# Table of Contents

<table>
<thead>
<tr>
<th>Topic</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Principles</strong></td>
<td></td>
</tr>
<tr>
<td>o Acute Confusional State (Delirium)</td>
<td>1</td>
</tr>
<tr>
<td>o Syncope</td>
<td>2</td>
</tr>
<tr>
<td>o Ataxia</td>
<td>5</td>
</tr>
<tr>
<td>o Dizziness &amp; Vertigo</td>
<td>8</td>
</tr>
<tr>
<td>o Headache</td>
<td>12</td>
</tr>
<tr>
<td>o Sleep Disorders</td>
<td>17</td>
</tr>
<tr>
<td>o Head Injury &amp; Coma</td>
<td>19</td>
</tr>
<tr>
<td><strong>CNS Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>o Cerebrovascular Disease</td>
<td>24</td>
</tr>
<tr>
<td>o Infections of the CNS</td>
<td>28</td>
</tr>
<tr>
<td>o Seizures &amp; Epilepsy</td>
<td>33</td>
</tr>
<tr>
<td>o Antiepileptic Drugs</td>
<td>37</td>
</tr>
<tr>
<td>o Dementia</td>
<td>39</td>
</tr>
<tr>
<td><strong>Movement Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>o Extrapyramidal Movement Disorders</td>
<td>45</td>
</tr>
<tr>
<td>o Hyperkinetic Movement Disorders</td>
<td>47</td>
</tr>
<tr>
<td><strong>Demyelinating and Autoimmune Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>o Demyelinating Diseases</td>
<td>50</td>
</tr>
<tr>
<td>o Immune-mediated Neuropathy</td>
<td>52</td>
</tr>
<tr>
<td><strong>Neurological Diseases with Peripheral Involvement</strong></td>
<td></td>
</tr>
<tr>
<td>o Cranial Nerve Disorders</td>
<td>55</td>
</tr>
<tr>
<td>o Autonomic Nervous System Disease</td>
<td>59</td>
</tr>
<tr>
<td>o Peripheral Neuropathy &amp; Radiculopathy</td>
<td>63</td>
</tr>
<tr>
<td>o Myopathy</td>
<td>69</td>
</tr>
<tr>
<td>o Motor Neuron Disease</td>
<td>71</td>
</tr>
<tr>
<td>o Spinal Cord Diseases</td>
<td>73</td>
</tr>
<tr>
<td><strong>Neoplastic Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>o Neurocutaneous Syndromes</td>
<td>78</td>
</tr>
<tr>
<td>o Intracranial Tumors</td>
<td>80</td>
</tr>
<tr>
<td><strong>Miscellaneous Neurological Diseases</strong></td>
<td></td>
</tr>
<tr>
<td>o Prion Diseases</td>
<td>82</td>
</tr>
</tbody>
</table>
ACUTE CONFUSIONAL STATE (DELIRIUM)

Definition:
- Disorders of consciousness include disorders in which the level of consciousness (arousal or wakefulness) is impaired, such as acute confusional states and coma, and those in which the level of consciousness is normal but the content of consciousness is altered, such as dementia and amnestic disorders.

Ethanol intoxication
- Osmolar gap +22 mOsm/L for every 100 mg/dl ethanol
- Hypoglycemia from depleting NAD+
- Give B₁ (thiamine)

Ethanol Withdrawal
0-2 days
- Tremulousness, agitation, 25% visual hallucinations. Treatment: diazepam, chlordiazepoxide
- Seizures (1-3%). 40% of these seizures are solitary. If repeated, alcohol is unlikely etiology.

3-5 days
- Confusion, agitation, autonomic instability (tachycardia), hallucinations (visual and tactile)
- Can last 3 days

Delirium
- Altered sensorium (vs. alcoholic hallucinosis): no recognition of real world
- Treatment: 10-20mg diazepam Q 5 minutes until calm. Give atenolol. Correct electrolytes.

