Functional Neuroanatomy (PP)

- functional systems
  - input
    - general (touch, pin, temp)
    - special (smell, taste, hearing)
  - processing
    - consciousness (alertness)
    - cognition (thinking)
  - output
    - voluntary
    - special (look, breathe, speak)
    - visceral (focus, salivate, urinate)
- neuron organization
  - simple (linear)
    - sensory (primary, secondary, tertiary neurons)
      - 0 - receptor
      - 1 - receptor to relay nucleus
2 - relay nucleus to thalamus
3 - thalamus to cortex

- motor (upper and lower motor neurons)
  - upper - cortex to brainstem or spinal cord
  - lower - brainstem or sc to NMJ
- corticobulbar tract
  - voluntary muscles of face
  - two UMN (one from each hemisphere) innervate LMN
- autonomic (first, second, third order)
  - hypothalamus -> CNS cell body
  - CNS cell body -> PNS cell body
  - PNS cell body -> end organ
  - complex
    - diffusely projecting - small lesion can have multiple effects
    - reciprocal circuits (feedforward and feedback)
    - distributed networks

Regional-Function Neuroanatomy: Brainstem and Cranial Nerves (PP)

- functions
  - conduit for many tracts
  - cranial
  - control
    - midbrain
      - eye movements: vertical gaze and vergence
      - visceral: periaqueductal gray (pain, pleasure)
      - motor: substantia nigra
    - pons
      - eye movements: horizontal gaze center
      - visceral: RAS, locus ceruleus, raphe nuclei (arousal, mood)
    - medulla
      - eye movements: horizontal gaze-holding center
      - visceral: respiratory and cardiovascular centers

- organization
  - front-back
    - ventral: long tracts (motor)
    - intermediate - tegmentum
      - long tracts (sensory)
      - cranial nerve nuclei
      - visceral centers
    - dorsal - tectum
      - CSF, aqueduct
      - colliculi: superior for saccades, inferior for hearing
  - peduncles
    - inferior cerebellar: sc -> cerebellum
    - middle cerebellar: cerebrum -> cerebral peduncles -> pontine nuclei
      - -> cerebellum
    - superior cerebellar: cerebellum -> cerebrum
  - top-bottom
- 2-2-4-4 for CNs - cerebrum, midbrain, pons, medulla
- midbrain
  - CN 3-4
    - control: **vertical gaze** and vergence, substantia nigra
- pons
  - CN 5-8
    - control: **horizontal gaze**, locus ceruleus, raphe nuclei
- medulla
  - CN 9-12
    - control: **gaze-holding**, respiratory/cardio centers
  - medial-lateral
    - **medial** - motor incl. medial longitudinal fasciculus
    - intermediate - visceral
      - special motor nuclei
      - autonomies
    - lateral - sensory
    - lateral medullary stroke
      - aka wallenberg syndrome
      - most common brainstem stroke
      - loss of somatic and visceral sensation
      - no hemiparesis because motor is medial

### Localization in Neurology (PP)

- acute stroke will cause flaccid weakness, so do not associate weakness with LMN dz unless there are also fasciculations and atrophy
- LMN/UMN dz signs

<table>
<thead>
<tr>
<th></th>
<th>LMN</th>
<th>UMN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>acute</td>
<td>chronic</td>
</tr>
<tr>
<td>weakness</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>bulk</td>
<td>normal</td>
<td>atrophic</td>
</tr>
<tr>
<td>tone</td>
<td>flaccid</td>
<td>flaccid</td>
</tr>
<tr>
<td>reflexes</td>
<td>decreased</td>
<td>decreased</td>
</tr>
<tr>
<td>babinski</td>
<td>flexor</td>
<td>flexor</td>
</tr>
<tr>
<td>clonus</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>fasciculations</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>aberrant regeneration</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

- **redudancy**
  - **motor**
    - most motor CNs are redundantly innervated
    - however, cranial nerves VII (below brow) and XII are not redundantly innervated by cerebrum, so cerebral lesions will cause unilateral deficits
  - **sensory**
    - most sensory CNs are not redundantly innervated
    - taste and hearing are redundantly innervated
• cortical somatotopic map (medial -> lateral): legs -> arms -> hands -> face
• crossing
  ◦ crossed: cerebral cortex to outside cerebrum
  ◦ not crossed: cortex to thalamus, brainstem to face or cerebellum, spinal cord to body or cerebellum
• what is the level
  ◦ supratentorial: aphasia, amnesia, agnosia, apraxia, anosmia, anopsia
  ◦ infratentorial: diplopia, dysarthria, dysphagia, dysphonia
  ◦ spinal: breathing, bowel, bladder, broken reflexes
• multiple lesions
  ◦ R hemiparesis and aphasia plus left eye blindness from ICA lesion
  ◦ vertigo, nausea, vomiting + visual field defect from PICA
  ◦ headache, blurred vision, diplopia from hydrocephalus
• timing
  ◦ seconds to hours
    ◦ vascular (eg stroke, TIA)
    ◦ electrical (eg seizure, migraine)
  ◦ days to weeks - infectious and inflammatory
  ◦ months to years - neoplastic and degenerative

Neurotransmitter Disorders in Neurology (PH)

• Glutamate
  ◦ 70% of synapses in brain
  ◦ Excitatory
  ◦ Cannot cross BBB
  ◦ 3 receptors
    ◦ NMDA - Ca and Na activate NOS, NO feeds back on presynaptic neuron making subsequent glutamate release easier
    ◦ AMPA - Na and Ca release causing depolarization
    ◦ Metabotropic - 2nd messengers
  ◦ EAAT: excitatory amino acid transporter
    ◦ major utilizer of energy in brain
    ◦ basis for PET
    ◦ expressed on astrocytes - inside astrocyte, Glu->Gln and can diffuse back into neuron
  ◦ AMPA receptors in postsynaptic membrane are an indicator of synaptic strength
  ◦ Stabilizes remaining synapses via release of trophic factors
• GABA (gamma-aminobutyric acid)
  ◦ Inhibiting
  ◦ Synthesize from Glu by losing a carboxyl group via glutamate decarboxylase
  ◦ 15% of synapses in brain
  ◦ Benzodiazepenes enhance the action of GABA by acting at receptor
  ◦ GABA pump in glial cells stops postsynaptic activation
  ◦ Inhibitory synapses tend to be on axon, whereas excitatory are on axonal processes
  ◦ Cl entry into neuron
• Seizures - imbalance between glutamate and GABA causing multiple activation
• Epilepsy - repeated seizures
• New memories are created by activation of excitatory synapses in the hippocampus
• Long term potentiation (LTP) - more AMPA receptors are expressed at synapse allowing easier depolarization
• Excitotoxicity - hippocampus, cortex, thalamus, cerebellum are susceptible
  ◦ Common causes: stroke, circulatory arrest, hypoxemia, hypoglycemia, trauma, mito. disorders
  ◦ Vicious cycle of Ca flooding in activating NOS and making mitochondria "sick," mitochondria dysfunction helps depolarize membrane allowing more activation
  ◦ Associated with NMDA receptor activation; it is only activated during depolarization+presence of glutamate
• Serotonin (5-HT)
  ◦ All comes from raphe nuclei in the pons
  ◦ SERT (transporter) responsible for reuptake into neuron
  ◦ SSRIs treat depression
  ◦ Involved in migraine headaches and depression
  ◦ Triptans are agonists for treatment of migraine
• Dopamine
  ◦ Mainly in the basal ganglia (caudate and putamen)
  ◦ Degeneration of nigro-striatal pathway is cause of Parkinson's dz
  ◦ Mesolimbic - pathways up to cortex
    • affect mood
    • reward
    • nucleus accumbens and humans
  ◦ cocaine blocks reuptake of dopamine
• Acetylcholine
  ◦ Nucleus basalis degeneration is associated with Alzheimer's
  ◦ Drugs block AChE to maintain excitation

Craniospinal Trauma and Herniation (P)

