horner syndrome**
 - Constricted pupil (miosis)
 - Drooping of eyelid (ptosis)
 - Absence of sweating of face (anhidrosis)



Wikipedia/Public Domain

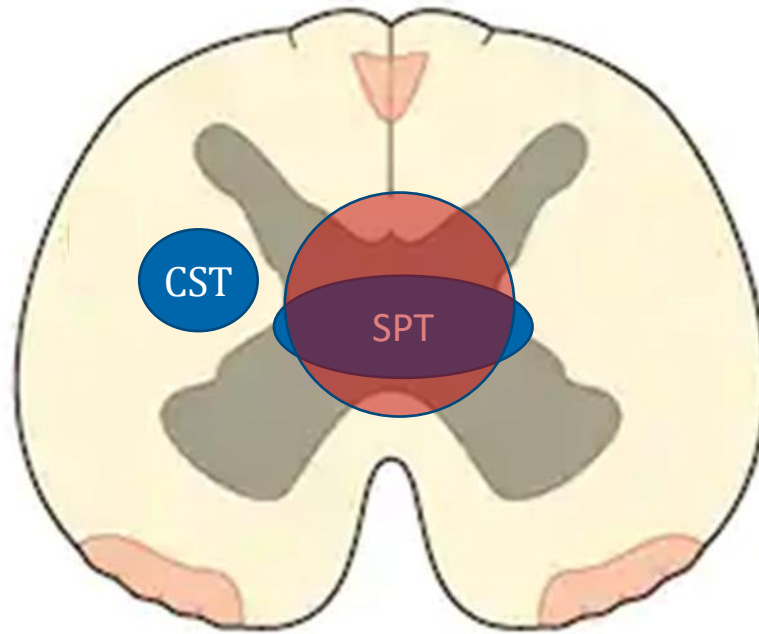
Central Cord Lesions

- **Loss of pain and temperature sensation**
 - Bilateral
 - At level of lesion
 - Crossing fibers of spinothalamic tract
- **Medial portion of corticospinal tract**
 - Weakness arm > leg
- Classic cause: syringomyelia



Syringomyelia

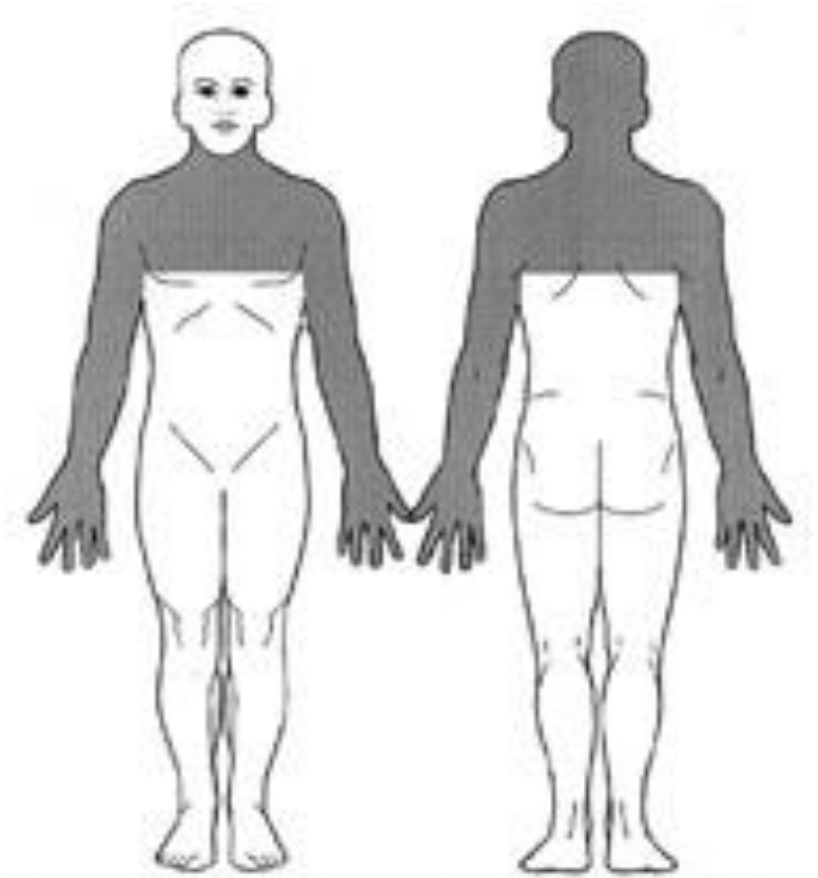
- **Syrinx**: fluid-filled space in spinal canal
- Central cord syndrome
- Diagnosis: MRI
- Treatment: surgery



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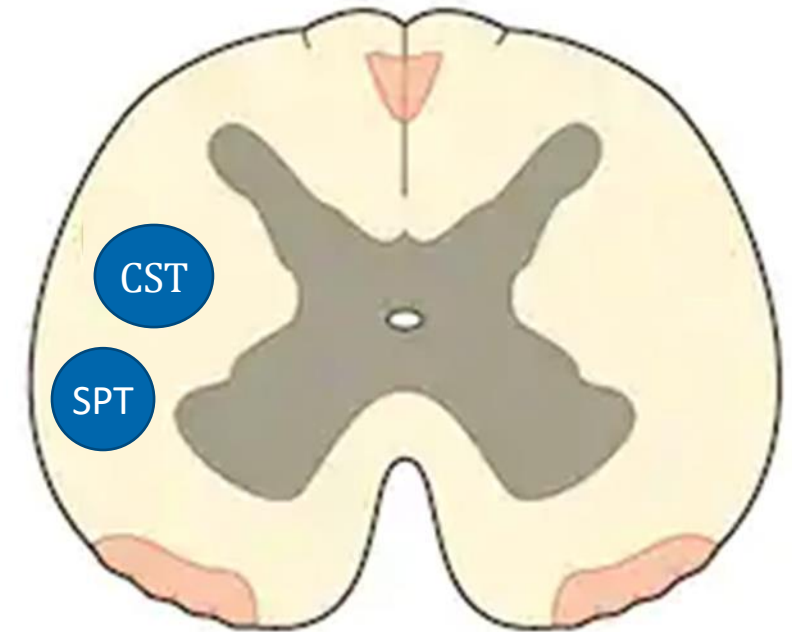
Syringomyelia

- Sensory symptoms only at level of the syrinx
- **Usually C8-T1**
 - Pin prick/temp loss in hands/back
 - Legs will be normal
- Loss of pain and temperature
 - Burns and cuts not felt
- Weakness may occur if CST involved
 - Usually arms > legs
- Horner syndrome may occur
- Position, vibration normal at all levels



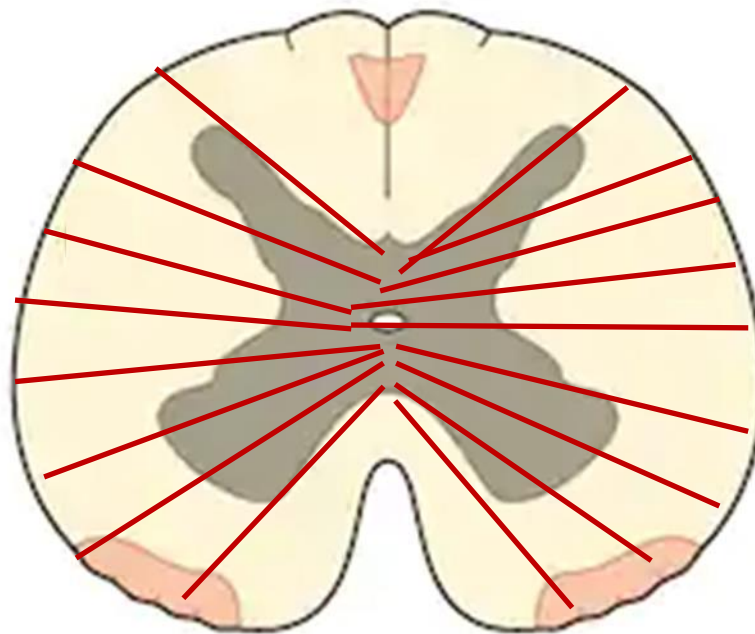
Ventral Cord Lesions

- Anterior two-thirds of cord
- Corticospinal tract
 - Bilateral paralysis below lesion
- Spinothalamic tracts
 - Bilateral loss of pain/temperature below lesion
- Descending autonomic tracts
 - Loss bladder control
- Classic cause: **spinal cord infarction**



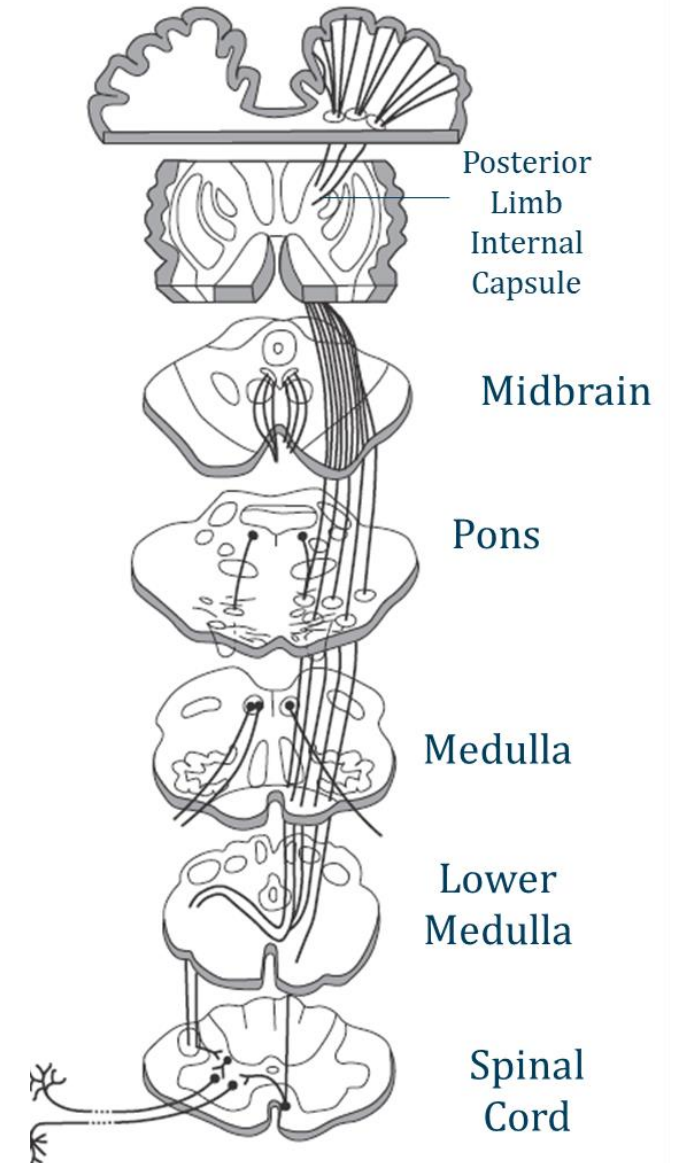
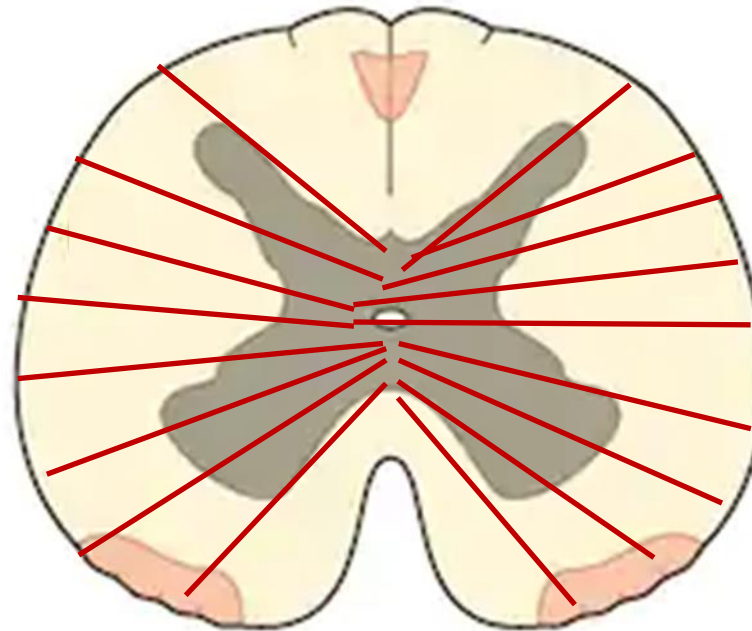
Anterior Spinal Artery Infarction

- Rare form of stroke
- Causes a ventral cord syndrome
- Loss of all but posterior columns
- Only vibration, proprioception
- Acute onset (stroke)



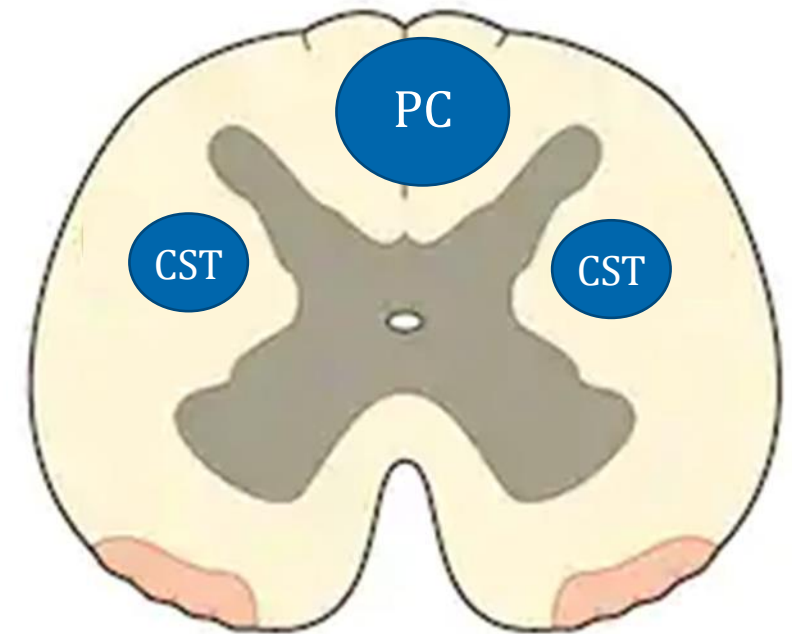
Anterior Spinal Artery Infarction

- Initial **spinal shock**
 - Flaccid bilateral paralysis (loss of LMN) below lesion
- Weeks later
 - **LMN defect at level of lesion (loss of DTRs)**
 - **UMN damage below lesion**



Dorsal Cord Lesions

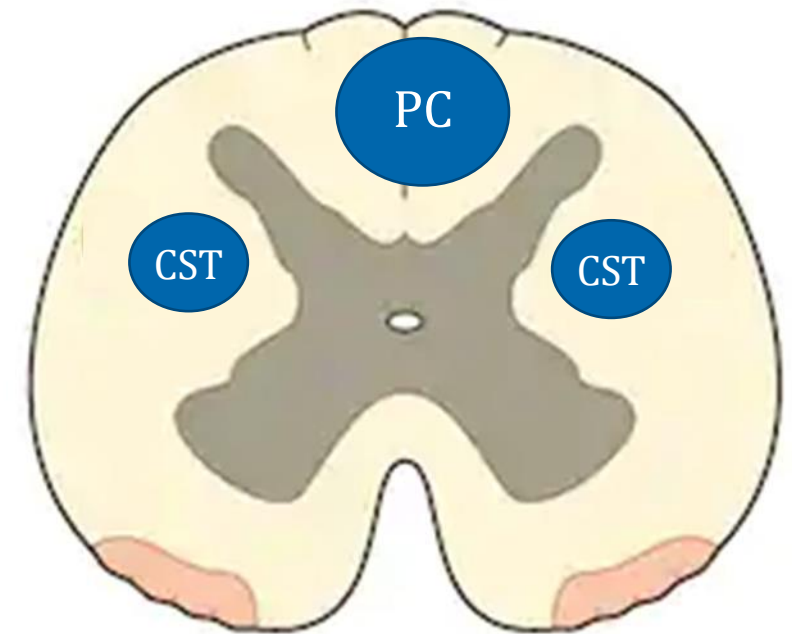
- Posterior columns
 - Loss of proprioception and vibration below lesion
- Can affect corticospinal tract
 - Motor weakness
- Classic causes:
 - SCD
 - Tabes Dorsalis



SCD

Subacute Combined Degeneration

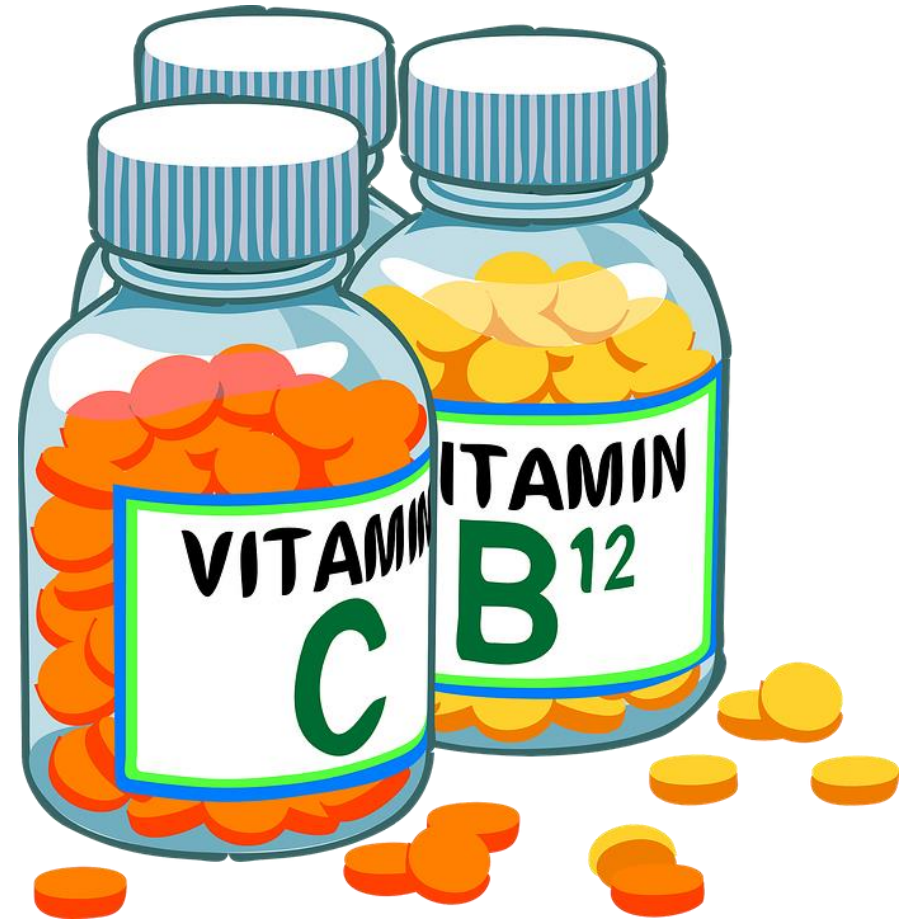
- Caused by **vitamin B12 Deficiency**
 - Anemia not always present
- Degeneration of **dorsal and lateral white matter**
 - Demyelination posterior columns
 - Loss of conduction in tracts
 - Loss of vibration/proprioception
 - Loss of lateral motor tracts
- Slowly progressive weakness
- Sensory ataxia
 - Loss of proprioception



SCD

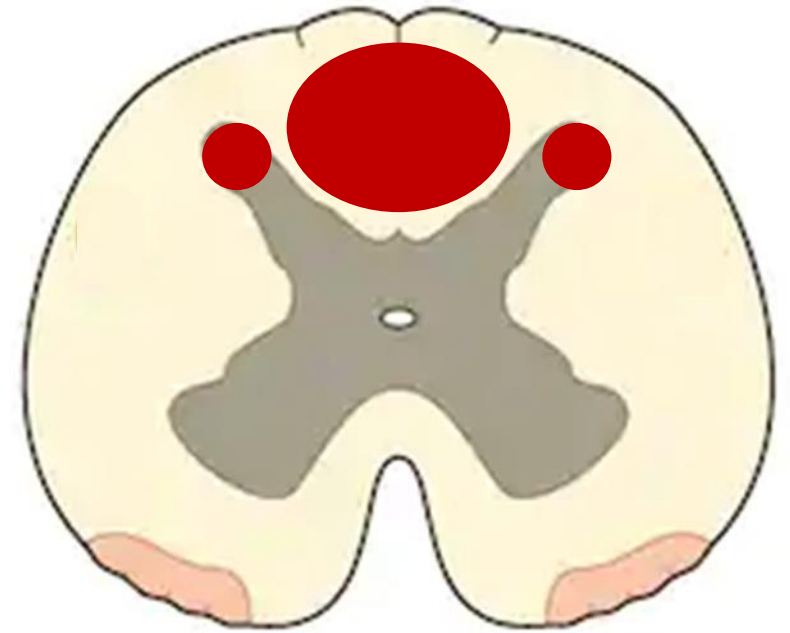
Subacute Combined Degeneration

- Classic presentation
 - Problems walking
 - Positive Romberg
 - Spastic paresis in legs
 - Lower extremity hyperreflexia
 - Positive Babinski



Tabes Dorsalis

- Tertiary syphilis (rare in modern era)
- Demyelination of posterior columns
 - Impairment of vibration and proprioception
 - Ataxia
- Loss of dorsal roots
 - Loss of pain sensation
 - Loss of peripheral reflexes



Tabes Dorsalis

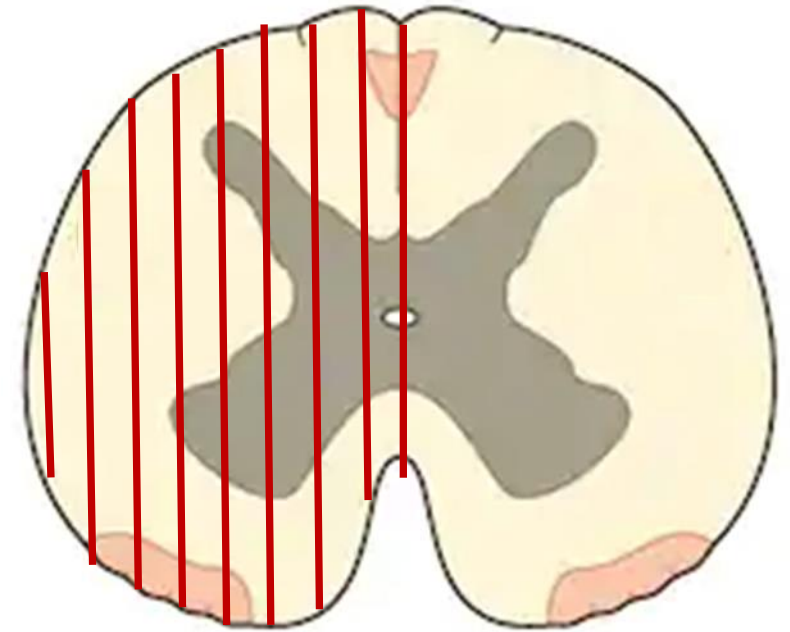
- **Sensory ataxia**
 - Loss of proprioception
- Hyporeflexia
- **Argyll-Robertson pupil**
 - Reacts to light but not accommodation
- **Shooting pains**
 - Sudden, severe pain
 - Limbs, back, or face



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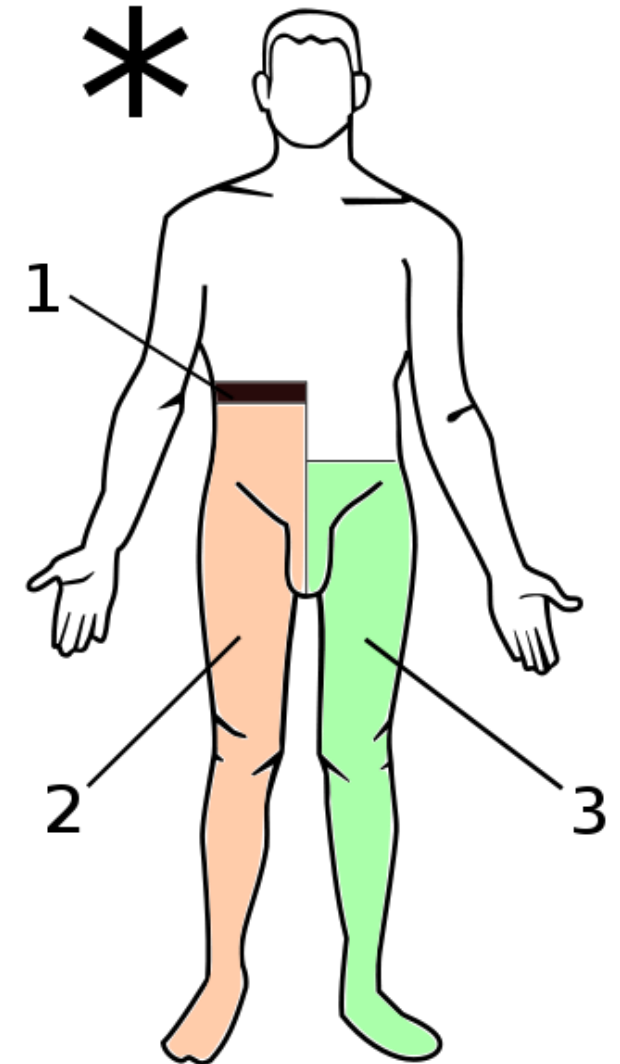
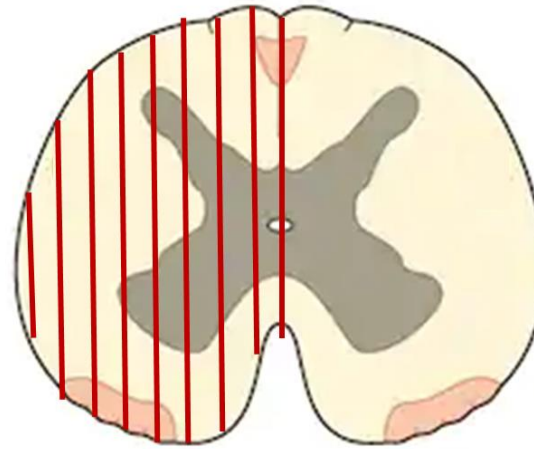
Brown-Sequard Syndrome

- Damage to half of spinal cord
- Causes:
 - Trauma (knife, bullet)
 - Multiple sclerosis
- Ipsilateral hemiparesis
 - Corticospinal tract
- Ipsilateral loss of proprioception/vibration
 - Posterior column damage
- Contralateral loss of pain and temperature
 - Spinothalamic tract



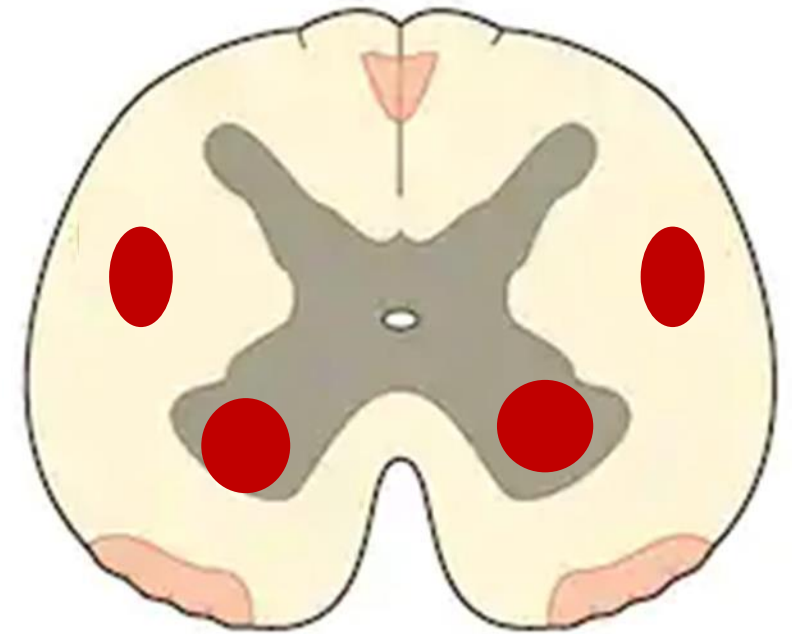
Brown-Sequard Syndrome

- 1: Level of lesion
 - LMN signs
 - Loss of ALL sensation
- 2: Loss of motor/posterior columns
 - UMN signs
 - Absent vibration/proprioception
- 3: Loss of pain/temp
- Horner syndrome may occur
- Weak side = side with lesion
- Complete sensory loss = level of lesion



Amyotrophic Lateral Sclerosis

- **Upper and lower motor neuron disease**
 - UMN (CST): Spasticity, exaggerated reflexes
 - LMN (anterior horns): Wasting, fasciculations
- Primary clinical feature: weakness
 - Limbs
 - Bulbar muscles: dysphagia, dysarthria
 - Difficulty swallowing, chewing or speaking common
 - Weak cough
 - Respiratory muscles
- Usually no sensory symptoms

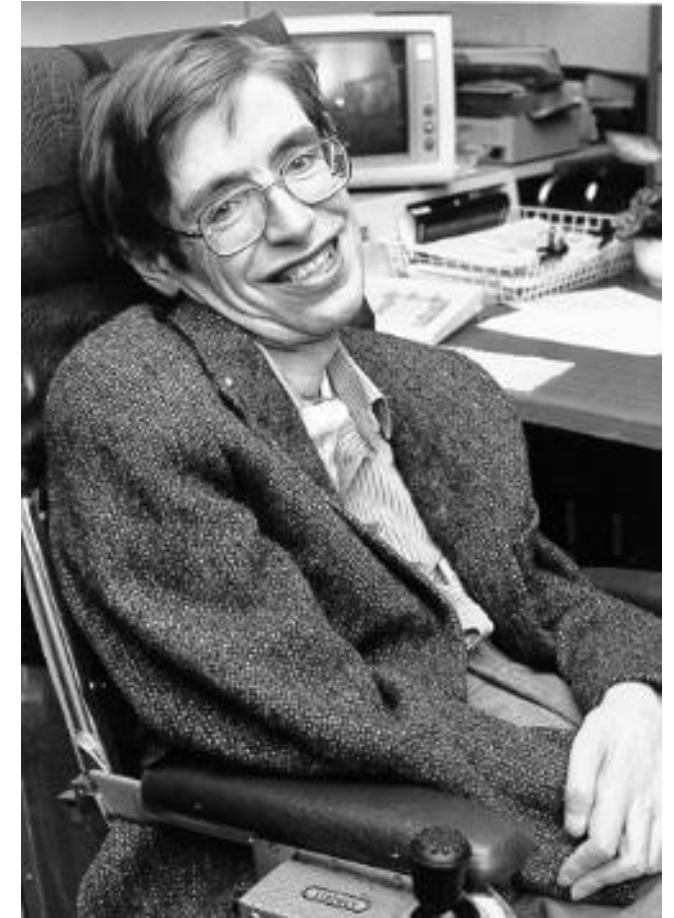


Amyotrophic Lateral Sclerosis

Clinical Features

- Most common 40-60 years old
- Usually sporadic (90% cases)
- Rarely familial: associated with SOD1 mutations
 - Superoxide dismutase type 1
 - Associated with free radical oxidative nerve injury
- Usually fatal 3-5 years
- Common cause of death: respiratory failure

Stephen Hawking

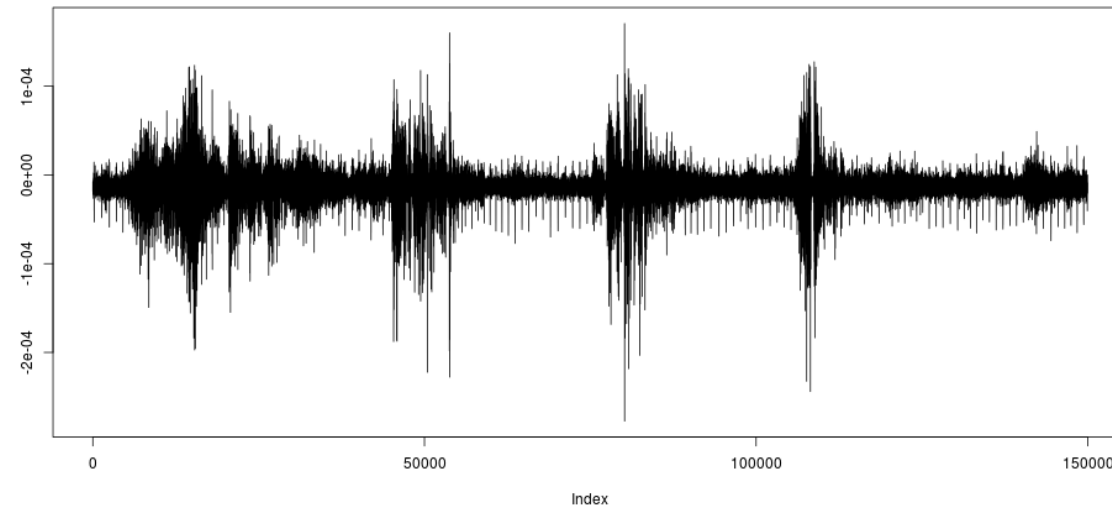


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Amyotrophic Lateral Sclerosis

Diagnosis

- Clinical diagnosis
- Brain imaging usually normal
- Electromyography (EMG)
 - Provides supportive evidence
 - Demonstrates denervation of muscle groups



Electromyogram

Amyotrophic Lateral Sclerosis

Treatment

- Treatment mostly supportive
- Riluzole
 - Blocks glutamate toxicity
 - Improved survival over 12 months
- Edaravone:
 - Free radical scavenger
 - Reduces oxidative stress
 - Improves symptoms



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Spinal Cord Compression

- Trauma, malignancy or infection
- Gradually worsening back pain
- Classically worse when lying in bed at night
- Symmetric lower extremity weakness
- Acute: diminished/absent deep tendon reflexes
- Chronic: **hyperreflexia with positive Babinski**



Public Domain

Spinal Cord Compression

- Tumor
 - Prostate, breast, lung, multiple myeloma
- Infection
 - Spinal epidural abscess
 - IVDU, cellulitis, uncontrolled diabetes
 - Fever
- Management:
 - Immediate steroids if high suspicion
 - Urgent MRI
 - Antibiotics for infection
 - Neurosurgical evaluation



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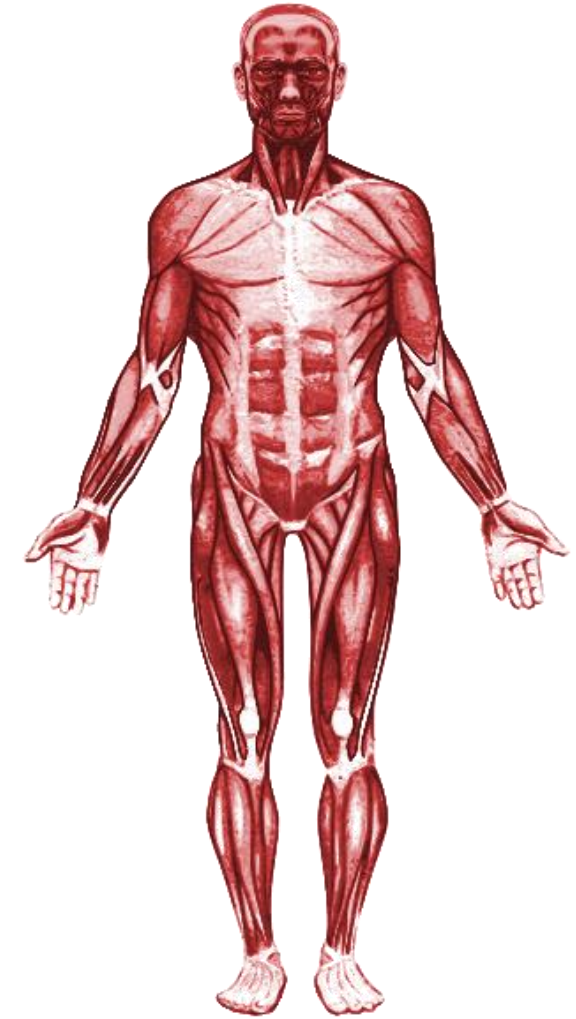
Neuromuscular Disease

Jason Ryan, MD, MPH



Muscular Dystrophies

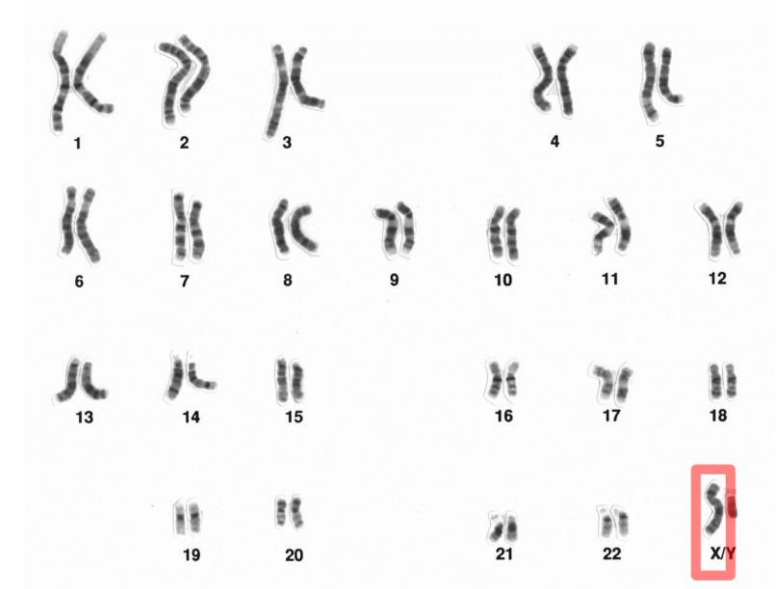
- Group of genetic disorders
- More than 30 types
- All result from defects in genes for muscle function
- Main symptom: **progressive muscle weakness**



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Duchenne and Becker Muscular Dystrophies

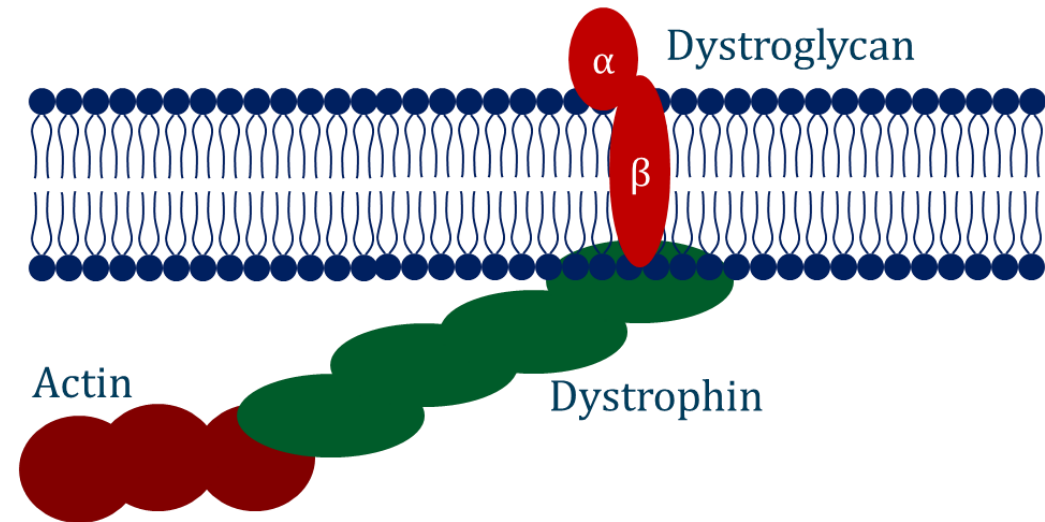
- Both **X-linked recessive disorder**
 - “X-linked muscular dystrophies”
 - All male carriers affected
 - New mutations in fertilized egg (no parental carrier)
 - Inherited from carrier mothers
- Both involve **DMD gene** and **dystrophin** protein