Myxedema Coma
- Delayed relaxation of deep tendon reflexes
- Treatment: replace thyroid hormone, rule out addisonian crisis (give hydrocortisone)

Thyrotoxic Crisis
- Agitation (common < 50): psychosis, hallucinations
- Apathetic (common > 50)
- Treatment: 1) Propanolol, 2) Iodine, 3) Hydrocortisone

Hyperosmolar Hyperglycemic Nonketotic Syndrome (HHNS)
- > 350 mOsm, ↑↑↑ glucose (800+ mg/dl), no ketones, no acidosis, positive neurologic signs/seizures

Wernicke Encephalopathy
- Triad: 1) Ophthalmoplegia (nystagmus, CN VI palsy), 2) Ataxia, 3) Confusional state (amnesia)
- Pathogenesis: neuron loss, demyelination, gliosis of gray matter.
  - Affected areas: Medial thalamus, mamillary body, periaqueductal gray matter, cerebellar vermis
- Treatment: 100mg B₁ (thiamine)
  - Horizontal nystagmus and ataxia are usually reversible (60%). Other symptoms are irreversible.

Hepatic Encephalopathy: ↑ GABA, often precipitated by GI bleed, infection, diuretics
- Somnolence, agitation, asterixis
- Nystagmus, tonic ↓ deviation of eyes, disconjugate movement. Seizures.
- CSF: ↑↑ glutamine (specific)
- EEG: Diffusely slow with triphasic waves
- Treatment:
  1. Correct electrolyte imbalances and glucose
  2. Correct coagulopathy: Fresh frozen plasma, Vitamin K
  3. Lactulose (acidify colon and ↓NH₄ absorption) and Neomycin (↓ NH₄ forming bacteria in colon)
  4. Flumazenil (benzodiazepine antagonist)

Uremia
- Tremor, asterixis, myoclonus, tetany. Seizures.
- Treatment:
  1. Hydration
  2. Protein/salt restriction
  3. Dialysis
- Dialysis disequilibrium syndrome: First hemodyalisis. Occurs due to hyposmolality

Sources
SYNCOPE

Definition: A transient (average = 12 seconds), self-limited loss of consciousness, usually associated with falling.

Etiology

- **Unknown (33%)**
- **Reflex syncope**: cardioinhibitory (↑ parasympathetic [vagal]), vasodepressor (↓ sympathetic), or both.
  - Subtypes
    - Neurocardiogenic (vasovagal) (50% of all syncope): more common in younger patients.
      - Triggers: temperature (vasodilation), alcohol, fatigue, pain, hunger, stress
      - **Prodrome**: pallor, diaphoresis, weakness, nausea, blurred vision (vs. orthostatic)
    - Situational
      - Triggers: micturation, defecation, coughing fits (COPD)
      - Carotid sinus hypersensitivity
        - Triggers: shaving, tight collar, turning the head to one side
    - **Diagnosis**: tilt-table study
  - **Glossopharyngeal Neuralgia (rare)**
    - Preceded by pain in oropharynx, tonsillar fossa, or tongue
    - Afferent CN IX to nucleus solitarius and activate dorsal motor nucleus of vagus
  - **Cardiovascular (18%)**: more common in the elderly.
    - Subtypes
      - Arrhythmias: brady (ex. sick sinus), tachy (ex. SVT, long QT, WPW - *prodromal palpitations*)
      - Structural lesion: valvular (ex. aortic stenosis), hypertrophic cardiomyopathy, atrial myxoma
      - Cerebrovascular disease: vertebrobasilar insufficiency, basilar migraine (see focal signs)
        - No prodrome
  - **Orthostatic (10%)**
    - Causes: drugs, autonomic insufficiency, dehydration
    - Posture is trigger (vs. NCS)
    - No prodrome
  - **Seizures (15%)**
    - Incontinence is far more common with seizures than in other types of syncope

Pathophysiology

- Minimum O₂ requirement to maintain consciousness: 50 ml/100 g brain tissue/min (12% of CO)
  - Easy to achieve in young, healthy, but elderly or comorbid conditions may jeopardize.
  - Sudden halt in cerebral blood flow for 6-8 seconds is sufficient to cause loss of consciousness
  - As little as 20% ↓ cerebral perfusion can cause loss of consciousness.
- Cerebral perfusion is mainly dependent on MAP, so anything which ↓ CO or ↓ TPR decreases perfusion.
  - MAP = CO x TPR.
  - Most important determinant of CO is preload, and venous pooling in limbs ↓ preload.
  - CO also impaired in arrhythmias and valvular disease.
  - Widespread vasodilation ↓ MAP dramatically in the reflex syncopal episodes.
  - Can also be due to ↑ cerebral vascular resistance (usually due to ↓ CO₂)