• injuries
  ◦ basal skull fractures
    • suggest severe trauma
    • sx
      • blood in ear canal
      • leak of CSF through nose
      • bruising behind the ear (Battle's sign)
  ◦ subarachnoid hemorrhage
    • most common consequence of head trauma
    • long-term complication is blockade of CSF circulation and hydrocephalus
  ◦ traumatic hemorrhage
    • more common in elderly due to amyloid deposition
    • site is commonly cerebral white matter
  ◦ axonal shearing occurs in acceleration/deceleration injuries (eg car crash)
  ◦ brain edema
  ◦ herniations
    • uncal, subfalcian, central, tonsilar types
    • commonly compress vasculature
• mechanisms and patterns
  ◦ blows to the head
scalp contusion and skull fracture
sub/epidural hemorrhages
falls
coup injury - brain lesion where head hits the ground (pretty small)
contrecoup injury - brain lesion opposite coup, extensive cortical damage
acceleration/deceleration
automobile and sports injuries
edema, maybe subarachnoid hemorrhage
diffuse axonal injury
long-term changes of brain trauma
chronic subdural hematomas
seizures
those with diffuse axonal injury:
hydrocephalus
brain atrophy
sensory, motor, cognitive, behavioral deficits
impaired CSF flow or reabsorption (normal pressure hydrocephalus)
mentia, gait apraxia, incontinence
spinal cord trauma
most involve compression secondary to vertebral fractures/dislocation
C4-C8 lesions are most common nonfatal spinal injury associated with head trauma
pathology
early - necrosis and hemorrhage that is most sever in center of cord
late
necrotic tissue replaced by cavity
degeneration of spinal pathways
mechanism of injury
first, mechanical disruption of neural membranes
second, ischemia and reperfusion injury, glutamate and Ca induced toxicity
Coma, Persistent Vegetative State, and Brain Death (PP)
domains of consciousness
wakefulness (cortex and medulla) - alertness, arousal, vigilance
awareness
consciousness (cortex)
attention, perception (thalamus)
coma
state of unarousable unresponsiveness
absence of voluntary or purposeful movement
can be expressed quantitatively
Glasgow coma scale
FOUR (full outline of unresponsiveness)
bilateral hemispheric, diencephalic, or brainstem injury
brain death
complete and irreversible loss of all brain activity
must exclude physiologic, metabolic, pharmacologic confounders
- extensive hemispheric or brainstem injury
  - vegetative state
    - arousal without awareness
    - bilateral cortical/thalamic injury with sparing of hypothalamus and brainstem
  - minimally conscious
    - arousal + rudimentary awareness
      - following commands
      - attending to stimuli
      - visual tracking
    - cortical or thalamic injury
  - delirium
    - acute onset of altered mental status
    - changes in level of consciousness
    - many causes
  - locked-in syndrome
    - does not affect consciousness at all
    - quadriplegia and anarthria, can still look up and blink
    - injury from pons or midbrain

**Cerebrovascular Disease (P)**

- blood flow is autoregulated in the brain such that neurons that are more active receive a greater share of blood
- vascular anatomy
  - ACA
    - anterior portion of medial wall of hemispheres
    - motor + sensory leg
    - perforating branches supply anterior caudate and putamen and anterior limb of IC
  - MCA
    - lateral parts of hemispheres, incl. frontal, parietal and temporal lobes
    - motor + sensory face and arms, language and FEFs affected
    - perforating branches supply posterior caudate and putamen, GP, genu and some of posterior IC
  - PCA
    - posterior portion of medial wall of hemispheres + occipital lobe + midbrain
    - perforating branches supply subthalamic nucleus, dorsal thalamus
  - ophthalmic artery is a branch of internal carotid artery
  - basilar artery
    - supplies the midbrain, pons, cerebellum
  - vertebral arteries
    - supply the medulla
  - 2 posterior spinal arteries supply the dorsal columns
  - 1 anterior spinal artery supplies the rest of the cord
- infarction
  - large vessel dz involves any of above
  - small vessel dz typically involves perforating branches, therefore, the deep nuclei (**lacunar infarcts**)
    - common causes
thrombosis from atherosclerosis in carotid - non hemorrhagic
emboli from plaque or heart - hemorrhagic and multiple
  ◦ hypertension increases risk
  ◦ vulnerable cells
    ▪ higher metabolism
      ◦ grey matter
      ◦ pyramidal cells of hippocampus and neocortex
      ◦ purkinje cells of cerebellum
    ▪ watershed areas
  ◦ pathological changes
    ▪ up to 4 hours: normal
    ▪ 4-6 hours: hyperchromatic
    ▪ 12-24 hours: visible grossly and attenuated on CT/MRI
    ▪ 24 hours: edema
    ▪ 1-4 days: necrotic glial cells, some neutrophils, edema, soft and well-demarcated grossly
    ▪ 5-7 days: macrophages and new blood vessels appear
    ▪ 8-14 days: cells pale and ghostly, reactive astrocytes appear, edema resolves, cavity forms

• primary intracranial hemorrhages
  ◦ hypertensive hemorrhage
    ▪ intraparenchymal
      ◦ deep grey matter
      ◦ pons
      ◦ cerebellum
        ▪ causes little necrosis
        ▪ may originate from Charcot-Bouchard aneurysms - microscopic dilatations near branch points of vessels
  ◦ amyloid angiopathy
    ▪ associated with AD
    ▪ relatively superficial, lobar distribution
  ◦ berry aneurysm
    ▪ subarachnoid bleeding and potentially infarcting vasospasm
    ▪ “worst headache of my life”
    ▪ occur at branch points in or near circle of Willis
    ▪ rx by clipping or coils
  ◦ arteriovenous malformation
    ▪ tangled masses of blood vessels
    ▪ subarachnoid and intraparenchymal hemorrhage

Cerebrovascular Disease Pathophysiology and Treatment (PP)

• ischemic stroke
  ◦ infarction from interrupted blood supply
  ◦ focal symptoms lasting > 24 hours
• transient ischemic attack
  ◦ no infarct on imaging
  ◦ ischemia that reverses within 24 hours
• hemorrhagic stroke - bleeding into parenchyma, ventricles, or CSF
• MCA stroke
- contralateral motor and sensory loss
- dysarthria, aphasia (if dominant hemisphere)
- neglect
- contralateral visual loss
- gaze deviation towards lesion

- ACA stroke
  - contralateral weakness of foot and leg
  - sensory loss of foot
  - frontal lobe signs (apathy, cognitive slowing)

- PCA stroke
  - contralateral hemianopsia
  - cognitive impairment

- cerebellar infarcts
  - vertigo, nystagmus
  - gait and limb ataxia
  - falling towards side of lesion

- basilar artery infarcts
  - pontine and midbrain ischemia
  - hemipontine - pure motor hemiparesis
  - bilateral - coma, quadriparesis

- stroke etiology
  - large artery atherosclerosis
    - large vessel TIAs are repetitive, stereotyped
    - carotid artery TIA
      - numbness and weakness of contralateral face and arm
      - aphasia if in dominant hemisphere
      - rx with carotid endarterectomy (removing plaque)
    - intracranial atherosclerosis treated with aspirin or other anti-coag
  - cardioembolic stroke
    - causes - Afib, LV thrombus, endocarditis, valve disorder
    - sx
      - sudden onset
      - maximal deficit at onset
      - commonly MCA territory
    - rx
      - no benefit from immediate anti-coag
      - treated with anti-coag for prevention of recurrence
  - small vessel dz / lacunar stroke
    - lacune in IC or pons - pure motor hemiparesis
    - lacune in thalamus - pure sensory stroke
    - rx
      - antiplatelet - aspirin, clopidogrel, dypiridamole
      - control risk factors - blood pressure, cholesterol, diabetes

- coagulation disorder

- acute stroke rx
  - supportive care
  - BP, glucose, fever control
  - pharmacotherapy
    - antithrombotics - first rule out hemorrhage
      - acute: heparin not helpful as it increases bleeding risk
      - prevention: aspirin or clopidogrel
    - statins
    - thrombolytic - rtPA
    - endovascular - thrombolysis and stenting under investigation
Cerebrovascular Disease: Pupil and Eye Movement Findings (PP)

- anatomy of eye movements
  - midbrain: vertical movement, vergence
  - pons: horizontal movement
  - medulla: gaze-holding
  - MLF connects these eye movement structures
  - saccades
    - generally involve eye-head movements, not eye-only movements
    - requires a pulse and step signal
      - para-pontine reticular formation (PPRF) - horizontal gaze center / "burst generator"
      - some cells act as the gas (excitatory burst neurons), others act as a brake (inhibitory burst neurons), and others act as a clutch (pause neurons)

- horizontal eye movements
  - signal starts in FEF (voluntary) -> saccade center -> contralateral horizontal gaze center
  - must ultimately activate CN 3 in midbrain and CN 6 in pons
  - CN6 nucleus -> travel through MLF -> contralateral CN3
  - cerebral gaze palsy results from lesion to FEF
  - internuclear ophthalmoplegia (INO) - lesion to MLF
    - overcome by convergence

- efferent and afferent pupils
  - anisocoria - asymmetric sized pupils
  - EW nucleus carries parasympathetics
  - 3rd nerve palsy
    - big ptosis, exotropia, dilated pupil
    - berry aneurysm can cause
  - Horner syndrome
    - baby ptosis on side of small pupil
    - carotid dissection can cause
  - relative afferent pupillary defect
    - defects in afferent innervation do not cause anisocoria