DMD

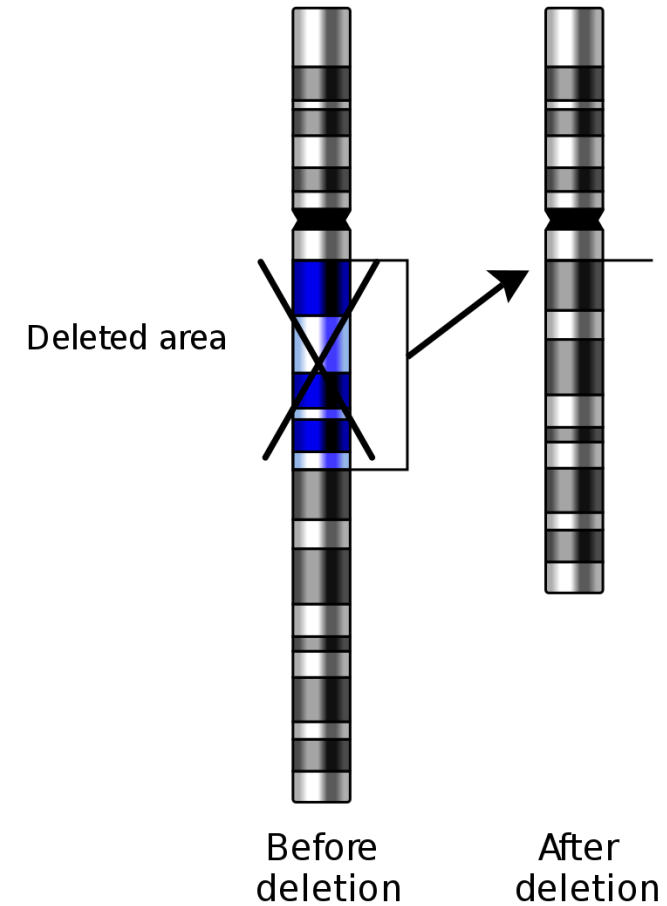
Duchenne Muscular Dystrophy

- **DMD gene**
 - Massive gene (2300kb)
 - 1.5% of the X chromosome
 - Among largest known genes
 - High mutation rate
- Codes for **dystrophin**
 - Connects actin to dystroglycan
 - Maintains muscle membranes



Dystrophin Gene Mutations

- Most mutations are **deletions**
- Duchenne: frameshift mutation
 - Alters DNA reading frame
 - Truncated or absent dystrophin protein
 - Severe disease
- Becker: non-frameshift mutation
 - Some functioning protein
 - Less severe disease



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DMD

Duchenne Muscular Dystrophy

- Affected boys normal first few years
- Weakness develops age 3-5
- Wheelchair usually by age 12
- Death usually by age 20
 - Usually due to respiratory failure
 - Sometimes heart failure

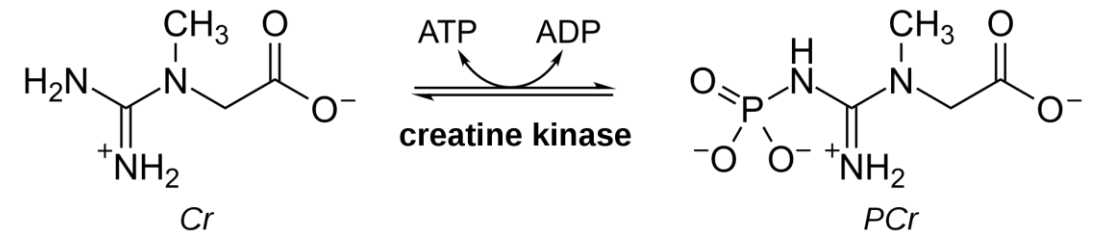


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DMD

Duchenne Muscular Dystrophy

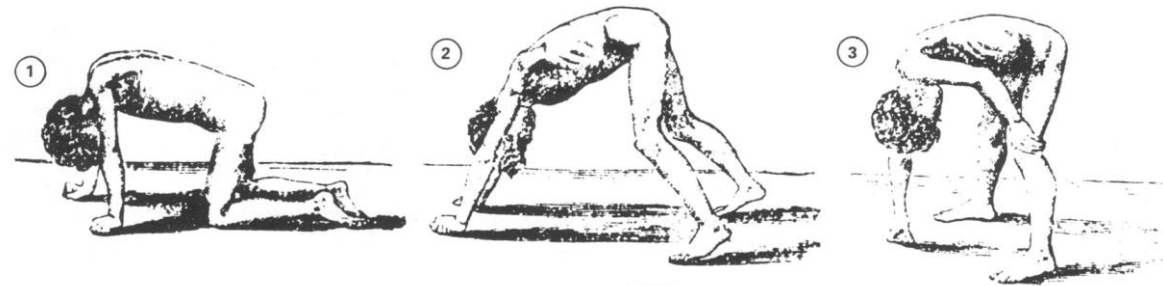
- Loss of dystrophin → **myonecrosis**
- **Creatine kinase** elevation
 - Common in early stages
 - Released from diseased muscle
- Other muscle enzymes also elevated
 - Aldolase
 - Aspartate transaminase (AST)
 - Alanine transaminase (ALT)



DMD

Duchenne Muscular Dystrophy

- **Proximal muscles** affected before distal limb muscles
- **Lower limbs** affected before upper extremities
- Affected children:
 - Difficulty running, jumping, climbing stairs
 - Use hands to push themselves up from chair (Gower's sign)
 - Waddling gait

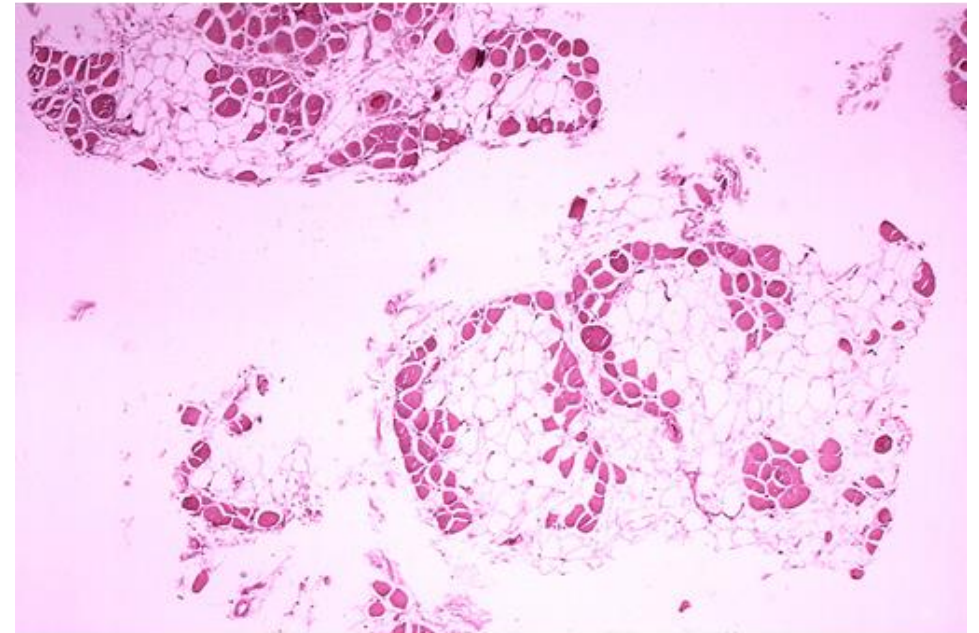


DMD

Duchenne Muscular Dystrophy

- Muscle replaced with **fat/connective tissue**
 - Calf enlargement
 - “Pseudohypertrophy”
- **Cardiomyopathy**
 - Depressed LVEF
 - Systolic heart failure
 - Myocardial fibrosis

Muscle Biopsy



Wikipedia/Public Domain

DMD

Duchenne Muscular Dystrophy

- Diagnosis: genetic testing
 - Usually with polymerase chain reaction
 - Identifies most common DMD gene abnormalities
- Muscle biopsy (rarely done)
- Treatment: **glucocorticoids**
 - Improve motor function
 - Delay loss of ambulation
- Multidisciplinary care
 - Physical therapy
 - Monitoring respiratory function



BMD

Becker Muscular Dystrophy

- Also X-linked recessive disorder
- **Milder form of muscular dystrophy**
- Later age of onset
- Remain ambulatory longer
- Often survive into 30s



Myotonic Dystrophy

- Autosomal dominant muscular dystrophy
 - Unrelated to dystrophin protein
- Type I (most common)
 - Abnormal **DMPK gene** (chromosome 19)
 - Dystrophia myotonica protein kinase
 - CTG expansion
 - Codes for **myotonic dystrophy protein kinase**
 - Abnormal gene transcribed to mRNA but not translated

Myotonic Dystrophy

- Most common MD that **begins in adulthood**
 - Often starts in 20s or 30s
- Progressive muscle wasting and weakness
- Prolonged muscle contractions (myotonia)
 - Unable to relax muscles after use
 - Cannot release grip
 - Locking of jaw
- **Facial muscles** often affected
 - Characteristic facial appearance
 - Long and narrow face
 - Hollowed cheeks



Herbert L. Fred, MD, Hendrik A. van Dijk

Myotonic Dystrophy

- **Multisystem disorder**
 - Many non-muscle features
- Intellectual disability
- Cataracts
- Cardiac arrhythmias
- Frontal balding
- Hypogonadism
- Insulin resistance

Cataract

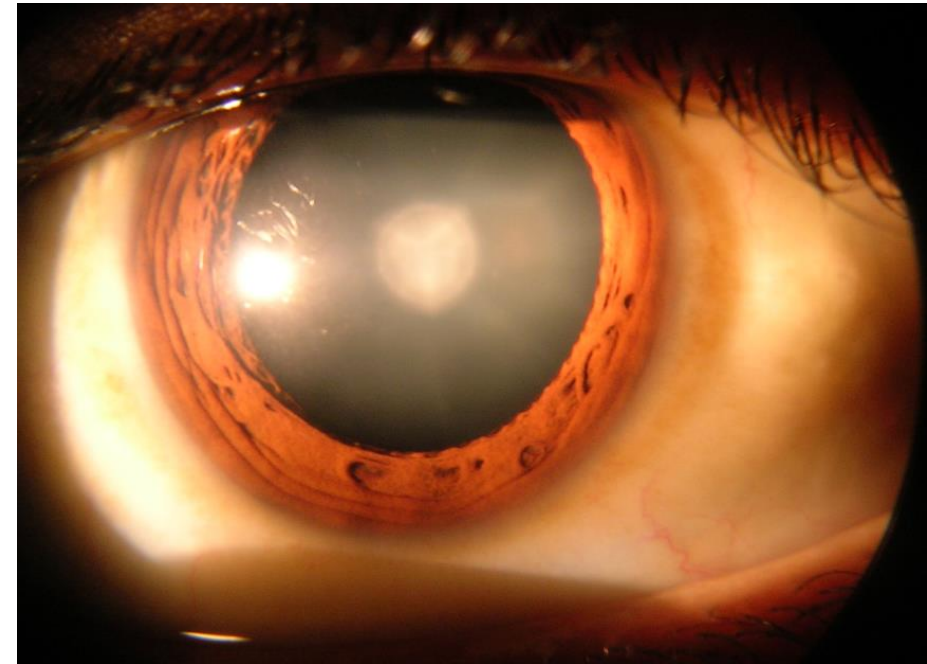


Image courtesy of Rakesh Ahuja, MD

Myotonic Dystrophy

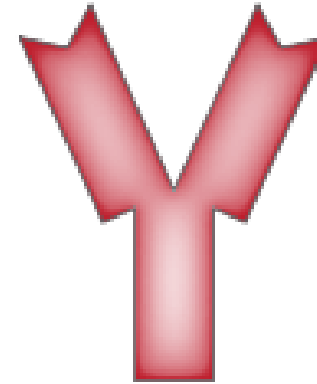
Diagnosis and Treatment

- Diagnosis: genetic testing
- Treatment: supportive
 - No disease-modifying therapies



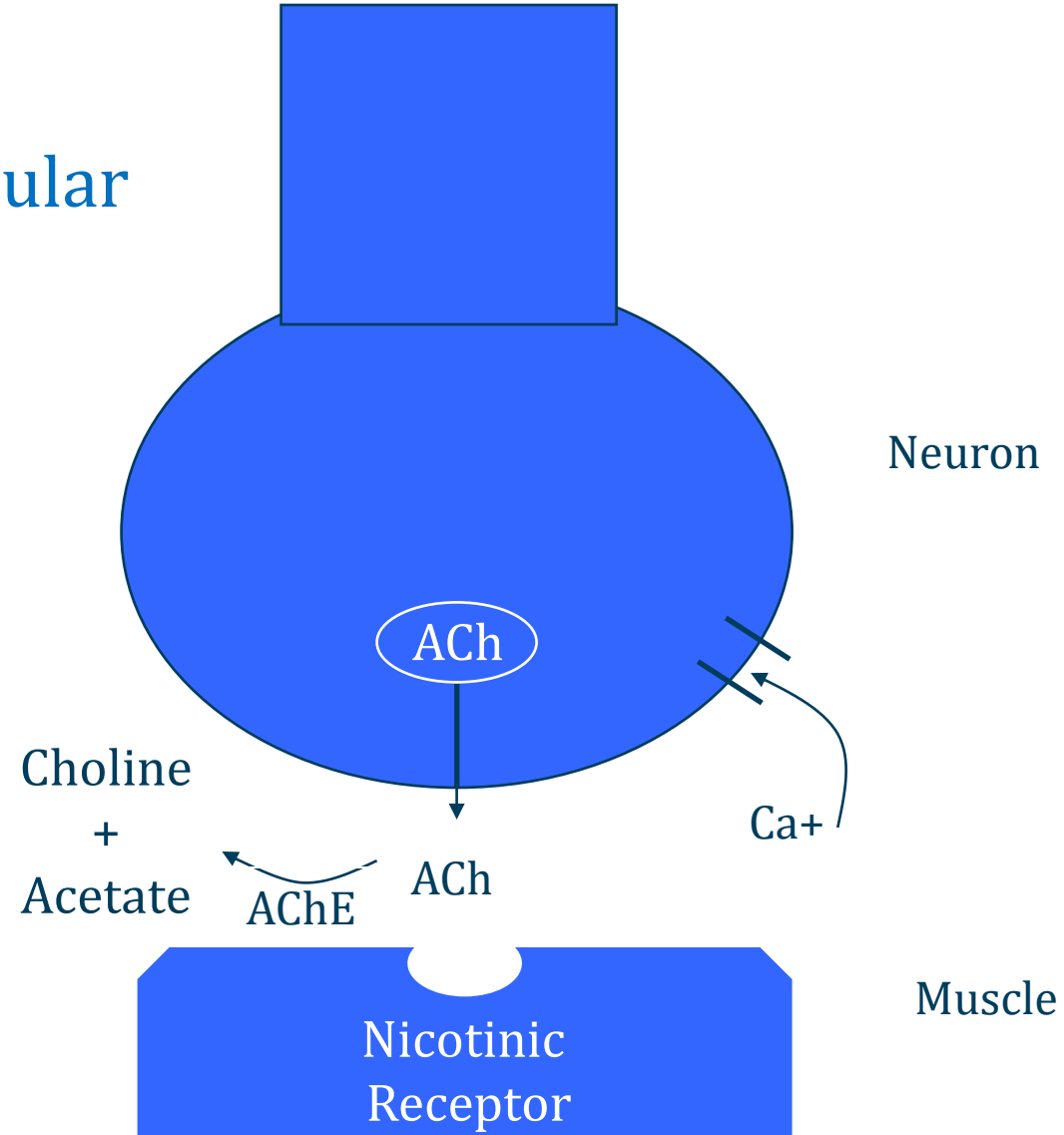
Myasthenia Gravis

- **Neuromuscular junction disorder**
- Autoimmune disease
- Antibodies block nicotinic ACh receptors
- Compete with ACh for receptor binding
- Muscle weakness
- More common in women
- Diagnosis: **acetylcholine receptor antibodies**



Martin Brändli /Wikipedia

The Neuromuscular Junction



Myasthenia Gravis

- **Bimodal age distribution**
- Women: peak 20s to 30s
- Men: peak 60s to 80s

Myasthenia Gravis

Clinical Features

- **Muscle fatigability**
 - Repeated nerve stimulation \rightarrow \downarrow ACh release
 - **Muscles weaken with use**
- **Diplopia and ptosis**
 - Extraocular muscle weakness
 - 50% patients present with eye complaints
- Speech, chewing and swallowing problems
 - 15% patients present with “bulbar symptoms”

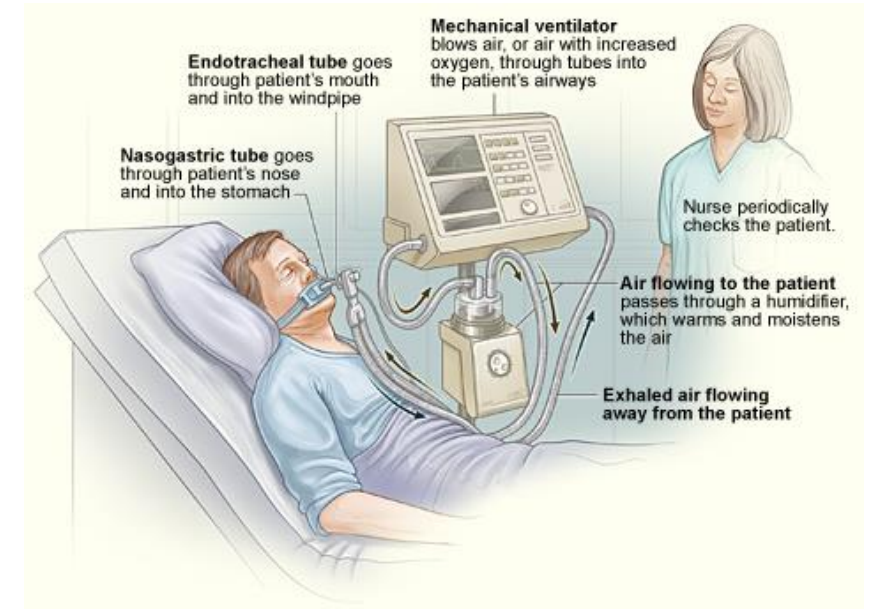


Andrewya/Wikipedia

Myasthenia Crisis

- Rapid, life-threatening worsening of weakness
- Most common precipitant: infection
 - Also surgery
- Can be caused by many drugs:
 - Hydroxychloroquine
 - Antibiotics: aminoglycosides, fluoroquinolones
 - Beta-blockers
- Requires **intubation or noninvasive ventilation**
 - Weakness of respiratory muscles
 - Severe bulbar muscle weakness → airway obstruction
- Treatment: **plasma exchange or IVIG**

Mechanical Ventilation



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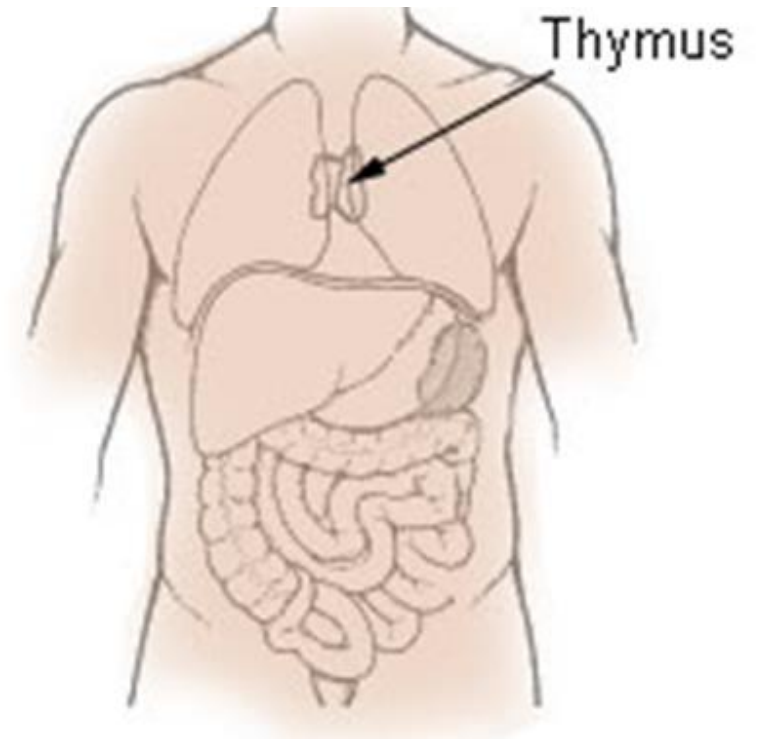
Myasthenia Crisis

- **Oral or nasogastric glucocorticoids**
- Moderate to high dose
- Given concurrently with plasma exchange or IVIG
- Alternatives: azathioprine, mycophenolate, or cyclosporine

Myasthenia Gravis

Disease Associations

- Most MG patients have **abnormal thymus**
 - Hyperplasia ~85%
 - Thymoma ~15%
- MG often resolves with thymectomy
- Thymectomy done for all thymomas
 - Nonthymomatous MG can also be cured with thymectomy
 - Nonthymomatous thymectomy often done patients < 60
- Key test: **imaging of mediastinum (CT or MRI)**
 - Anterior mediastinal mass (terrible Ts)



Public Domain/Wikipedia

Myasthenia Gravis

Drugs

- Some drugs worsen neuromuscular transmission
- Should be avoided by patients with MG
- **Antibiotics**
 - Aminoglycosides
 - Fluoroquinolones
- **Na channel blocking drugs**
 - IV local anesthetics (e.g., lidocaine)
 - Procainamide
 - Quinidine
- **Beta-blockers**

Myasthenia Gravis

Pregnancy

- Most women with MG tolerate pregnancy well
- MG can worsen in pregnancy and postpartum
- Flares most likely in **first trimester** and **first month postpartum**

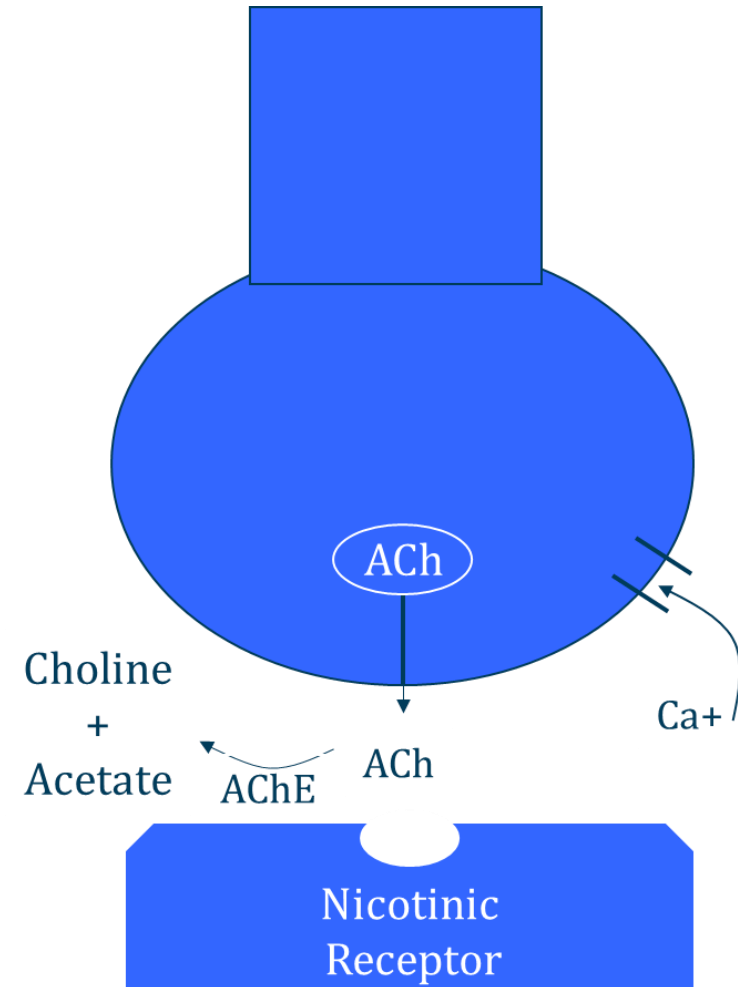


Øyvind Holmstad/Wikipedia

Myasthenia Gravis

Chronic Treatment

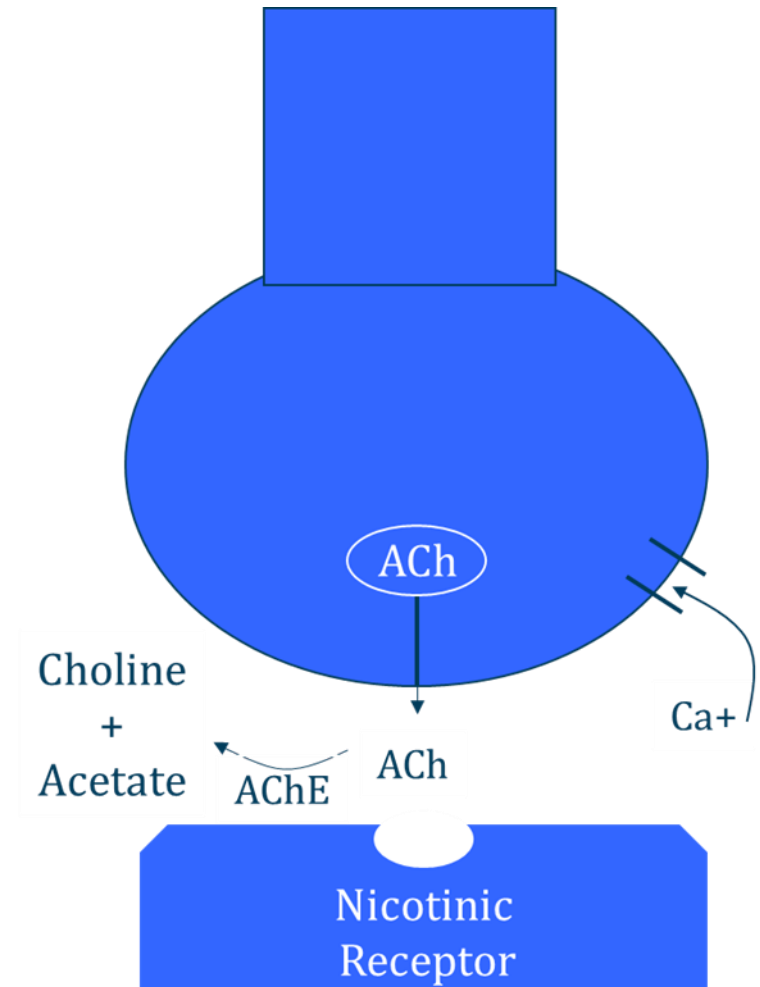
- **Acetylcholinesterase inhibitors**
 - First line: pyridostigmine
 - ↓ ACh metabolism
 - ↑ ACh levels in NMJ
- Immunosuppressants
- Thymectomy in appropriate patients



LEMS

Lambert-Eaton Myasthenic Syndrome

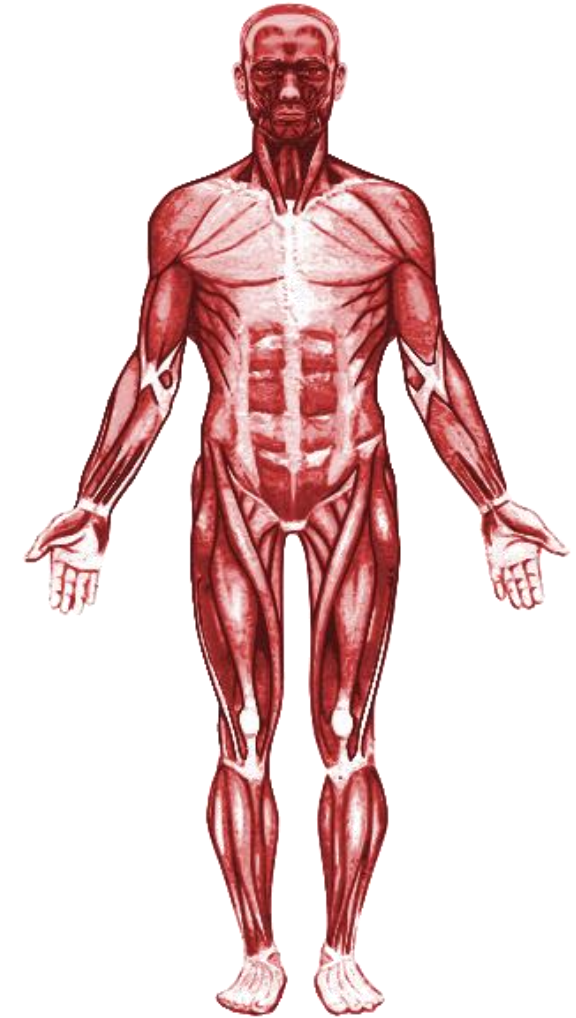
- Also a disorder of NMJ (less common)
- Paraneoplastic syndrome (small cell lung cancer)
- Antibodies against pre-synaptic Ca channels
- Prevent ACh release
- Diagnosis: **VGCC antibodies**
 - Antibodies to voltage-gated calcium channel (VGCC)
- Key test: imaging for lung mass



LEMS

Clinical Features

- Slow-onset **symmetric proximal muscle weakness**
 - Also seen in myositis
 - Normal CK levels
 - No muscle pain/myalgia
- Difficulty walking or rising from chair
- Difficulty combing hair



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LEMS

Clinical Features

- **Muscle use → improved symptoms**
 - Contrast with myasthenia gravis
 - More depolarization → more ACh release
 - Detected by motor nerve conduction studies
 - ↑ compound motor action potentials (CMAPs) with repeated stimulation

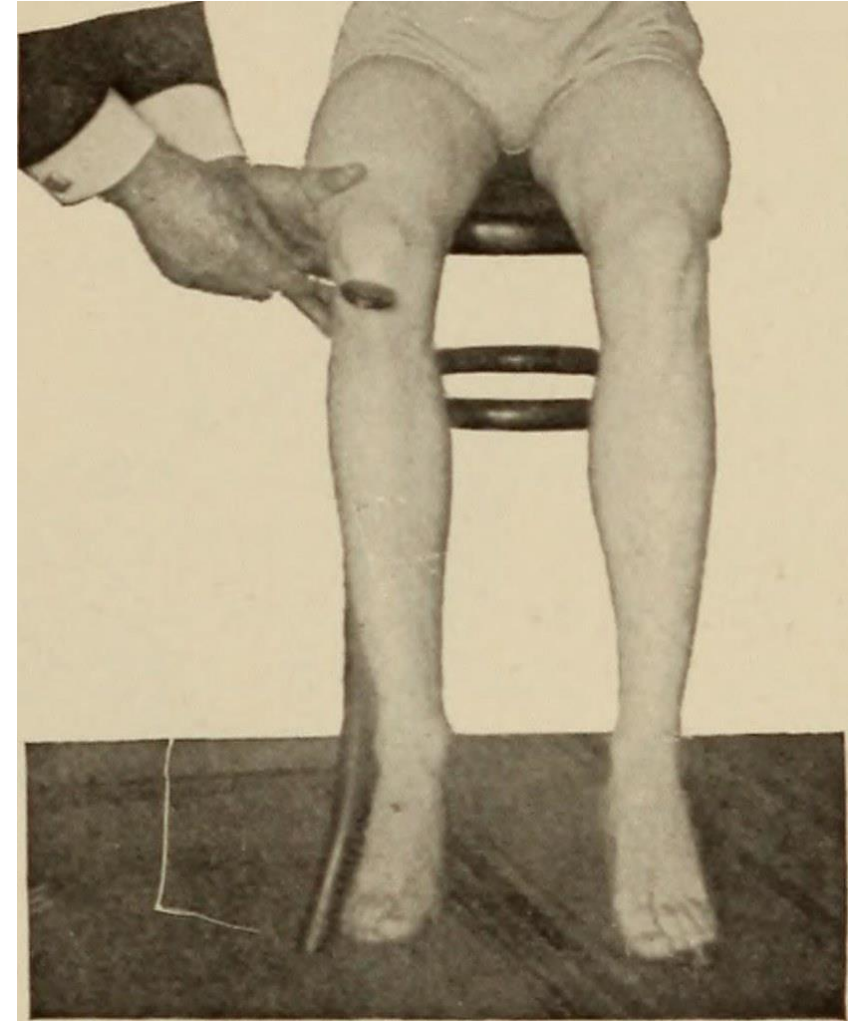


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LEMS

Clinical Features

- Diminished or absent deep tendon reflexes
 - Contrast with MG



Flickr/Public Domain

LEMS

Clinical Features

- Autonomic dysfunction common
- Classically dry mouth from ↓ salivation
- Erectile dysfunction, constipation
- Impaired pupillary light response

Xerostomia (Dry Mouth)

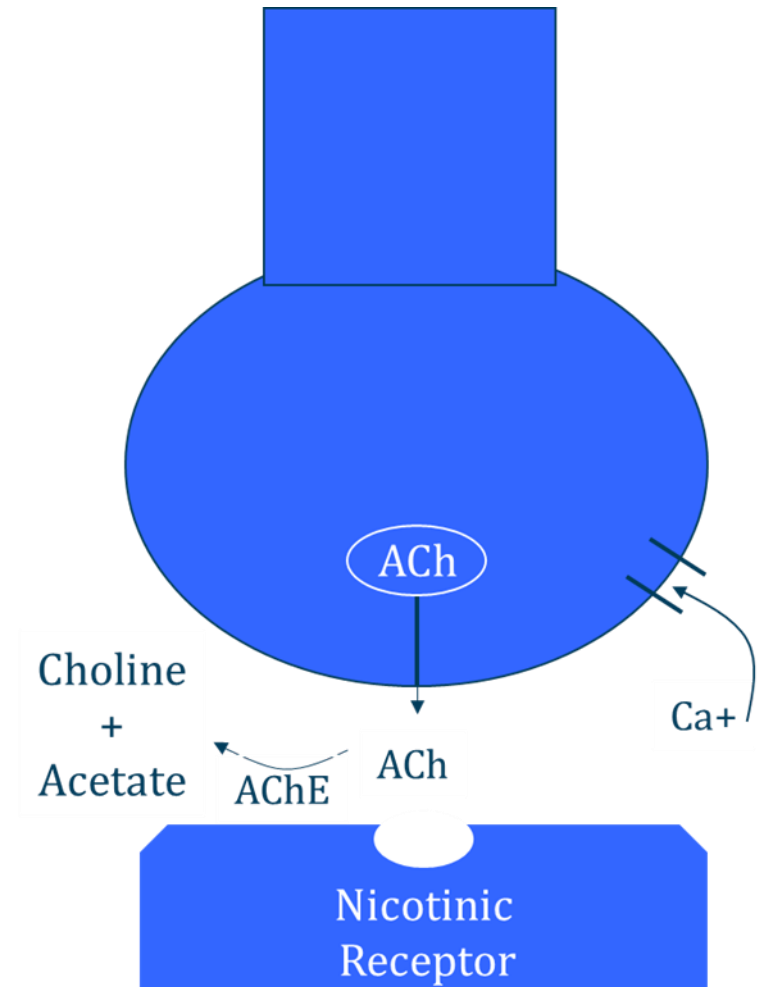


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LEMS

Treatment

- Treat (or locate) underlying malignancy
- **Amifampridine** (3,4-diaminopyridine or 3,4-DAP)
 - Inhibits potassium channel efflux presynaptic neuron
 - Slows repolarization
 - Prolonged depolarization → ↑ ACh release
- Alternative: guanidine (same mechanism)
- Pyridostigmine
- Acute, severe LEMS: IVIG



NMJ Syndromes

	Myasthenia	Lambert-Eaton
Cause	ACh receptor Ab	Calcium channel Ab
Muscle Use	Worsens	Improves
Eye Symptoms	Classic	Less common
Proximal Muscles	Rare	Common
Autonomic Symptoms	Absent	Common

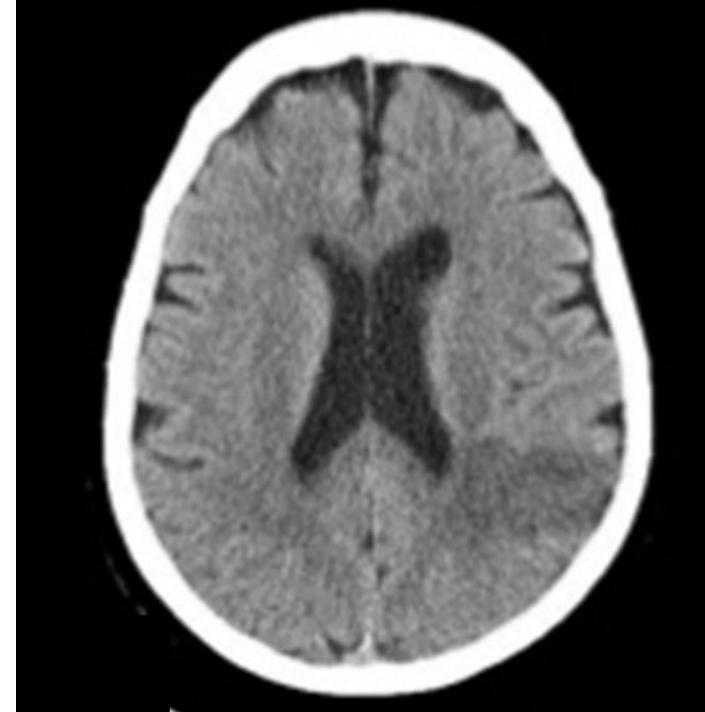
Ventricular Pathology

Jason Ryan, MD, MPH

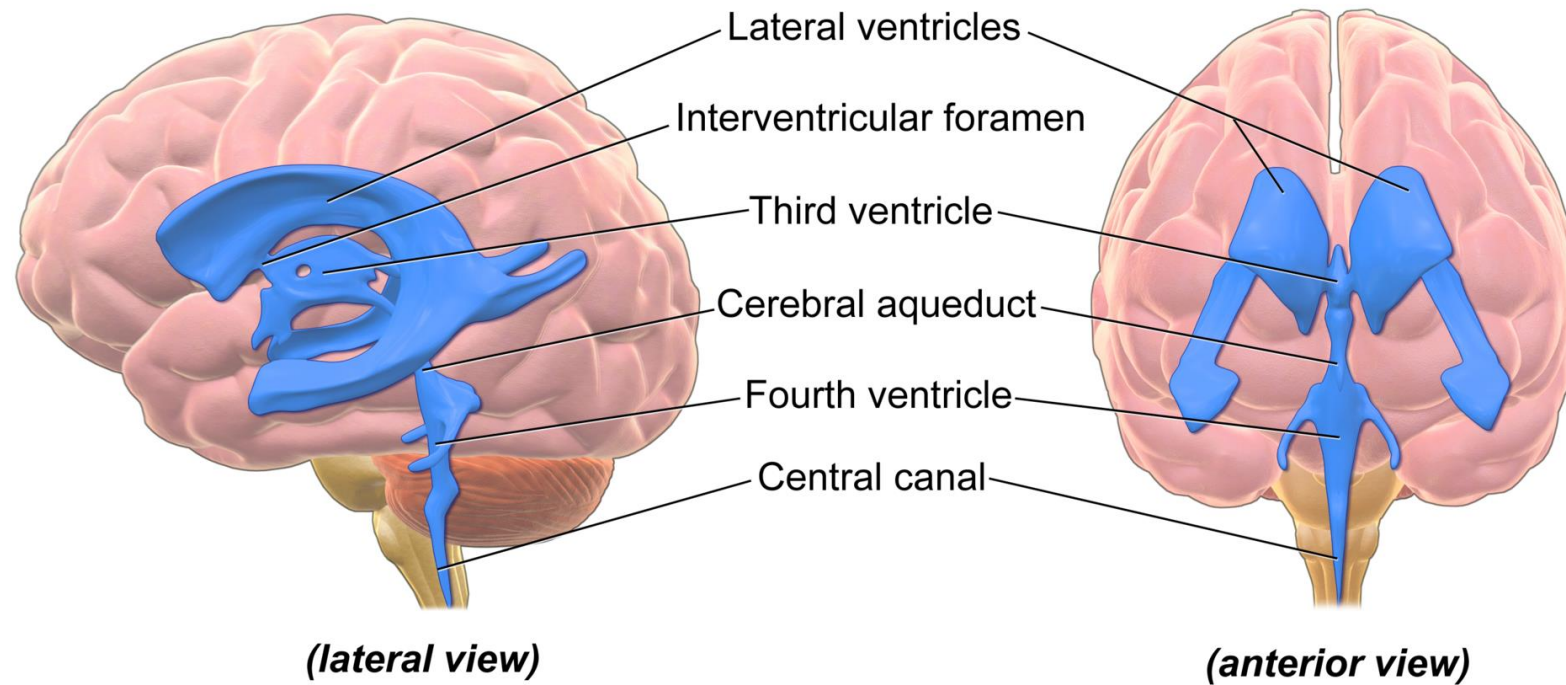


CNS Ventricles

- Four structures that contain CSF in brain
 - Two lateral ventricles
 - 3rd ventricle
 - 4th ventricle
- Continuous with central canal of spinal cord