Approach to the patient with syncope

1. Rule out life-threatening causes
   - Cardiac: EKG/Holter monitoring and echocardiogram if suspected valvular lesion
   - Seizure: syncope has no postictal state and prodromal period is distinct from aura
     - EEG: no epileptic activity in syncope (even in presence of syncopal myoclonic jerks), only generalized slowing with prompt recovery.
2. History and physical: Look for triggers
3. Tilt-table study
   - Orthostatic
     - Normal neurological exam: postganglionic autonomic insufficiency
     - Abnormal neurological exam: peripheral neuropathy (ex. DM), MSA if CNS findings
4. CBC, metabolic panel
5. Review medication
SYNCOPE

Sources

● Step-up to Medicine, Agabegi, 2nd edition, 2008
● First Exposure to Neurology, Kirschner, 2007
ATAXIA

Cerebellum

1. Anatomy: Lateral regions control upper extremities, midline regions control lower extremities
   - Lobes: anterior, posterior, flocculonodular (archicerebellum - vestibular nuclei)
   - Deep nuclei: (FGED about it - medial to lateral) festigial, globose, emboliform, dentate
   - Superior pedicle: mostly efferent
     - Efferent from dentate nuclei to thalamus (dentothalamic) and SC via red nuclei (rubrospinal)
       - Controls contralateral motor cortex, thusly ipsilateral side of the body
     - Afferent from ventral spinocerebellar tract: From lower limbs (golgi tendon organs)
   - Middle pedicle: Afferent from contralateral pontine nuclei
   - Inferior pedicle: Afferent
     - Dorsal spinocerebellar tract: From lower limbs (muscle spindles)
     - Cuneocerebellar tract: From upper limbs
     - Olivocerebellar tract: timing

Cerebellar function

1. Maintenance of posture
2. Maintenance of muscle tone
3. Coordination of voluntary activity

Cerebellar dysfunction

1. Dysequilibrium: gait and trunk ataxia (Greek: “lack of order”)
2. Hypotonia
3. Dyssynergia: loss of coordinated muscle activity
   - Intention tremor (NOT resting tremor)
   - Nystagmus: coarse (>3mm), toward side of the lesion. (vs. vestibular)
   - Dysdiadokinesia: Inability to perform rapid alternating movements
   - Dysrhythmokinesia: Rebound phenomenon (Stewart-Holmes Test)
     - Fail to relax bicep after passive resistance released - hit self in head with own hand

Approach to the patient

- **Ataxia**: gait problem, scanning speech, visual blur (nystagmus), hand incoordination, and intention tremor
  - Positive Romberg sign (lose balance when eyes closed and must rely on proprioception)
  - Vertiginous ataxia (not true ataxia): dizziness, light-headedness, or the perception of movement

1. What is the timeline (acute, subacute, chronic)?
2. What is the distribution (symmetric, focal)?

Symmetric Ataxia: Gradual, bilateral increase in symptoms: biochemical, metabolic, immune, or toxic etiology

- **Acute** (hours-days)
  - Drugs: alcohol, phenytoin, lithium, barbiturates, chemotherapy and other drugs
  - Toxic exposures: gasoline/glue sniffing, spray paint, mercury, bismuth
  - Postinfectious (esp. varicella): gait ataxia and mild dysarthria (reversible)
    - Poliovirus, coxsackievirus, echovirus, EBV, toxoplasmosis, Legionella, Lyme
- **Subacute** (weeks-months)
  - Alcoholism
  - Malnutrition: deficiency of B₁ or B₁₂ or E
  - Hyponatremia
  - Paraneoplastic syndromes: opsoclonus (small saccades about fixed point), myoclonus, ataxia
    - Breast and ovarian: anti-Yo
    - SCLC: Anti-PQ type voltage-gated calcium channels, Anti-Hu (anti-mRNA from cancer)
    - Hodgkin disease: anti-Tr
  - Autoimmune:
    - Speech & gait: anti-glutamic acid decarboxylase (GAD) (also in Stiff Man Syndrome + DM-1)
    - Anti-gliadinin (and anti-endomysium) (Celiac disease)
- **Chronic** (months-years)
  - Inherited ataxia
  - Metabolic disorder: hypothyroidism
  - Chronic infection: Meningovascular syphilis and tabes dorsalis
Focal Ataxia