Demyelinating Disease (PP)

- Other focal disorders
  - Subacute combined degeneration (SCD) - Vit B12 deficiency leads to peripheral neuropathy and spinal cord syndrome
  - Acute disseminated encephalomyelitis (ADEM) - post-infectious
  - Central pontine myelinolysis (CPM) - rapid correction of [Na]
  - Progressive multifocal leukencephalopathy (PML) - JC virus infection in immunocompromised

- Multiple sclerosis
  - Epidemiology
    - Onset early to middle adult years with lifelong course
    - Most prevalent non-traumatic neurological disease of young and middle-aged
Increased prevalence in temperate higher latitudes
Polygenetic dz + environmental trigger
Three implicated genes: HLA-DR2, IL2, IL7

Presentation
- usually relapsing and remitting (RR, 90%), but also secondary progressive and primary progressive
- demyelination occurs even during remission
- Early - paresthesias, diplopia, urinary urgency, mild weakness
- Later - para/quadri-plegia, dysarthria, impotence, cognitive impairment
- Other - fatigue, seizure, neuralgia

Pathology
- Gross - multiple, irregularly-shaped, sharp-edged plaques; predilection for periventricular area
- LM - loss of perivenous myelin w/lymphocytes; subsequent proliferation of astrocytes and lipid macrophages

Diagnosis
- 2 or more episodes of neurological dysfunction or progression for more than 6 months with no other cause
- MRI - Dawson's fingers, contrast enhancement suggests breakdown of BBB
- CSF - elevated or oligoclonal IgG

Pathogenesis
- autoreactive T cells traffic into CNS
- release cytokines causing further inflammation and demyelination

Treatment
- INF-Beta - antagonizes INF-Gamma
- Glatiramer acetate - looks like myelin and acts as a decoy
- Natalizumab - mab against adhesion molecule critical for T cell migration into CNS
- Immunosuppressives incl. methotrexate, IVIg

Paraneoplastic Neurological Disorders (PP)

Examples of PND
- Cachexia
- Hypercalcemia
- Cushing's syndrome
- Trousseau's syndrome - hypercoagulability

Neurological syndromes
- CNS
  - Limbic encephalitis - memory deficits
  - Subacute cerebellar degeneration - ataxia
- PNS
  - Subacute sensory neuronopathy
- NMJ
  - Lambert-Eaton myasthenic syndrome - fatigue, muscle weakness

PND Pathogenesis
- Autoimmune attack on NS resulting from production of Abs against cancer
- Commonly from SCLC, thymoma, testicular, ovarian, breast cancers
- Effect of Ab may be immune destruction of tissue or functional effect
- Thymomas are associated with myasthenia gravis
• Diagnosis - involves suspicion of cancer with PND symptoms and demonstration of onconeural Abs
• Treatment
  ◦ surgical resection of cancer
  ◦ treatment of immune mechanism - steroids, plasma exchange, IVIg, immunosuppression, rituximab
  ◦ treat secondary problems

CNS Infections (PP)

• lumbar puncture

<table>
<thead>
<tr>
<th></th>
<th>pressure</th>
<th>cells</th>
<th>protein</th>
<th>sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>viral meningitis</td>
<td>normal</td>
<td>lymphocytes</td>
<td>+</td>
<td>normal</td>
</tr>
<tr>
<td>bacterial meningitis</td>
<td>normal or +</td>
<td>PMN</td>
<td>++</td>
<td>---</td>
</tr>
<tr>
<td>subacute meningitis</td>
<td>normal</td>
<td>lymphocytes</td>
<td>++</td>
<td>normal to -</td>
</tr>
</tbody>
</table>

• causes
  ◦ Gm-'s in neonates
  ◦ neisseria, strep pneumo in adults
  ◦ enteroviruses
  ◦ lack of immune defenses in CNS leads to rapid spread
  ◦ sx - headache, fever, nuchal rigidity
  ◦ dx - lumbar puncture except when
    ◦ > 60 yo, immunocompromised
    ◦ abnormal consciousness or focal findings
  ◦ rx
    ◦ community-acquired: cefotaxime + vanco
    ◦ high death rate even with rx
    ◦ most viral forms are self-limited (not herpes simplex though)
  ◦ chronic variety
    ◦ lasts 4 weeks or more
    ◦ may also present with seizures, dementia
    ◦ TB in HIV-infected is a cause

• infx of brain parenchyma
  ◦ bacterial abscess
    ◦ mixed flora of aerobic and anaerobic bacteria (strep, staph, enterobacteria, and bacteroides are common)
    ◦ sx - headache, focal signs, seizures
    ◦ dx - enhancing rim on MRI
    ◦ rx - Abx and drainage
    ◦ spinal abscesses are medical emergencies and can develop in diabetics and drug users
  ◦ encephalitis
    ◦ commonly caused by viruses
    ◦ pathogenesis
      ◦ HSV - retrograde travel from ganglia
      ◦ arbovirus - travels through blood from arthropod bite
    ◦ sx
- fever, headache
- nausea, vomiting
- seizures
- dx - CSF PCR, **early diagnosis of HSV is essential since it is treatable**
- rx - **acyclovir for HSV**

- infx in immunocompromised
  - cryptococcal meningitis
    - neck stiffness uncommon
    - elevated intracranial pressure from obstruction of CSF flow
  - cerebral toxoplasmosis
    - necrotic multifocal abscesses appear as ring-enhancing lesions on CT
  - primary CNS lymphoma
    - EBV
    - progressive neurological deterioration
  - progressive multifocal leukencephalopathy
    - JC virus
    - dx is multiple asymmetric areas on MRI
    - sx - hemiparesis, hemianopsia, aphasia, ataxia
  - listeria monocytogenes
  - CMV encephalitis
    - focal signs and meningismus uncommon
    - dx with PCR

- chronic infxs
  - spirochetes
    - syphilis
      - dx with RPR
      - rx with IV PCN
    - lyme dz
  - retroviruses
    - HIV-associated dementia
      - progressive subcortical dementia
      - rare if CD4 > 500
    - CJD - presents later in life as a progressive dementia
    - vCJD - young adults present with behavioral changes

---

**Tumors of the Brain, Spinal Cord, and Meninges (P)**

- **Meningioma**
  - Well-circumscribed, often non-invasive, attached to dura
  - Originate from normal whor cells in arachnoid layer
  - Characteristic calcifications in center of whorls called psammoma bodies
  - Usually no known etiology, but can result from radiation therapy
  - Associated with neurofibromatosis, particularly NF2 mutation
  - Cytogenetics - loss of chromosome 22
  - Radiology - "dural tails"
  - Can invade bone or brain
  - Generally affects middle-aged females
- **Glioblastoma (astrocytoma)**
Question of whether astrocyte undergoes neoplastic change of if they arise from stem cells
- Immunohistochemistry for GFAP
- Radiology - Large masses with necrotic center and ring-enhancing under contrast
- Intraaxial, infiltrating, non-resectable, with mass effect, affecting brain parenchyma
- High grade ones are hemorrhagic with neovascularization
- Generally affects middle-aged males
- May originate from radiation
- Multiforme - great variations in histology
- Pseudopalisading (cells line up around necrotic center) and vascular proliferation
- Usually presents with headache
- Metastasis rare, but can go to liver

- Medulloblastoma
  - Arises from external granular cells in cerebellum due to high prolif. rate
  - Histology
    - sometimes densely cellular, unstructured
    - other times neuroblastic rosettes
    - may be nodular (desmoplastic)
  - May seed in the CSF and affect spinal cord
  - Treatment - chemo and radiation to neuraxis

**Dangerous Causes of Headaches (PP)**

- Cephalalgias - pains in the head, face, ears, eyes, nose, throat, etc.
- Primary
  - no disease other than the headache
  - migraine, tension, cluster, etc.
  - central pain systems - 5th nucleus, periaqueductal gray, thalamus
- Secondary
  - caused by something else
  - meningitis, brain tumor, aneurysm
  - stimulation of peripheral pain systems - nociceptors
- Referred pain patterns mean that where the pain is does not correspond to where the pathology is
- Dangerous headaches
  - **Systemic Disease** - malignancy, AIDS
  - **Neurologic Symptoms** - altered mental status, diplopia, NOT visual aura
  - **Onset** sudden
  - **Older** than 50 years
  - **Pattern change**
- Rules of thumb
  - Persistent headaches may be bad
  - Abrupt-onset headaches are often bad
  - w/fever are usually bad
  - w/diplopia are almost always bad
  - with change in mental status are always bad (not migraine)
- Headache is not common presentation for brain tumor, but may be a concern in the case of raised ICP
• **DATA CAN save lives** (these are Threatening, Time-Dependent, Treatable, and Tricky)