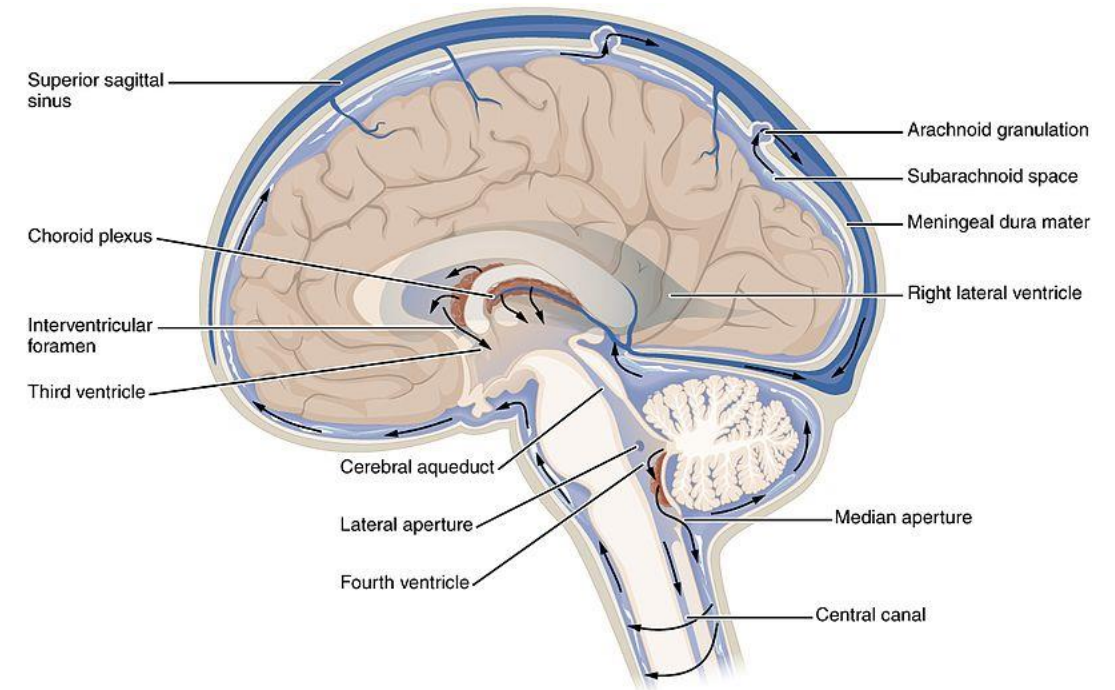


Ventricles



Cerebrospinal Fluid

- Clear, colorless fluid
 - Mechanical protection
 - Shock absorber
 - Circulates nutrients removes waste
- Production
 - Ependymal cells of choroid plexus (ventricles)
- Absorption
 - Arachnoid villi
- Drains to superior sagittal sinus
 - Then to venous system



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Hydrocephalus

- Dilation of ventricles
- Excessive accumulation of CSF
- Diagnosis: CT scan (or MRI)
 - Will show ventriculomegaly

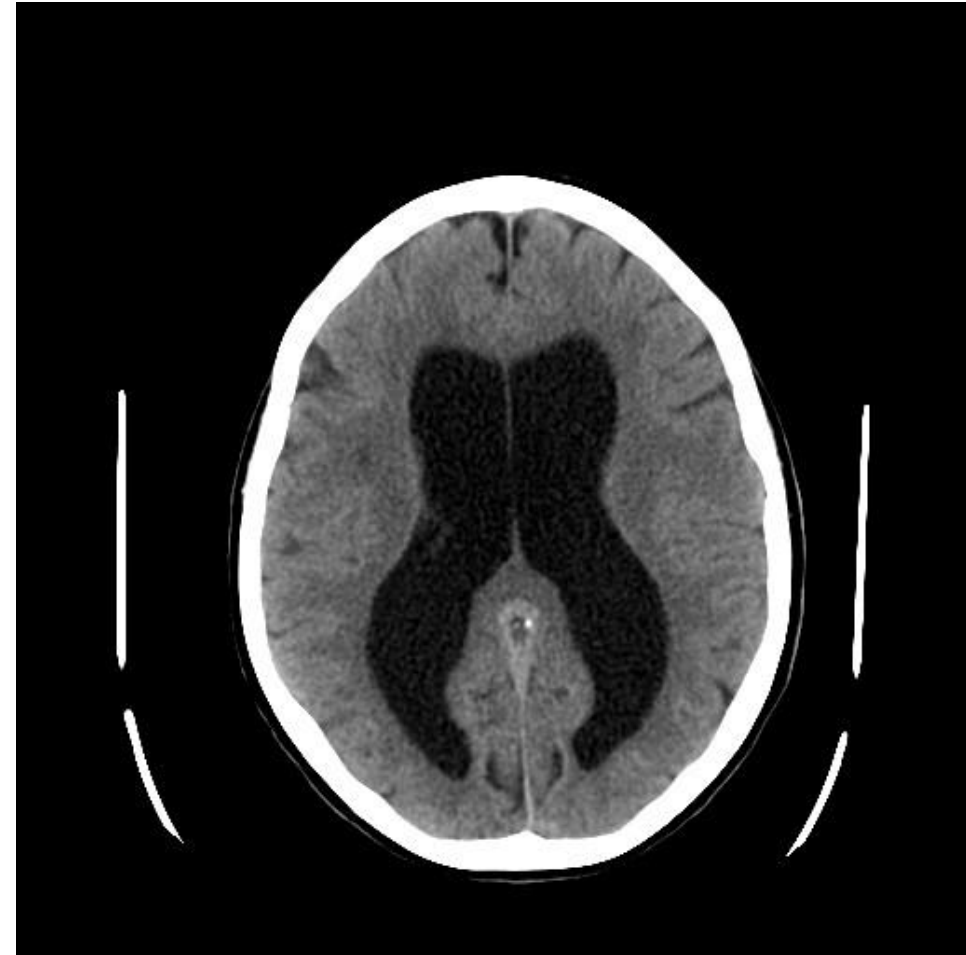


Image courtesy of Lucien Monfils

Hydrocephalus

- Communicating
 - CSF not being absorbed
 - Ventricles CAN communicate
- Non-communicating
 - Blockage to flow
 - Ventricles CAN'T communicate

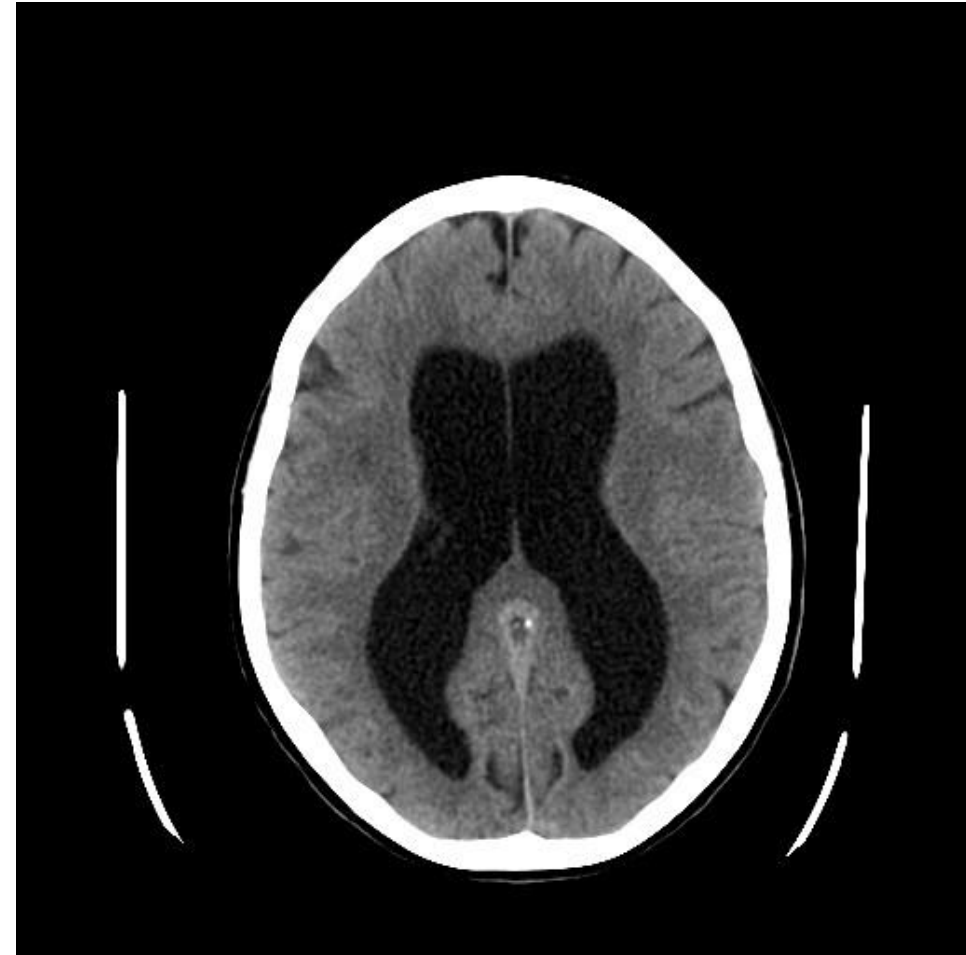
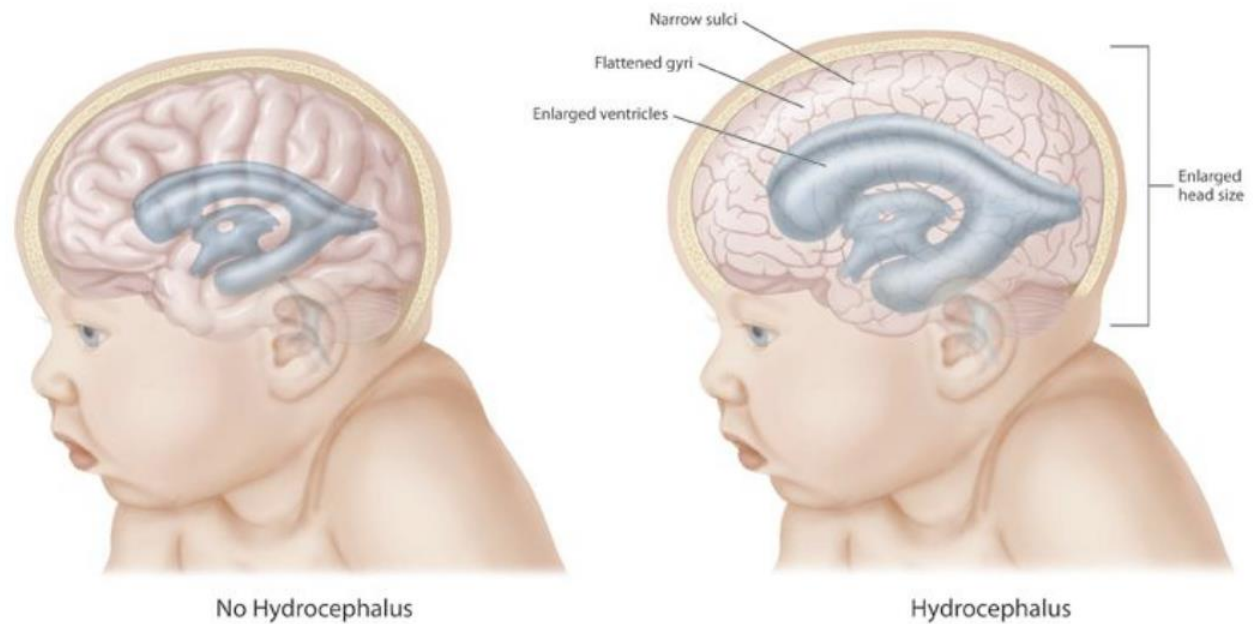


Image courtesy of Lucien Monfils

Non-Communicating Hydrocephalus

- Structural blockage of CSF flow within ventricles
- Often congenital
- Many etiologies
- Three worth knowing:
 - Aqueductal stenosis
 - Chiari Malformations
 - Dandy-Walker malformation



Aqueductal Stenosis

- Stenosis of cerebral aqueduct
- Blocked drainage from 3rd to 4th ventricle
- Congenital narrowing
 - X-linked (boys)
- Inflammation due to intrauterine infection
 - Rubella, CMV, toxo, syphilis
- Presentation: **enlarging head circumference**



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Chiari II Malformation

- Downward displacement of the cerebellar tonsils and medulla
- Obstructs outflow of CSF
- 4th ventricle displaced
- Enlarged lateral and 3rd ventricles

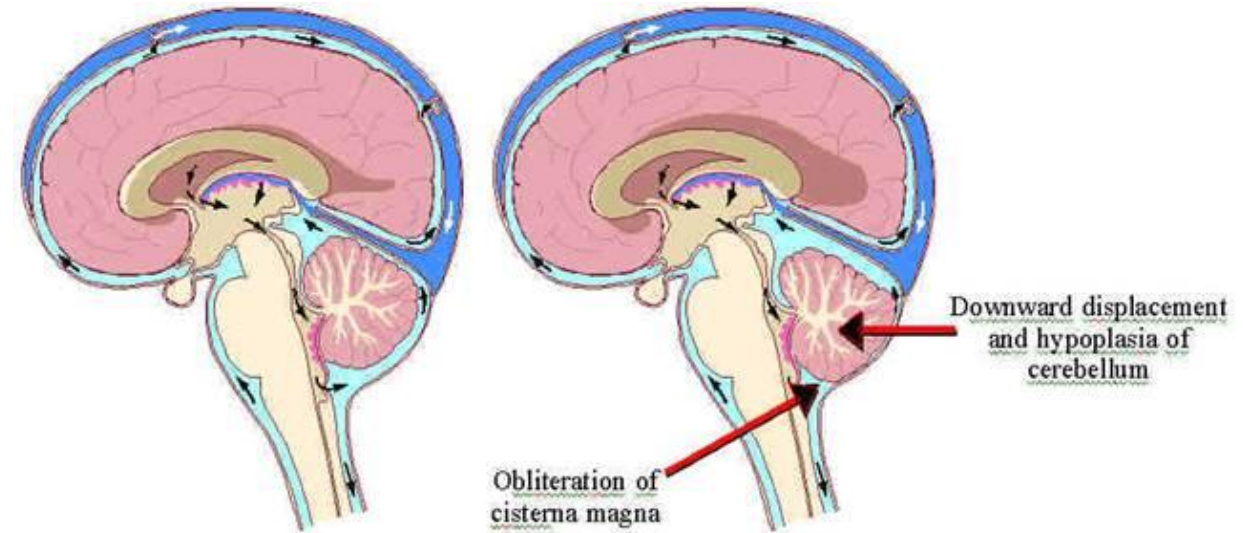
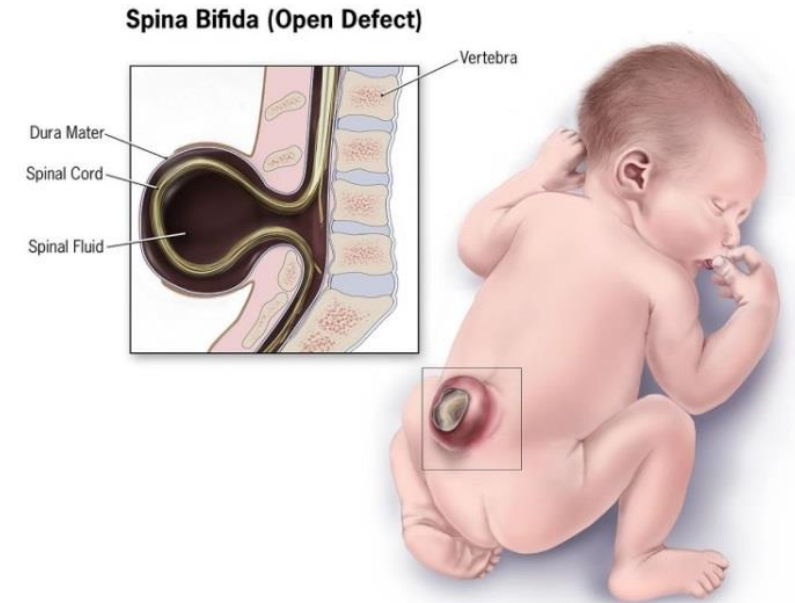


Image courtesy of obinno59

Myelomeningocele

(Spina Bifida)

- **Neural tube defect**
- Failure of spine and meninges to close around cord
- Myelomeningocele: cord/meninges outside spine
- **Almost always has Chiari II malformation**
- Hydrocephalus major cause morbidity
- Obstruction 4th ventricular outflow



Dandy-Walker Malformation

- Developmental anomaly of the **fourth ventricle**
- Hypoplasia or agenesis of cerebellar vermis
- Cysts of 4th ventricle → hydrocephalus
- Massive 4th ventricle, small cerebellum
- Many associated symptoms/conditions
- Affected children
 - Hydrocephalus (macrocephaly)
 - Delayed development
 - Motor dysfunction (crawling, walking)



Public Domain

Communicating Hydrocephalus

- ↓ CSF absorption by arachnoid
- ↑ intracranial pressure
- CT Hallmark: **dilation of ALL ventricles**
- Scarring after **meningitis**
- **Intraventricular hemorrhage**
 - Occurs in premature infants

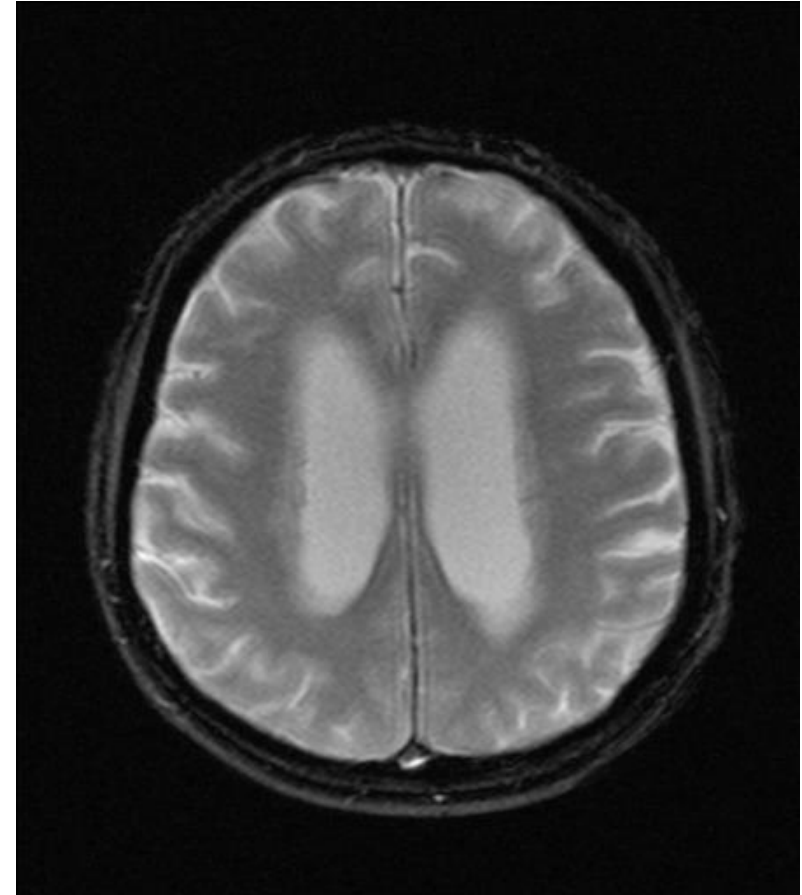


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NPH

Normal Pressure Hydrocephalus

- **Enlarged ventricles on imaging**
- **Normal opening pressure on LP**
- Suspected mechanism: impaired absorption CSF
- Older adults, usually > 60
- Classic triad:
 - Urinary incontinence, gait disturbance, dementia
 - Wet, wobbly, and wacky

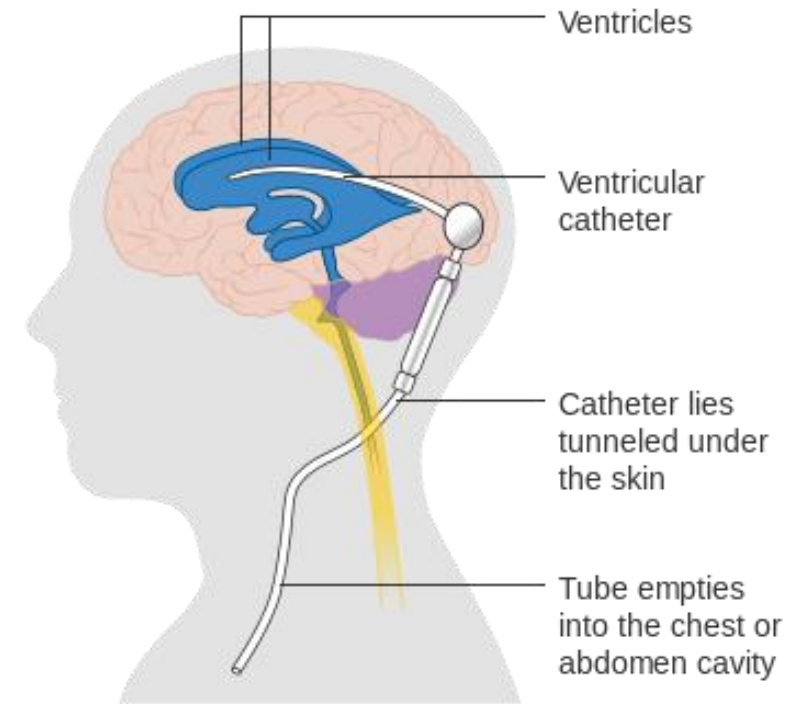


Nevit Dilmen/Wikipedia

NPH

Normal Pressure Hydrocephalus

- Key finding: **slow, wide-based gait**
- Gait disturbance can resemble Parkinson's
 - But no rest tremor, masked facies or bradykinesia
- Diagnosis: MRI
 - Ventriculomegaly
 - No cortical atrophy
- Treatment: **ventriculoperitoneal (VP) shunt**
 - Drains CSF to abdomen

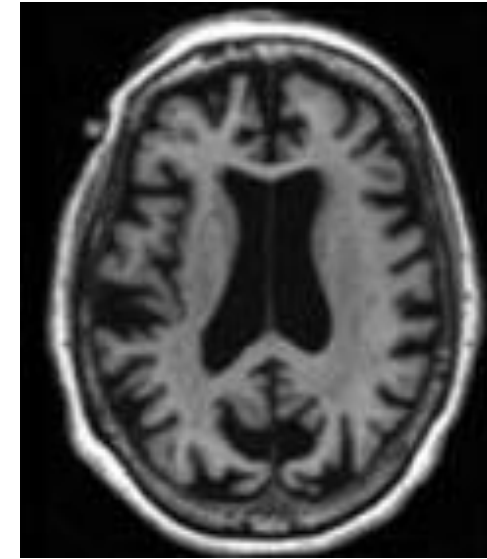


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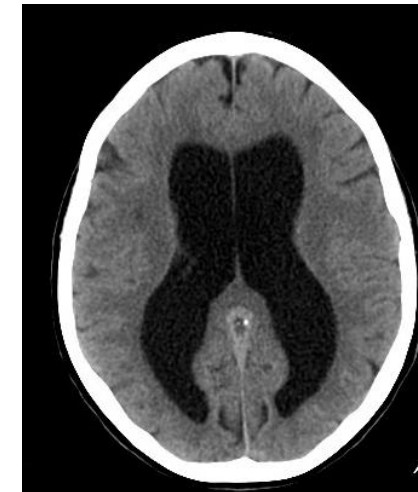
Hydrocephalus Ex-Vacuo

- Ventricular enlargement that occurs with:
 - Age
 - Cortical atrophy (Alzheimer's, Pick, HIV)
- Brain shrinkage
- Usually after age 60
- Increase size of ventricles
- **IN PROPORTION to increase size of sulci**
- If out of proportion: hydrocephalus

Hydrocephalus Ex-Vacuo



Hydrocephalus



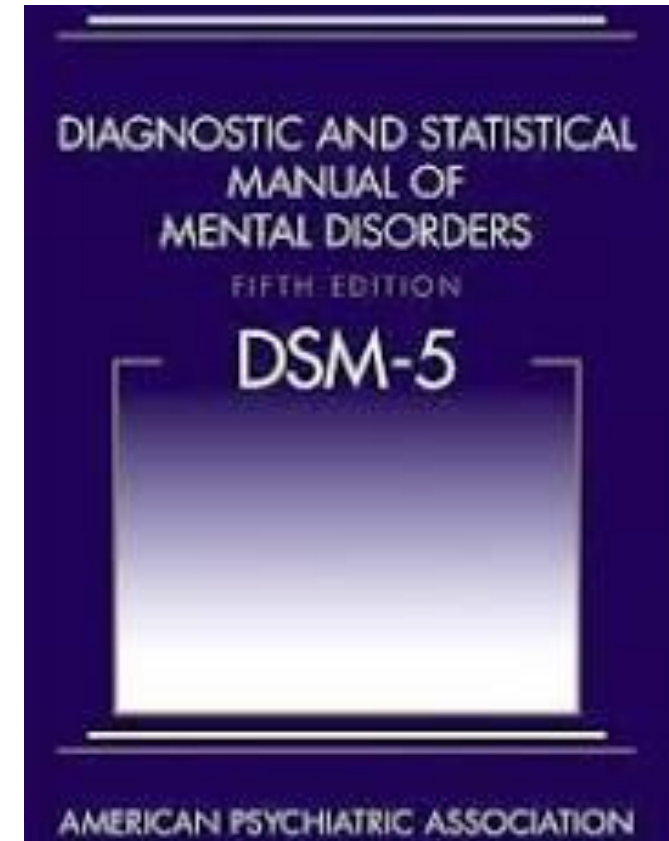
Dementia

Jason Ryan, MD, MPH



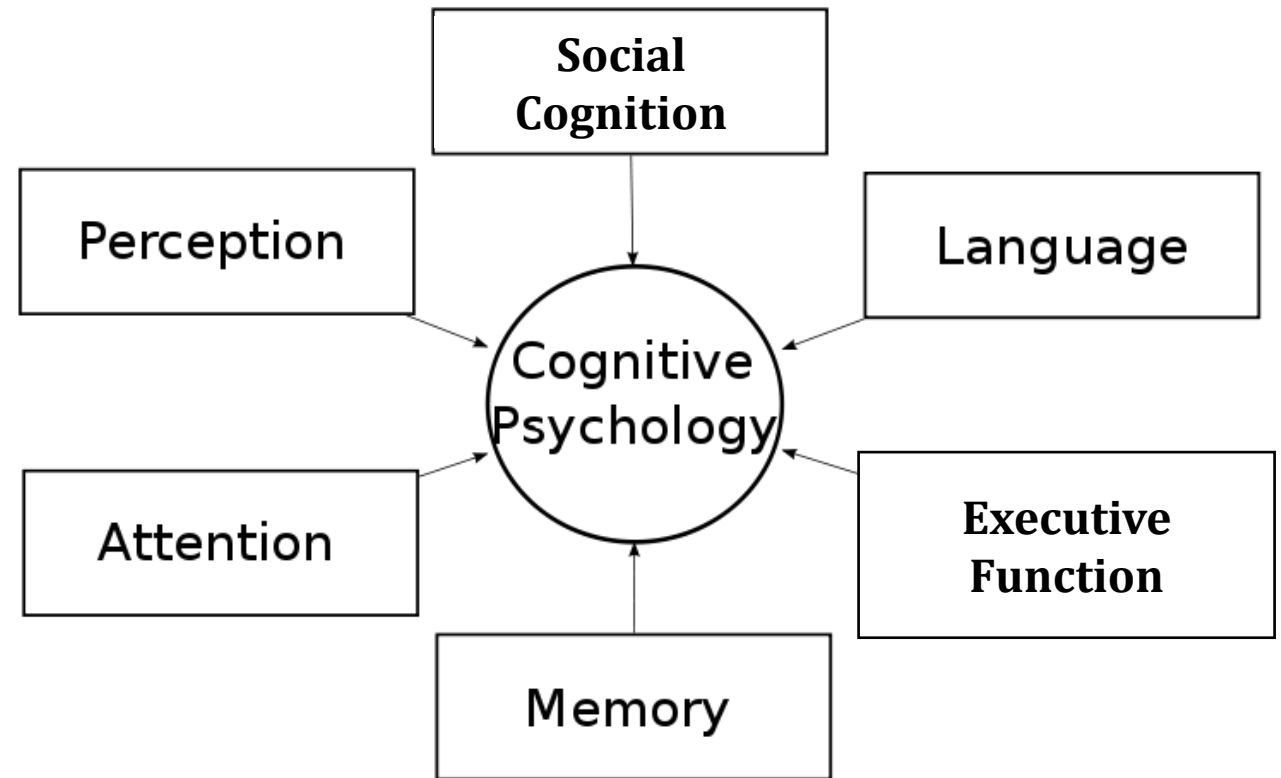
Neurocognitive Disorders

- DSM-V: Mild neurocognitive disorder
- DSM-V: Major neurocognitive disorder (dementia)



DSM-V Neurocognitive Domains

- Executive function
 - Planning, decision making
- Perceptual-motor function
 - Visual perception
 - Motor coordination
- Language (naming, word finding)
- Learning and memory (recall)
- Social cognition
 - Recognition of emotions
 - Insight into behaviors
- Complex attention
 - Sustained attention



Activities of Daily Living

- Basic activities of daily living (ADLs)
 - Basic self care tasks
- Instrumental activities of daily living (IADLs)
 - Tasks required to remain independent
- Advanced activities of daily living (AADLs)
 - Participate in family, social, or work-related roles

BADLs

Basic Activities of Daily Living

- Feeding
- Bathing
- Dressing
- Toileting
- Transferring
- Walking

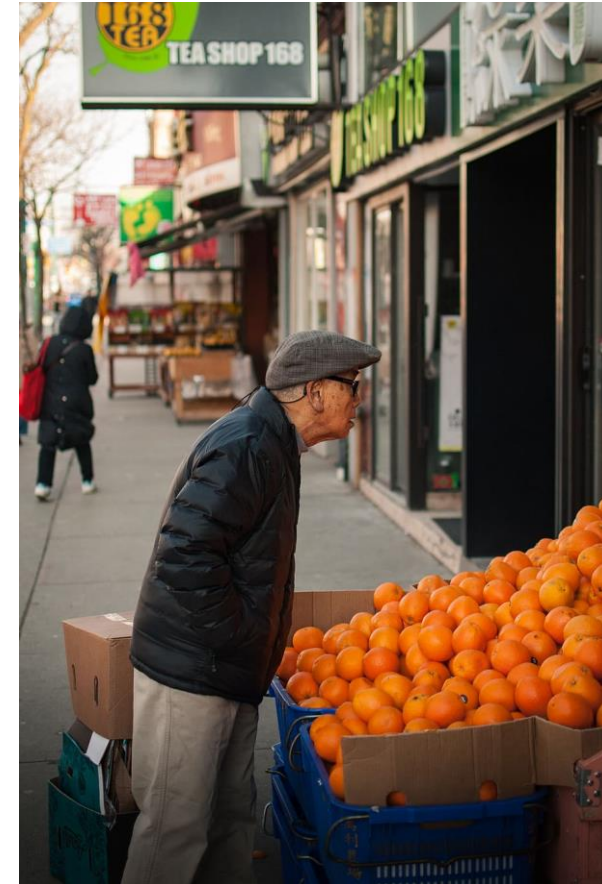


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IADLs

Instrumental Activities of Daily Living

- Shopping for groceries
- Driving or using public transportation
- Using the telephone
- Housework
- Home repair
- Preparing food
- Laundry
- Taking medications
- Managing finances




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Mini Mental Status Exam

Neurocognitive Testing

- Oriented to time, place
- Repeat three objects, remember them
- Serial 7s or spell WORLD backwards
- Name an object pointed out
- Repeat a phrase
- Draw an object shown
- Point system
- ≥ 27 out of 30 is normal

Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day of the week? Month?"
5		"Where are we now: State? County? Town/city? Hospital? Floor?"
3		The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____
5		"I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, ...) Stop after five answers. Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the floor." (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence must contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

Normal Aging

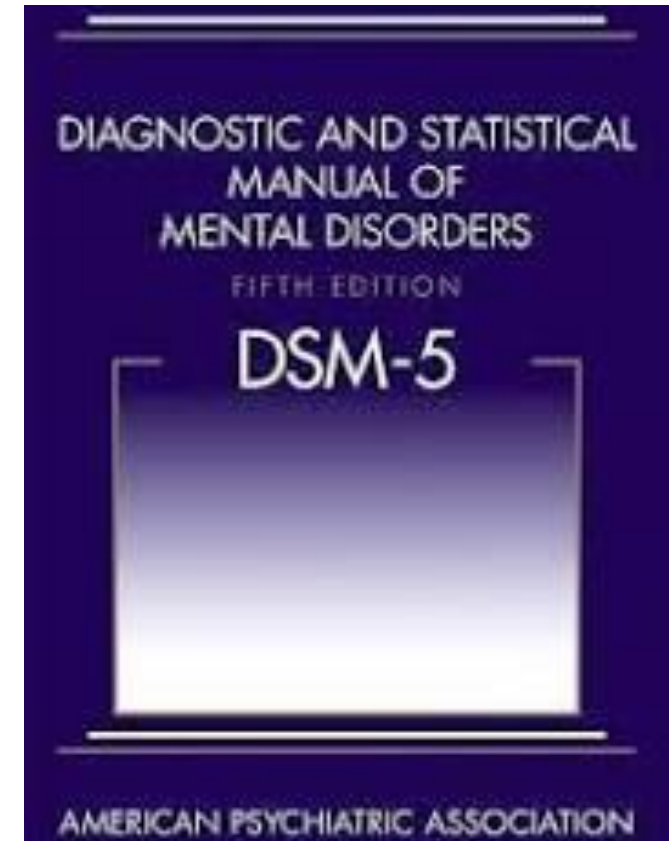
- Occur after 60 years of age
- Mild cognitive changes
- Minimal or no change on MMSE
- **Usually no loss of functional abilities in daily life**
- Often problems with executive function
 - Attention span
 - Problem solving
 - Learning new information



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DSM-V Neurocognitive Impairment

- Mild
 - Usually impaired memory
 - Often frustrating to patient
- Major (dementia)
 - One or more cognitive areas
 - Interferes with functioning
 - Patient may be unaware
 - Problems with IADLs/ADLs
 - MMSE usually <24/30



Dementia vs. Delirium

- Dementia
 - Chronic, progressive cognitive decline
 - Usually irreversible
- Delirium
 - Acute
 - Waxing/waning
 - Usually reversible



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Dementia

- Gradual decline in cognition
- No change level of consciousness
- Usually irreversible (unlike delirium)
- Memory deficits
- Impaired judgment
- Personality changes



Dementia

Four A's

- Amnesia
- Aphasia
 - Inability to communicate effectively
 - Forgets words
 - Can't understand (may nod to pretend)
- Apraxia
 - Inability to do pre-programmed motor tasks
 - Can't do their job
 - Later: chewing, swallowing, walking
- Agnosia
 - Inability to correctly interpret senses
 - Can't recognize people
 - Can't interpret full bladder, pain



Picpedia.org

Dementia

Causes

- Alzheimer's disease - 60% of cases
- Multi-infarct dementia (stroke) ~20% of cases
- Rare causes
 - Lewy body dementia
 - Pick's disease
 - Normal pressure hydrocephalus
 - Creutzfeldt-Jakob
 - HIV
 - Wilson's disease

DEMENTIA

Dementia

Reversible Causes

- **Hypothyroidism**
- **Vitamin B12 deficiency**
- Folate deficiency
- Thiamine deficiency
- Normal pressure hydrocephalus
 - Incontinence, wide-based gait
- Chronic subdural hematoma
- Depression

Depression-Related Cognitive Impairment

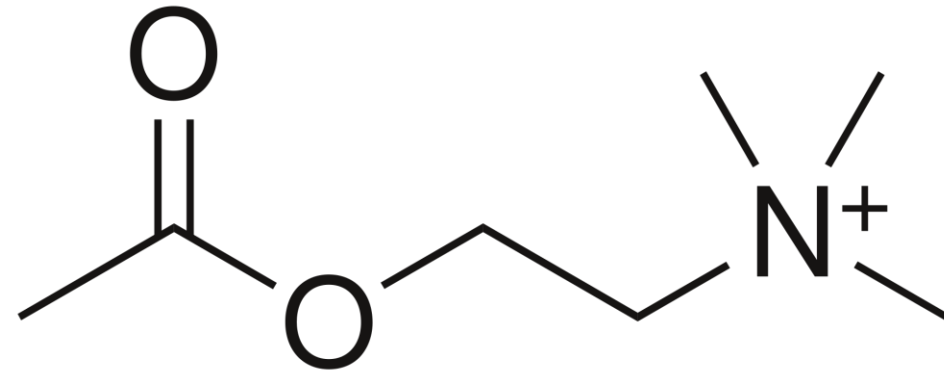
Pseudodementia

- DSM-V: Difficulty thinking and concentrating and/or making decisions

	Dementia	Pseudodementia
Mood	Variable	Depressed
Onset	Slow	Rapid
Progression	Slow	Rapid
Disability	Diminished by patient	Emphasized by patient
Answers to Questions	Tries but unable	"I don't know"
Suicide Risk	Low	High

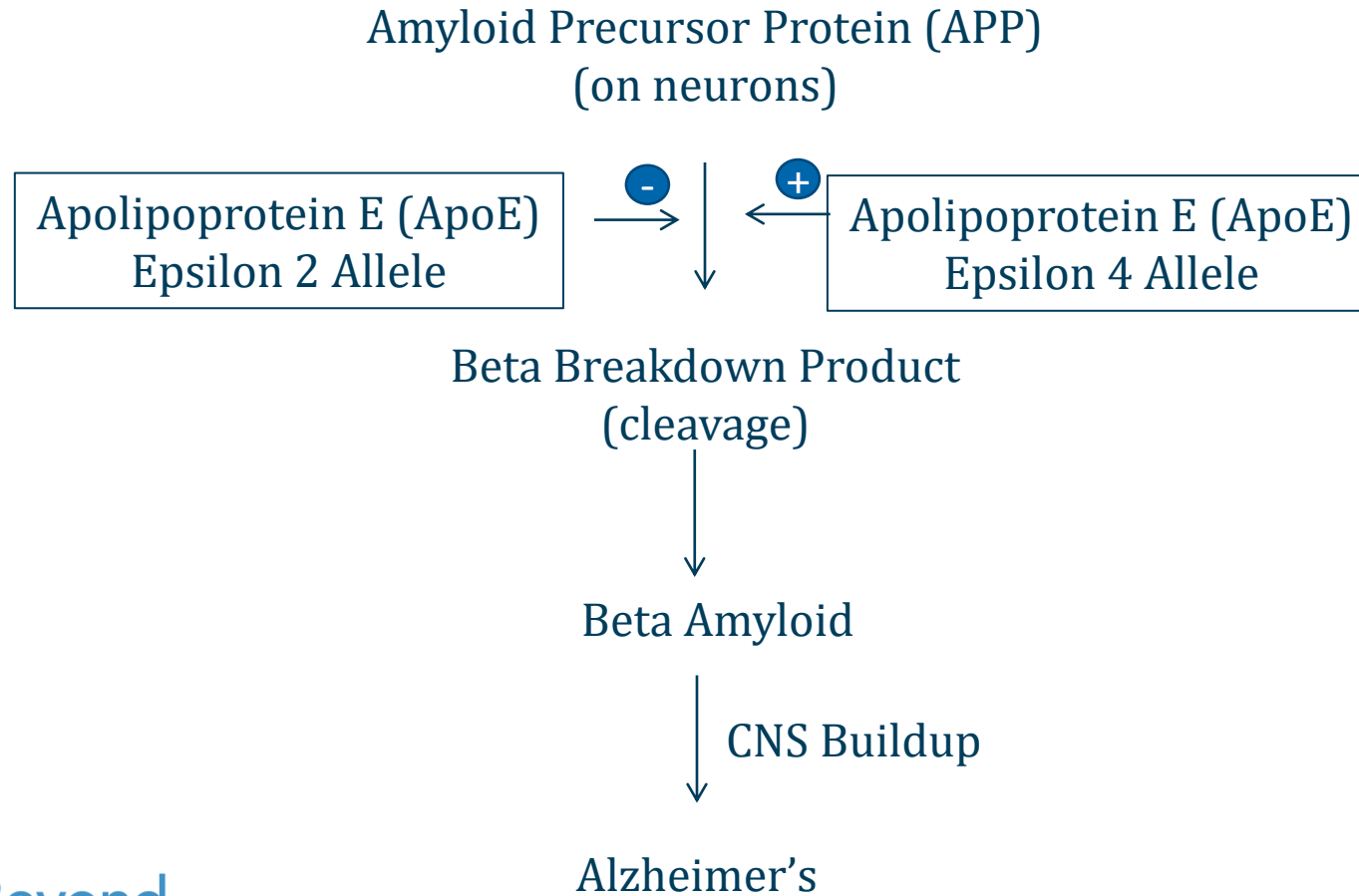
Alzheimer's Disease

- **Most common cause dementia**
- Degeneration of cortex
 - Especially parietal and temporal lobes
 - Contrast with basal ganglia in movement disorders
 - Generalized → no focal deficits
- Associated with loss of **acetylcholine activity**