- Space occupying lesion
  - Headache
  - Impaired level of consciousness
  - Ipsilateral cranial nerve palsies
  - Contralateral weakness
- Ischemic infarction or hemorrhage
  - Cerebellar symptoms ipsilateral to lesion
- Lymphoma or progressive multifocal leukoencephalopathy (PML) in a patient with AIDS
- Congenital
  - Chiari malformation
    - Type 1: cerebellar tonsils extend below the foramen magnum
      - Not symptomatic until adulthood if ever. Symptoms referable to cerebellum.
    - Type 2: cerebellar vermis lies well below the foramen magnum (worse)
      - Symptomatic at birth: hydrocephalus, myelomeningocele and/or mental retardation
    - Posterior fossa cyst (Dandy-Walker) (Giant cisterna magna)
      - Agenesis of cerebellar vermis (ataxia), obstructive hydrocephalus, mental retardation

Inherited Ataxias

- Spinocerebellar Ataxias (SCAs): mostly autosomal dominant, mostly due to CAG repeat expansion
  - CAG = glutamate. Polyglutamine proteins (ataxins) produce a toxic gain of function
  - MRI: Cerebellar folia atrophy
    - Type 1: ataxic type (most common) subtype
      - Onset before 20
      - True cerebellar deficits: dysarthria and gait and extremity ataxia
      - Fasiculations also present
    - Type II: ataxic type (most common) subtype
      - Onset 10-30
      - True cerebellar deficits: dysarthria and gait and extremity ataxia
      - Sensory loss involving pain, touch, vibration, and position senses
      - No extrapyramidal findings
    - Type III MJD: ataxic-amyotrophic type
      - Onset in 40-60
      - True cerebellar deficits: dysarthria and gait and extremity ataxia.
    - SCA type 7
      - Retinal pigment degeneration (vs. other SCAs)
        - Onset as blue-yellow confusion and proceeds to total blindness
- Episodic ataxia (Autosomal dominant)
  - Type 1: Ataxia with myokymia and nystagmus brought on by startle, change in posture, exercise
    - K⁺ channel mutation on chromosome 12
  - Type 2: Lasts hours-days. In addition to startle, can be brought on by fatigue.
    - Ca²⁺ channel mutation on chromosome 14
  - Treatment: Acetazolamide, anticonvulsants
● **Friedreich ataxia** (most common inherited ataxia - 50% of cases)
  ○ Autosomal recessive mutation in *frataxin* on chromosome 9
    i. GAA triplet in first intron
  ○ Classic form or Vitamin E deficiency syndrome
  ○ Median age of death: 35 years
  ○ **Pathophysiology**
    i. Degeneration of:
      ● Spinocerebellar tracts: ataxia
      ● Posterior columns: loss of vibration sense and light touch
      ● Lateral corticospinal tract: loss of pain and temperature sensation
      ● Dorsal root ganglion neurons: DTR ↓
    ii. *Cerebellum itself is spared.*
  ○ **Signs & symptoms**
    i. “Cerebellar” signs: Dysarthria, ataxia, staggering gait, nystagmus, dysmetria
    ii. Mental retardation
    iii. **Cardiomyopathy** (90%): cardiomegaly, conduction defects
    iv. Diabetes (20%)
    v. Hyporeflexia
    vi. Skeletal abnormalities: Scoliosis, pes cavus (high arch), pes equinovarus (club foot)
    vii. **MRI:** atrophy of spinal cord

● **Ataxia-Telangiectasia**
  ○ Autosomal recessive
  ○ Onset < 10
  ○ **Signs & symptoms**
    1. Telangiectasias
    2. Ataxia
    3. Nystagmus
       Myoclonic jerks
       Areflexia
       Distal sensory deficits
       **Thymic hypoplasia:** IgA and IgG2 immunodeficiency. Recurrent pulmonary infections
       Endocrine disorders: type 1 DM
  ○ Increase in cance

● **Sideroblastic anemia with ataxia** (X-linked recessive)

● **Mitochondria ataxias**

Management of ataxias
● Focal lesions are neurosurgical emergencies
● Progressive: CSF titers for infection (Lyme, syphilis, etc)
● Weight loss: work-up of paraneoplastic syndrome antibodies
● Malabsorption: vitamin deficiency or anti-gliadinin
● Episodic ataxia: Acetazolamide

Sources
● PreTest: Neurology, Anschel, 2009
● High-Yield Neuroanatomy, Fix, 2nd Edition
● Waxman SG, "Chapter 13. Control of Movement" (Chapter). Waxman SG: Clinical Neuroanatomy, 26e
Vertigo: the sensation of motion while motionless.