  ◦ Dissection of the carotid or vertebral arteries
    • any age
    • ~50% h/o trauma
    • frontal headache
    • Horner's syndrome
    • TIAs (dizziness) and pain
    • 50% stroke rate within 90 days
    • Diagnose by angiography
    • Treat with anticoagulation

  ◦ Arteritis (giant cell, aka temporal arteritis)
    • most older than 65
    • gradual onset headache
    • associated with fatigue, fever, weight loss, arthralgias
    • jaw claudication
    • risk of permanent visual loss
    • Diagnose by ESR/CRP or temporal artery biopsy
    • Treat with steroids

  ◦ Thrombosis of the dural venous sinuses
    • any age
    • gradual or abrupt onset
    • when lying flat (increased ICP)
    • pulsatile tinnitus
    • lose venous pulsations and papilledema
    • hypercoagulable
    • 50% stroke rate within 1 month
    • Diagnose by LP, venography
    • Treat by anticoagulation

  ◦ Aneurysm
    • any age, more common over age 40
    • rapid onset with association with exertion
    • neck stiffness, photophobia
    • diplopia
    • may be no neurological findings
    • Diagnose with CT then LP then angiography
    • Treat with surgical clip or endovascular occlusion

  ◦ Carbon monoxide
    • dizziness, lethargic, lightheaded
    • diagnose with CO detectors and COHb levels

  ◦ Colloid cyst of the 3rd ventricle
    • any age
    • intermittent, severe, abrupt-onset, brief
    • bifrontal location
    • may be relieved by lying down (acts like ball valve)
    • associated with syncope
    • Diagnose with CT or MRI
    • Treat with surgery

  ◦ Angle closure glaucoma
    • any age, some drugs
    • more common in Eskimos and Chinese
    • often darkness is trigger
    • blurred vision (cloudy cornea), red eye
    • untreated can go blind
- Diagnose with gonioscopy
- Treat with iridotomy

- Angina
  - referred pain patterns to head, may be no chest pain
  - Diagnose with EKG, stress test, angiography
  - Treat with CABG

- Norepinephrine neoplasm (pheochromocytoma)
  - any age with peak at middle age
  - episodic, abrupt onset
  - palpitations, dizziness, sweating
  - hypertension, tremors
  - Can cause MI, stroke, death
  - Diagnose with plasma free metanephrines
  - Treat with surgical resection

- Only colloid cyst may be excluded by CT scan

- I's
  - Infections
  - ICP - hydrocephalus, high altitude, hypertension
  - Infarcted pituitary

- Categorizing headaches
  - Episodic
    - Benign (most) - migraines
    - Dangerous (A CAN)
  - Continuous
    - Benign (most) - med overuse
    - Dangerous - meningitis (DAT, I3)

<table>
<thead>
<tr>
<th>Episodic</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aneurysm</td>
<td>Dissection</td>
</tr>
<tr>
<td>CO</td>
<td>Arteritis</td>
</tr>
<tr>
<td>Colloid cyst</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>Angle closure</td>
<td>Infections</td>
</tr>
<tr>
<td>Angina</td>
<td>ICP</td>
</tr>
<tr>
<td>Norepinephrine neoplasm</td>
<td>Infarcted pituitary</td>
</tr>
</tbody>
</table>

**Migraine and Other Primary Headaches (PP)**

- Migraine
  - Chronic disorder of hyperexcitable brain function with recurring "sick headaches"
  - Last 4 - 72 hours
  - Epidemiology
    - F > M, 13% population
    - peak prevalence 25-55
    - 90% of patients with chief complaint of intermittent headache have migraine
- Migraine causes most "sinus" headaches and thunderclap headache
  - Presentation - recurring with
    - Severity
    - UniLateral
    - Throbbing
    - Activity causes worsening
    - Nausea
    - Sensitivity to light/sound
  - Pathogenesis (multiple related mechanisms)
    - Trigeminocervical complex (TGC) believed to be responsible for generating headache
    - Cortical spreading depression
      - slow-moving, cell-cell propagated wave of electrochemical activity that may initiate migraine and are probably responsible for auras
      - opens BBB
    - Pain
      1. Trigeminal sensory neurons activated, release CGRP and inflammatory factors
      2. Mast cell activation and more inflammation
      3. Vasodilation + edema + leakage of plasma protein
      4. TGN nociceptors activated -> Trigeminal nucleus caudalis -> thalamus -> PAIN
      5. Peripheral sensitization -> central sensitization and hyperactivity -> involvement of other brain systems (Photophobia, nausea, etc.)
  - Genetics
    - rare single gene mutations (hyperexcitable channelopathies)
    - caucasian > AfAm
    - high concordance with family members
  - Treatment
    - Acute
      - Triptans
        - serotonin agonists
        - reverse vasodilation and block neurogenic inflammation
        - Calcitonin Gene Related Peptide antagonists (see pathophys above)
    - Preventive
      - Common aggravators - menstruation, alcohol, lack of sleep, stress
      - Can modify threshold through avoiding aggravators or medication
      - Halt an aura with TMS
  - Cluster Headache
    - Epidemiology
      - Rare, onset in teens
      - smoking a risk factor
      - alcohol can trigger
    - Presentation
      - rapid onset, relatively short duration, usually unilateral
      - Multiple attacks per day, then remission, often seasonal
      - May become chronic (no remissions)
"suicide headaches" - very painful with high sympathetic activation (people do stupid things)

- Pathogenesis
  - Posterior-inferior hypothalamus and cranial parasympathetic activation (vasoactive intestinal peptide)
  - Internal carotid artery swelling affects sympathetic outflow

- Treatment
  - acute: O2, serotonin agonists
  - preventative: Verapamil, anticonvulsants, lithium
  - Hallucinogens
  - Deep brain stimulation?

- Tension-type
  - Epidemiology
    - very prevalent
    - mild
  - Presentation
    - no nausea/vomiting
    - bilateral, no measurable muscle tension
    - usually no photo/phonophobia
  - Treatment - NSAIDs, acetaminophen
  - Pathogenesis poorly understood

Vertigo and the Pathphysiology of Bedside Vestibular Eye Signs (PP)

- Anatomy - "labyrinth"
  - 3 semicircular canals - angular movements
    - anterior canal - 45 degrees medial to lateral from dorsal to ventral, perpendicular to the floor
    - horizontal canal - mostly parallel to floor
    - posterior canal - 45 degrees lateral to medial from dorsal to ventral, perpendicular to the floor
  - Otolith organs - linear movements
  - VOR reflex - vestibular nuclei connected to oculomotor nuclei -> 3rd and 4th move the eyes vertically, 6th and 3rd move the eye horizontally

- Normal physiology
  - Movement of endolymph causes neuronal firing
  - Head impulse - move head quickly and see if fixation is maintained
  - Otolith-ocular reflect
    - vestige of when we were lateral-eyed animals
    - inhibited by cerebellum
  - Gaze holding center
    - natural resting position of eyeballs is straight ahead
    - requires EOM force to keep eyes eccentric
    - force generated by gaze holding center and calibrated by the cerebellum

- Vestibular system defects
  - Symptoms
    - Dizziness - broken balance system, ears tell you one thing and brain another
- non-vestibular DDx of dizziness - orthostatic, cardiac, intoxication, post-concussive, panic attack
- vestibular DDx of dizziness - vestibular neuritis, brainstem/cerebellar stroke, migraine, bilateral vestibulopathy, BPPV

- Vertigo
  - hallucination of head movement
  - implies asymmetry
  - motion intolerance, nausea/vomiting, bouncing vision, diplopia, unsteady walking

- Signs
  - Nystagmus - from Greek, movement of someone dozing
    - pendular
      - slow oscillation
      - rare, usually congenital
    - jerk
      - slow movement, fast restore
      - common among dizzy patients
      - vestibular lesions or gaze-holding deficits
  - abnormal VOR response, ataxic gait and tendency to fall

- Pathophysiology of jerk nystagmus
  - Vestibular
    - slow phase is the pathologic manifestation of vestibular asymmetry
    - quick phase is reset of cerebrum's desire to maintain eyes straight ahead
    - tonic asymmetry produces perpetual slow phase drift
    - never changes direction
  - Gaze-holding nystagmus
    - slow movement towards natural eye position is pathology of gaze-holding center
    - jerk back the other way as a reset
    - centripetal drift, no asymmetry
    - changes directions
  - Can be mixed type as well