Acetylcholine

Beta Amyloid



Alzheimer's Disease

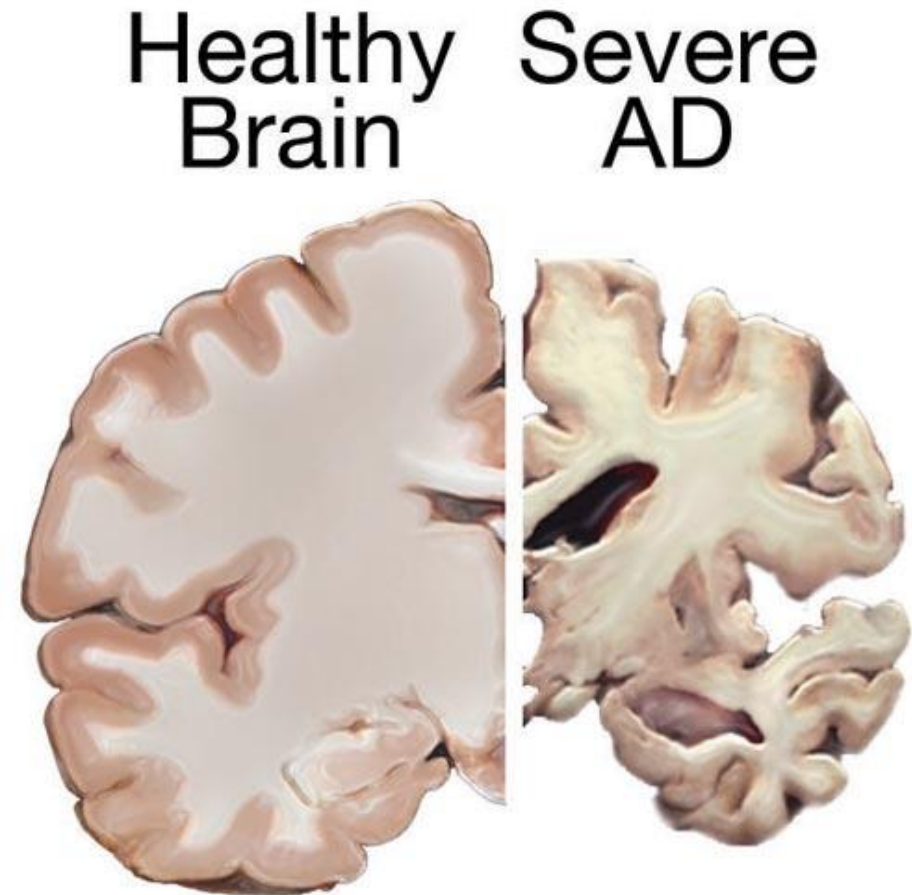
- Major risk factor: **age**
 - Most cases > 65 years old
 - ApoE4 allele
- Rare early-onset Alzheimer's
 - Down syndrome – APP on Chromosome 21
 - Amyloid precursor protein gene mutations
 - Presenilin 1, 2 gene mutations



Pexels.com

Alzheimer's Brain

- Cortical atrophy
- Gyri narrow
- Sulci widen
- **Hydrocephalus ex vacuo**
 - Ventricles appear larger due to atrophy



Alzheimer's Pathology

Neurofibrillary Tangles

Hyperphosphorylated Tau protein in Neuron

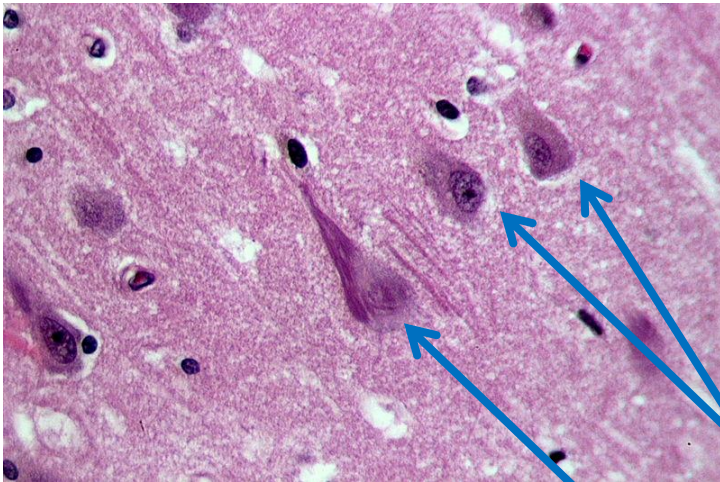


Image courtesy of Patho

Normal neuronal cell bodies
with nuclei

Neuronal cell body (with nucleus)
containing neurofibrillary tangle in
(cytoplasm - dark purple stuff)

Beta Amyloid Plaques

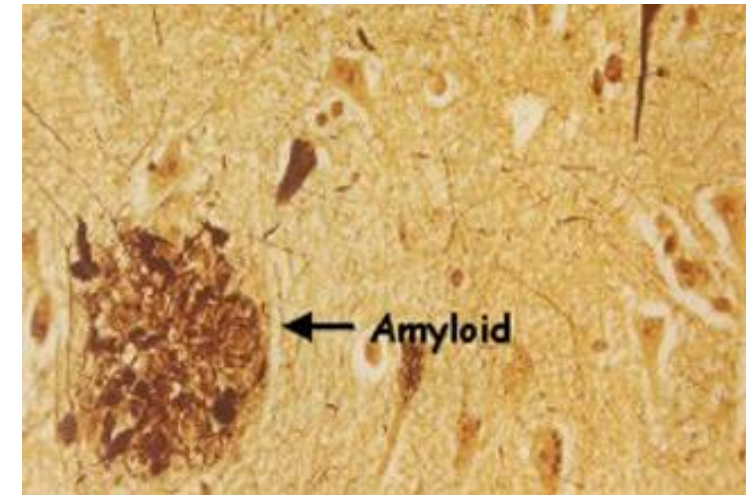


Image courtesy of Neurofractal

Alzheimer's Symptoms

- Initial symptom often **memory impairment**
 - Patient may not notice cognitive decline
 - Often brought in by family member
- Slowly progresses to other cognitive domains
- Late disease: behavioral problems
 - Apathy, social disengagement, irritability
- **Diagnosis: clinical**
- Confirmed at autopsy

Alzheimer's Drugs

- **Acetylcholinesterase inhibitors**

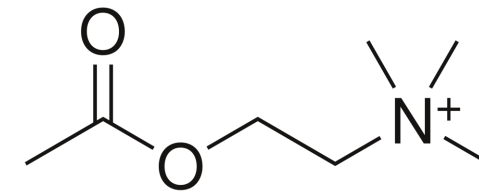
- Donepezil, galantamine, rivastigmine
- Side effects: Nausea, dizziness, insomnia
- Mild-moderate dementia

- Memantine

- NMDA receptor blocker
- N-methyl-D-aspartate receptor (glutamate receptor)
- Side effects: Dizziness, confusion, hallucinations
- Moderate-severe dementia

- Vitamin E

- Believed to protect against oxidation



Acetylcholine



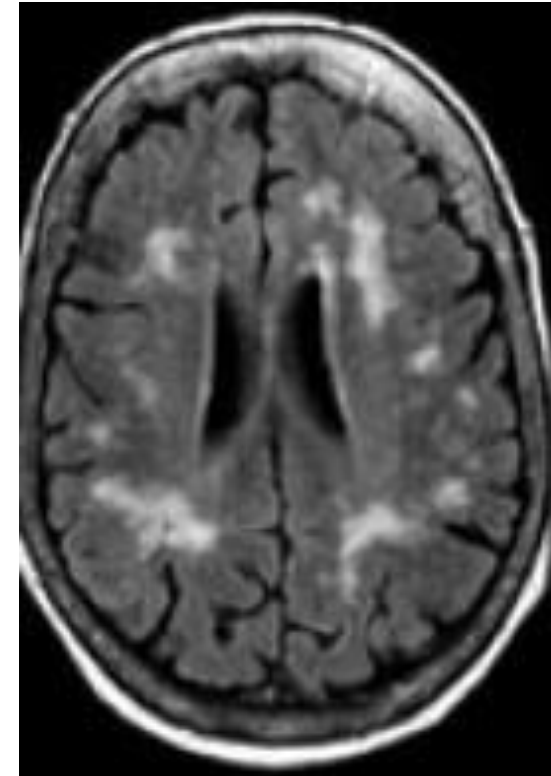
Acetylcholinesterase

Acetate + Choline

Vascular Dementia

Multi-infarct Dementia

- Second most common cause
- **Dementia after multiple strokes**
- Strokes may be overt or “silent”
- Vascular risk factors:
 - Hypertension
 - Hypercholesterolemia
 - Diabetes
 - Smoking

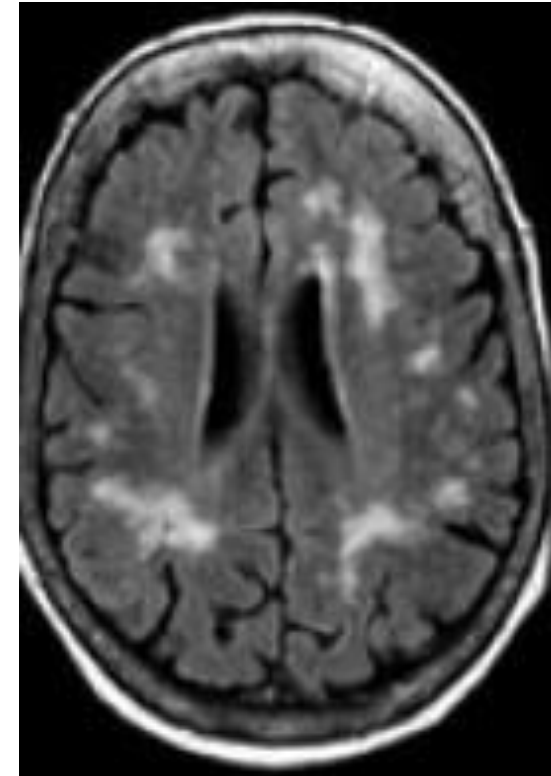


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Vascular Dementia

Multi-infarct Dementia

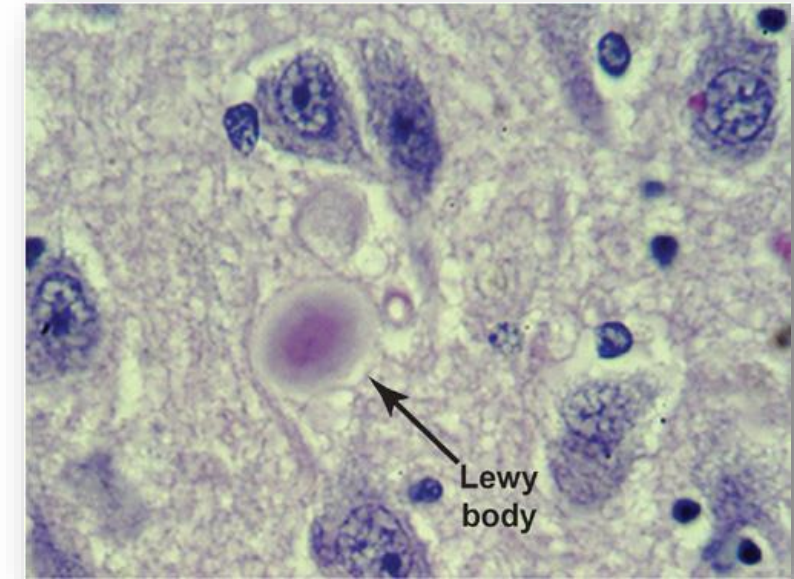
- Often has **associated motor deficits**
 - Weakness
 - Abnormal reflexes
- Onset may be rapid/abrupt
 - Contrast with Alzheimer's
- MRI: multiple infarcts
- Treatment: control risk factors



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Lewy Body Dementia

- Lewy body: protein alpha-synuclein
- Found in basal ganglia in Parkinson's
- In cortex cause Lewy body dementia
- Triad
 - Dementia
 - **Parkinson's symptoms**
 - Hallucinations
- Diagnosis: clinical
- Limited evidence for cholinesterase inhibitors
 - Only Alzheimer's and Lewy Body treated with AChE inhibitors



Charles E. Driscoll, MD

Lewy Body Dementia

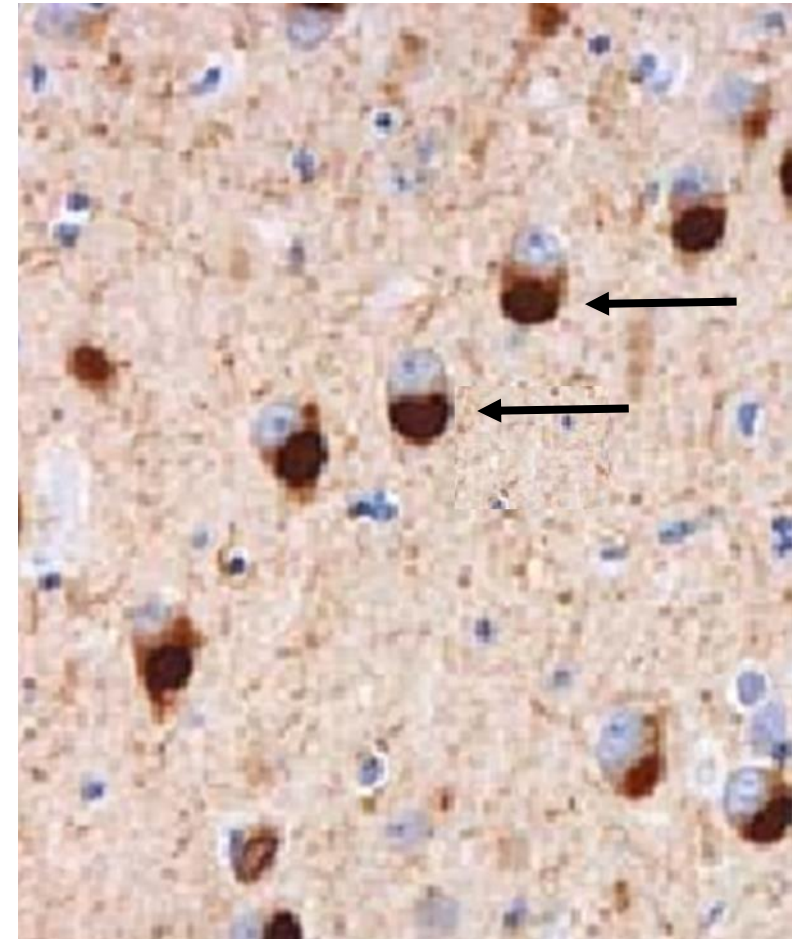
- 1-year rule
- Parkinson's disease dementia (PDD)
 - At least 1 year of Parkinson's before dementia symptoms
- Dementia with Lewy bodies (DLB)
 - Dementia within less than 1 year of Parkinson's symptoms

Pick's Disease

Frontotemporal Dementia

- Rare cause of **early-onset dementia**
 - Usually 50s to 60s
- Affects frontal and temporal lobes
 - Frontal: **change in personality, behavior**
 - Temporal: aphasia
 - Memory deficits not prominent until late
- Path: Pick bodies
 - Spherical tau proteins
- Abnormal accumulation of TDP-43 protein
 - TAR DNA-binding protein 43

Pick Bodies
(labeled anti-tau antibodies)

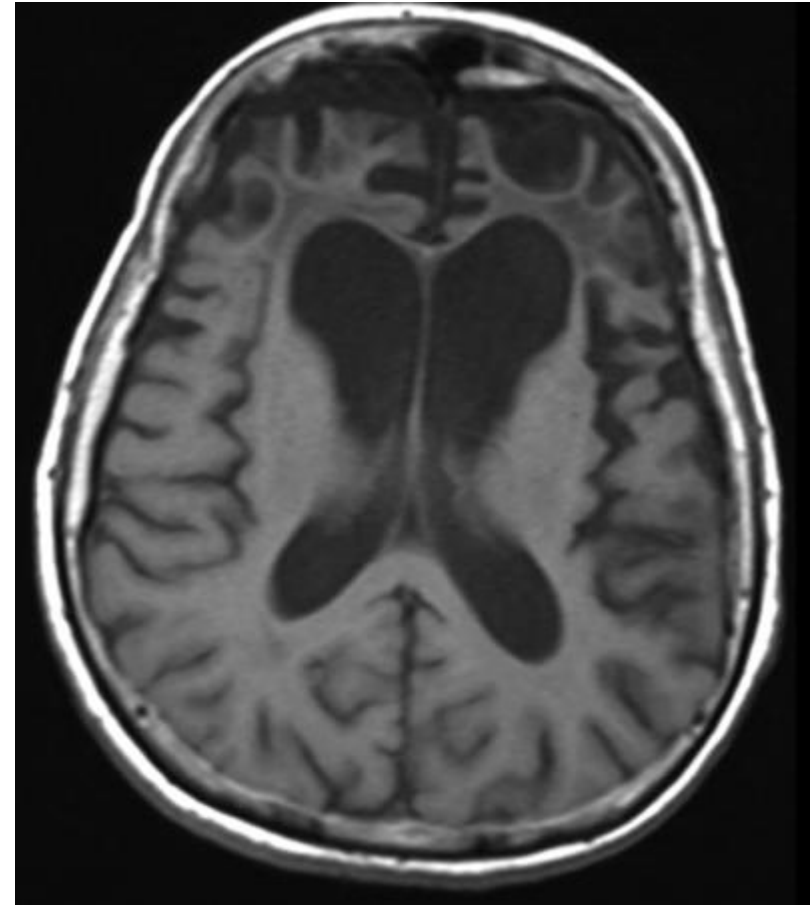


Cairns et al./Public Domain

Pick's Disease

Frontotemporal Dementia

- Diagnosis: clinical
- MRI: frontal or temporal atrophy
- No disease-modifying therapies

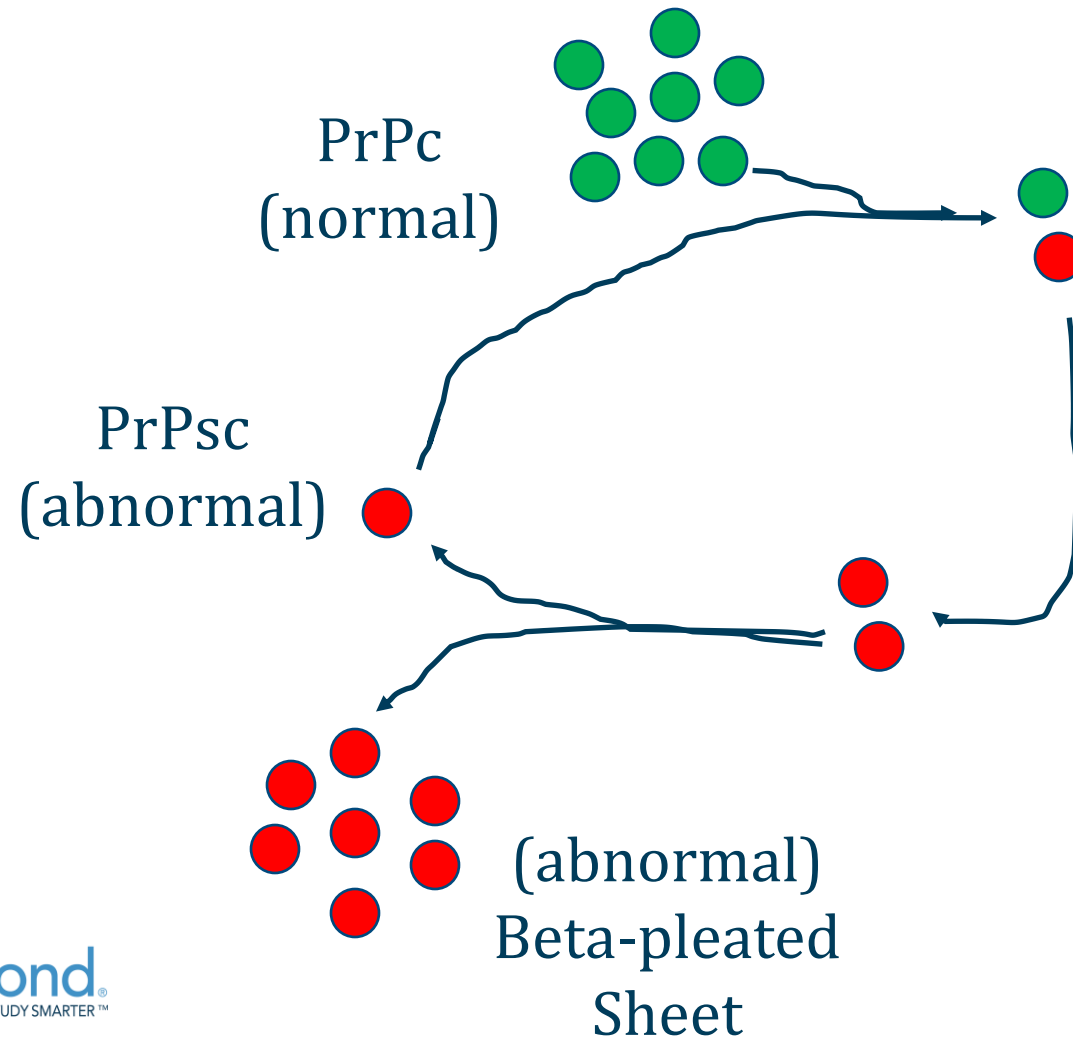


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Prion Diseases

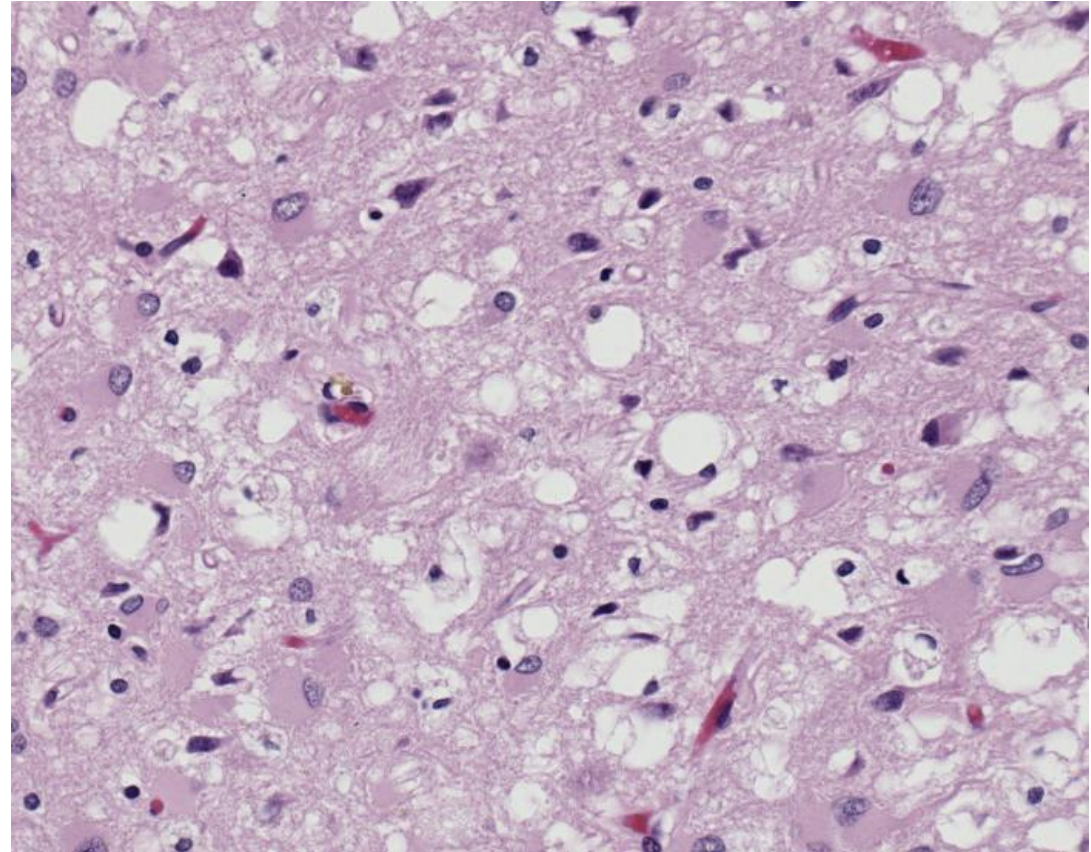
- Neurodegenerative diseases
- Caused by abnormal variants of proteins (prions)
- PrPc = normal cell-surface glycoprotein
- PrPSc = misfolded PrPc
- PrPSc leads to more PrPSc → disease
- PrPSc acquired from:
 - Sporadic protein change
 - Transmission
 - Rarely familial
- Prions difficult to eradicate with decontamination

Creutzfeldt-Jakob



Creutzfeldt-Jakob

- Classic prion disease
- “Spongiform encephalopathy”
- Intracellular vacuoles
- Mad Cow Disease



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Creutzfeldt-Jakob

- **Rapidly progressive dementia**
 - Weeks to months
- Death within a year
- Classic features
 - Behavior changes
 - Ataxia
 - Motor dysfunction
 - **Myoclonus when startled**
- Diagnosis
 - Brain biopsy (gold standard)
 - Clinical criteria

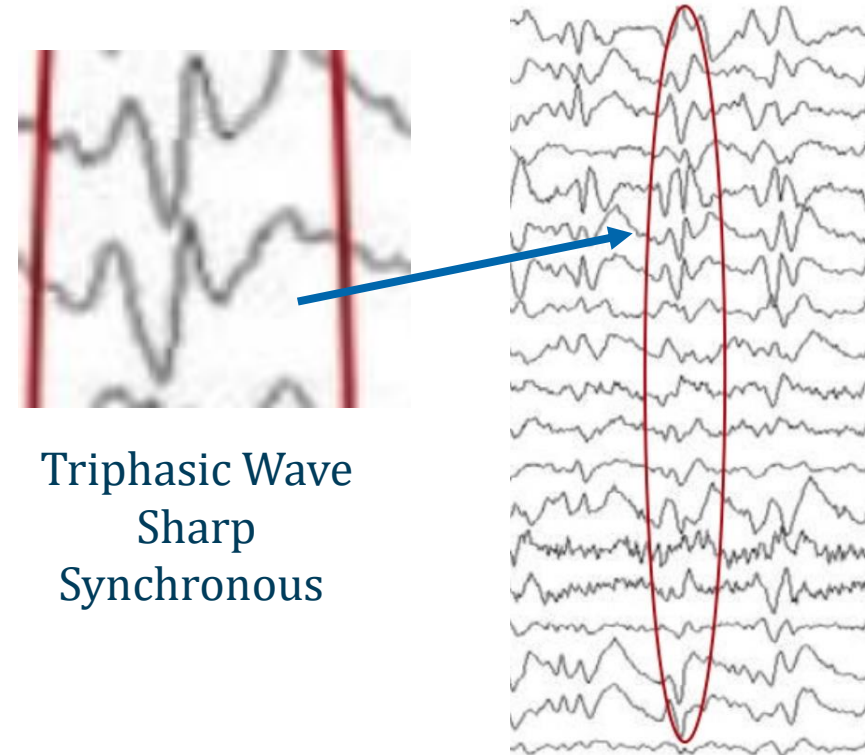
Key Features

Rapid Progression
Myoclonus

Creutzfeldt-Jakob

Supportive Evidence

- EEG
 - Periodic **sharp, triphasic synchronous** discharges
- MRI:
 - Excludes other diagnoses
 - May show abnormal signal in **caudate/putamen**
- CSF
 - **Positive RT-QuIC**
 - Real-time quaking-induced conversion
 - Misfolded prion protein converts normal PrP to misfolded form
 - Aggregates form → formation monitored in real time with fluorescent dye



Creutzfeldt-Jakob

Supportive Evidence

- **14-3-3 proteins**
 - Family of proteins found in brain
 - Appears in CSF of CJD patients
 - Included in WHO diagnostic criteria

Altered Mental Status

Jason Ryan, MD, MPH



Altered Mental Status

- Change in cognitive and psychological functioning
- Usually accompanied by behavioral changes
- Commonly develops **acutely in hospitalized patients**
- Clinical syndrome – not a diagnosis



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Delirium

- **Most common cause AMS in hospital**
- Loss of focus/attention
- Disorganized thinking
- Hallucinations (often visual)
- Sleep-wake disturbance
 - Up at night
 - Sleeping during day



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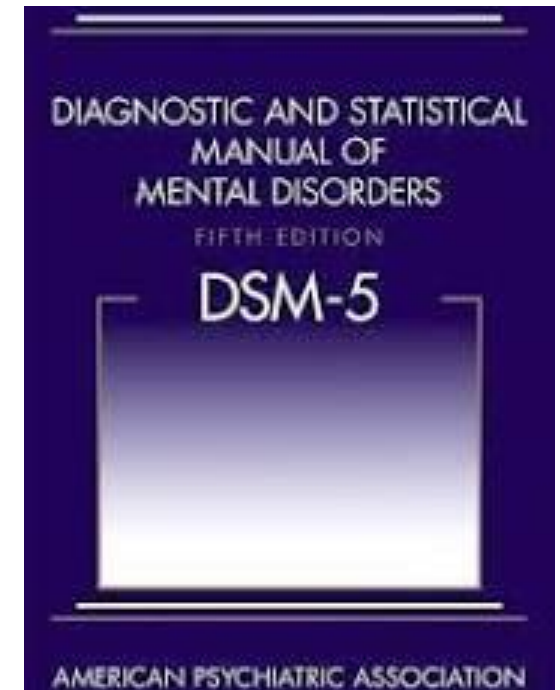
Altered Mental Status

Terminology

- Altered mental status
- Delirium
- Encephalopathy

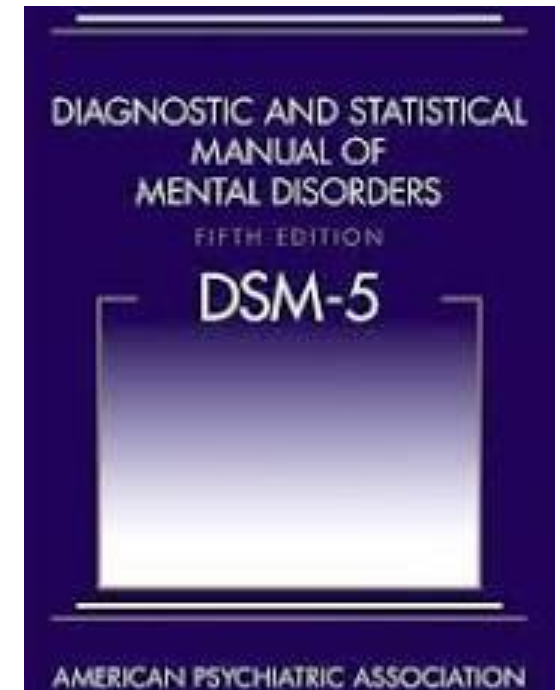
DSM-V Delirium Definition

- Disturbance in attention - can't focus or sustain attention
- Characteristic features
 - Develops rapidly, usually over hours to days
 - Represents a change from baseline
 - Fluctuates over time
- Disturbance in cognition: memory, orientation, language



DSM-V Delirium Definition

- Not better explained by another disorder
- Does not occur with reduced level of arousal (coma)
- Evidence that disturbance caused by:
 - A medical disorder
 - Substance use or withdrawal
 - Medication side effect



Dementia vs. Delirium

- **Dementia**
 - Chronic, progressive cognitive decline
 - Usually irreversible
- **Delirium**
 - Acute
 - Waxing/waning
 - Usually reversible

Delirium Causes

- **Medical disorders**
 - Infection
 - Renal failure
 - Electrolyte disturbances
 - Many, many others
- Substance use or withdrawal
- Medication side effect
- **Workup of delirium: identify underlying cause**

Sundowning

- Variant of delirium
- Behavioral deterioration in evening or at night
- Common in **hospitalized patients with dementia**
- Likely related to unfamiliar setting



PxHere/Public Domain



Pexels/com/Public Domain

Delirium

Prevention

- **Orientation protocols**
 - Clocks
 - Calendars
 - Windows
 - Frequent reorientation
- Avoid polypharmacy
 - Benzodiazepines, sleeping medications
- Avoid physical restraints
 - Use one-to-one sitter if necessary
- Minimize sleep disruptions
 - Noise
 - Nursing staff



Delirium

Treatment

- **Treat underlying cause**
 - Electrolyte abnormalities
 - Hypo/hyperglycemia
 - Thiamine deficiency
 - Hypercarbia
 - Hypoxemia
- Haloperidol
- Other antipsychotics



Coma

- **Unresponsive and unarousable**
- Many causes
 - Trauma
 - Drugs
 - Toxins
- Diagnosis and workup based on suspected cause
- Assessed using the **Glasgow coma scale**



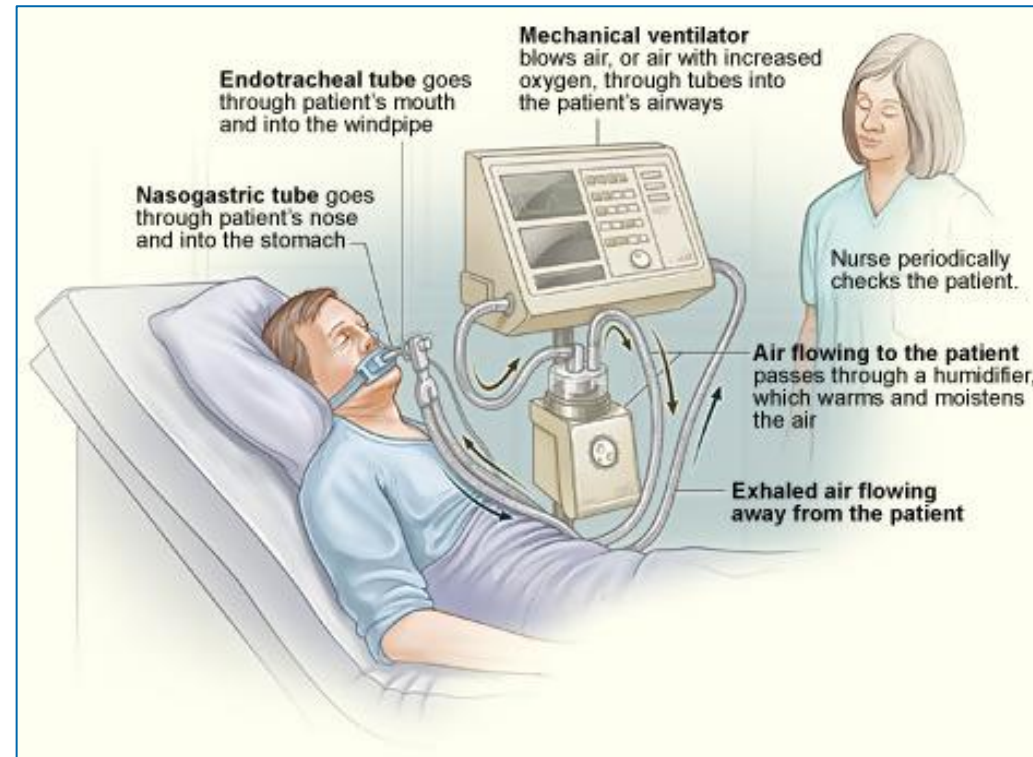
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Glasgow Coma Scale

- Three tests: eye, verbal and motor
- GCS score: 3 to 15
- Eye (1-4 points)
 - Does not open, opens to painful stimuli, opens to voice, opens spontaneously
- Verbal (1-5 points)
 - No sound, incomprehensible sounds, inappropriate words, confused, oriented
- Motor (1-6 points)
 - No movements, decerebrate posturing, decorticate posturing, withdrawal to pain, localizes to pain, obeys commands

Mechanical Ventilation

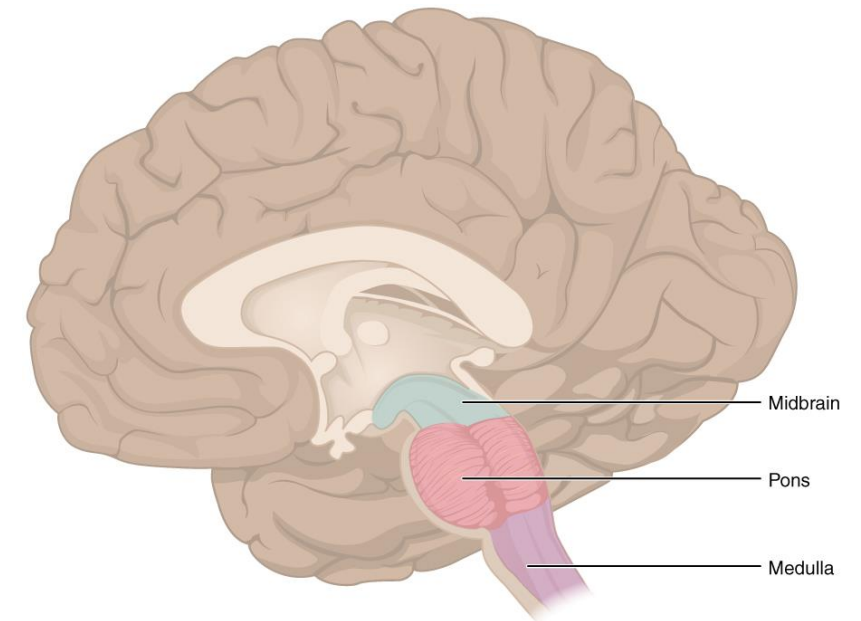
- GCS 8 = intubate



Mechanical Ventilation

Locked-In Syndrome

- Mimics coma
- Patient is conscious but paralyzed
- Sparing of respiratory muscles and eye movement
- Caused by ventral pons infract/hemorrhage
- Usually due to basilar artery stroke
- Diagnosis: **voluntary vertical eye movements**



Wikipedia/Public Domain

Persistent Vegetative State

- **Wakefulness**
- No awareness of environment
- No response to visual, auditory, or painful stimuli
- Normal sleep-wake cycle
- Preserved reflexes and autonomic function
- Common cause: **severe anoxic brain injury**

Brain Death

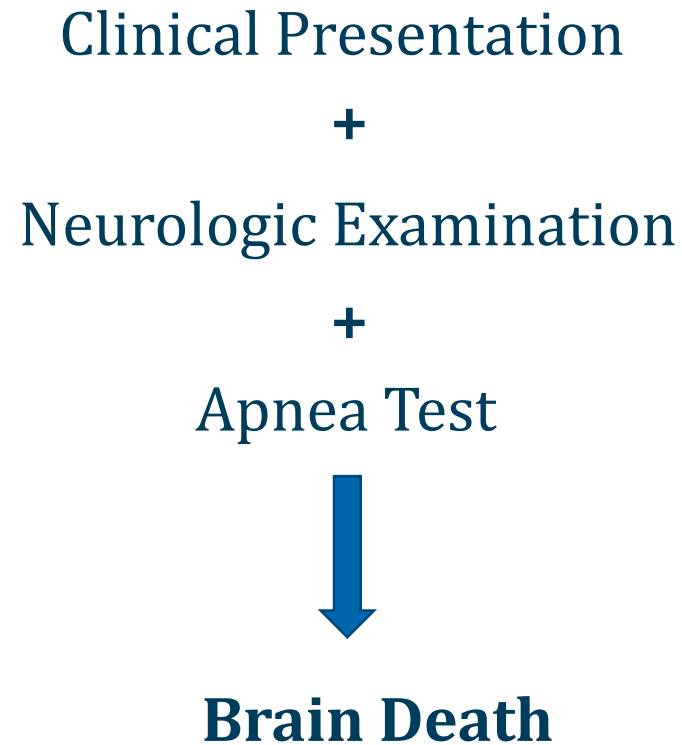
- Irreversible cessation of cerebral and brainstem function
- Legally equivalent to cardiopulmonary death in the US
- Do not need to continue care