- **Physiologic vertigo**: Occurs in normal individuals under the following circumstances
  - Intersensory mismatch among the three stabilizing systems (vestibular, somatosensory, visual)
    - Movie “chase scene”: visual stimulus is unaccompanied by vestibular or somatosensory cues
  - Vestibular system experiences unadapted, unfamiliar head movements (ex. seasickness)
  - Unusual head/neck positions (ex. painting a ceiling)
  - Following a spin

- **Pathologic vertigo**: lesions in the visual, somatosensory, or vestibular systems
  - Signs & symptoms: jerk nystagmus, nausea, postural unsteadiness, gait ataxia.
  - Visual vertigo: new or incorrect eyeglasses or sudden EOM paresis resulting in diplopia
  - CNS normally rapidly counteracts the vertigo
  - Somatosensory vertigo (rare) due to peripheral neuroapthy
  - Vestibular vertigo (most common): either due to labyrinth or central lesion
  - Vestibular ataxia: occurs with gravity-dependent movement (vs. cerebellar - all movement)

**Anatomy & Physiology**

- **Vestibular apparatus**: 3 semicircular canals, otolithic apparatus (utricle and saccle)
  - Semicircular canals (kinetic labyrinth): angular acceleration
    - Horizontal canal: detects axial (horizontal) rotation
    - Anterior and posterior canals: detect vertical rotation
  - Otolithic apparatus (static labyrinth): linear acceleration. Utricle for horizontal, saccule for vertical
  - Supplied by labyrinthine artery off of AICA (usually)

- **Pathway**
  - From labyrinth hair cells to CN VIII vestibular ganglion bilpolar cells to ipsilateral vestibular nuclei
  - Vestibular nucleus in pons-medulla has connections to four targets:
    1. **Cranial nerves III, IV, VI**: Vestibuloocular reflex: maintain visual stability during head motion.
      - Intact VOR exonerates CN VI in pons and CN III + IV (midbrain via MLF) from pathology
      - These CN connections explain why problem here results in nystagmus
      - Lesion in MLF results in internuclear ophthalmoplegia (IOP) (ex. MS demyelination)
        - On attempted lateral gaze, paramedian pontine reticular formation (PPRF) abducens nucleus (CN VI) complex fires attempting to laterally abduct the eye, but nystagmus results.
        - Connection between PRPP-CN VI nucleus and contralateral CN III nucleus (medial longitudinal fasiculus) is demyelinated
        - The “affected” eye is unable to adduct medially (CN III), paralyzed in midline.
        - Summary: abducting eye = nystagmus, adducting eye = paralyzed.
    2. **Spinal cord** (anterior & lateral vestibulospinal tracts): maintain postural stability
      - Anterior: lower part of MLF. Cervical cord only. Neck movement/VOR. (Bilateral)
      - Lateral: extends to entire cord. Controls limbs in postural stability. (Ipsilateral only)
    3. **Cerebral cortex** (via thalamus): provides conscious awareness of movement
    4. **Cerebellum**: modulates VOR (primarily flocculus and nodulus)

- Three systems contribute to spacial orientation and posture. Compensate for each other’s deficiencies.
  - 1) Visual system, 2)Somatosensory system, 3) Vestibular system

- **Coordination of signals in cortex**
  - When head is straight and immobile, the right and left labyrinths should give equal tonic signal
  - During acceleration, one side increases its firing rate and the other decreases its firing rate
  - These signals are projected to the cortex, combined with the visual and somatosensory systems to create the conscious sense of rotational movement.
  - After cessation of prolonged rotation, firing frequencies reverse. Sense of rotation experienced.
    - Physiologic postrotational vertigo (ex. facing the wrong way in a car)
  - Peripheral vertigo can be compensated by plasticity of cortex, but central vertigo cannot be.
### Dizziness & Vertigo