- Neuritis vs. Stroke (peripheral vs. central)
  - both present with acute vestibular syndrome - dizziness/vertigo, nausea/vomiting
  - Stroke
    - brainstem or cerebellum
    - usually AICA or PICA since inferior cerebellum is vestibulocerebellum
  - Main difference is based on physical exam of eyes - 1 of the signs positive
    - Head Impulse Test
      - abnormal in neuritis, normal in stroke
      - pathway skips the cerebellum
      - but it does travel through medulla
    - Skew deviation
      - tests otolith-ocular reflexes
      - damage to cerebellum prevents cerebellar suppression
      - look for vertical separation of eyes when one is covered
  - Nystagmus
- superimposition of vestibular and gaze-holding nystagmus
- Alexander's law
  - nystagmus that is worse in direction of fast phase, better in direction of slow phase
  - not obeyed in case of stroke

**Gait Disorders and Ataxis (PP)**

- Myelopathic gait - "runway model"
  - UMN pathology
  - both legs cross due to increased adductor tone (scissoring gait)
  - steps are short (shuffling)
  - step height reduced (scuffing)
- Hemiplegic gait
  - leg swings outward because ankle is plantar flexed
  - knee may hyperextend
- Neuropathic gait
  - excessive knee flexion for clearance
  - hyperextension in stance
  - steppage gait
  - foot slap
- Cerebellar ataxic gait
  - wide-based
  - trunk sway
  - irregular stepping and foot placement
- Ataxia
  - incoordination of limbs
  - mechanisms - inborn errors, nutritional, channelopathy, DNA repair, immune, PND, histone acetylation, anticipation (dependent on number of copy repeats, spinocerebellar ataxia, SCA)
  - workup
    - thyroid function tests
    - B12, magnesium, vitamin E, thiamine
    - test for gluten sensitivity
    - thyroglobulin, antineuronal Abs
    - nucleotide repeats for autosomal dominant SCAs

**Neuromuscular Disorders I (PP)**

- radiculopathy - disease of nerve root as it exits spinal cord
- myelopathy - disease of the spinal cord
- Amyotrophic lateral sclerosis
  - neuronopathy
  - Presentation
    - upper motor neuron signs
      - brisk jaw reflex, brisk gag reflex
      - pseudobulbar features (emotional lability with easy laughter or crying)
      - hyperreflexia, Babinski sign
      - spasticity
- lower motor neuron signs
  - weakness
  - atrophy
  - fasciculations
  - combination of acute and chronic denervation as determined by EMG
- sensation is normal
- autonomic functions spared
- no visual system involvement
- progression to other muscles in the same region

- Spinal muscular atrophy
  - deletion of SMN1 gene - role in RNA splicing
  - Presentation
    - infant weakness ("floppy baby")
    - poor feeding, respiratory insufficiency
    - spares muscles of eyes and face
    - lower motor neuron disorder - lose reflexes
    - poor intellect

- Spinal radiculopathy - localized findings

- Disorders of the peripheral nerve
  - axon degeneration
  - demyelination
  - sensory neuronopathy (DRG)
  - paraneoplastic

- Myasthenia gravis
  - affects neuromuscular junction
  - simplified NMJ as a result of loss of receptors from Ab destruction
  - Presentation
    - fatigue following exertion
    - **diplopia** (distinguishes from ALS, but can have MG without it), dysarthria, dysphagia, dyspnea
    - proximal weakness
  - Diagnosis
    - 85% with anti-AChR Abs
    - administration of edophonium - an AChE inhibitor that results in increased Ach in cleft and transient improvement of symptoms
    - repetitive nerve stimulation
    - single fiber EMG
  - Treatment
    - suppress the immune system - steroids, IVIG
    - plasmapheresis
    - AchE inhibitors

- Polymyositis
  - inflammatory myopathy
  - T-cell mediated (CD8>CD4)
  - usually older than 20 yo
  - Presentation
    - dysphagia
    - elevated CK
    - small increase in incidence of malignancy
    - interstitial lung disease

- Dermatomyositis
  - affects blood vessels
  - CD4 and macrophages > CD8
Presentation
- similar to polymyositis
- heliotrope rash - nondescript facial or shawl-type rash
- Groton’s papules (knuckles)

Inclusion body myositis
- affects men over 50
- weakness of wrist flexors and quadriceps
- refractory to corticosteroid therapy (ie they won't work)

Duchenne muscular dystrophy
- Onset in first decade
- calf pseudohypertrophy
- proximal muscle weakness
- cardiomyopathy

Muscular Dystrophy and Targeted Molecular Therapeutics (PP)

- muscular dystrophy - hereditary disease of muscle with progressive weakness and wasting
- heterogenous group of disorders
- function of basal lamina-cytoskeletal link
  - structural stability
  - signal transduction
- Common features
  - absence or altered function of muscle fiber structural component
  - dystrophic changes - rounds of necrosis, degen, and regen with remodeling and fatty infiltration
  - many due to disruption of basal lamina-cytoskeletal link
- Duchenne muscular dystrophy
  - x-linked mutation in dystrophin
    - largest in human genome
    - subsarcolemmal protein
    - breakage in cytoskeletal link
    - 30% new mutations
    - Becker muscular dystrophy - milder phenotype that results from mutation that preserves reading frame and protein-protein interactions
  - Diagnose by lack of dystrophin on immunohistochemistry
  - Gower’s maneuver - way of getting up from the ground without using hip flexors
- limb girdle muscular dystrophies
  - sx
    - hip and shoulder girdle weakness
    - early onset, rapidly progressive
    - cardiomyopathy
  - mutations in structural proteins
  - most autosomal recessive
  - eg sacroglycanopathy
  - phenotype/genotype heterogeneity
    - fukutin-related protein mutations
      - LGMD2I - adult onset
- MCD1C - congenital
- facioscapulohumeral muscular dystrophy
  - one of the most common adult musc. dys
  - autosomal dominant
  - deletion in telomeric region of chromosome 4q
  - sx - variable severity
    - sloping shoulders
    - scapular winging
    - loss of ambulation
- myotonic muscular dystrophy
  - one of the most common adult musc. dys.
  - cognitive, ophthalmologic, cardiac, GI involvement
  - myotonic face - long face
  - trinucleotide repeat disorder (anticipation)
- rx
  - maintaining muscle strength - exercise, prednisone
  - reduce cardiac load
  - pulmonary management - PEEP

### Pathology of Neurodegenerative Disease (P)
- Alzheimer Dz
  - most common neurodegen dz and cause of dementia
  - slowly progressive course with early memory loss
  - loss of cortical fnacs
  - Epidemiology
    - elderly
    - women
    - ~5-10 yr survival
  - Pathology
    - Gross findings
      - Diffuse cortical atrophy
      - Hippocampal atrophy
    - Microscopic
      - Plaques
        - amyloid-beta
        - abnormal neurites from multiple neurons+reactive microglia
        - most important feature for dx
        - decreased synapses within plaques
      - Neurofibrillary tangles
        - cytoplasmic inclusion
        - Tau protein
        - accumulation of amyloid-beta in blood vessels as well
    - Dx - plaques and tangles
    - Plaques
      - Amyloid beta
        - derived from amyloid precursor protein (APP), a transmembrane protein
        - created by abnormal cleavage by beta-, gamma-secretases
        - smaller oligomers are more toxic
- Genetics
  - APP - first discovered
  - Presenilin 1 - 40% of cases
  - Presenilin 2
  - ApoEpsilon4 - risk factor for late onset, NOT causative
  - all increase proportion of Abeta42 (as opposed to Abeta40)
  - Down syndrome and other variations in APP can increase likelihood
- Tangles
  - begin in medial temporal lobe, hippocampus and spread
  - S1 and M1 affected last
  - hippocampus circuitry: neocortex->entorhinal cortex->dentate gyrus->CA3->CA1->subiculum
  - tangles first appear in entorhinal ctx and CA1, de-eff and de-aff hippocampus
  - Tau protein
    - microtubule associated
    - hyperphosphorylation causes self-aggregation
- Parkinson's dz
  - second most common neurodegen dz
  - Microscopic findings
    - loss of pigmented dopaminergic neurons in substantia nigra
    - Lewy bodies - dark circle with clear halo of displaced pigment
    - Lewy neurites
  - Affected areas
    - substantia nigra - basal ganglia
    - locus ceruleus - pons
    - dorsal nucleus of vagus - medulla
  - alpha-synuclein
    - normal presynaptic protein
    - accumulates as misfolded protein in Lewy bodies/neurites
  - Genetics
    - alpha-synuclein - dominant, always with Lewy bodies
    - Parkin - early onset, recessive
    - LRRK2 - most common, dominant, sometimes Lewy bodies
  - Presentation
    - most do not have dementia
    - overlap between Parkinson's and Alzheimer's
  - Dementia with Lewy bodies
    - second most common neurodegen dementia
    - similar onset and survival to AD
    - distinguished from AD by
      - visual hallucinations
      - parkinsonism
      - fluctuation in symptoms
- Amyotrophic Lateral Sclerosis (ALS)
  - affects UMN and LMN
  - progressive weakness and atrophy
  - Epidemiology
    - middle age onset
    - male>female
    - 3-5 yr survival
  - Pathology
    - Gross findings
atrophy of ventral roots
• atrophy of motor ctx in rare cases
• Microscopic findings
  • loss of myelinated axons in CST
  • loss of m. axons in ventral roots
  • loss of motor neurons
  • eosinophilic inclusions
• TDP-43 inclusions
  • found throughout nucleus
  • inclusions in other degen dzs (eg most common form of frontotemporal dementia)
  • spectrum from ALS to FTLD: ALS has more inclusions in motor neurons and FTLD more in cortical neurons
• Genetics
  • superoxide dismutase - never have TDP inclusions
  • TDBP - gene for TDP-43
• Huntington’s dz
  • chorea or akinetic-rigid form
  • personality change, depression, dementia
• Epidemiology
  • young to middle-age
  • 10-30 yr survival
• Pathology
  • Gross
    • atrophy of striatum, particularly caudate
    • corresponding dilation of ventricles
    • cortical atrophy later
  • Microscopically
    • neuronal loss (>50%) and reactive astrocytosis
    • intranuclear inclusions of huntingtin
• Huntingtin
  • polyglutamine repeats
  • anticipation