Needpix.com

Brain Death

Diagnosis

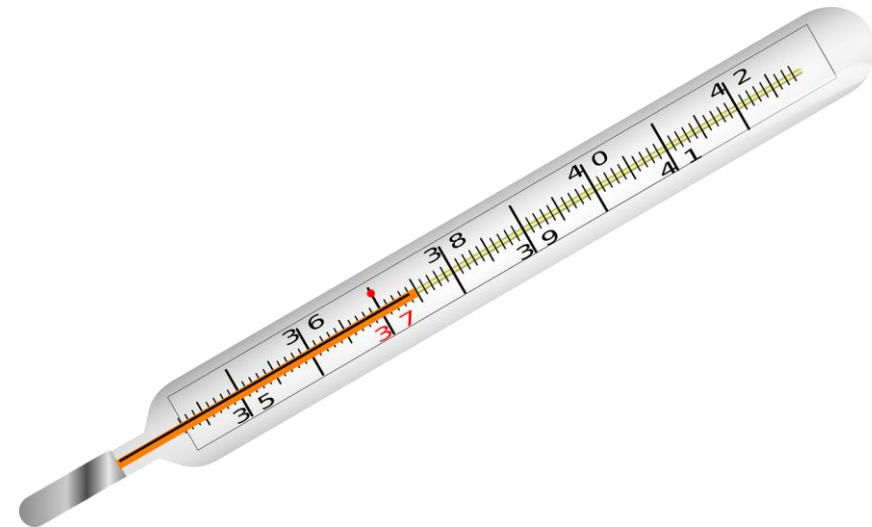


*Brain death should be confirmed
by two different attending physicians

Brain Death

Clinical Presentation

- Clinical or imaging evidence of acute CNS catastrophe
- Exclusion of other conditions
 - Electrolytes
 - Acid-base
 - Endocrine
 - Circulatory (e.g., shock)
- No drug intoxication or poisoning
- Core temperature normal ($>97^{\circ}\text{F}$)
- Systolic blood pressure > 100 mmHg



Brain Death

Neurologic Examination

- Coma
- Absent high-level motor response (no withdrawal to pain)
- Absent pupillary light reflex, corneal reflex
- Absent oculovestibular (caloric) reflex
- Absent cranial nerve and primitive reflexes (gag, jaw jerk, sucking, rooting, etc.)
- DTRs may be intact (spinal cord)

Brain Death

Apnea Test

- Performed after other criteria have been met
- Preoxygenate
- Disconnect from ventilator
- Positive test:
 - No respiratory movements for 8 – 10 min
 - ABG: PaCO₂ > 60 mmHg or > 20 mmHg from baseline

Headache

Jason Ryan, MD, MPH



Headache Causes

- CNS Tumors
- CNS Bleeds (SAH)
- Hydrocephalus
- Inflammation (temporal arteritis)
- In clinical practice, must rule all these things out
- History, neurologic exam are key
- Lack of papilledema very important



Public Domain

Common Primary Headache Disorders

- Tension
- Migraine
- Cluster
- All diagnosed clinically



Pexels/Public Domain

Tension Headache

- **Most common headache subtype**
- Etiology not clear, probably multifactorial
- Bilateral, constant pain
- Pain is pressing, tightening around head
- 30 min to several hours
- Lack of photophobia, phonophobia, or aura
- Chronic when occurs > 15 days/month



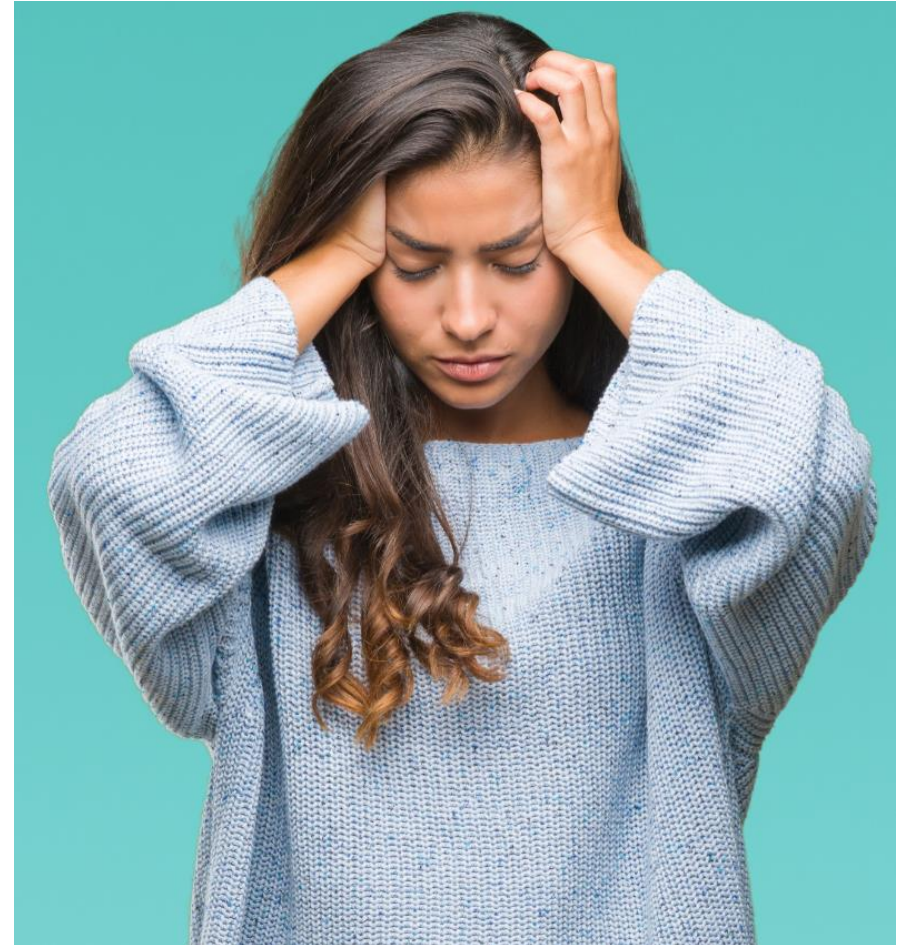
Tension Headache

- First-line treatment: **NSAIDs**
 - Often combined with **caffeine**
- Prophylaxis for chronic tension HA
 - Strongest evidence: **amitriptyline**



Migraine Headache

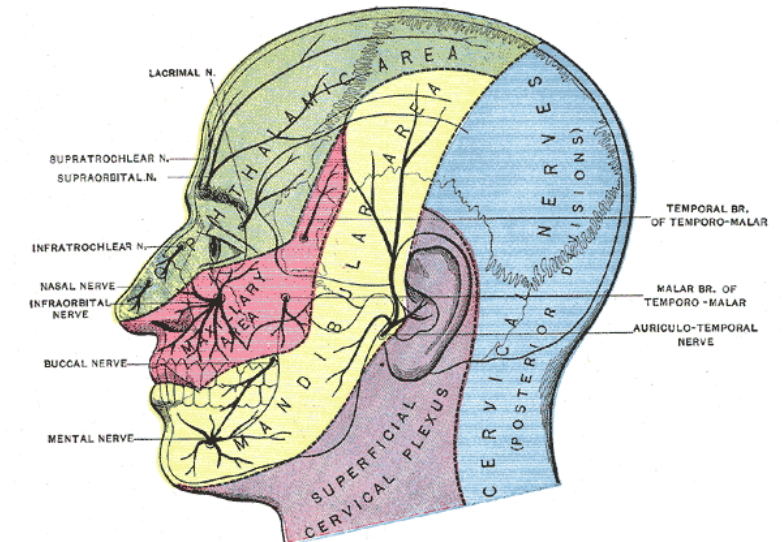
- Episodic headache
- Progresses through phases
 - Prodrome
 - Aura
 - Headache



Migraine Pathophysiology

- Still incompletely understood
- **“Cortical spreading depression”**
 - Wave of nerve depolarization
 - Spreads across the cerebral cortex
- Activates **trigeminal nerve**

Trigeminal Nerve Dermatomes



Wikipedia/Public Domain

Migraine Headache

Prodrome

- About 75% of migraine patients
- 1 – 2 days before headache
- Yawning
- Depression
- Irritability
- Food cravings
- Constipation
- Neck stiffness



Wikipedia/Public Domain

Migraine Headache

Aura

- About 25% of migraine patients
- Gradual development of non-headache symptom
 - Specific to patient: patients often recognize their aura
- Classically precedes HA but may be at same time
- Often visual
 - Bright, dark spots
 - “Scintillating scotoma”
- Sensory: tingling in limb or face
- Auditory: tinnitus



Migraine Headache

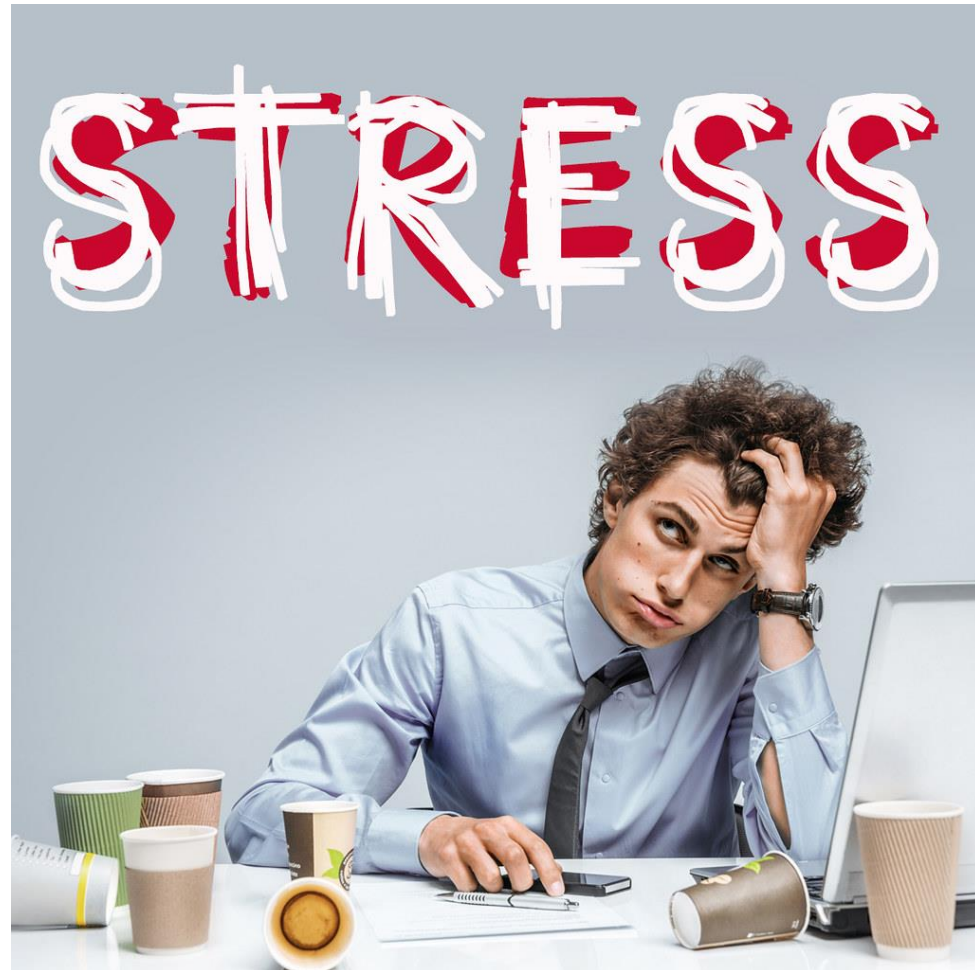
Headache Features

- Pulsating
- Unilateral
- Throbbing
- Often nausea, vomiting
- Photophobia, phonophobia
- Last for hours
- Disabling

POUND
Pulsatile
hOurs
Unilateral
Nauseating
Disabling

Triggers

- Stress
- Fasting
- Menstruation
- Weather changes
- Alcohol
 - Especially wine



Flickr/Public Domain

Oral Contraceptive Pills

- Migraines and exogenous estrogen **increase risk of stroke**
 - Especially migraines with aura
- Women with migraines **should not use estrogen-containing OCPs**



BruceBlaus/Wikipedia

Migraine Treatment

- Abortive therapy
- Prophylactic Therapy

Abortive Therapy

- **Triptans**
 - Sumatriptan, zolmitriptan, eletriptan, others
 - Serotonin agonists
 - Inhibit trigeminal nerve activity
 - ↓ vasoactive peptide release
- Use for > 10 days per month: **overuse headache**
- Can cause **serotonin syndrome**
 - When combined with MAO inhibitors
 - Lower risk with SSRI or SNRI drugs

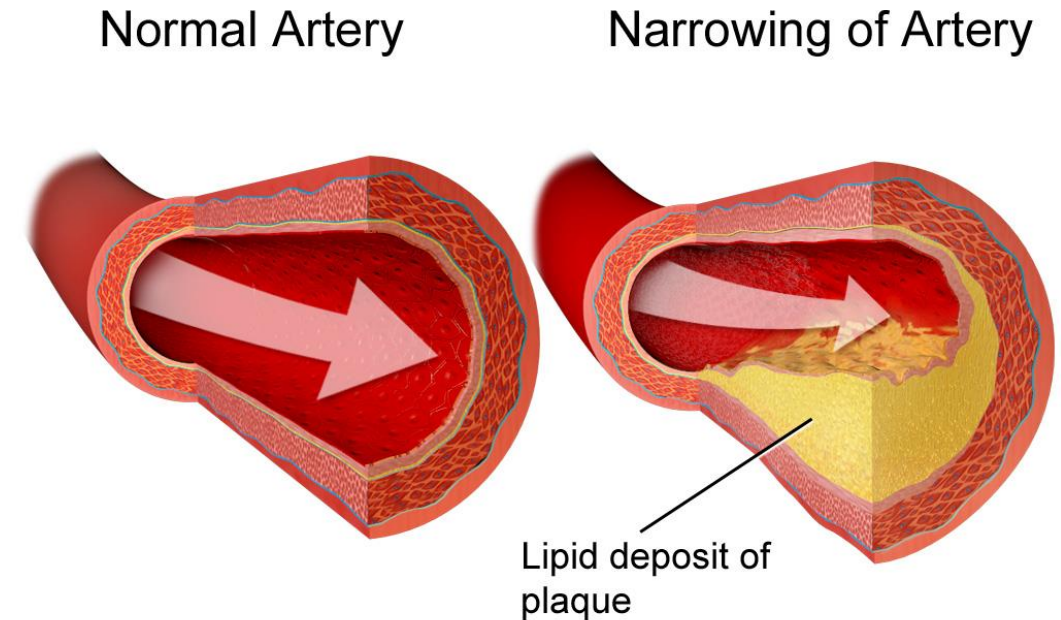


Wikipedia/Public Domain

Triptans

Contraindications

- Triptans cause vasoconstriction
- Contraindicated:
 - Peripheral vascular disease
 - Coronary artery disease
 - Cerebrovascular disease
 - Uncontrolled hypertension
- Exception: lasmiditan
 - Selective serotonin 1F receptor agonist
 - No vasoconstrictor activity



Coronary Artery Disease

Abortive Therapy

- High dose NSAIDs
- Antiemetics
 - **IV metoclopramide**
 - IV or IM chlorpromazine
 - IV or IM prochlorperazine
 - Dopamine antagonists
 - Improve nausea and pain
 - May cause dystonia



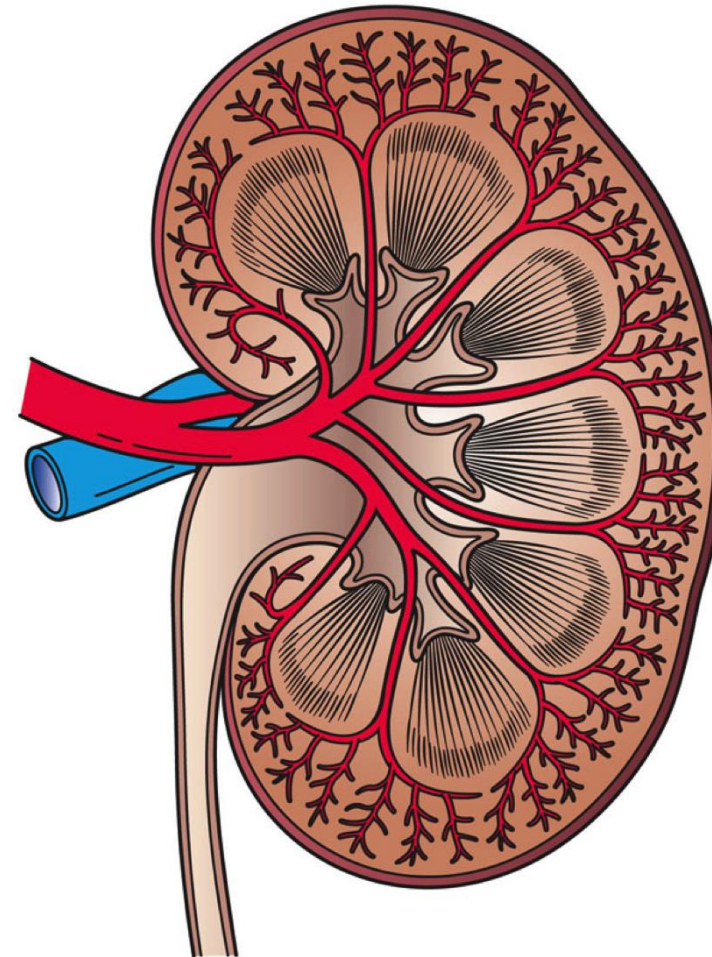
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Preventive Therapy

- Usually for patients with > 3 headaches per month
- Avoid triggers
- Healthy lifestyle
 - Sleep, diet, exercise
- Many drug classes shown to reduce migraine frequency
 - Anticonvulsants (topiramate and valproate)
 - Beta-blockers (propranolol)
 - Antidepressants (amitriptyline and venlafaxine)

Topiramate

- Anticonvulsant
- Very effective for migraine
- Mental dulling/sedation
- **Kidney stones**
 - Weak carbonic anhydrase inhibitor
 - Leads to more Ca in urine
 - May ↑ risk kidney stones
 - Patients need to hydrate



Wikipedia/Public Domain

Pregnancy and Migraines

- Usually less headaches while pregnant
- Avoid anticonvulsants
 - Especially valproate (neural tube defects)
- Abortive therapy
 - Acetaminophen is safest
 - NSAIDs second line
 - Triptans for moderate to severe symptoms
- Prevention
 - Beta-blockers



Øyvind Holmstad/Wikipedia

Cluster Headache

- Very rare headache disorder
- Poorly understood mechanism
- Seen primarily in men
- More common in smokers
 - Although quitting does not alter disease course



Cluster Headache

- Excruciating, unilateral headache **behind eye**
- Autonomic dysfunction
 - **Lacrimation, rhinorrhea**
 - Ptosis, miosis
- Unlike migraine: no aura, no nausea/vomiting
- Comes in clusters: attacks daily for few weeks
- Circadian rhythm:
 - Daily attacks (same time of day)
- **Attacks last 15 min to several hours**
 - Contrast with trigeminal neuralgia: < 1 min



Shutterstock

Cluster Headache

- First-line treatment: **oxygen, triptans**
 - Mechanism for oxygen unclear
 - May be related to O₂-induced vasoconstriction
 - O₂ also inhibits neuronal activation in the trigeminal nucleus
- Poor response to indomethacin (NSAID)
- Prophylaxis of chronic cluster headache: **verapamil**
 - Drug of choice
 - Highly effective



Public Domain

Paroxysmal Hemicrania

- Unilateral, severe headache
- Similar to cluster headache

	Paroxysmal Hemicrania	Cluster Headache
Gender predominance	Females	Males
Frequency of attacks	>15 in 24 hours	1 to 4 in 24 hours
Duration of attacks	~15 minutes	> 30 minutes
Response to indomethacin	Good	Poor

Medication Overuse Headache

- Headache 15 or more days per month
- In patients with **pre-existing headache disorders**
- Overuse of drugs for acute treatment of headache:
 - NSAIDs
 - Triptans
 - Opioids
- Treatment: **discontinue the overused medication**

Low Pressure Headache

- Drop in CSF pressure leading to headache
- Common after **lumbar puncture**
- Common after **epidural anesthesia**
- Classic feature: **postural headache**
 - Improved lying flat
 - Worse sitting up

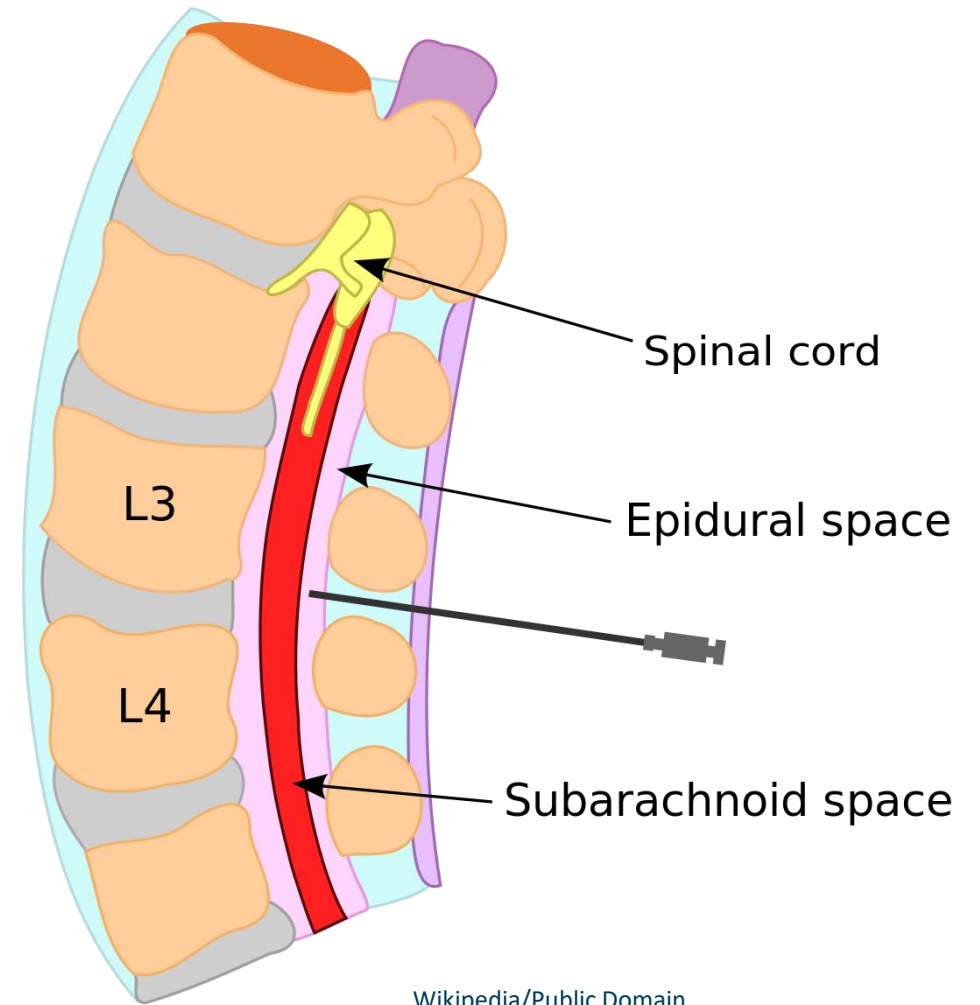
Lumbar Puncture



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Low Pressure Headache

- Diagnosis: clinical
- Treatment: NSAIDs +/- **epidural blood patch**
 - Infusion of blood into epidural space
 - Clots over dural CSF leaks
 - Often immediate symptom relief



Syncope

Jason Ryan, MD, MPH



Syncope

- Transient loss of consciousness
- Caused by inadequate cerebral blood flow
- Common reason for emergency evaluation



The Faint
Pietro Longhi, 1744

Vasovagal Syncope

Neurocardiogenic Syncope

- Sudden increase parasympathetic outflow via the vagus nerve
- Sudden decrease in sympathetic outflow
- Bradycardia, vasodilation, hypotension
- Triggers
 - Emotional stress
 - Pain
 - Fear
 - Heat
 - Prolonged standing

Sinus Bradycardia



Vasovagal Syncope

Neurocardiogenic Syncope

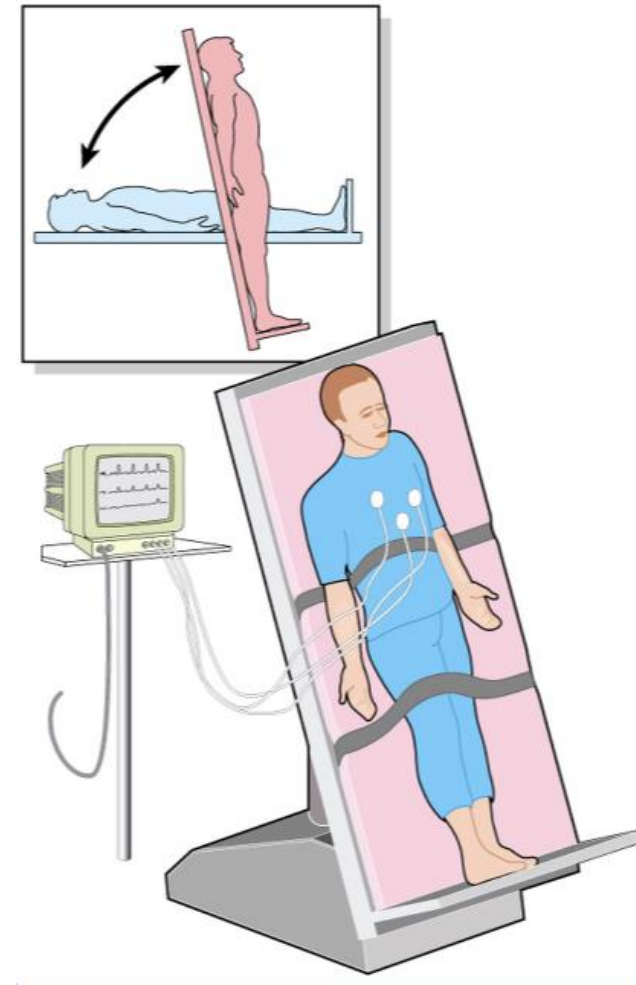
- **Preceded by classic prodrome**
 - Nausea
 - Diaphoresis
 - Pallor
 - Feeling faint
- Ultimately leads to syncope
- **Rapid return to consciousness**
 - Contrast with seizure
- On awakening patient **often feels tired**
 - Result of diffuse vasodilation



Vasovagal Syncope

Neurocardiogenic Syncope

- **Diagnosis: clinical**
 - Trigger
 - Prodrome
 - Rapid return to consciousness
 - Post-syncope fatigue
 - No evidence of other causes
- No associated EKG changes
- Rarely used test: tilt-table test
 - Patient placed supine
 - Rapidly lifted upright
 - Pulse and blood pressure monitored



Vasovagal Syncope

Neurocardiogenic Syncope

- Benign condition
- Mainstay of treatment: **reassurance**
- Rarely used treatments:
 - Counter-pressure maneuvers
 - Salt tablets
 - Fludrocortisone (mineralocorticoid)
 - Midodrine (alpha-1 agonist)

Situational Syncope

- Variant of vasovagal syncope
 - Associated with abnormal autonomic tone
 - Has triggers and prodrome
- Coughing
- Sneezing
- Urination
- Defecation
- Swallowing



Carotid Sinus Syncope

- Carotid sinus hypersensitivity
- Pressure on carotid artery baroreceptors in neck
- Leads to excessive fall in heart rate and hypotension
- Diagnosis: clinical
 - Pressure on carotid sinus reproduces symptoms
- Treatment:
 - Patient education
 - Rarely requires pacemaker



Orthostatic Syncope

- Syncope with standing
- Exaggerated fall in blood pressure due to gravity
- Many causes
 - Hypovolemia (poor fluid intake, diuretics)
 - Autonomic failure (diabetes, Parkinson's)
 - Medications (beta blockers, alpha blockers)
- Improves with intravenous fluids



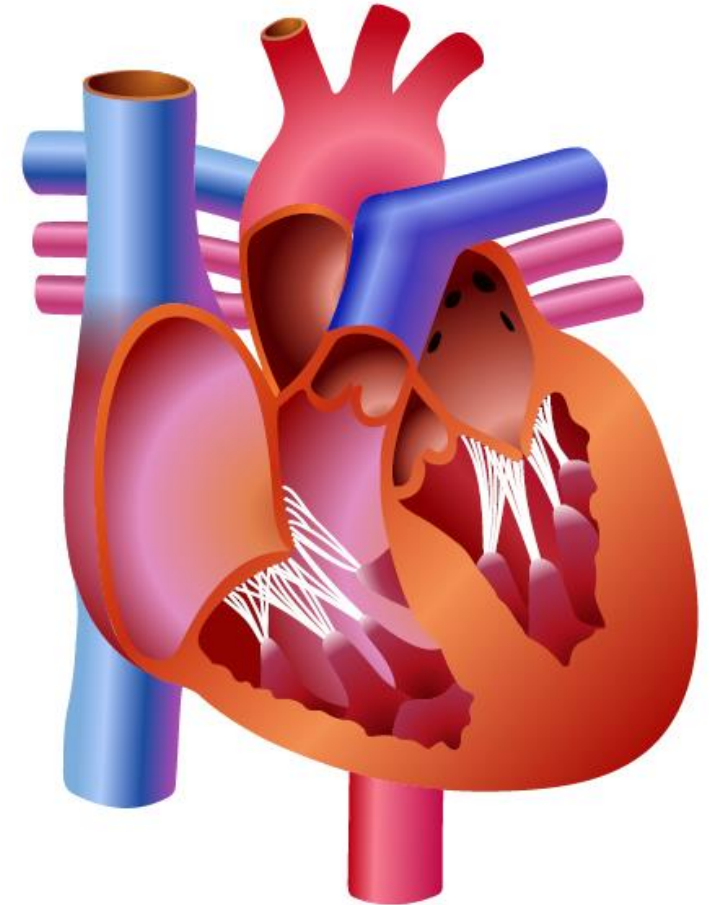
Neurogenic Orthostatic Hypotension

- Loss of autonomic nervous system function
- Supine hypertension
- Orthostatic hypotension
- Occurs in 20 to 60% of Parkinson's patients
- More common with levodopa treatment
- Complex treatment
 - Cautious use of antihypertensives
 - Fludrocortisone (mineralocorticoid)
 - Midodrine (alpha-1 agonist)



Cardiogenic Syncope

- Sudden fall in cardiac output
- Often abrupt onset without prodrome
- Sometimes preceded by palpitations or chest pain
- Only form of syncope that may occur supine
- Risk factors: **history of cardiac disease**
- Causes:
 - Ischemia (very rare)
 - Arrhythmia
 - Outflow obstruction



Cardiogenic Syncope

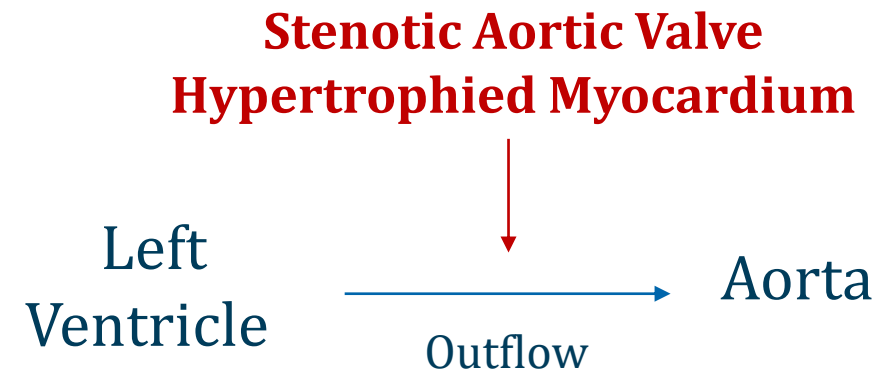
- Rarely caused by **ischemia**
 - Almost always has associated chest pain and/or EKG changes
- Many underlying **heart rhythm causes**
 - Bradycardia (sinus, AV block)
 - Tachycardia (SVT, VT)
- Diagnosis: EKG and history
- Treatment based on cause

Complete AV Block



Cardiogenic Syncope

- **Outflow obstruction**
 - Aortic stenosis
 - Hypertrophic cardiomyopathy
- **Syncope occurs with exertion**
 - Red flag
- Diagnosis:
 - Exam (murmur)
 - **Echocardiogram**



Syncope

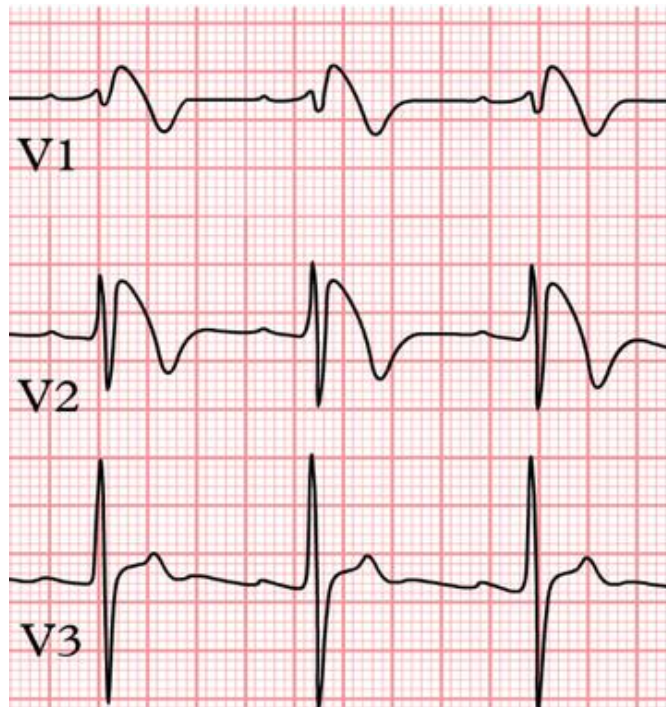
Important EKG findings

Finding	Significance
Sinus bradycardia	Sick sinus syndrome
Prolonged PR interval	AV conduction disease
Bundle branch blocks	AV conduction disease
Q waves	Risk of ventricular tachycardia
Prolonged QT interval	Risk of torsades de pointes
Epsilon wave	ARVD
Coved ST elevation V1-V3	Brugada syndrome
Arrhythmias (A fib, SVT, VT)	

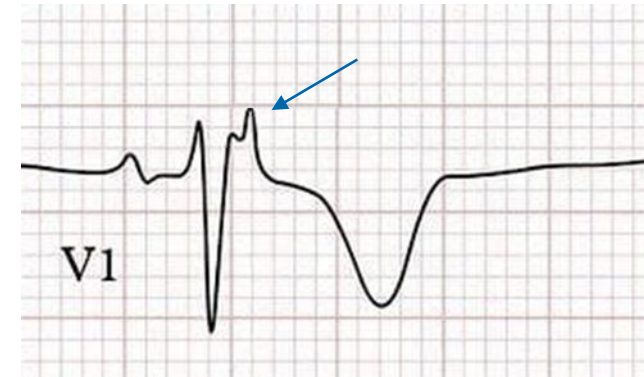
Syncope

Important EKG findings

Brugada Syndrome



Epsilon Wave ARVD



Syncope

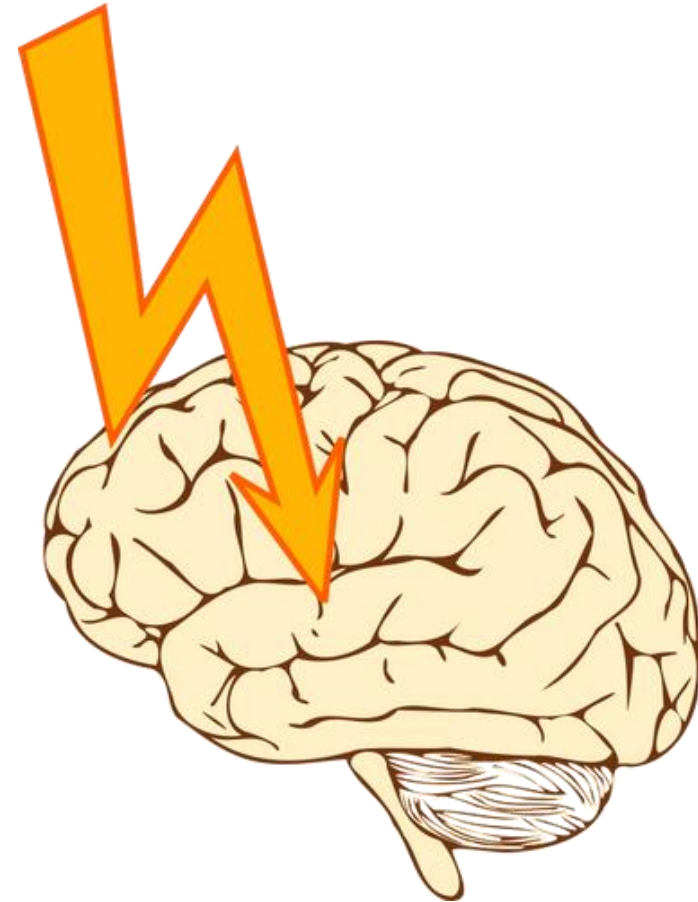
Rare Causes

- Pulmonary embolism
- Subarachnoid hemorrhage
- Shock
- Atrial myxoma

Syncope

Mimics

- Seizure
 - Tonic-clonic activity
 - Tongue biting
 - Incontinence
 - **Post-ictal state**
- Mechanical fall +/- head trauma
- Narcolepsy



Public Domain

Syncope

Workup

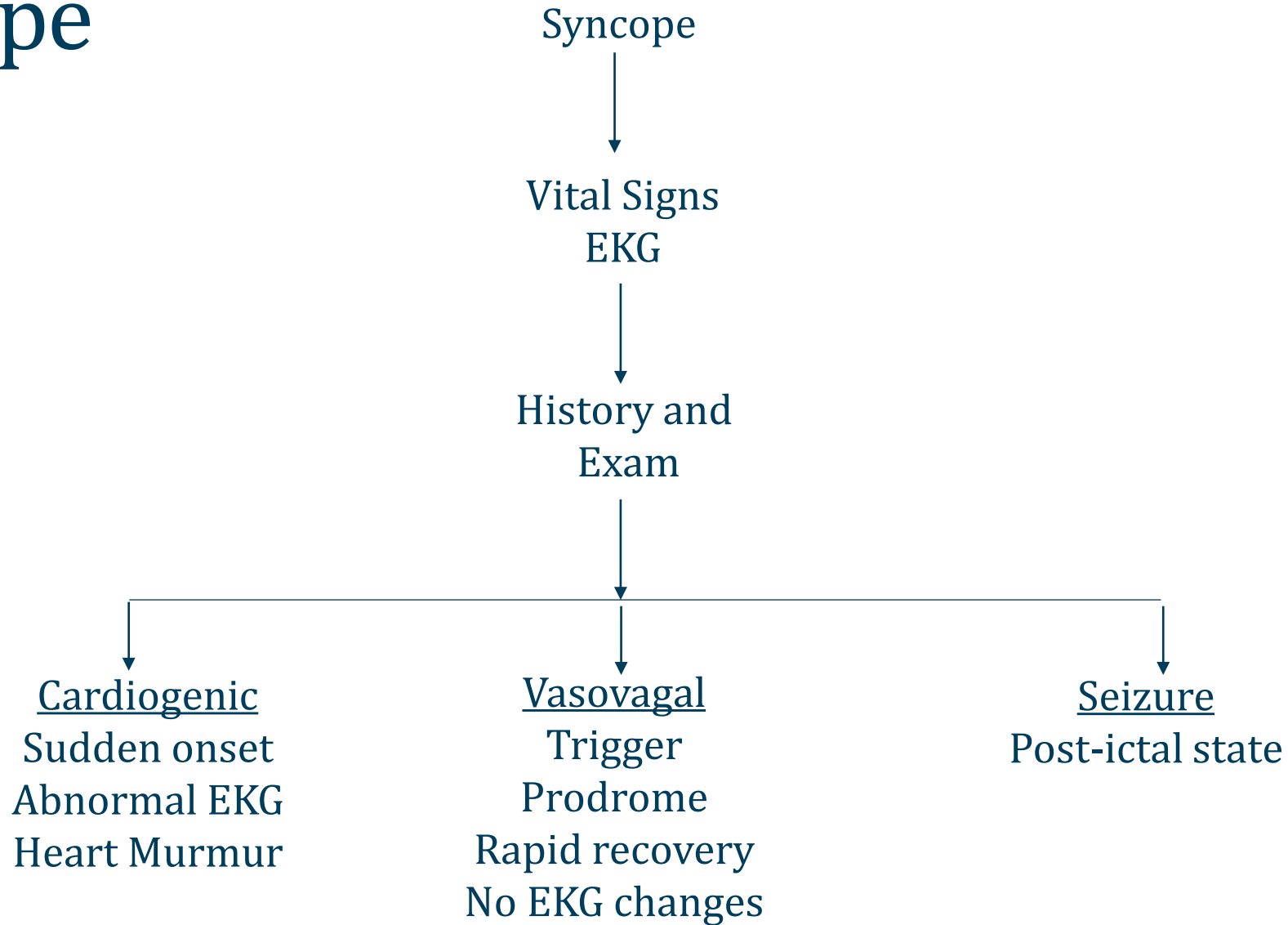
- Two most important steps:
 - Check EKG
 - Assess for history of cardiac disease
- **History is *extremely* important**