<table>
<thead>
<tr>
<th>Sign or Symptom</th>
<th>Peripheral (Labyrinth)</th>
<th>Central (Brainstem or Cerebellum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction of nystagmus</td>
<td>Unidirectional. Fast phase is opposite lesion</td>
<td>Bidirectional or unidirectional</td>
</tr>
<tr>
<td>Purely horizontal nystagmus</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Vertical nystagmus</td>
<td>Never present</td>
<td>80% sensitive for cerebellar, CN VIII nucleus</td>
</tr>
<tr>
<td>Visual fixation</td>
<td>Inhibits nystagmus and vertigo</td>
<td>No inhibition</td>
</tr>
<tr>
<td>Severity of vertigo</td>
<td>Marked</td>
<td>Often mild</td>
</tr>
<tr>
<td>Direction of spin</td>
<td>Toward fast phase, away from lesion</td>
<td>Variable</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>Finite but recurrent</td>
<td>May be chronic (may be continuous)</td>
</tr>
<tr>
<td>Tinnitus and/or deafness</td>
<td>Often present</td>
<td>Usually absent</td>
</tr>
<tr>
<td>Tullio effect (worse w/sound)</td>
<td>Sometimes present</td>
<td>Not present</td>
</tr>
<tr>
<td>Associated CNS abnormalities</td>
<td>None</td>
<td>Extremely common (e.g., diplopia, hiccups, cranial neuropathies, dysarthria)</td>
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### Etiology

- **BPPV**
- **Infection (labyrinthitis)**
- **Ménière's**
- **Neuronitis**
- **Ischemia**
- **Trauma**
- **Toxins**
- **Vascular**
- **Demyelinating**
- **Neoplasm**

### Labyrinthine dysfunction

- **Acute unilateral labyrinthine dysfunction** (acute labyrinthitis)
  - **Signs & symptoms**: brief vertiginous attacks for several days. Self-limited.
  - **Etiology**: infection (HSV-1 most common), trauma, and ischemia (labyrinthine artery off of AICA)
  - Postinfections (after URI): Often associated with hearing loss or tinnitus. (vs. neuronitis)
  - Vertebrobasilar insufficiency: with associated nausea but no hearing loss
  - **Treatment**: Prednisone
- **Recurrent unilateral labyrinthine dysfunction** (can be positional)
  - **Ménière syndrome**: Vertigo *with* signs of cochlear disease (tinnitus & hearing loss)
  - Endolymphatic hydrops: Ménière syndrome, syphilis, trauma
  - Sporadic (most common), and inherited (Ménière disease) mutation in cochin
  - Vertigo ↓ as hearing loss ↑. Hearing loss is in the low frequency range.
  - **Treatment**: HCTZ, triamterene (K⁺-sparing diuretic)
- **Vestibular neuronitis**: Vertigo *without* signs of cochlear disease (no hearing loss) (vs. labyrinthitis)
  - Early attacks are long (2 days - 2 weeks) but shorten as disease progresses.
  - Can happen after recent URI.
- **Acute bilateral labyrinthine dysfunction**: toxins (mercury, lead), drugs (aminoglycosides, phenytoin)
- **Benign paroxysmal positional vertigo (BPPV)** (peripheral positional vertigo) (most common) Severe vertigo..
  - **Etiology**: Idiopathic (most common), head trauma
  - **Diagnosis**: Dix-Hallpike maneuver has 83% PPV in diagnosing BPPV
  - **Treatment**: 93% of primary care visits for vertigo
  - **Latency of 3-40 seconds after position achieved. Goes away on repeated stimulation** (all peripheral)
DIZZINESS & VERTIGO

- **Perilymphatic fistula**: brought on by valsalva/exertion and associated with sensorineural hearing loss
  - History of head trauma, surgery, or barotrauma.
  - Hennebert’s sign: vertigo caused by pushing on tragus and external auditory meatus
- **Central positional vertigo**: No latency, does not extinguish on repeated trials (vs. BPPV). Vertigo is mild.

**Vestibular nerve dysfunction**
- Auditory portion of CN VIII is usually affected too (unilateral tinnitus or sensorineural hearing loss)
- Usually less severe and not usually paroxysmal
- Central mechanisms usually can compensate for the vertigo, but not for the auditory symptoms
- **Etiology**: Schwannoma (acoustic neuroma) or meningioma

**Central Vertigo**
- Lesions of brainstem or cerebellum. Usually cause “neighborhood signs” by occupying space
  - Acute onset: could be infarction.
  - Chronic onset: acoustic neuroma, meningioma, cholesteatoma.
    - CN V and VII are most often compressed leading to facial palsy and/or numbness.
- Migraine auras.
- Vestibular epilepsy (rare): secondary to temporal lobe epileptogenesis.