Pharmacology of Parkinson Disease (PH)
• dopaminergic neurons project from substantia nigra to basal ganglia and cortex
• PD affects many neural systems, ie not just dopaminergic
• no drugs have been proven to slow dz progression
• polypharmacy is the norm
• Replacement therapy - L-Dopa
  • Tyrosine -TH-> L-Dopa -AADC-> dopamine
  • dopamine can’t cross BBB
  • AADC is ubiquitous, can inhibit AADC in periphery decreasing necessary L-Dopa
  • Sinemet
    • combination of carbidopa/L-Dopa
    • short t1/2
    • reduces tremor, rigidity, bradykinesia, but not much improvement in postural instability
• Toxicity
  • nausea, dyskinesia, hallucinations,
- motor/psychiatric complications with time
  - abnormal mvts, freezing, confusion
  - probably due to disease progression, but maybe due to pulsatile nature

- **MAOI**
  - Selegiline
    - inhibits metabolism by irreversibly binding MAO-B (MAO-A is in the periphery)
    - twice-daily
    - Toxicity: rare weight loss
    - complex pharmacokinetics
      - metabolites are amphetamines
  - Azalect
    - like selegiline
    - different metabolites

- **COMT inhibitors** - Entacapone
  - reversible selective inhibitor of COMT
  - Toxicity: GI complaints, urine turns reddish brown
  - short t1/2
  - does not cross BBB so only acts peripherally

- **Dopamine receptor agonists**
  - Toxicities: nausea, somnolence, hallucinations, orthostatic hypotension
  - Pramipexole
    - short t1/2
    - Toxicity: mental status changes in elderly, daytime somnolence, compulsive gambling

- **Anti-cholinergics**
  - might be effective by preventing ACh antagonism of dopamine
  - used predominantly early on

---

**Neuromuscular Disorders II: Peripheral neuropathy (P/PP)**

- sural nerve is the most commonly biopsied nerve (behind lateral malleolus)
- nerve anatomy
  - nerve layers
    - epineurium - surrounds fascicles
    - perineurium - blood-nerve barrier
    - endoneurium
  - A fibers
    - alpha - motor
    - beta - sensory
      - conduct at 120 m/s
    - delta - pain
      - small myelinated fibers
      - conduct at 15-30 m/s
  - C fibers
    - unmyelinated
    - pain, autonomic signal
    - conduct at 1 m/s
    - 1 micron in diameter, limit of LM
• General peripheral neuropathy
  ◦ as many as 10% people have it
  ◦ diabetes is most common cause
  ◦ important questions
    ▪ focal or diffuse
    ▪ axonal or demyelinating
      • EMG nerve conduction test (only large fibers), cannot determine by exam
      • skin biopsy to assess small fiber
    ▪ heritable or acquired

• Pathology
  ◦ Schwann cells will wrap collagen fibers in the absence of nerves
  ◦ Wallerian degeneration - active degradation of nerve distal to cell body after injury
    ▪ early phase - little visible change
    ▪ mid phase
      • axon stays in place for 48-72 hours after injury
      • neurofilaments dissolve and myelin ovoids form
    ▪ late phase
      • schwann cells divide and proliferate
      • macrophages digest myelin
  ◦ demyelination
    ▪ segmental; damage to schwann cells
    ▪ macrophages digest myelin
    ▪ thickness of axon always proportional to diameter of axon so thinly myelinated axons are indicative
    ▪ onion bulbs are evidence of cycles of myelin destruction/repair, appears grossly as nerve hypertrophy
  ◦ vascular pathology
    ▪ patchy, but may be confluent
    ▪ phase I: perivascular inflammation and macrophages inside vessel
    ▪ phase II: necrosis and invasion of vessel wall
    ▪ phase III: vessel occlusion
    ▪ amyloid
      • distortion of vessel wall
      • depletion of small myelinated axons with preservation of large ones

• some causes
  ◦ Guillaine-Barre - most common neuron-targeted autoimmune dz
  ◦ connective tissue dzs (eg Ehlers-Danlos)
  ◦ metabolic (eg diabetes, renal)

• rx
  ◦ NSAIDs and acetaminophen are not effective against neuropathy
  ◦ anti-depressants
  ◦ anti-convulsants
  ◦ narcotics

The Clinical Spectrum of Movement Disorders (PP)

• levadopa can cause an irregularly irregular dyskinesia
• DBS can resolve movement disorders
• Parkinson's disease
  ◦ Epidemiology
    ▪ 1% of population over 65
    ▪ 10% occur before age 40
  ◦ destruction of >80% dopamine signaling neurons in substantia nigra
  ◦ Lewy bodies are pathological hallmark
  ◦ Etiology
    ▪ interaction between genes and environment
    ▪ some single gene varieties
  ◦ pathogenesis
    ▪ loss of dopaminergic SNc neurons
    ▪ direct (stimulatory) pathway no longer excited
      • D1 of striatum -(-)> GPi -(-)> thalamus
    ▪ indirect (inhibitory) pathway no longer inhibited
      • D2 of striatum -(-)> GPe -(-)> STN -(+)> GPi -(-)> thalamus
  ◦ Diagnosis - mostly clinical
    ▪ parkinsonism
      ▪ bradykinesia
      ▪ festinating gait
      ▪ rigidity - "cogwheeling"
    ▪ rest tremor
      ▪ instability, loss of reflexes, "masked face"
      • MRI to rule out other causes
      • response to L-dopa treatment
  ◦ Treatment
    ▪ ablative surgery of GPi
    ▪ deep brain stimulation of STN
  ◦ other causes of parkinsonism
    ▪ drug-induced
    ▪ vascular
    ▪ hydrocephalus - treatable with shunt
• Tremor
  ◦ essential tremor
    ▪ most common movement disorder
    ▪ no known cause
    ▪ average age of onset is 45
  ◦ physiologic tremor
    ▪ Diagnose
      ▪ clinical
      ▪ family hx
      ▪ EMG
    ▪ Treatment
      ▪ medications are effective
      ▪ surgical options
• primary dystonia
  ◦ sustained muscle contractions particularly of agonist/antagonist pairs
  ◦ most are genetic
  ◦ stereotyped and patterned abnormal movements
  ◦ dx
    ▪ rule out drugs
    ▪ MRI
    ▪ Test for Wilson's
• L-dopa trial
  ◦ varieties
    ▪ Wilson dz
    ▪ DOPA-responsive dystonia
    ▪ glutaric acidemia
  ◦ focal
    ▪ cervical dystonia
      ▪ most common focal
      ▪ F>M age 40-60
    ▪ primary limb
    ◦ rx - DST, L-dopa
• myoclonus
  ◦ sudden, involuntary sock-like movement caused by muscle contraction
  ◦ rx - treat underlying cause
• chorea
  ◦ involuntary, unpattered and unsustained movements with variable timing and distribution
  ◦ varieties
    ▪ inherited (eg Huntington)
    ▪ metabolic or drug-related
    ▪ stroke involving STN
• tics and tourettes
  ◦ rx with depletors of dopamine

Alzheimer Disease and the Pathobiology of Dementia (P)