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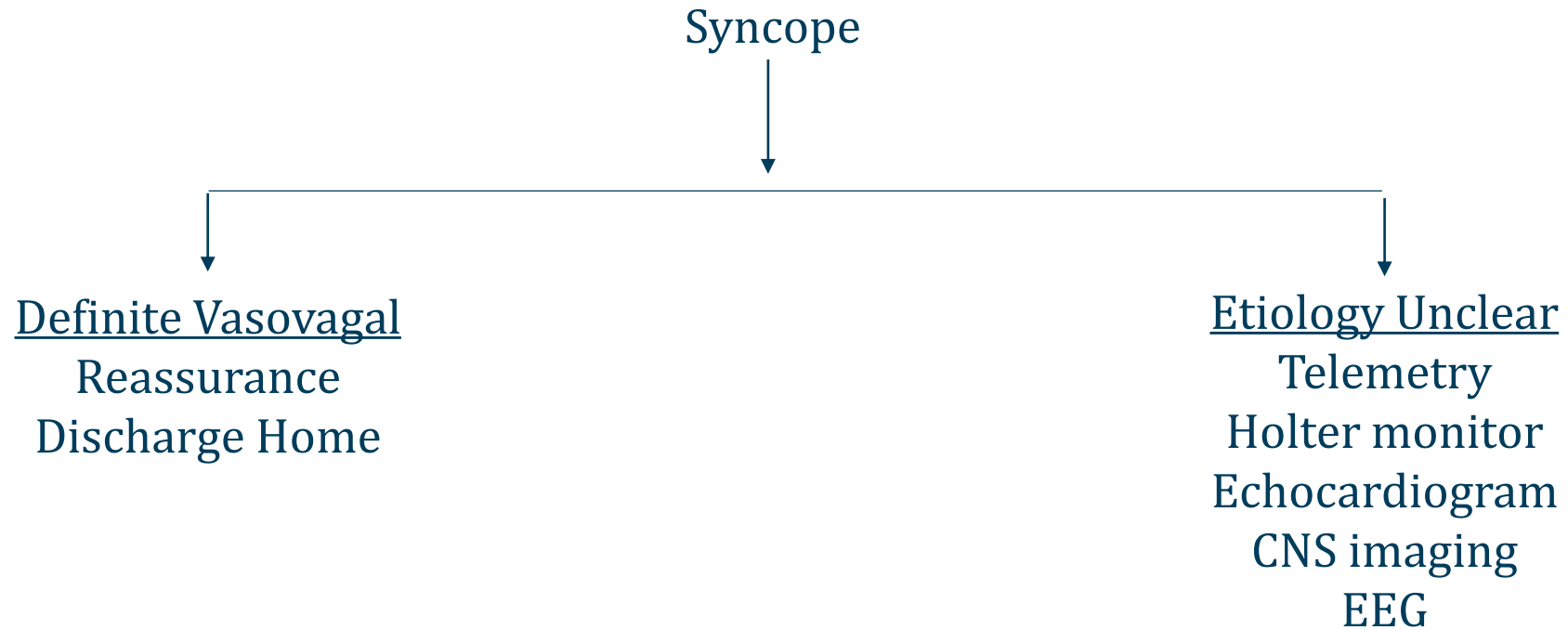
Syncope

Workup



Syncope

Workup



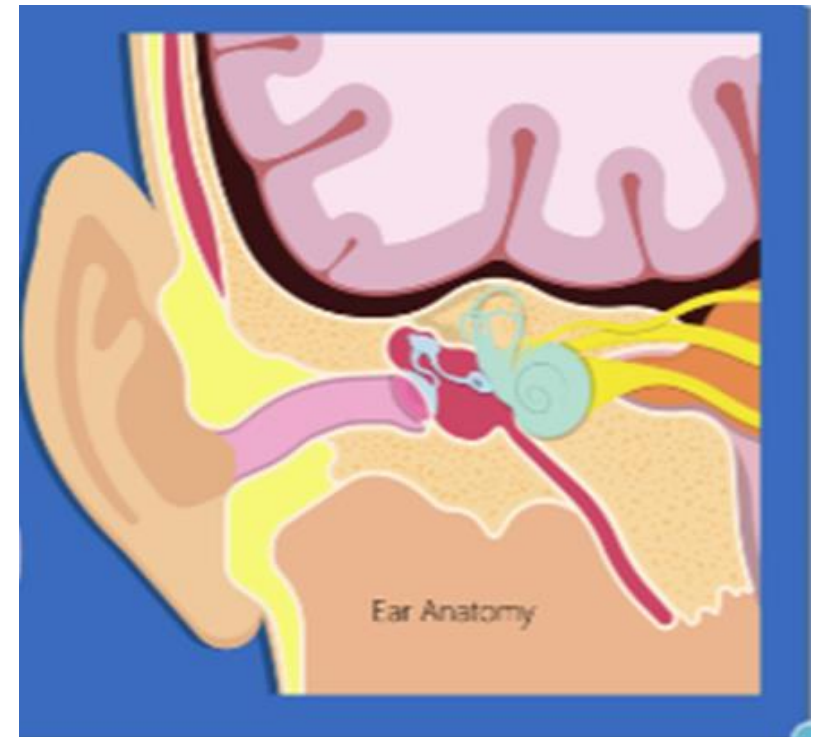
Vertigo

Jason Ryan, MD, MPH



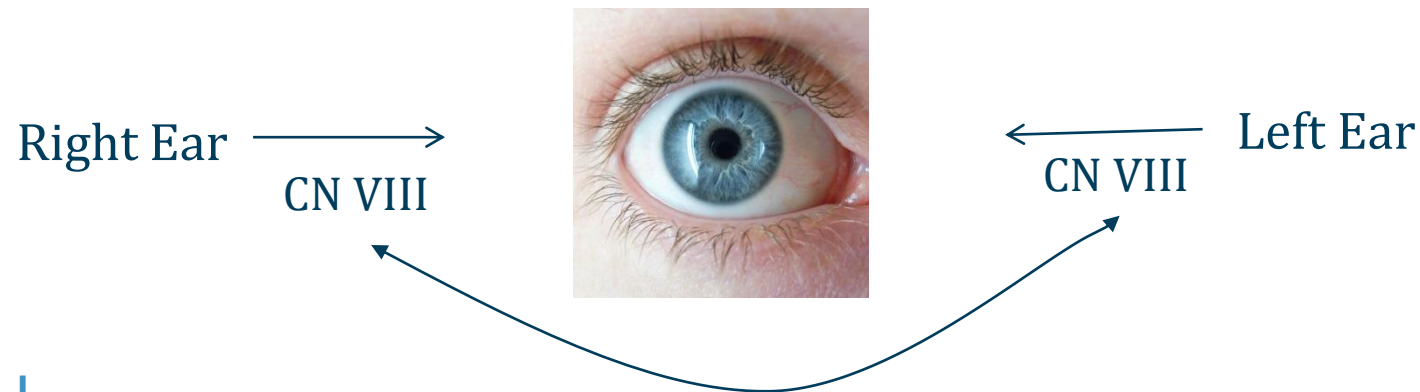
Vertigo

- Sensation of **room spinning** when head still
- Caused by abnormalities of the vestibular system
- Peripheral: dysfunction of inner ear/cranial nerve VIII
- Central : dysfunction of cerebellum or brainstem
- Often associated with nausea and vomiting



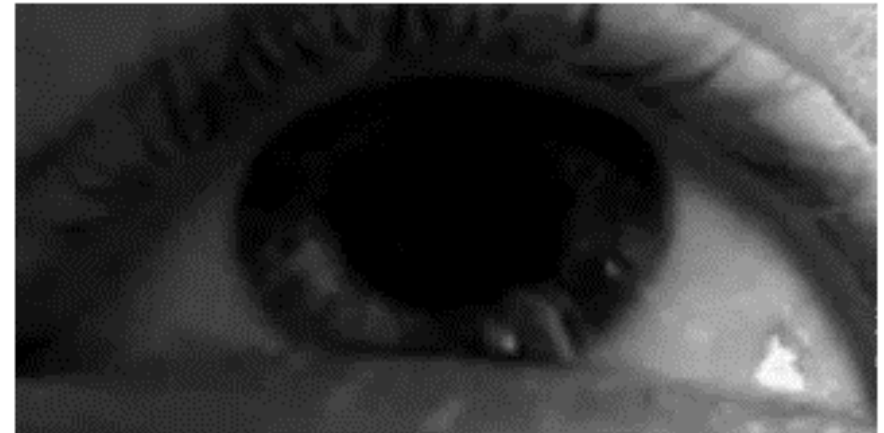
Nystagmus

- Rhythmic beating of the eye
- Associated with vestibular dysfunction and vertigo
- Vestibulo-ocular reflex: focuses eyes when body moves
- Vestibular dysfunction → disrupts reflex
- Eyes move slowly one direction → fast correction



Nystagmus

- “Jerk” nystagmus named for fast direction
 - Left/right (“horizontal”)
 - Torsional/rotational
 - Upbeat/downbeat (“vertical”)
- Peripheral vestibular dysfunction
 - Horizontal or torsional
 - Never purely vertical
- Central vestibular dysfunction
 - Can cause purely vertical



EyeWiki

Nystagmus

- Peripheral nystagmus
 - Fatigable (stops < 1 min)
 - Inhibited by gaze fixation
 - Latency period (2-30s)
- Central nystagmus
 - Not fatigable (lasts > 1 min)
 - Not inhibited by gaze fixation
 - Immediate



EyeWiki

Skew Deviation

- Vertical misalignment of the eyes
- Not due to oculomotor muscle dysfunction
- Side of lesion: downward and inward rotation
- Opposite site: upward and outward rotation
- Associated with brainstem lesions



Public Domain

Head Thrust Test

Head Impulse Test

- Patient focuses on examiner's nose
- Head turned quickly by examiner
- Peripheral lesions:
 - Eyes move away
 - Quickly return to nose at end of rotation
 - "Corrective saccade"
 - Caused by abnormal vestibulo-ocular reflex
- Central lesions: eyes remain focused on nose



Pexels/Public Domain

Central vs. Peripheral Vertigo

- Peripheral = benign (usually)
 - Inner ear problem
 - Benign positional vertigo (BPV)
 - Vestibular neuritis
 - Meniere's disease
- Central = dangerous
 - Brainstem or cerebellar lesion
 - Vertebrobasilar stroke/TIA
 - Cerebellar infarction/hemorrhage
 - Tumor (posterior fossa)



Peripheral Vertigo

Clinical Features

- Abrupt onset
- Nausea and vomiting common
- Corrective saccades on head tilt test
- Peripheral nystagmus features
- No other neurologic symptoms



Central Vertigo

Clinical Features

- Usually gradual onset (exception: stroke)
- Generally milder
- Nausea/vomiting less common
- Central nystagmus features
- Skew deviation
- Normal head tilt test
- Other CNS symptoms (weakness, sensory)
- Vascular risk factors (age, diabetes)



Central Vertigo

HINTS Exam

- **H**ead **I**mpulse
 - Abnormal = peripheral
- **N**ystagmus
 - Unidirectional, horizontal = peripheral
- **T**est of **S**kew
 - Absent = peripheral
- If all indicate peripheral, rules out central vertigo
- If any one indicates central → further workup
- Used in patients with *ongoing* vertigo

Acute Vertigo

Symptomatic Treatments

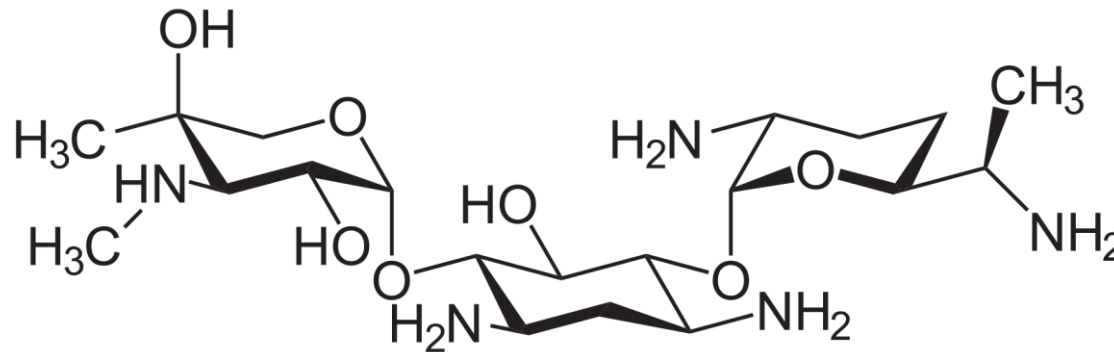
- Antihistamines
 - Meclizine – drug of choice, less sedating
 - Dimenhydrinate (Dramamine)
 - Diphenhydramine (Benadryl)
 - All have some anticholinergic effects
- Benzodiazepines
- Antiemetics
 - Ondansetron
 - Metoclopramide



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Aminoglycosides

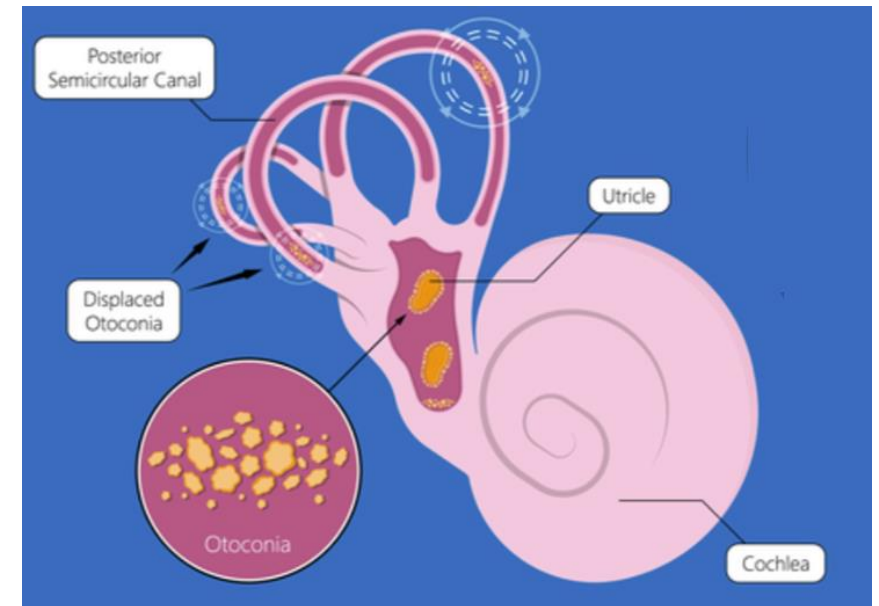
- Famous for vestibular toxicity
- Damaging to inner ear
- Cause peripheral vertigo
- Can also cause bilateral hearing loss



Gentamycin

Benign Positional Vertigo

- Vertigo with head turning or position changes
- Due to canalithiasis: calcium debris in semicircular canals
- Diagnosis: Dix Hallpike Maneuver
- Treatment: Epley maneuver to reposition otoconia



Benign Positional Vertigo

Dix-Hallpike Maneuver

- Used in patients without vertigo/nystagmus at rest
- Done to reproduce vertigo and cause nystagmus
- Seated patient
- Extend neck, turn head to side
- Rapidly lie patient down on table
- Let head hang over end of table

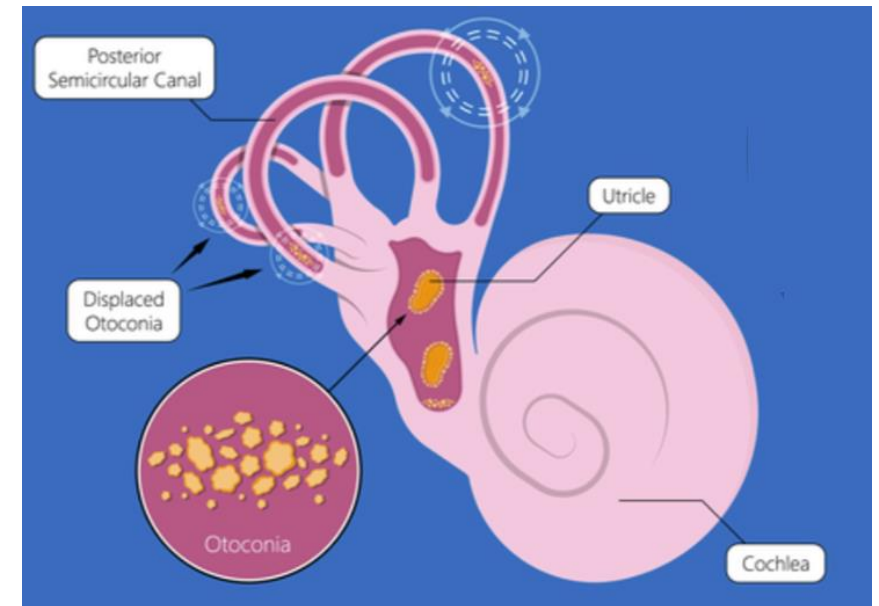
Benign Positional Vertigo

Dix-Hallpike Maneuver

- No symptoms for 5-10 seconds
- Vertigo develops
- Torsional nystagmus develops
- Symptoms resolve with sitting up
- Fewer symptoms with repeated maneuvers

Epley Maneuver

- Repositions particles in semicircular canals
- Allows stones to exit inner ear
- Similar to Dix-Hallpike maneuver
 - Sit on a bed, turn head 45 degrees
 - Quickly lie back, keeping head turned
 - Alter head position every 30 seconds
 - Sit up



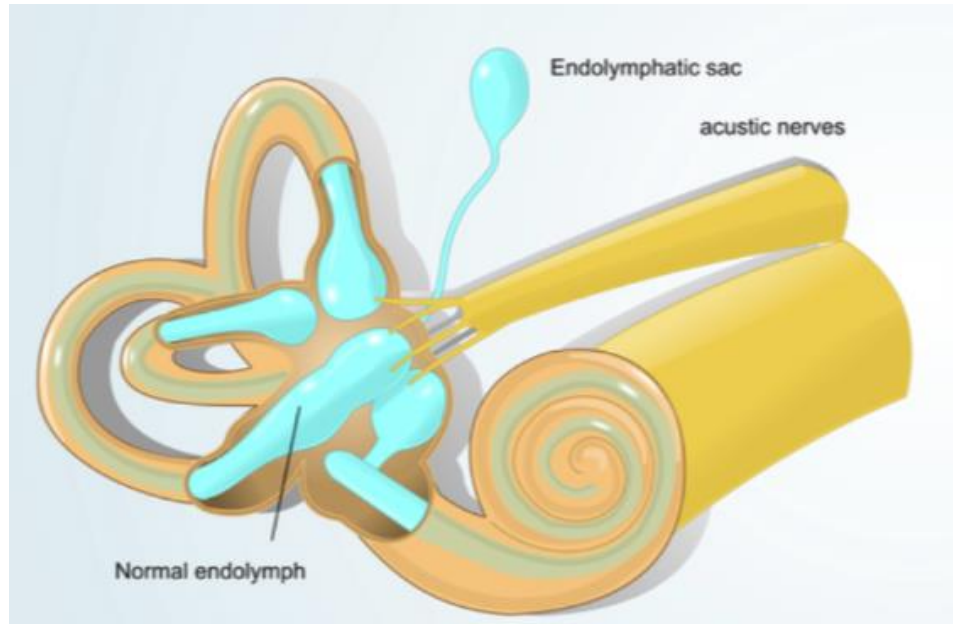
Vestibular Neuronitis

Labyrinthitis

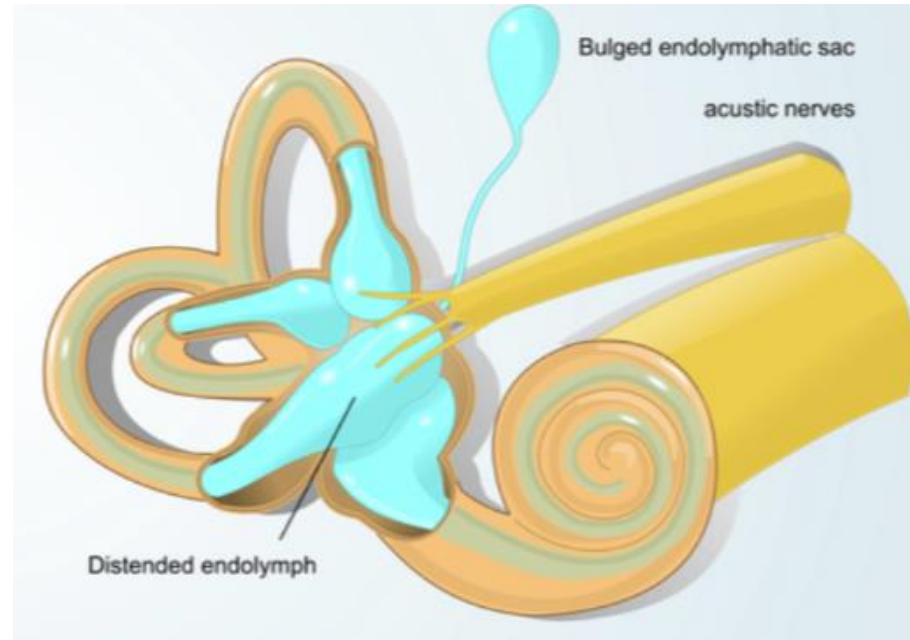
- Peripheral cause of vertigo
- Neuropathy of vestibular portion CN VIII
- **Benign, self-limited**
- Usually viral or post-inflammatory
- Diagnosis: clinical
- Treatment:
 - Meclizine (antihistamine)
 - Antiemetic for nausea
 - Rarely corticosteroids

Meniere's Disease

- Endolymph fluid accumulation (hydrops)
- Swelling of the labyrinthine system



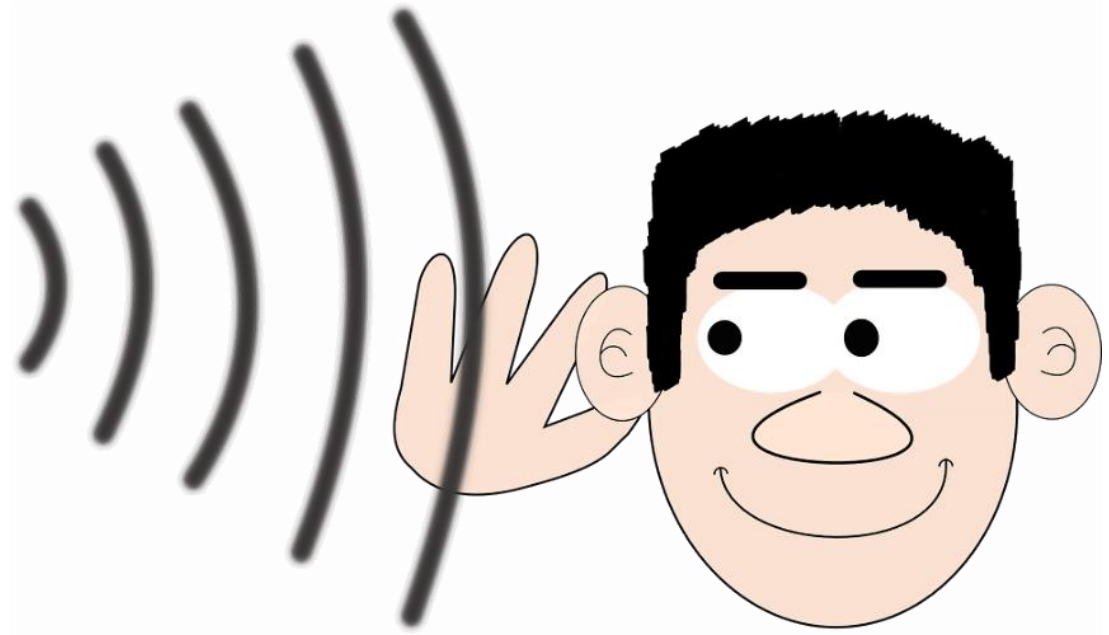
Normal



Meniere's

Meniere's Disease

- Tinnitus
- Sensorineural hearing loss
- Vertigo
- Diagnosis: clinical



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Meniere's Disease

Treatment

- Acute episodes of vertigo:
 - Meclizine
 - Antiemetics
- Chronic treatment:
 - **First line: diet and lifestyle modification**
 - Avoid high salt – decrease swelling
 - Avoid caffeine, nicotine–vasoconstrictors, ↓ flow from inner ear
 - Avoid alcohol – causes fluid shifts in inner ear
 - Diuretics: hydrochlorothiazide, furosemide, acetazolamide
 - Surgery

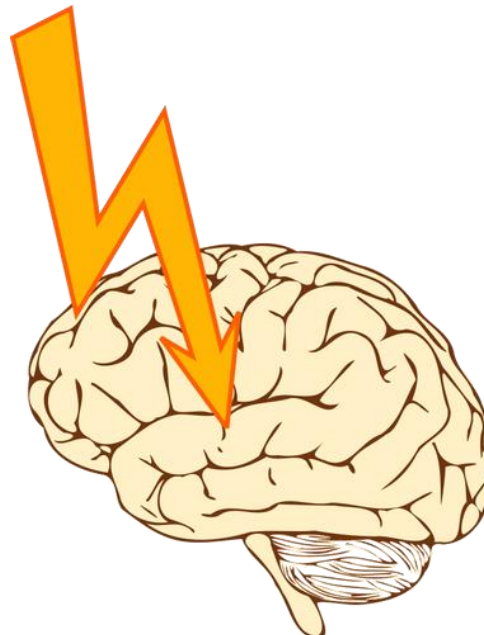
Seizures

Jason Ryan, MD, MPH



Seizure

- Sudden alteration in behavior
- Transient CNS electrical activity in cerebral cortex



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Seizure

Clinical Features

- Abnormal motor activity
- Abnormal sensation
- Loss of consciousness
- Tongue biting
- Incontinence
- Perioral cyanosis (children)



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Psychic Symptoms

- Higher cortical areas affected
- Sudden emotional changes
- Feelings of familiarity ("deja-vu")
- Anxiety
- Fear



Wikipedia/Public Domain

Autonomic Symptoms

- Epigastric "rising" sensation
- Sweating
- Piloerection
- Pupillary changes

Auras

- Warning before major seizure
- Auras = simple, partial seizures
- Seizure affects enough brain to cause symptoms
- Not enough to interfere with consciousness
- Symptoms depend on area of brain
 - Occipital lobe: flashing lights
 - Motor cortex: muscle jerking

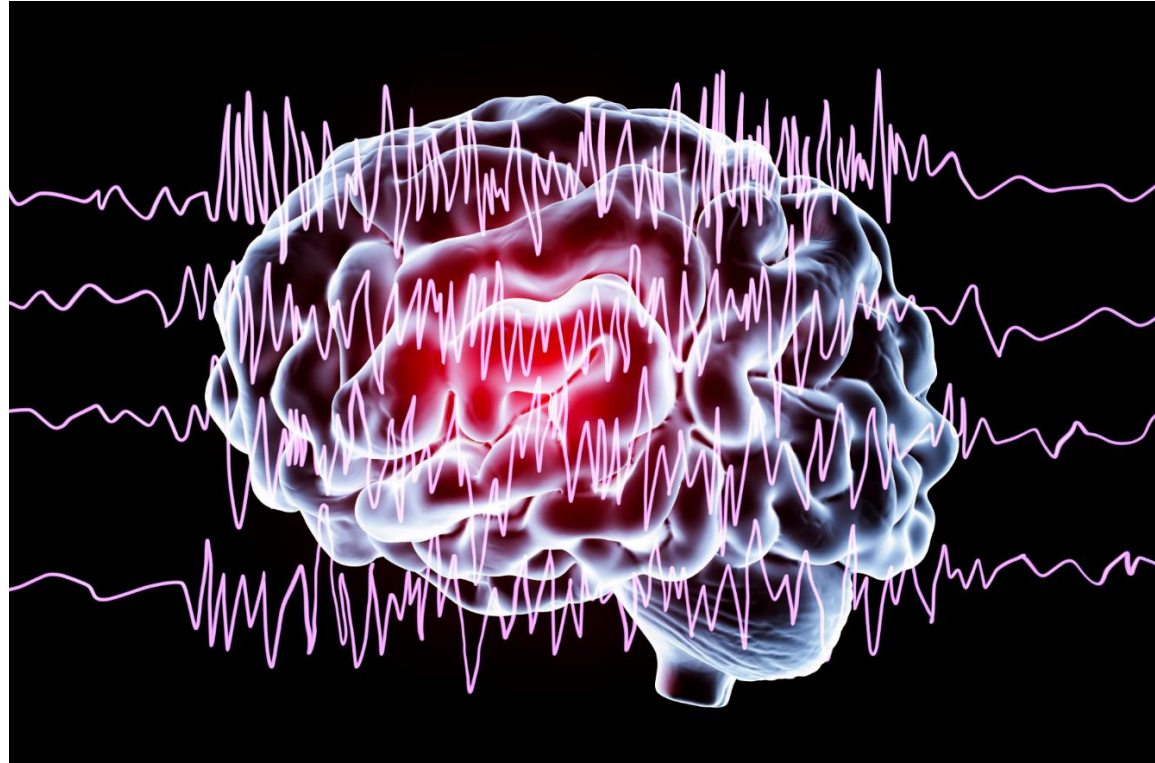


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Seizure

Types

- Simple seizures
 - Awareness maintained
- Complex seizures
 - Loss of awareness



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Seizure Muscle Activity

- Tonic: sustained muscle tone
- Clonic: myoclonic muscle jerks
- Atonic: loss of muscle tone

Partial Seizures

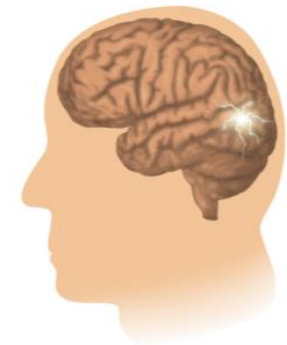
- Involves discrete area of brain
- Focal body area with seizure activity
- Motor, sensory, autonomic, psychic
- **Simple partial** – no alteration consciousness
 - Often recurrent, uncontrollable twitching
 - No impaired consciousness
- **Complex partial** – alteration consciousness
- Partial seizures may secondarily generalize

Types of Epilepsy

Generalized



Focal



Shutterstock

Generalized Seizures

- Entire brain affected
- May begin as partial seizure

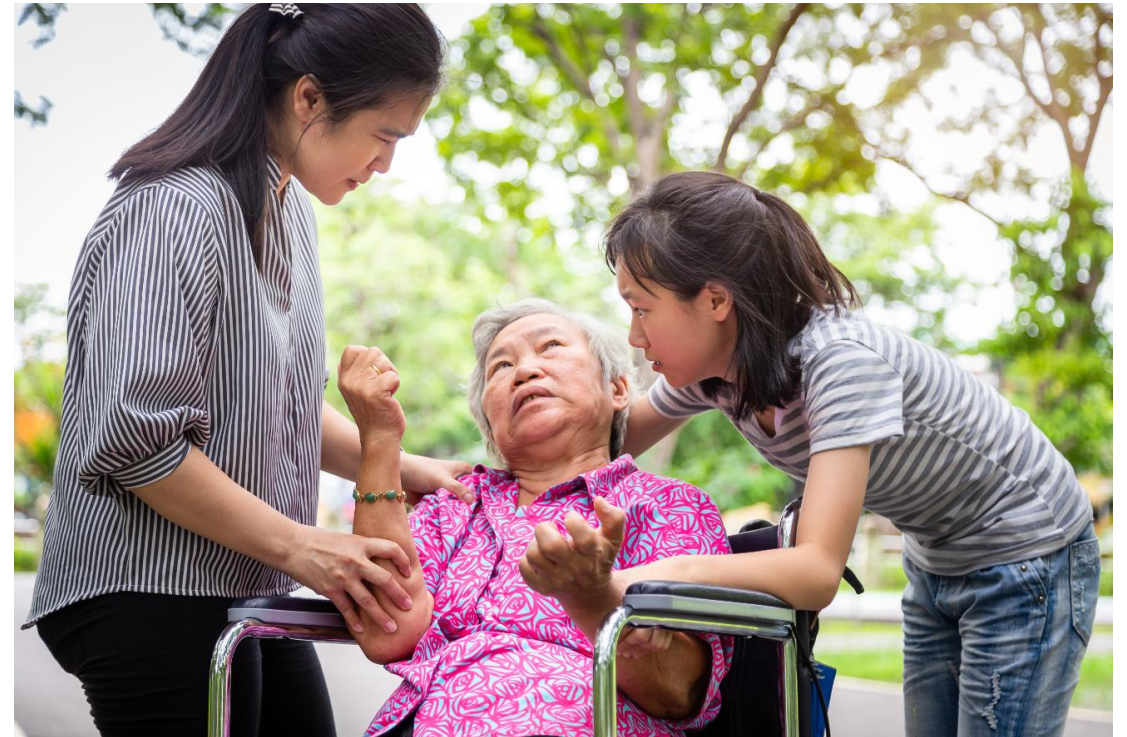
Type	Features
Grand Mal or Tonic-Clonic	Unconsciousness, convulsions, muscle rigidity
Petit Mal or Absence	Brief loss of consciousness
Myoclonic	Repetitive, jerking motion
Tonic	Muscle stiffness and rigidity
Atonic or Drop Seizure	Loss of muscle tone

Jacksonian Seizure

- Type of simple, partial seizure
- No change in alertness
- Involves one area of motor cortex
- **Involves one side of the body**
- **Progresses in a predictable pattern**
 - Example: starts with twitching or tingling sensation of finger
 - Spreads (“Jacksonian march”) to entire hand

Postictal State

- Follows seizures
- Period of brain recovery
- **Confusion, lack of alertness**
- Focal neurologic deficits may be present
- Variable time from minutes to hours
- **Key distinction from syncope**



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Todd's Paralysis

- **Persistent muscle weakness following a seizure**
- Can last up to hours
- Example:
 - Motor seizure of left arm
 - Postictal weakness for several hours
 - Can raise concern for stroke

Status Epilepticus

- Life-threatening emergency
 - Lactic acidosis
 - Cortical laminar necrosis → permanent neurologic disease
- Old definition: 30 minutes continuous seizure activity
- Modern definition:
 - ≥ 5 minutes of continuous seizures
 - Or ≥ 2 seizures with incomplete recovery of consciousness
- Usually occurs with generalized tonic-clonic activity



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Seizure Causes

- Many people have 1 seizure
- Often “provoked”
 - Fever (children)
 - Lack of sleep
 - Drugs, alcohol
 - Hypoglycemia
- Other more serious causes: tumors, strokes
- Epilepsy: multiple, unprovoked seizures

Seizure Causes by Age Group

Infants < 6mo	Children	Adults
CNS disease* Metabolic* Epilepsy rare	Febrile Epilepsy	Stroke Infection CNS mass Withdrawal Intoxication Metabolic New epilepsy rare

CNS Disease: hypoxic-ischemic encephalopathy, CNS hemorrhage

Metabolic: hypoglycemia, electrolyte abnormalities

Withdrawal Seizures

- Alcohol
- Benzodiazepines
- Barbiturates
- Anticonvulsant drugs



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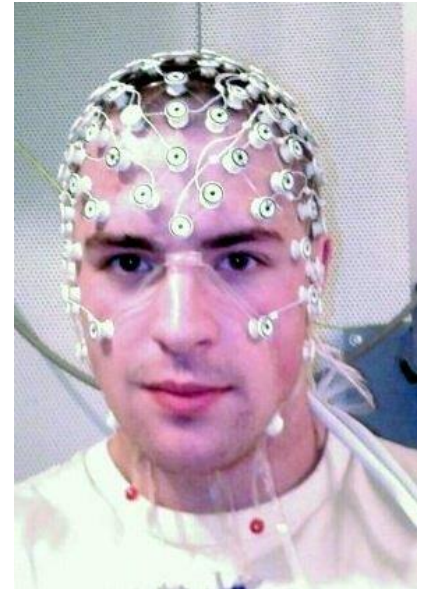
Seizure Workup

- **Blood work**
 - Calcium, sodium, glucose
 - CBC
 - Renal function
 - Liver function tests
- Toxicology screen
- EKG (cardiac syncope)
- Brain imaging (CT or MRI)
- Sometimes lumbar puncture (LP)
- EEG

EEG

Electroencephalogram

- Records voltage changes in brain
- Different leads
 - Frontal, parietal, occipital
- Characteristic patterns
- **Done only if all else negative**



Driving

- Risk of recurrence while driving
- Guidelines vary in length of seizure-free interval required for safety
- Most sources: no driving for **6-12 months** after unprovoked seizure



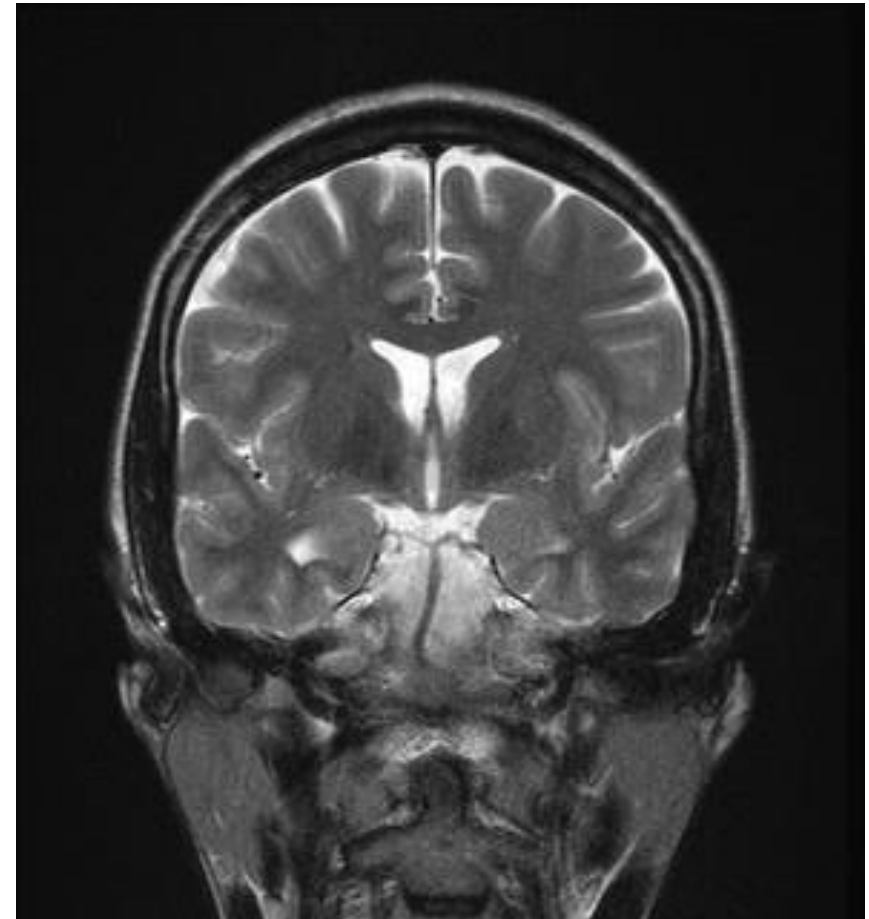
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Seizure Management

- Move bystanders and objects out of way
- Loosen tight clothing around neck
- Do not force mouth open
- Place on side to avoid aspiration
- Most are self limited (~2 minutes)

Temporal Lobe Epilepsy

- **Most common site focal seizures**
- Causes complex partial seizures
- Due to mesial temporal sclerosis
 - Most commonly from hippocampal sclerosis
 - Mechanism unclear
- Hand movements: picking, fidgeting
- Chewing, **lip smacking**
- Impaired consciousness/confusion
- Diagnosis: MRI

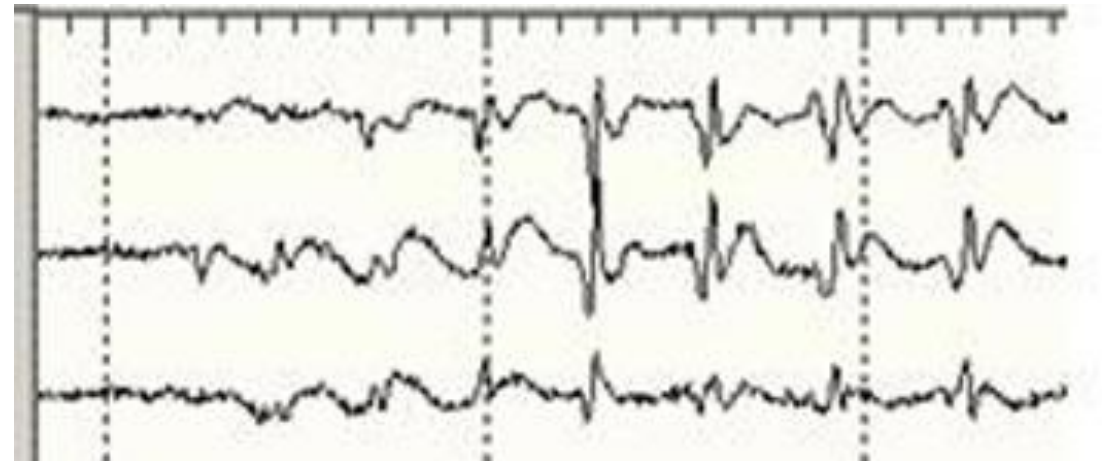


Wikipedia/Public Domain

Childhood Absence Epilepsy

- Sudden impairment of consciousness
- No change in body/motor tone
- Seconds in duration
- Usually remits by puberty
- Classic EEG finding:
 - **3 Hertz spike wave activity**
- No post-ictal confusion
- First-line treatment: **ethosuximide**