• Memory
  ◦ hippocampus - consolidation (short-term)
  ◦ cortex - storage (long-term)
• Types of memory loss
  ◦ age-associated memory impairment
  ◦ Mild Cognitive Impairment - significant memory loss, but still functional
  ◦ Dementia
    ▪ memory loss and loss of another cognitive ability
    ▪ loss of function
    ▪ causes include AD, vascular lesions, Lewy body dz, AIDS, alcohol
• Alzheimer Disease
  ◦ plaques of beta-amyloid
  ◦ tangles of Tau protein
  ◦ both cause cell death, inflammation, and atrophy
  ◦ atrophy of hippocampus and cortex
• Vascular lesions - strokes contribute to late-onset Alzheimer dz symptoms of dementia
• Obstructive sleep apnea
  ◦ associated with silent brain infarcts
  ◦ increased inflammation
  ◦ increased stroke risk
• Dementia
  ◦ Risk factors
• MI, hypertension, CVA
• AD
• Obstructive sleep apnea
• Diabetes or metabolic syndromes
• inflammation
  ◦ Presentation
    • activities of daily living
    • behavior
    • cognition
  ◦ Diagnosis
    • MMSE and history
    • Blood test, B12, TSH, RPR (syphilis), EKG, head CT - rule out other things
    • clock-drawing test
    • PET scan
  ◦ Treatments
    • medications - AchEI are mildly beneficial
    • nursing home
• Damage to the hippocampus from hypoxia, diabetes, HBP, trauma, depression, aging

Focal Cognitive Syndromes (PP)

• causes of impaired attention
  ◦ closed head injury
  ◦ delirium
  ◦ right hemisphere stroke
  ◦ dementia
• delirium
  ◦ Presentation
    • subacute onset
    • fluctuating level of consciousness
    • disorientation to place and time (not person)
    • hallucinations and occupations
  ◦ Causes
    • systemic disease - infx, RF, LF
    • medication side-effects (benzo, antiCh)
    • drug/alcohol withdrawal - delirium tremens
  ◦ Diagnosis
    • no diagnostic test
    • waxing and waning consciousness, impaired attention
• Unilateral spatial neglect
  ◦ viewer-centered
    • supramarginal gyrus
    • angular gyrus
    • frontal cortex
    • right dorsal stream
  ◦ stimulus-centered
    • temporal lobe (aka ventral stream)
• HIV dementia - "subcortical" dz
  ◦ Presentation
    • motor slowing
- memory impairment
- visuo-constructional impairment
- fluctuating attention
- preserved language and other cortical fncts

- aphasia
  - usually multi-modal (ie reading, writing, etc.) but can be modality specific
  - global aphasia
    - all modalities severely impaired
    - no speech or comprehension
    - recurrent utterances
    - most severe type of aphasia
    - Cause
      - MCA stroke
      - involves Broca's area and much of Wernicke's
  - partial aphasia
    - Broca's
      - nonfluent, effortful speech (telegraphic)
      - poor articulation with sparse output
      - good comprehension
      - damage to superior division of left MCA
    - Conduction
      - difficulty with repetition
      - fluent, paraphasic speech (almost the right word, but not quite)
      - decent comprehension
      - working memory problem
      - usually left upper, parietal lobe lesion
    - Wernicke's
      - fluent, paraphasic
      - speech lacking in content
      - poor comprehension and repetition
      - posterior, superior temporal lobe
      - inferior division of left MCA
    - Transcortical aphasias
      - all have spared repetition
      - transcortical motor - like Broca's
      - transcortical sensory - like Wernicke's
      - mixed transcortical - like global
  - Etiology
    - acute - stroke
    - gradual onset - degenerative disorders
      - primary progressive
      - CJD

- apraxia
  - acquired deficit of purposeful movements
  - Causes
    - stroke in left hemisphere
    - cortical dementia
    - cortico-basal degeneration
    - parietal lobe lesion

- agnosia
  - disorder of recognition
  - generally modal specific
visual agnosia - basilar artery stroke with bilateral temporo-occipital involvement

- amnesia
  - anterograde - impaired learning of new info
  - retrograde - impaired recall of old info
  - Global amnestic syndrome
    - herpes simplex encephalitis
    - alcohol associated amnesia
      - Wernicke's encephalopathy - acute
        - eye movement abnormalities
        - ataxia
        - confusional state
      - Korsakoff's syndrome - chronic
        - thiamine (B1) deficiency
        - severe anterograde amnesia
        - disorientation
    - iatrogenic
    - advanced Alzheimer
    - hypoxia/ischemia
    - transient global amnesia
      - anterograde
      - preserved consciousness
      - self-limited course possibly due to stroke in hippocampus
      - unknown etiology
  - anosognosia
    - inability to recognize one's deficits
    - seen in severe, diffuse brain injury

### Epilepsy and Seizure Disorders (PP)

- epilepsy - recurrent seizure
- Epidemiology
  - 2nd most common disorder "that neurologists see"
  - all age groups
- epileptic syndromes include seizure type and cause
- Classification
  - partial - focal region
    - simple - no alteration or loss of consciousness
    - complex - altered consciousness
  - Presentation
    - most common present as temporal lobe partial seizure
    - auras - nausea, deja vu, odors with no change in consciousness
  - generalized - begin from both sides
    - absence seizure - petit mal
    - tonic-clonic, grand mal - convulsions
    - primary generalized
      - no known cause
      - not progressive

<p>| complex partial | absence |</p>
<table>
<thead>
<tr>
<th>adult or childhood onset</th>
<th>childhood onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>aura</td>
<td>no aura</td>
</tr>
<tr>
<td>minutes long</td>
<td>seconds long duration</td>
</tr>
<tr>
<td>post-ictal state/slow recovery</td>
<td>no post-ictal state</td>
</tr>
<tr>
<td>focal EEG abnormalities</td>
<td>may go into spontaneous remission</td>
</tr>
</tbody>
</table>

- **Epilepsy**
  - Risk factors
    - head injury
    - stroke
    - infection
    - AD
  - typically self-limited lasting < 2 minutes
  - Mechanism
    - hyperexcitability
    - repetitive firing of action potential
    - paroxysmal depolarizing shift (PDS)
    - cell injury that can affect any type of neuron
  - Diagnosis
    - History
    - EEG - often normal in between, but looking for focal abnormalities
    - MRI
  - Treatment
    - antiepileptic drugs - if uncontrolled after 3 drugs, chances of finding one that works is <5%
    - seizure surgery
    - ketogenic diet
    - neurostimulation (eg vagus nerve stimulation)

---

**TNDs, TIAs, and Neuro-electrical Auras:**

**Pathogenesis of Episodic Neurological Symptoms (PP)**

- **Transient neurological deficits**
  - mechanical (usually history of triggers)
    - fluid dynamic
    - compressive
    - ex: Benign paroxysmal position vertigo
      - episodic **vertigo** and nausea triggered by head movements
      - single, excited semicircular canal (posterior)
      - "rocks" in the posterior semicircular canal
      - characteristic **upbeat nystagmus** upon recumbency is diagnostic (Dix-Hallpike test)
      - Epley Canalith repositioning can cure most patients
  - ischemic (usually spontaneous)
    - global
    - focal
    - ex: TIA
      - quick onset
- lasts < 24 hrs
- mechanisms can be cardiac embolism, athero-embolism, low flow stenosis
- risk for stroke highest in early stages post-event
- **big blood vessel diseases are bad for the brain**
  - neuroelectrical
    - ephaptic (direct connection between neurons, not synapse)
    - channelopathic
    - ex: migraine with aura
      - aura often has positive leading edge, negative wake, and slow tempo
      - 5-30 minute duration (~same length as seizures)
    - familial hemiplegic migraine
      - prolonged auras with motor manifestation
      - progression typical (V->S->M->C)
      - mutations in ion channels
      - episodic neurologic dysfunction on short time scale
  - Spreading Depression Hypothesis - migraine wave of excitation spread by extracellular fluid (not synaptic)
    1. cortex irritated
    2. spreading depression triggered
    3. depolarizing wave
    4. hyperpolarizing wave
    5. decreased metabolic demand
    6. decreased caliber of vessels (spasm)
    7. headache
      - explains spatial/temporal characteristics, absence of tissue ischemia, sensitivity to triggers, dovetails with channelopathy theory
  - **Symptoms**
    - are described as "neurological" - paresthesias, limb-shaking, paralysis, dizziness, etc.
    - last seconds to hours to a few days
    - can be of any quality
    - sometimes triggered
    - indicative of TIA, seizure, or migraine

**Developmental Disorders in Children (PP)**

- neurulation defects
  - anencephaly
  - spina bifida
    - types
      - myelomeningocele - part of CNS outside body
      - meningocoele - failure for neural tube to close but CNS still inside
      - spina bifida occulta - incomplete vertebra formation
  - most spontaneous
  - folate supplementation decreases incidence
  - screening
    - alphafetoprotein - made by fetal liver
    - ultrasound
• sx
  • spinal cord lesion - motor, sensory, bowel, bladder defects
  • hydrocephalus from tension pulling brainstem down and impaired flow (Arnold-Chiari)
• associations
  • cognitive impairment
  • orthopedic malformations
  • urologic/renal problems
  • pressure ulcers and osteomyelitis
• tethered cord - sc pinned to spot but infant continues to grow causing stretch cord syndrome
  ◦ encephalocele - possible disorder of anterior neural tube closure
• defects in neural tube segmentation
  ◦ holoprosencephaly
    • incomplete midline cleavage of forebrain
    • facial anomalies
  ◦ microcephaly
    • present at birth
    • variable mental retardation, decrease in neuronal number
    • sloping forehead
• neuronal migration defects
  ◦ lissencephaly - no gyral folds
• cerebral palsy
  ◦ **abnormal control of movement and posture** - limited, stereotypic, and uncoordinated
  ◦ does not imply causation
  ◦ induced by pre/postnatal events
  ◦ may exist with mental retardation, autism, others
• degenerative dzs
  ◦ may result from metabolic, mitochondrial, vascular dz
  ◦ classify by biochemical abnormality
  ◦ findings evolve over time
  ◦ gray matter
    • intellectual deterioration
    • dementia
    • seizures
    • retinal involvement
    • ataxia
    • eg Tay-Sachs
      • progression
        • normal at birth, deterioration at 6 months
        • first, startle to sounds
        • blindness and cherry red spot over the macula
        • late, megalencephaly
        • lysosomal storage dz - GM2 gangliosides accumulate in neuron due to hexosaminidase A mutation
        • no curative rx
  ◦ white matter
    • peripheral neuropathy
    • spasticity, hyperreflexia
    • ataxia
    • eg metachromatic leukodystrophy
      • progressive demyelinating
      • defect in arylsulfatase A
Anticonvulsants (PH)

- seizures - sustained, repetitive neuronal depolarization
- Mechanisms
  - bind opening/closing channels more avidly, so neurons that are more rapidly firing are affected most
  - block rapidly opening/closing V-dependent Na channels
    - Phenytoin
    - Carbamazepine
    - Lamotrigine
    - Valproic acid
  - block V-dependent Ca channels (eg ethosuximide, commonly used for absence seizures)
  - Increase activity of GABA
    - most powerful but have side effects
    - activate GABA receptor
      - barbiturates - "-barbitals"
      - benzodiazepines - "-zepams"
      - block reuptake of GABA - tiagabine
      - block metabolism of GABA
  - Decrease activity of glutamate
    - block AMPA receptor
      - topiramate
      - dextromethorphan
      - interferes with memory limiting use
      - block NMDA receptor - felbamate
    - bind to synaptic vesicles - levetiracetam
- spectrum
  - for generalized, focal, partial seizures
    - carbamazepine
    - phenytoin
    - lamotrigine
    - phenobarbitol
  - generalized absence
    - ethosuximide, lamotrigine
    - carbamazepine may make generalized absence seizure worse!
  - valproic acid is very versatile and useful for all seizure types
- Pharmacogenetics
  - mutations in Na channels that cause seizures
    - Dravet syndrome
    - Generalized epilepsy with febrile seizures
  - so don't use Na channel drugs in those cases
- Barbiturates
  - Action: activates GABA receptor
  - Metabolism: liver, long t1/2
  - Toxicity: powerful but with cognitive and behavioral effects (eg depression)
  - Kinetics: linear kinetics (blood level / dose)
- Phenytoin
- Action: blocks active Na channels
- Metabolism: saturable liver metabolism
- Toxicity:
  - sedation
  - ataxia, nystagmus
  - gum hypertrophy
  - increased hair
- Michaelis-Menton kinetics (non-linear), zero-order elimination

- Carbamazepine
  - one of the most widely prescribed
  - action: blocks Na channels
  - metabolized in liver, induces its own metabolism, also induced by phenytoin
  - few side effects

- Valproic acid
  - blocks sodium channel, enhances GABA receptors
  - simple fatty acid
  - hepatic metabolism as fatty acid
  - fatal hepatic necrosis in children <2 yo

- Lamotrigine
  - 2-ring structure
  - block Na channel
  - glucuronidated in liver
  - metabolism inhibited by Valproic acid
  - few side effects but can produce severe skin rash

- Status Epilepticus
  - 30 min of continuous seizure or 2 or more seizures without full recovery
  - medical emergency
  - can cause brain damage
  - Treatment (in order of administration)
    1. benzodiazepenes - Lorazepam
    2. phenytoin
    3. phenobarbital
    4. midazolam
  - Side effects
    - sedation, coma
    - bradycardia, arrhythmias
    - skin, venous damage - "Purple glove" syndrome, S-J syndrome

- Anticonvulsants and pregnancy
  - anticonvulsants are teratogens
    - valproic acid associated with neural tube malformations
    - mechanism
      - antagonize folic acid
      - increase free radicals
      - decrease activity of epoxide hydrolase, which detoxifies anticonvulsant metabolites
  - induce metabolism of birth control drugs
  - alterations in metabolism of endohormones can cause ovarian dysfunction

- children often outgrow epilepsy and the need for anticonvulsants
General Anesthesia (PH)

- Classification
  - Inhaled
    - N2O
    - Potent, volatile agents - halothane, sevoflurane, isoflurane, desflurane
  - Intravenous
    - induction agents - propofol, ketamine, thiopental
    - continuous infusions - propofol

- anesthesia - **reversible** state of **unconsciousness**
  - hyponosis - loss of awareness
  - amnesia
  - analgesia
  - immobility - metric for potency
  - depth
    1. analgesia, amnesia - lose responsiveness at .3x MAC
    2. delirium
    3. surgical anesthesia - ~1x MAC
    4. medullary depression (OD) - 2-4x MAC

- Minimum alveolar concentration (MAC) - measure of potency
  - conc that abolishes movement to a noxious stimulant in 50% (=ED50)
  - potency = 1/MAC
  - decreased by old age, other sedatives, hypothermia
  - genetic variation
  - given average MAC, but anesthesiologist adjusts with careful observation
  - 95% CI = MAC +/- 25%

- Pharmacokinetics
  - partial pressure (PP) matters for drug effect, not concentration
  - PP rises at equal rates for all compartments but with phase delay (brain < muscle < fat)
  - some molecules do not go into solution and do not generate partial pressure
  - highly soluble gas will not have high partial pressure
  - so insoluble gases can have a higher PP gradient and induce anesthesia faster
  - time constant to reach partial pressure is proportional to solubility*volume/flow
  - takes 3 time constants for alveolar PP to reach equilibrium PP
  - equilibration b/w Palv and Part is essentially instant
  - fat dissolves anesthesia well acting as a drug depot and making it take longer to wake someone up
  - reached equilibrium when Pin = Pout
  - speed of drug induction determined by Fa/Fi
  - examples
    - nitrous oxide is only a partial anesthetic
    - desflurane can only be given after partial anesthetic since it is an irritant

- Malignant hyperthermia - the only anesthetic dz
  - autosomal dominant
  - point mutation in RYR1 (ryanodine receptor) in 50% of patients
  - Presentation
    - muscle rigidity
- Increased temp, HR, PCO2
- Decreased pH
- Rhabdomyolysis
  - Therapy - dantrolene (a muscle relaxant)
  - Diagnostic - contracture test (caffeine)
- Delivering IV anesthetic
  - Rapidly induce sleep, useful for emergencies
  - Does not provide all 4 components of anesthesia so combined with other sedatives, opioids
- GABA IV anesthetics
  - Thiopental
  - Propofol - can cause anaphylaxis, vein irritation
  - Etomidate - can cause apnea
- Ketamine
  - Phencyclidine derivative
  - Blockade of NMDA
  - Wide-eyed, but unresponsive to command
  - Stimulates sympathetics
  - Profound cutaneous analgesic
  - Good in resource-poor locations
- Dexmedetomidine
  - Central alpha2 adrenergic agonist
  - Continuous IV infusion
- Remifentanil
  - Ultra-short acting IV opioid
  - Metabolized in plasma by plasma cholinesterase
- Classes
  - Group 1 drugs
    - Etomidate, propofol, barbiturates
    - Target specific GABA receptors
    - Binds to different part of receptor
    - Linked to hypnosis and amnesia
    - Slowing of EEG
  - Group 2 drugs
    - Less specific and target glutamate and K channels
    - N2O and ketamine
    - Linked to analgesia
  - Group 3 drugs
    - Volatile anesthetics
    - Least selective, target many molecular sites