3Hz Spike and Wave



Juvenile Myoclonic Epilepsy

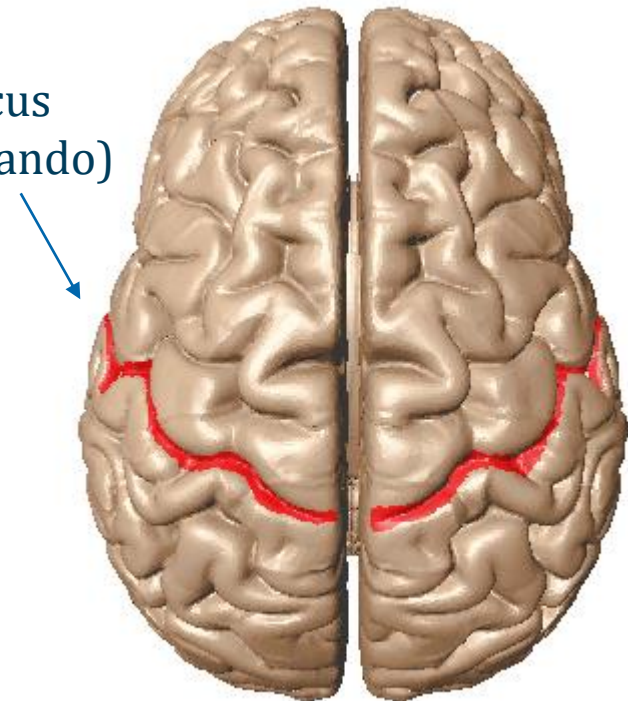
- Childhood epilepsy syndrome
- Myoclonic, tonic-clonic and absence seizures
- Absence seizures first (~5 years of age)
- Myoclonic seizures later (~15 years)
- Grand mal seizures soon after
- Hallmark:
 - **Myoclonic jerks on awakening from sleep**
 - Shock-like, irregular movements of both arms

Benign Rolandic Epilepsy

Benign epilepsy with centrotemporal spikes (BECTS)

- **Most common form of childhood epilepsy**
- Occurs in children 6 – 10 years old
- Origin near fissure of Rolando
- Focal seizure disorder
 - Often start in face
 - Spread to other body parts
- No loss of consciousness
- **EEG: centrotemporal sharp waves**
- Often remits within a few years

Central Sulcus
(Fissure of Rolando)



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Lennox-Gastaut Syndrome

- Childhood epilepsy syndrome
- Occurs in children 3 to 5 years old
- Multiple seizure subtypes
 - Tonic
 - Atonic
 - Myotonic
 - Absence
- Associated with intellectual disability
- EEG: generalized, slow (< 2.5 hertz) spike-wave pattern

Febrile Seizures

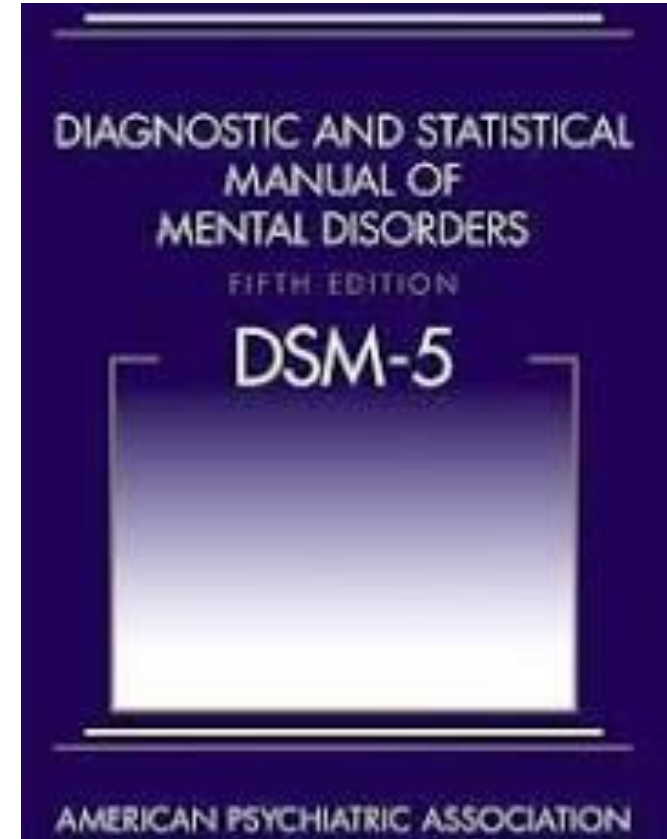
- Common: 2-4% children < 5 years old
- Most commonly generalized, tonic-clonic
- Child loses consciousness, shakes
- This is NOT considered epilepsy
- Children at risk for more febrile seizures
- Overall prognosis generally good
 - Small increased risk of epilepsy

Febrile Seizures

- **Diagnosis: clinical**
- MRI, EEG rarely done
- Lumbar puncture only if suspicion of meningitis
- Acute treatment for prolonged seizures: IV lorazepam
- **If child recovers, can reassure and discharge home**
- Long-term antiepileptic medications not required

Psychogenic Nonepileptic Seizures

- Clinical presentation of seizure
- No underlying CNS disease identified
- Normal EEG during seizure
- Treatment: psychotherapy
- Form of conversion disorder in DSM-V



Seizure Treatment

Jason Ryan, MD, MPH



Seizure Treatment

- **Status epilepticus**
 - Goal is to “break” seizure
 - Life-threatening emergency
 - Arrhythmias, lactic acidosis, hypertension
 - Continuous seizure > 30 min
 - ≥ 5 minutes of continuous seizures
 - Or ≥ 2 seizures with incomplete recovery of consciousness
 - Usually occurs with generalized tonic-clonic activity
- **Preventing seizures**
 - Goal is to prevent seizure occurrence
 - Used in patients with recurrent seizures

Status Epilepticus

- Check airway, breathing, and circulation (ABCs)
- **First-line treatment: IV lorazepam**
 - Alternative: diazepam
 - Multiple doses may be used
- Loading of intravenous antiseizure drug:
 - Fosphenytoin, valproate, and levetiracetam
 - Prevent recurrent seizures
- If still seizing: phenobarbital
- Often requires general anesthesia and intubation



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Antiepileptic Drugs

AEDs

Na Channel Blockers	GABA Activators	Other Mechanisms
Phenytoin Fosphenytoin Carbamazepine Oxcarbazepine Lacosamide Lamotrigine	Benzodiazepines Barbiturates Thiopental Tiagabine Vigabatrin	Gabapentin Levetiracetam Topiramate Valproic acid Ethosuximide Primidone

Choosing AEDs

- **Status Epilepticus**
 - Benzodiazepines
- **Absence seizures**
 - Ethosuximide
- No other AEDs have specific indications
- No head-to-head trials

AEDs

Common Side Effects

- Teratogenicity
- Rash and Stevens-Johnson Syndrome
- Induction liver P450 enzymes
- Reduced bone density
- Many drugs require blood level monitoring

AEDs and Pregnancy

- Women with epilepsy may require drugs in pregnancy
- All anti-seizure drugs may affect fetus
 - **Neural tube defects**
 - Congenital heart disease
 - Cleft palate
 - Short fingers
 - Abnormal facial features
- Drugs used in pregnancy:
 - Levetiracetam
 - Lamotrigine



Øyvind
/Wikipedia

Seizure Drugs

Teratogenicity

- Highest risk drugs
 - **Valproic acid** (↑↑ neural tube defects)
 - **Carbamazepine**
 - Phenytoin
 - Phenobarbital
- Many anti-seizure drugs associated with ↓ folic acid
 - Leads to neural tube defects
 - **High-dose folic acid supplementation recommended**
- Folate supplementation in pregnancy
 - Normal-risk mothers: 400 mcg/day
 - High risk mothers: 4mg/day



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Stevens-Johnson Syndrome

- Rare, life-threatening skin condition
- Extensive skin necrosis and sloughing
- Can be triggered by many AEDs
 - Carbamazepine
 - Lamotrigine
 - Phenytoin
- More common with **HLA-B*1502 allele**
 - High frequency in **Asian populations**
 - Pre-treatment screening sometimes done

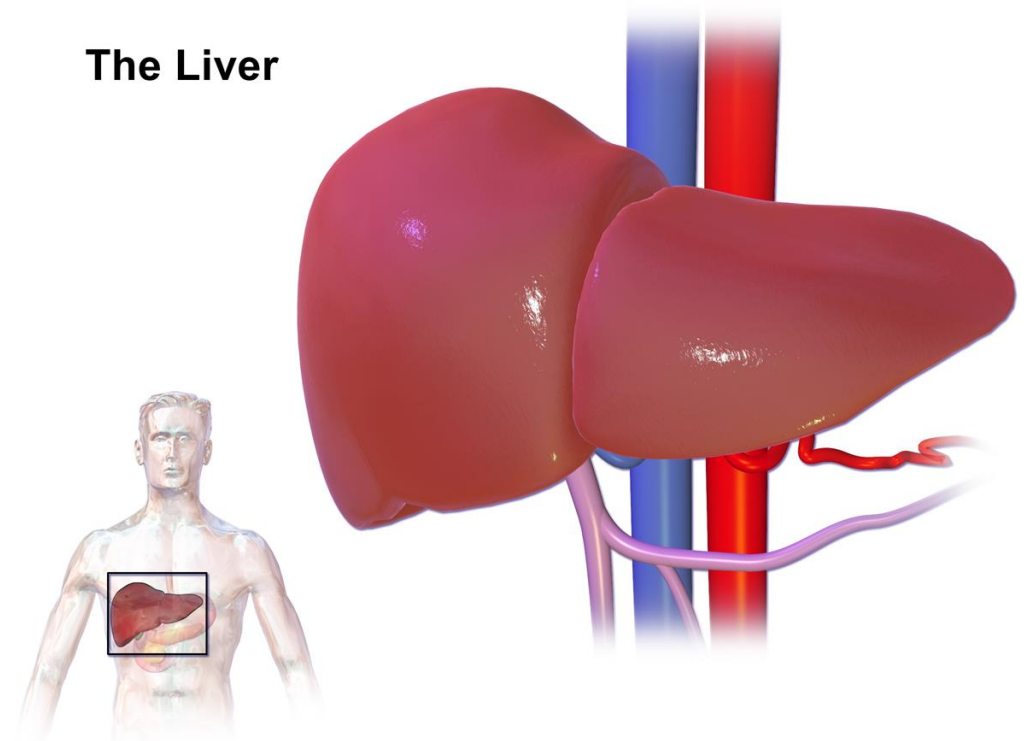


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Cytochrome P450

- Intracellular hepatic enzymes
- Metabolize many drugs
- If inhibited → drug levels rise
- If induced → drug levels fall
- **Several AEDs induce CYP450**
 - Carbamazepine
 - Phenobarbital
 - Phenytoin

The Liver



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Bone Density

- Many AEDs associated with **reduced bone density**
- Multiple mechanisms
- Induction of P450 enzymes may lead to ↓ vitamin D levels
- AEDs that lower bone density are **P450 inducers**
 - Carbamazepine
 - Phenobarbital
 - Phenytoin



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Blood Level Monitoring

- Used for monitoring of many AEDs
- Phenytoin
- Carbamazepine
- Ethosuximide
- Lamotrigine
- Levetiracetam
- Valproic acid



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Ethosuximide

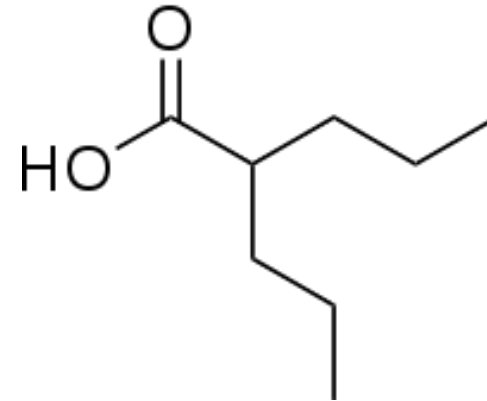
- Blocks thalamic T-type Ca channels
- Drug of choice: **childhood absence seizures**
- Most common side effect: upset stomach (nausea/vomiting)
- Rare side effects: drowsiness



Dolbex/Flickr

Valproic Acid

- **Na-channel and GABA effects**
 - Blocks Na channels
 - ↑ synthesis, ↓ breakdown GABA
- Also a mood stabilizer
 - Bipolar disorder
 - Acute mania



Valproic Acid

Valproic Acid

- Highly teratogenic
- Associated with spina bifida
- Nausea / vomiting
- Hepatotoxic
- Thrombocytopenia (bleeding)
- Tremor
- **Weight gain**



Tibor Végh

Phenytoin

- Inactivates Na channels
- Blood level monitoring critical
- **Gingival hyperplasia**
- **Body hair growth**

Gingival Hyperplasia



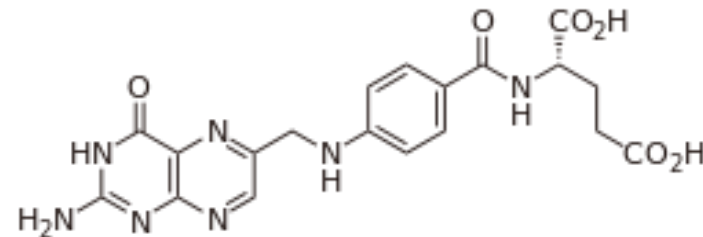
Lesion/Public Domain

Hirsutism



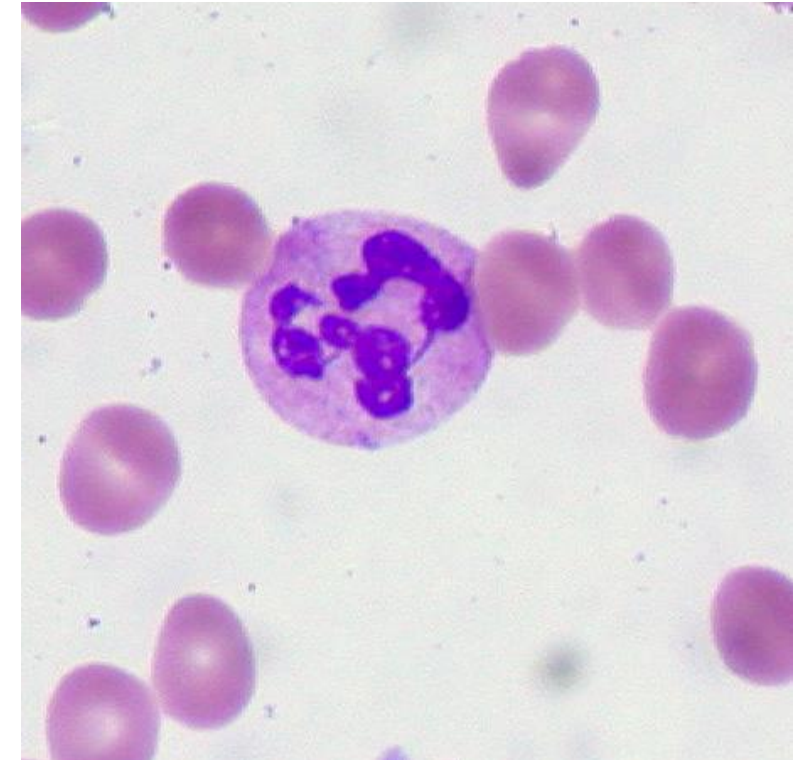
Phenytoin

- **Causes folic acid depletion**
- Teratogenic
- Megaloblastic anemia
- Reduces bone density
- **Neurologic effects**
 - Confusion
 - Blurry vision
 - Ataxia



Folic Acid

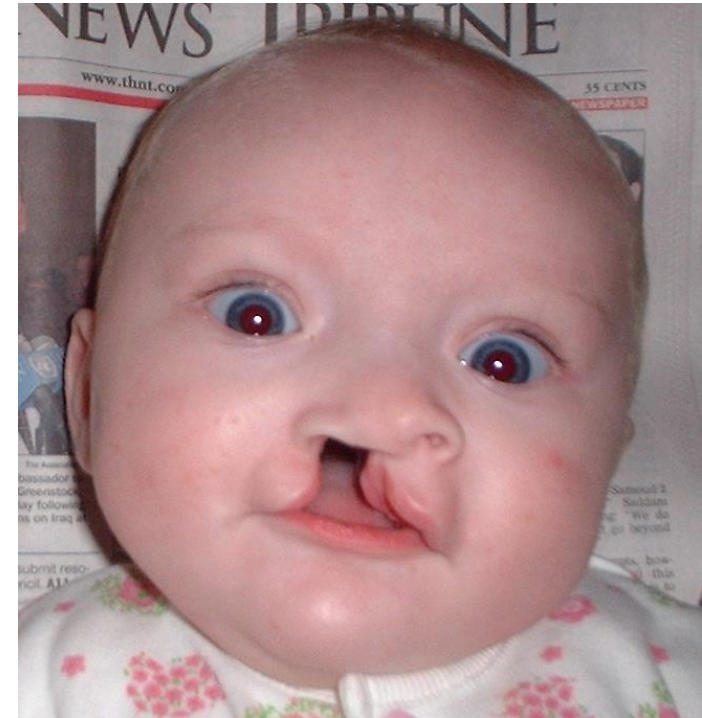
Megaloblastic Anemia
Hypersegmented Neutrophil



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Fetal Hydantoin Syndrome

- Associated with **phenytoin** use in pregnancy
- **Growth deficiency**
- Abnormal facial features
 - Broad, short nose
 - Wide-spaced eyes
 - Malformed ears
 - **Microcephaly**
 - Classically **cleft lip and cleft palate**



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Phenytoin

Acute Toxicity/Overdose

- Altered mental status
- Nystagmus
- Ataxia
- Abnormal reflexes
- Often due to **concomitant drug**
 - P450 metabolism (e.g., TMP-SMX)
 - Heavily albumin bound (e.g., valproic acid)
- Often in patients with **liver/kidney disease**



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Fosphenytoin

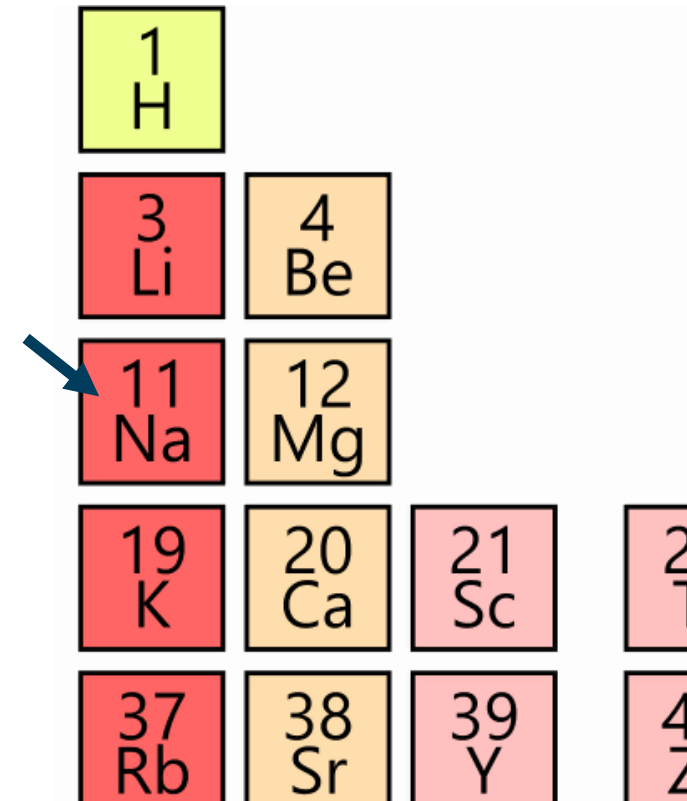
- IV phenytoin can cause “purple glove syndrome”
 - Purple-black skin discoloration distal to injection site
- Fosphenytoin
 - Prodrug of phenytoin
 - Lower incidence purple glove syndrome
 - Rapid onset of action
- Used in treatment of status epilepticus



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Carbamazepine

- Na channel blocking drug
- Many similarities with phenytoin
- Blood levels monitoring critical
- Stevens-Johnson syndrome (HLA-B*1502)
- Bone marrow suppression
- Liver toxicity
- **SIADH (hyponatremia)**



1 H			
3 Li	4 Be		
11 Na	12 Mg		
19 K	20 Ca	21 Sc	22 Ti
37 Rb	38 Sr	39 Y	40 Zr

Barbiturates

Phenobarbital, Pentobarbital, Thiopental

- GABA activators
- Used as sedatives in past
- Now largely replaced by benzodiazepines
- Narrow therapeutic index
- Inducers of P450 system
- Dangerous used **together with alcohol**
 - Cause respiratory and CNS depression
 - Drug have similar effects to alcohol (CNS depressants)



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Levetiracetam

- Exact mechanism unknown
- Useful for many types of seizures
- Blood levels can be monitored
- Drug titrated to clinical effect
- Well tolerated with few important or serious side effects
- Most adverse effects mild
- Most often occur during initial therapy
- Most common adverse effect: somnolence

Gabapentin

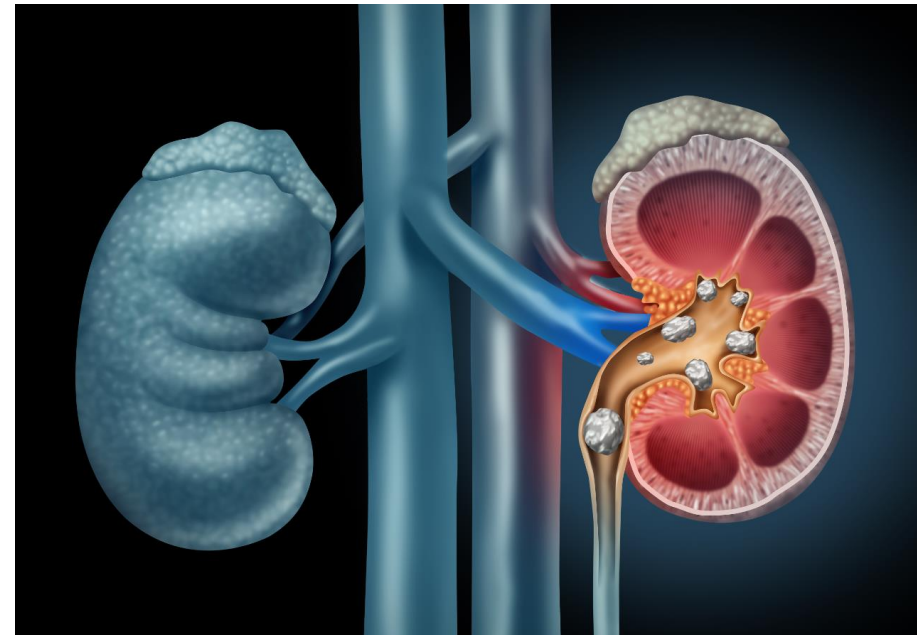
- Affects Ca channels
- Major adverse effect: **sedation**
- **Excreted entirely in urine**
- Increased toxicity with low GFR



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Topiramate

- Na and GABA effects
- **Mental dulling, sedation**
- Weak carbonic anhydrase inhibitor
 - Causes mild metabolic acidosis
- **Kidney stones**
 - Reduced urinary citrate excretion
 - Increased urinary free calcium



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CNS Malignancy

Jason Ryan, MD, MPH



CNS Malignancy

- Primary brain tumors (~30%)
- Metastasis (~70%)
- Most common sources:
 - Lung
 - Breast
 - GI tract
 - Kidney
 - Melanoma

CNS Malignancy

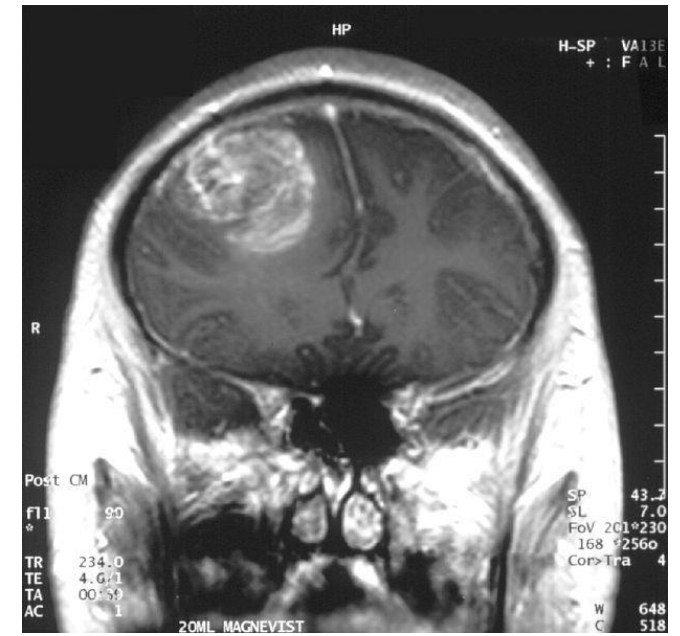
Clinical Features

- May be asymptomatic
- Most common presenting features:
 - Seizures
 - Slowly progressive focal deficits
- Can raise intracranial pressure
 - Papilledema
 - Vomiting
 - Headache: worse with bending, coughing or Valsalva
- Headache classically early morning (rare finding)

CNS Malignancy

Diagnosis

- Best initial test: CT or MRI
- Most accurate test: **contrast-enhanced (gadolinium) MRI**
 - Best at visualizing soft tissue structures and vascularity
- Biopsy for histologic diagnosis



Christaras A/Wikipedia

CNS Malignancy

Treatment

- Varies based on type of tumor
- Surgery
- Radiation
 - Whole brain radiotherapy (WBRT)
 - Stereotactic radiosurgery (SRS)
- Chemotherapy
- Glucocorticoids for ↓ ICP

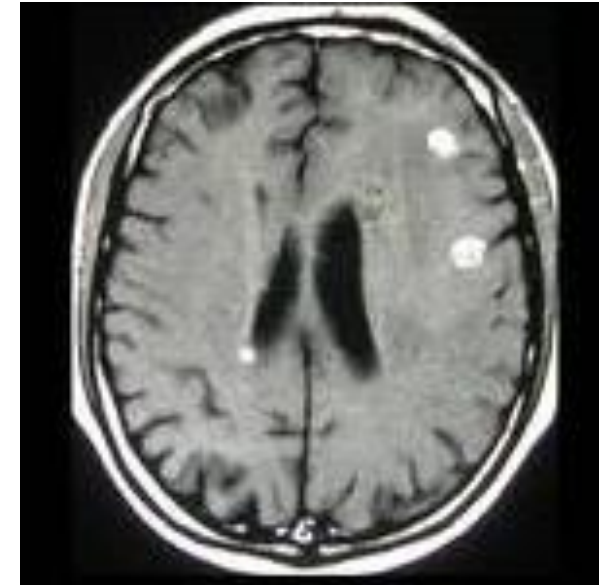


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Brain Metastasis

- One or more lesions
- Usually at gray-white matter junction
- Generally very poor survival (months)
- Survival predictors: age < 65, limited extracranial disease
- Single brain lesion often **treated with surgery**
 - Can significantly improve prognosis
 - Followed by radiation
- Multiple lesions often treated with radiation

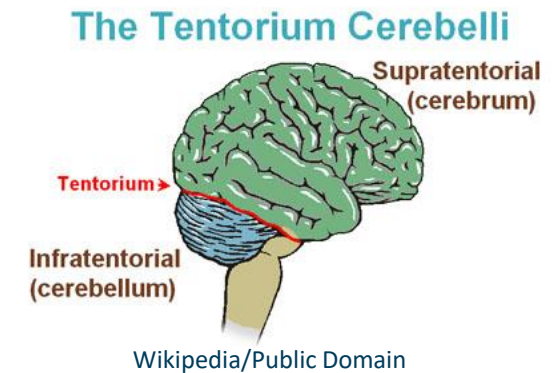
Metastatic Melanoma



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Primary Brain Tumors

- Adult tumors: supratentorial
- Childhood tumors: infratentorial



Adults	Children
Glioblastoma Meningioma Vestibular Schwannoma Oligodendroglioma	Pilocytic Astrocytoma Medulloblastoma Ependymoma Craniopharyngioma Pinealoma

Glioblastoma

- **Most common primary brain tumor in adults**
- Derives from astrocytes
- Occurs in cerebral cortex
- **Butterfly appearance on MRI**
 - Tumor spanning corpus callosum
- Rapidly progressive
- Usually fatal < 1 year
- Half of patients > 65 years old
- Older age = worse prognosis



A.Prof Frank Gaillard/Wikidoc

Glioblastoma

Treatment

- Surgical resection
- Neoadjuvant (pre-surgery) radiation
- **Temozolomide**
 - Oral alkylating agent
 - Given daily during radiation
 - Followed by post-radiation cycles



A.Prof Frank Gaillard/Wikidoc

Meningioma

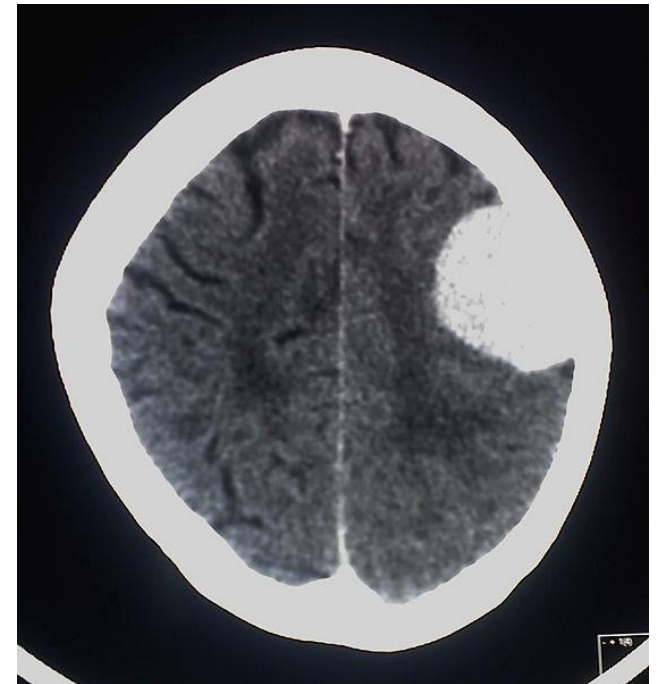
- Second most common brain tumor in adults
- From arachnoid cells
- Forms along dura
- “Extra-axial” - external to brain
- Can have dural attachment ("tail")
- Usually benign (no metastasis) and resectable
- Treatment: observation or surgical resection



Dr Paresh K Desai/Wikidoc

Meningioma

- Often asymptomatic
- Tissue compression can cause focal defects or seizures
- Classically affects female more than males
 - Expresses estrogen receptors
- Prior radiation to head is risk factor
 - Childhood malignancies
 - Latency period ~20 years

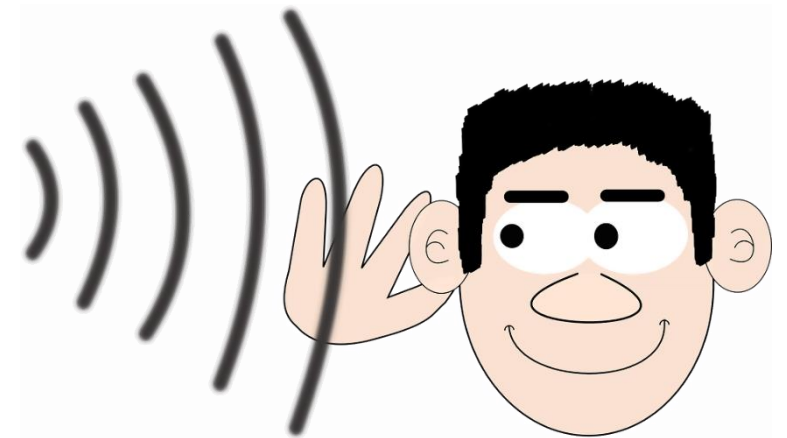


Nephron/Public Domain

Vestibular Schwannoma

Acoustic Neuroma

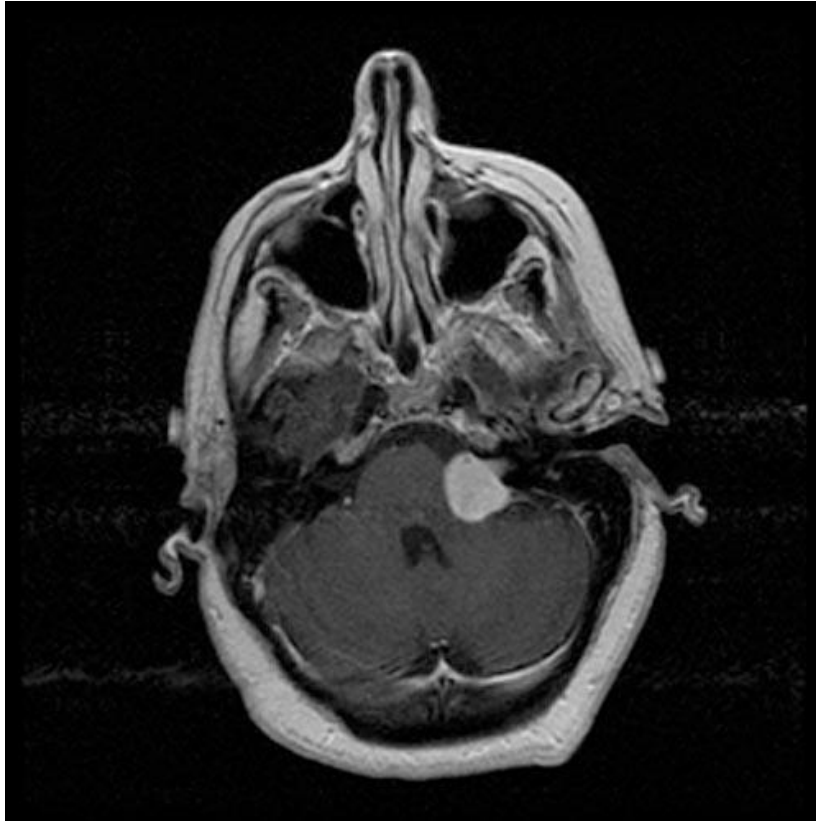
- 3rd most common adult primary brain tumor
- Derives from Schwann cells of PNS
- Occurs at cerebellopontine angle
- Cochlear nerve lesions: **hearing loss, tinnitus**
- Vestibular nerve lesions: **ataxia, rarely vertigo**
- Rarely compresses trigeminal (V) or facial (VII) nerves
 - Facial paralysis or paresthesias
- Treatable with surgery and radiation



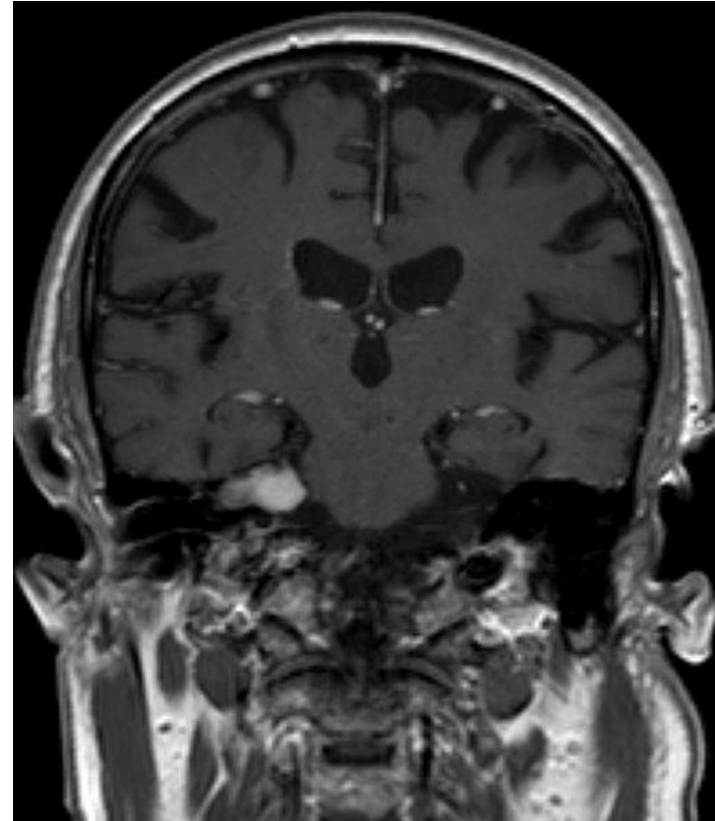
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Vestibular Schwannoma

Acoustic Neuroma



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Neurofibromatosis

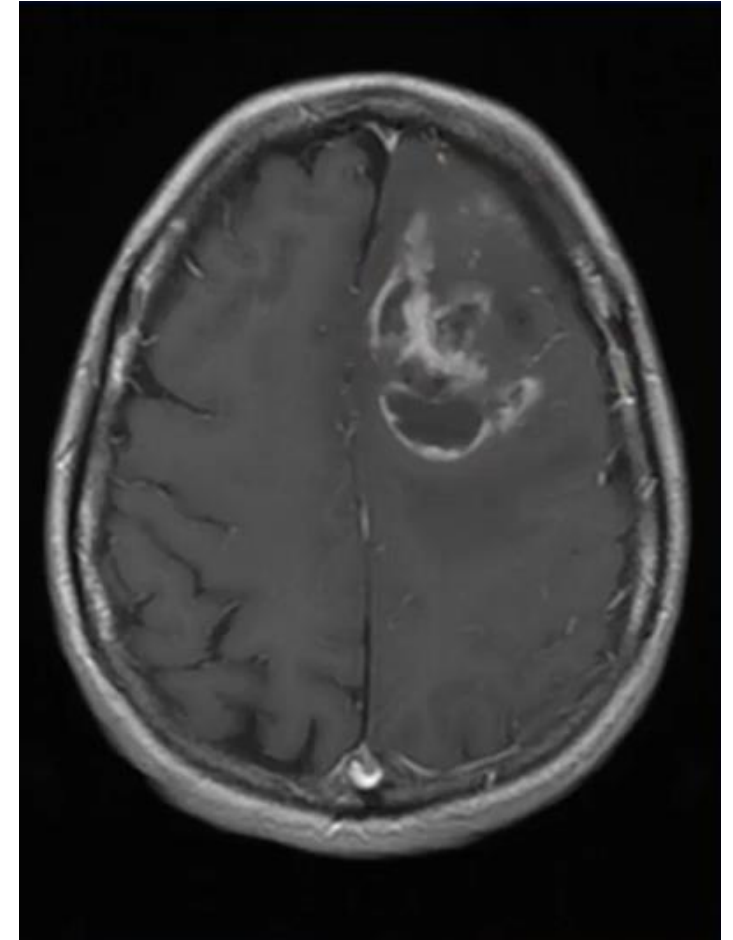
- Neurocutaneous disorder
- Autosomal dominant disease
- Mutation NF1 /NF2 genes
- Neurofibromas
- Type 2 (less common):
 - **Bilateral schwannomas (almost all patients)**
 - **Meningiomas**



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Oligodendroglioma

- Rare, slow-growing tumors of oligodendrocytes
- **Most patients 25 to 45 years old**
- White matter of the cerebral hemispheres
- Usually in frontal lobe
- Most common presenting symptom: **seizure**
- Contrast with glioblastoma
 - Older patient
 - Fast growing
 - Worse prognosis



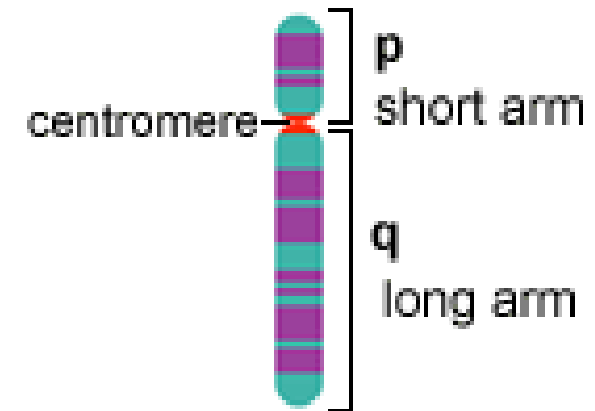
LearnNeuroradiology

Glioma Classification

Glioblastomas and Oligodendrogliomas


- Based on histopathologic appearance and molecular parameters
- **IDH1/IDH2 mutations**
 - Isocitrate dehydrogenase type 1 and type 2
 - Occur in many oligodendrogliomas
 - Associated with good prognosis
- **Deletion of 1p and 19q**
 - Occur in oligodendrogliomas
 - Strong predictor of survival
- Contrast with glioblastomas:
 - Wild type IDH (no mutation)
 - No deletions

Short and Long Arms of a Chromosome



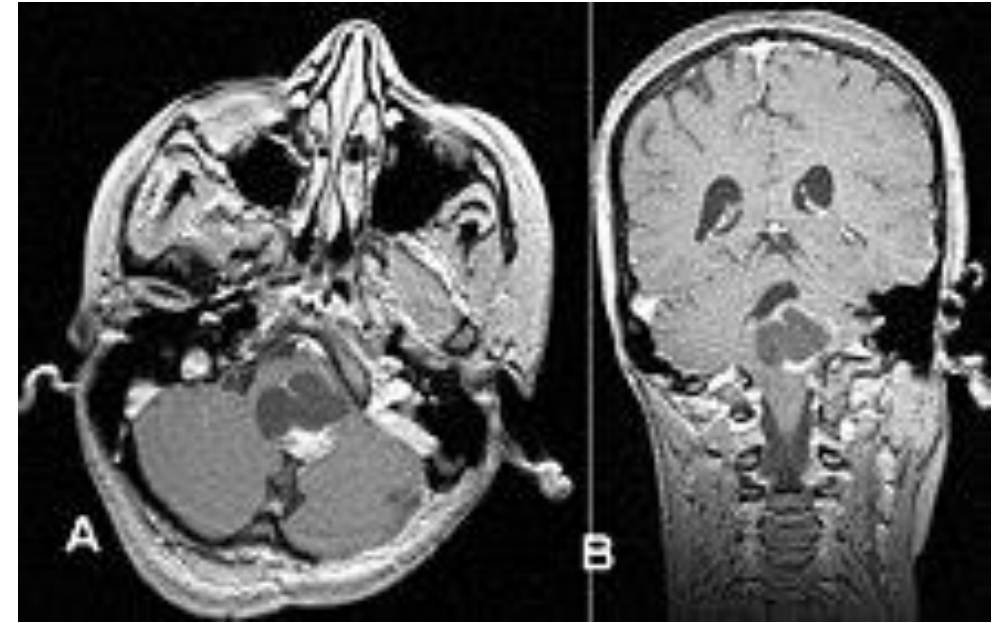
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Childhood CNS Tumors

- Usually infratentorial
 - Often near cerebellum
 - Pilocytic astrocytoma
 - Medulloblastoma
 - Ependymoma
 - Craniopharyngioma
 - Pinealoma
- Cerebellar
- 

Pilocytic Astrocytoma

- Low-grade astrocytoma
- Pilocytic: fiber-like cells
- Usually in posterior fossa (cerebellum)
- Presents with cerebellar dysfunction: **ataxia**
- Usually slow-growing, well-defined
- Often successfully treated with surgery
- Cure rates of 90 to 95%



Wikipedia/Public Domain

Medulloblastoma

- Most common childhood brain tumor
- Highly malignant primary brain tumor
- Usually occurs in children
- Usually occurs in cerebellum
 - Often midline causing **truncal ataxia**
- Treatment: surgery, radiation, chemo
- 75% children survive to adulthood
 - Many with complications of treatment



Medulloblastoma

- Can compress 4th ventricle → hydrocephalus
 - Symptoms of ↑ ICP
 - Headache, nausea, vomiting
- Can spread to CSF
 - Nodules in dura of spinal cord: “drop metastasis”
 - Often occur in lower spinal cord, cauda equina
 - Back pain, focal lesions can occur

Ependymoma

- Ependyma: epithelial lining of ventricles
- Found in brain and the spinal cord
- Often found in 4th ventricle
- Can cause hydrocephalus
- Treatment: surgery and radiation



Hellerhoff

Craniopharyngioma

- Rare supratentorial childhood tumor
- Bimodal age distribution
 - Children 10 - 14 years old
 - Adults 55 – 65 years old
- Suprasellar
 - Sella turcica depression in sphenoid bone

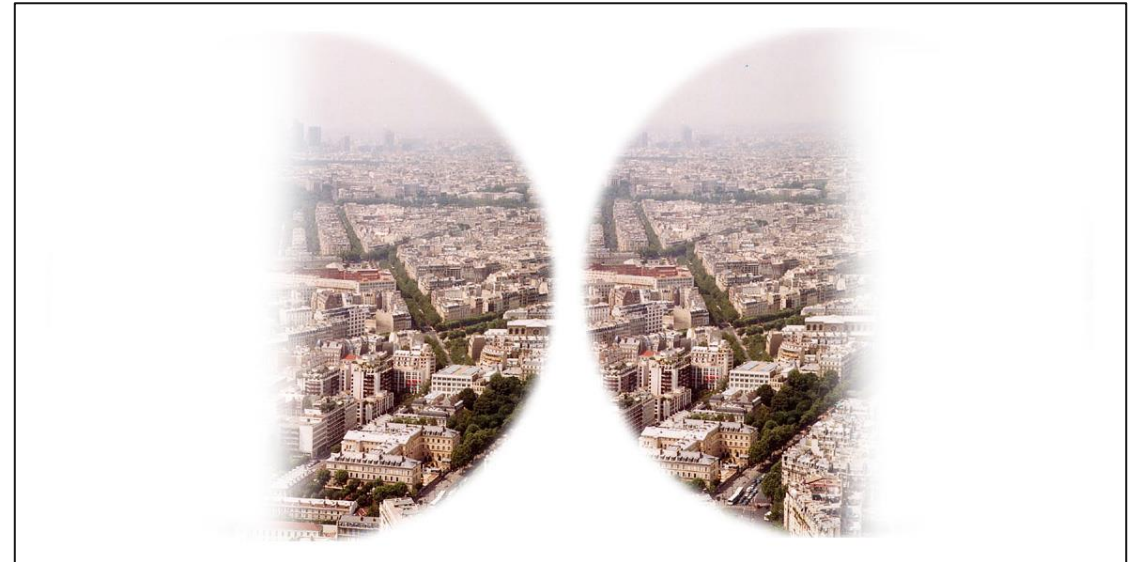


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Craniopharyngioma

- Benign
- Symptoms from compression
- Visual field defects
 - Can compress optic chiasm
 - Bitemporal hemianopsia
- Behavioral change (frontal lobe)
- Pituitary dysfunction
 - Hyperprolactinemia
 - Diabetes insipidus
 - Panhypopituitarism

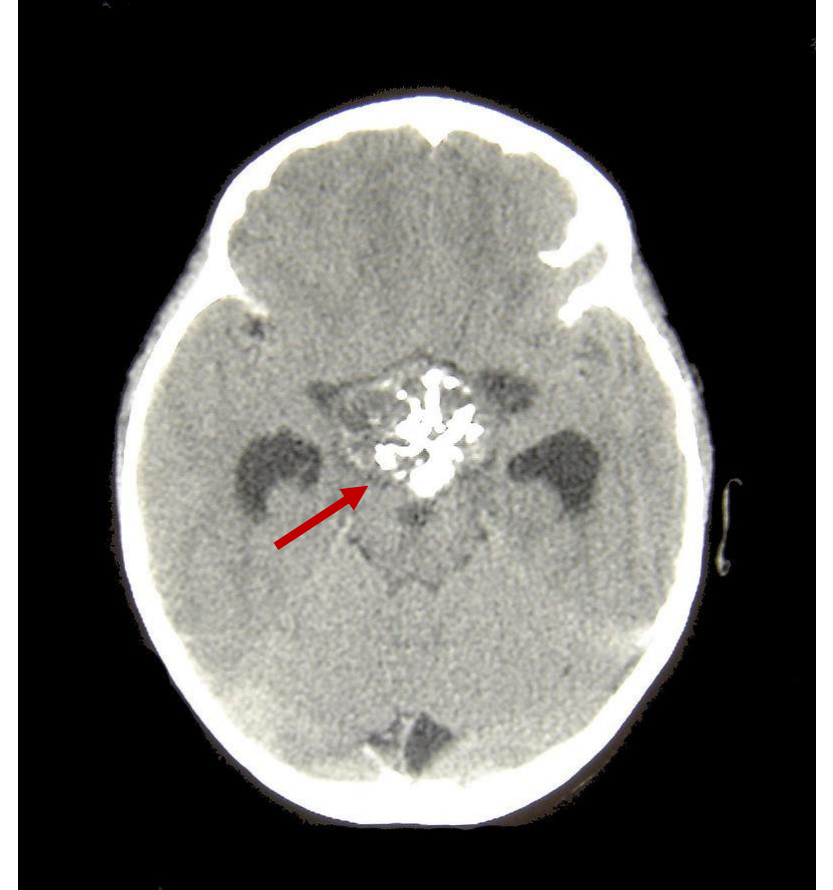
Bitemporal Hemianopsia



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Craniopharyngioma

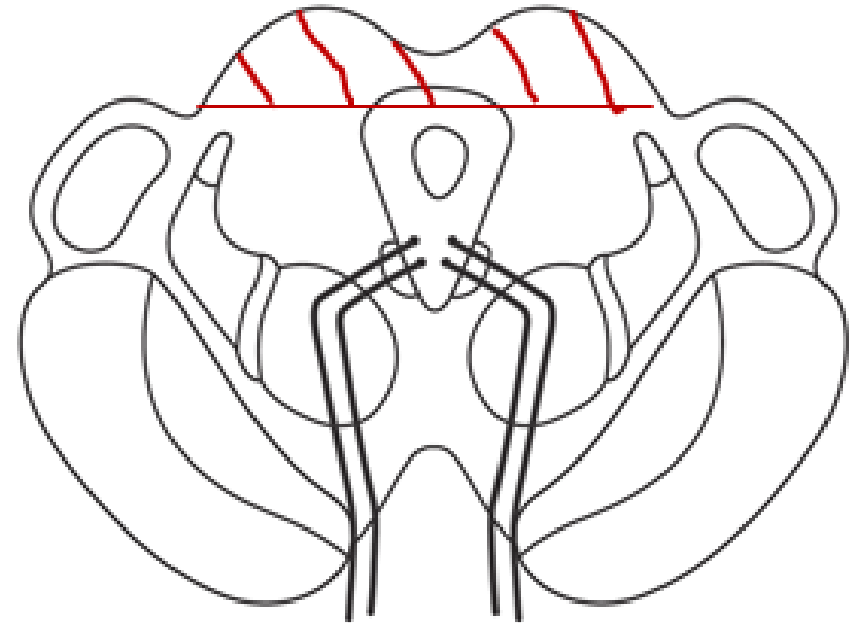
- Derived from remnants of **Rathke's pouch**
 - Invagination of the ectoderm
 - Protrudes from roof of mouth
 - Also forms anterior pituitary
- Often calcified and cystic
- Treatment: surgery plus radiation



Matthew R Garnett

Pinealomas

- Occur in children 1 to 12 years old
- Many types, but often **germ cell tumors**
- Compression **pretectal area of midbrain**
- Cause obstructive hydrocephalus
 - ↑ ICP
 - Headache
 - Nausea/vomiting
 - Papilledema



Pinealomas

- **Parinaud syndrome**
 - Paralysis of upward gaze
 - Pseudo-Argyll-Robertson pupils
 - React to accommodation but not light
- **Can produce β -HCG**
 - May cause precocious puberty
 - Differential for PP includes CNS lesions
- GCTs highly responsive to **radiation therapy**
 - Survival rates > 90% in localized cases



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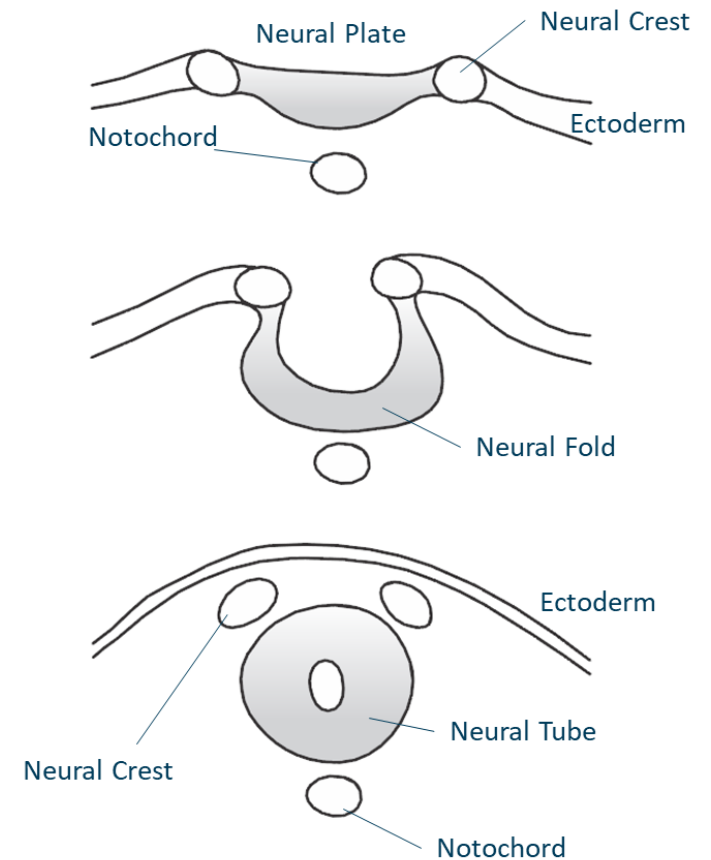
Congenital Neurology

Jason Ryan, MD, MPH

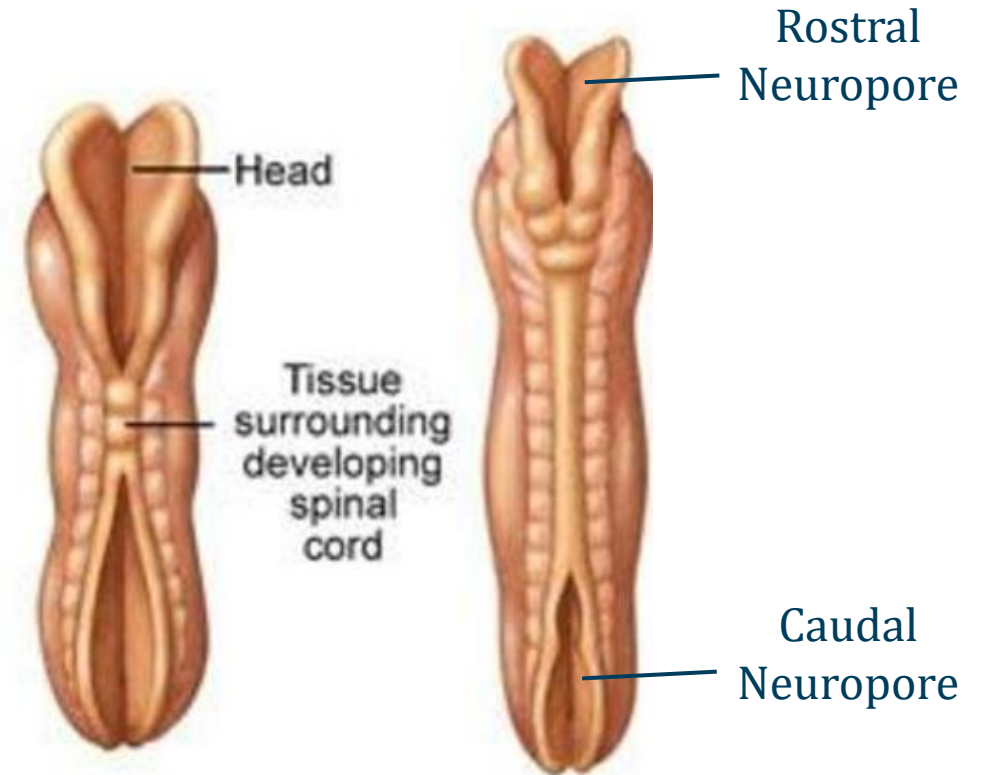
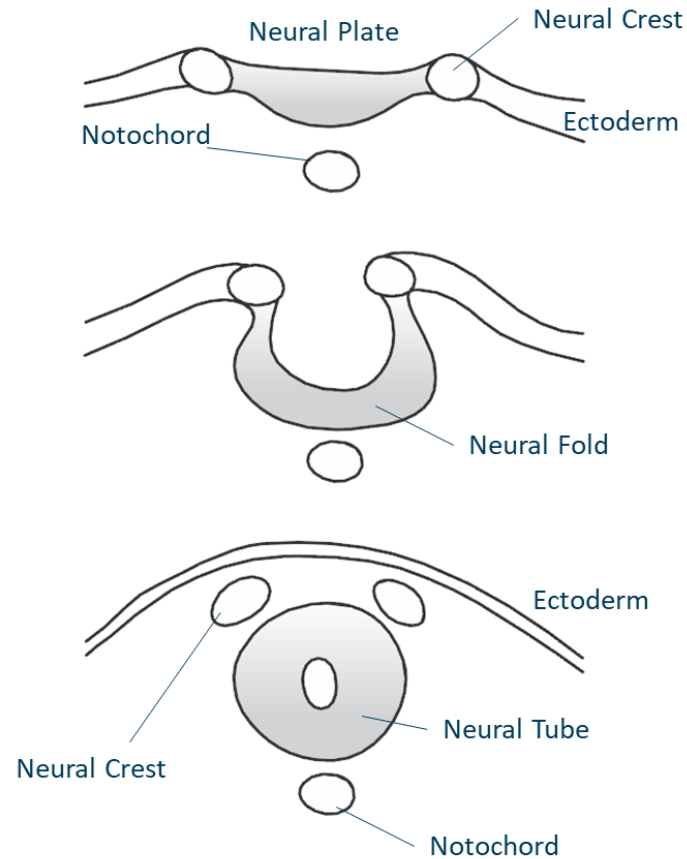


Neural Tube

- Embryonic precursor to central nervous system
- Forms brain and spinal cord
- Begins as neural plate → neural fold
- Neural fold “closes” to form neural tube
- Process complete by 28 weeks gestation
- Neuropores = cranial and caudal open ends of tube
 - Last structures to close
- Failure to close causes **neural tube defect**



Neural Tube



Neural Tube Defects

- **Spina Bifida**
 - Caudal neuropore fails to close posteriorly
 - Bones do not close around spinal cord/meninges
 - Also called spinal dysraphism (dysraphism = incomplete fusion)
- **Anencephaly (“without head”)**
 - Rostral neuropore fails to close anteriorly
 - Absence of major portions brain/skull

Neural Tube Defects

Risk Factors

- **Low folic acid intake** during pregnancy
- **Antiepileptic drugs**
 - Especially valproic acid and carbamazepine
- Folate in pregnancy
 - Normal-risk mothers: 400 mcg/day
 - High-risk mothers: 4mg/day
- High risk conditions:
 - Prior NTD in offspring
 - NTD in either parent
 - Valproate or carbamazepine

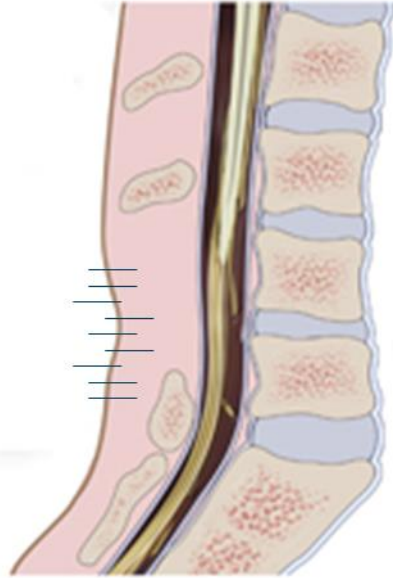


Flickr

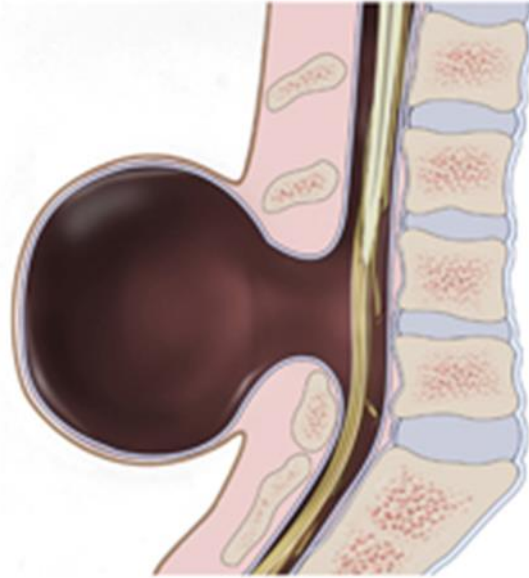


Øyvind Holmstad/Wikipedia

Spina Bifida



Spina bifida occulta
Absent vertebral bodies
No herniation



Meningocele
Herniation of meninges

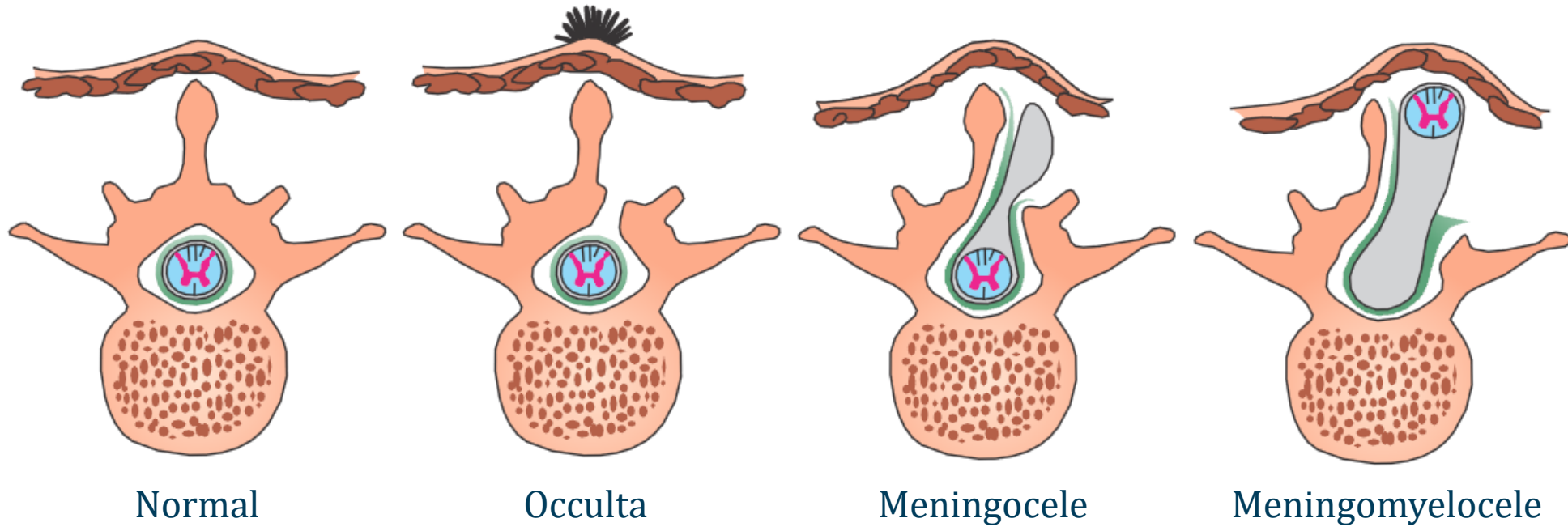


Meningomyelocele
Herniation of meninges
and spinal cord



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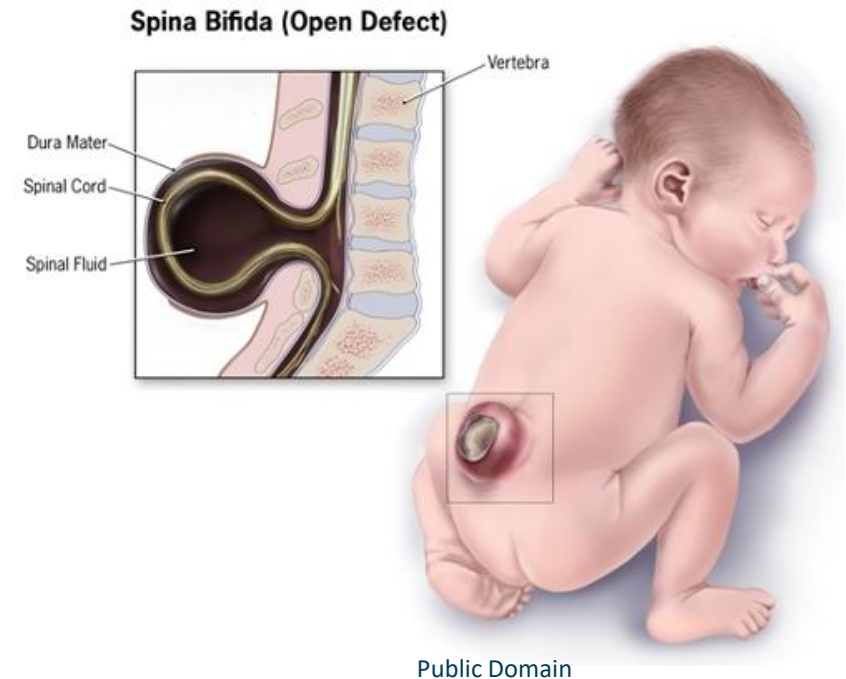
Spina Bifida



Spina Bifida

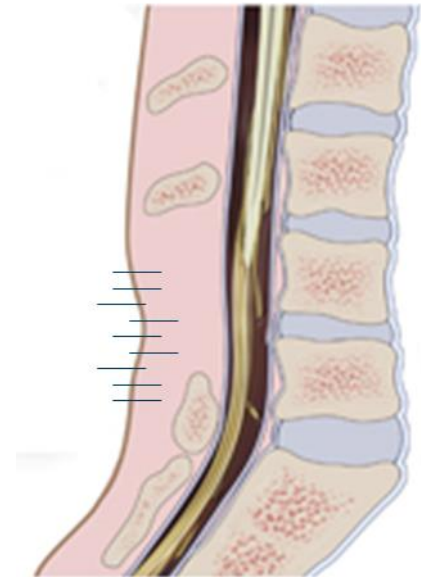
Clinical Features

- May damage spinal cord nerves
- Motor/sensory dysfunction
- Urologic symptoms (e.g. urinary incontinence/retention)
- Treatment: surgery



Spina Bifida Occulta

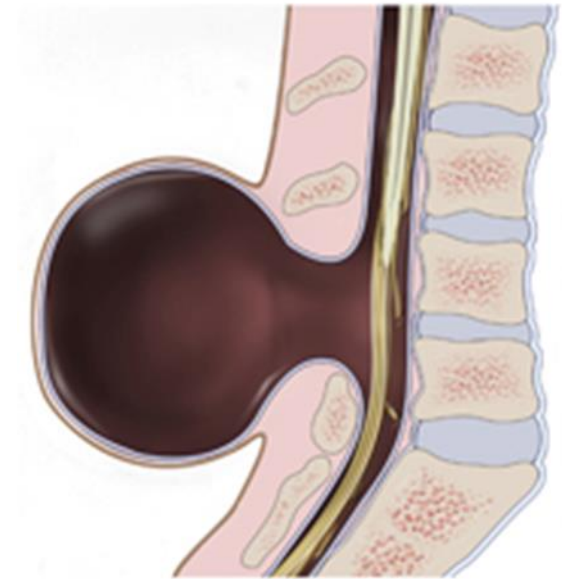
- Failure of fusion of vertebral bodies
- No herniation of meninges or spinal cord
- Often has skin abnormalities: **dimple, tuft of hair**
- Usually asymptomatic
- Can cause neurologic dysfunction
- “Tethered cord syndrome”
 - Cord normally loose in spinal canal
 - Tethered cord does not move
 - Reduces blood flow → nerve damage



Spina bifida occulta
Absent vertebral bodies
No herniation

Meningocele

- Herniation of meninges but not spinal cord
- Least common type of spina bifida
- Usually asymptomatic
- Treatment: surgical repair
- Good prognosis



Meningocele

Herniation of meninges

Meningomyelocele

- Herniation of meninges and spinal cord
- Severe neurologic deficits
- Almost always has **Chiari II malformation**
- Prenatal screening: ↑ AFP
- Prenatal diagnosis: ultrasound
- Treatment: surgery in utero or at birth



Meningomyelocele
Herniation of meninges
and spinal cord



Wolfgang Moroder

Anencephaly

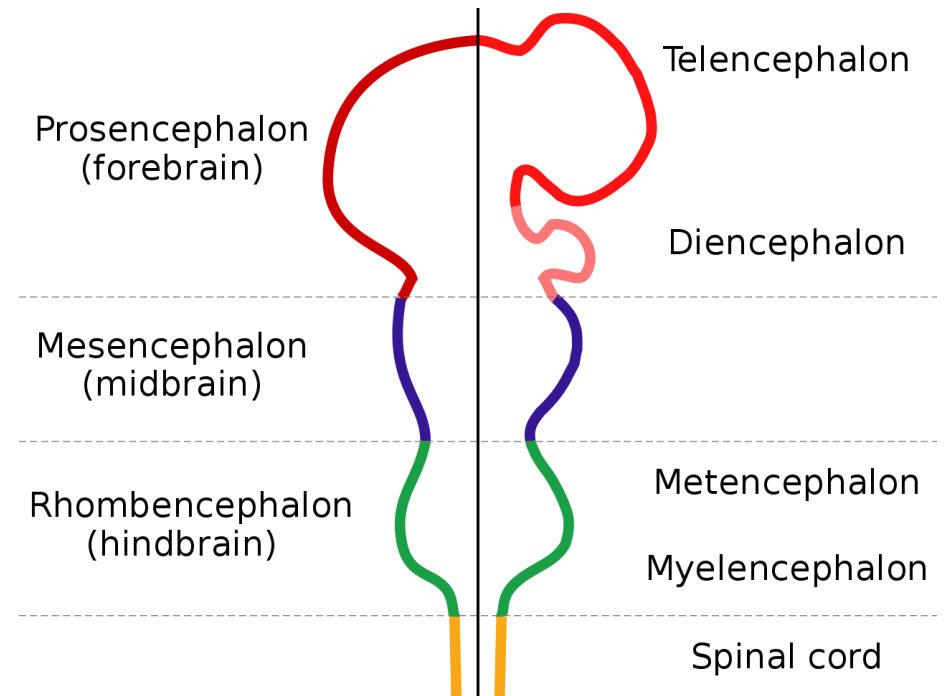
- Rostral neural tube defect
- Forebrain/brainstem exposed in utero
- CNS fails to develop normally
- Not compatible with life
- Stillbirth or death shortly after birth
- Ultrasound:
 - Open calvaria
 - Frog-like appearance of fetus
- Mother will have polyhydramnios
 - Baby can't swallow amniotic fluid normally



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Holoprosencephaly

- Cephalic malformation
- Failure of cleavage of prosencephalon
 - Also called forebrain
 - Includes cerebral hemispheres
- Left/right hemispheres fail to separate
- Associations:
 - Trisomy 13 (Patau syndrome)
 - Trisomy 18 (Edward's syndrome)
 - Fetal alcohol syndrome

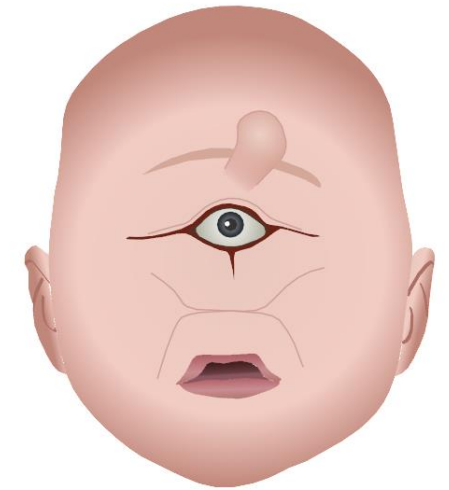


Holoprosencephaly

- Often associated with facial abnormalities:
 - Cleft lip/palate
 - Cyclopia
- Facial defect severity ~ brain defect severity
- Severe defects not compatible with life



Mild
Cleft Lip



Severe
Cyclopia

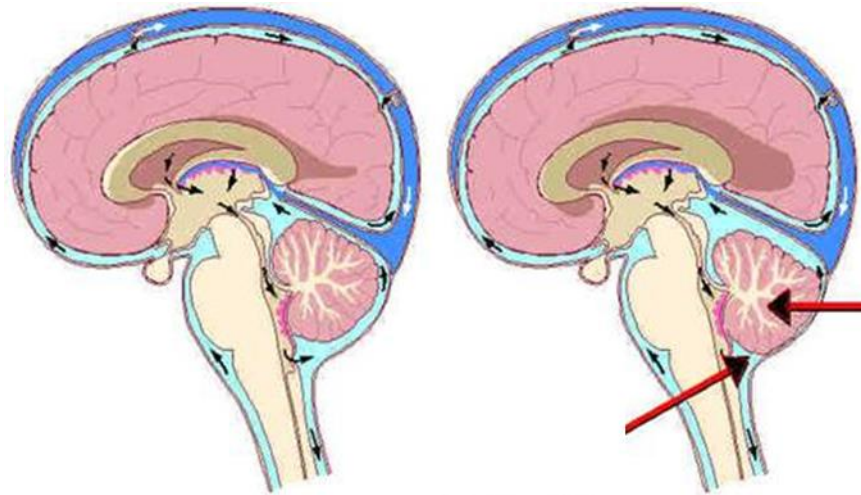
Encephalocele

- Brain or meninges herniate through skull defect
- Least common neural tube defect
- Most common site: occipital bone
- Treatment: surgery



Chiari Malformations

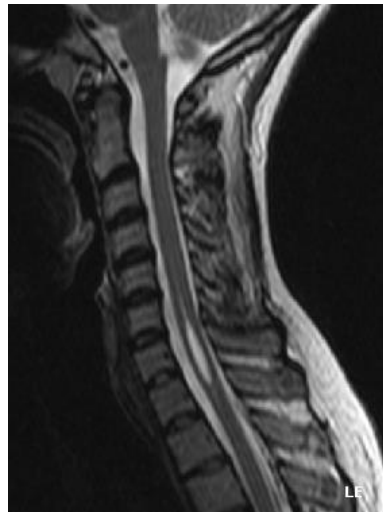
- Anatomic anomalies of cerebellum
- Group of congenital disorders
 - Chiari I through IV
- Downward displacement of cerebellum



Chiari I Malformation

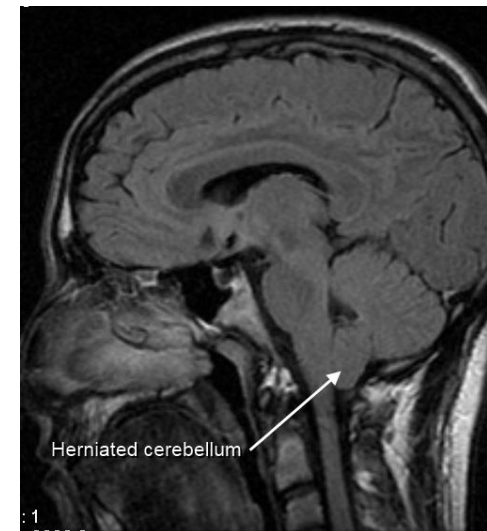
- Abnormal shape of cerebellar tonsils
 - Tonsils = small rounded structure at bottom of cerebellum
- Tonsils displaced below foramen magnum
- Associated with syringomyelia

Syringomyelia



Public Domain

Chiari I



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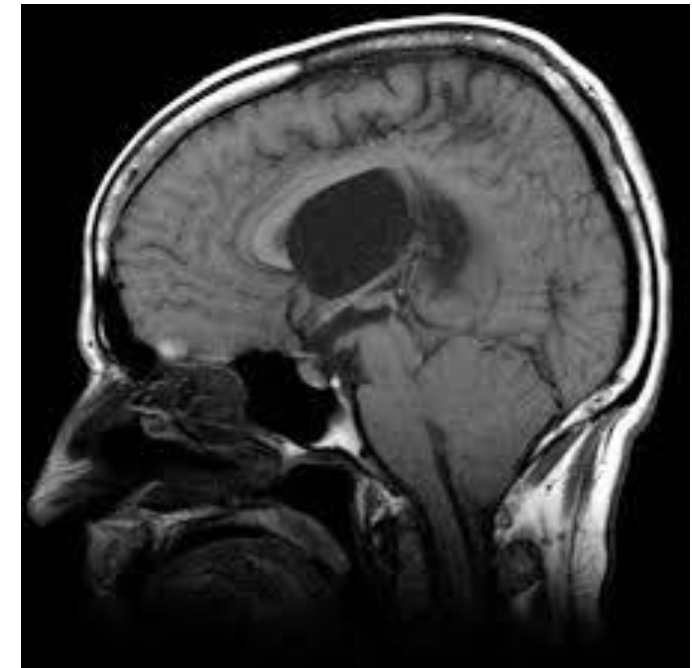
Chiari I Malformation

- Usually no symptoms until adolescence/adulthood
 - Mean age 18 years
- Headaches
 - Due to meningeal irritation
 - Worse with cough: “cough headache”
- Cerebellar dysfunction (ataxia)
- Cranial nerve dysfunction (brainstem compression)

Chiari II Malformation

Arnold-Chiari Malformation

- Downward displacement cerebellar vermis and tonsils
- Through foramen magnum into upper spinal canal
- **Spinal meningocele**
- Almost always occurs with Chiari II
 - Usually detected prenatal/birth
- Almost all cases have **hydrocephalus**



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Chiari II Malformation

Arnold-Chiari Malformation

- **Hydrocephalus in infants**
 - Large head circumference on growth curves
 - Anterior fontanelle distended
 - Sutures widely split
 - Abnormal percussion: “cracked pot” sound or Macewen’s sign
- Myelomeningocele → paralysis below defect



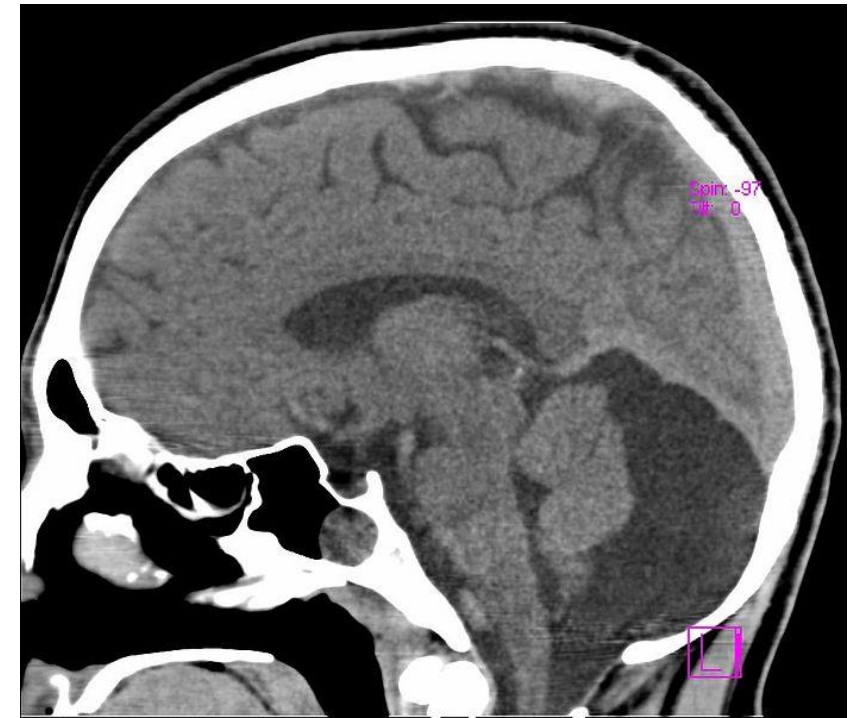
Meningomyelocele

Herniation of meninges
and spinal cord

Dandy Walker Malformation

- Hypoplasia or agenesis of **cerebellar vermis**
- **Enlarged 4th ventricle**
- Cysts of 4th ventricle → hydrocephalus
- Imaging findings:
 - Small cerebellum
 - Dilated 4th ventricle

Dandy Walker Malformation



Public Domain

Dandy Walker Malformation

- Often detected by ultrasound in utero
- Many, many associated symptoms/conditions
 - Heart, facial or limb defects
 - Spinal bifida
- Affected children
 - Hydrocephalus
 - Delayed development
 - Motor dysfunction (crawling, walking)
 - Ataxia

Dandy Walker Malformation