**Psychogenic Vertigo**
- Usually occurs with panic attacks or agoraphobia (fear of crowds, open spaces)
- Not accompanied by nystagmus.
- Associated with hyperventilation syndrome.

**Miscellaneous Head Sensations**
- People who complain of “dizziness“ which is not presyncope or vertigo.
- Etiology: hyperventilation syndrome, hypoglycemia, somatic symptoms of clinical depression
  - Hyperventilation syndrome associated with anxious individuals. There is associated paresthesia.
- Gait disorder can even be reported as dizziness
  - Multiple-sensory-defect dizziness (Benign dysequilibrium of aging):
    - Elderly who complain of dizziness only when walking.
    - 3 systems contribute to orientation & posture (visual, somatosensory, vestibular)
      - ↓ proprioception, ↓ vision create overreliance on aging vestibular apparatus

**Otosclerosis**
- **Conductive** (and/or sensorineural) hearing loss, vertigo. Onset <30
- **Treatment**: NaF, Vitamin D, Calcium gluconate, Surgery (stapedectomy)

**Approach to the patient with dizziness**
1. **Differentiate**: true vertigo (hallucinatory “room spinning”), presyncope, and miscellaneous sensations
   - Dizziness can mean lightheadedness, spinning, giddiness, or even confusion, blurred vision, HA
2. **Is the patient taking any drugs that can cause vertigo?** (ex. aminoglycosides, phenytoin, cisplatin, diuretics)
3. **Determine if vertigo is peripheral or central** (see table): Suspected central lesions require imaging.
4. **Progression of symptoms**
   - Start severe and get better: acute vestibular neuritis
   - Start mild and get worse: Ménière syndrome
5. **Provoking factors**
   - Position (turning in bed, hyperextending neck): BPPV, acute labyrinthitis, MS, fistula, tumor
   - Recent viral URI: acute vestibular neuritis or acute labyrinthitis
   - Associated with headache: basilar migraine (Bickerstaff) (30% of migraine patients have vertigo)
   - History of trauma (barotrauma - ex. scuba diving): perilymphatic fistula
   - No provoking factors (spontaneous): Acute vestibular neuritis, Ménière, migraine, CVA, MS
6. **Associated symptoms**
   - Aural fullness: Acoustic neuroma, Ménière syndrome
   - Ear pain: Acoustic neuroma, otitis media, herpes zoster oticus (Ramsay-Hunt syndrome)
   - Facial palsy: Acoustic neuroma, herpes zoster oticus (Ramsay-Hunt syndrome)
   - Imbalance: Acute vestibular neuronitis (moderate), cerebellopontine angle tumor (severe)
7. **Duration of vertiginous attacks**
   a. Seconds: peripheral. late vestibular neuritis, early Ménière
   b. Seconds-minutes: BPPV, perilymphatic fistula, TIA
   c. Hours: Late Ménière, perilymphatic fistula, migraine, acoustic neuroma
   d. Days: Early acute vestibular neuronitis, migraine, multiple sclerosis, CVA
   e. Weeks: Psychogenic

8. **Neurological exam**
   a. Auditory symptoms: high hearing loss and/or tinnitus
      i. **Unilateral hearing loss**
      1. Sensorineural: Acoustic neuroma, herpes zoster oticus, perilymphatic fistula, CVA
      2. Conductive: cholesteatoma
      ii. **Bilateral hearing loss**
      1. Sensorineural: Ménière syndrome (low-frequency loss)
      2. Conductive: otosclerosis
   b. Cephalic ischemia: reproduced with maneuvers producing orthostatic hypotension, valsala
   c. Neighborhood signs: diplopia, hiccups, dysarthria, facial palsy suspect central lesion
   d. Establish the side of the abnormality: Electronystagmography (calorics): COWS
      i. Compare nystagmus on two sides. Inability to produce nystagmus = “dead labyrinth”

9. **MRI if central suspected** (neighborhood signs, does not extinguish, chronic course) or neuro exam abnormal
   a. Not necessary with monosymptomatic vertigo or BPPV

10. **Provocation studies**
   a. Valsalva: ↓ cerebral blood flow, reproduces ischemic symptoms
   b. Hyperventilation for 1 minute: points to hyperventilation syndrome (pschogenic)
   c. Vestibular function: rapid rotation and abrupt cessation in a swivel chair
      i. Compare with symptomatic dizziness
   d. If positional, examine patient in the appropriate position.
   e. Shake head with Frenzel glasses (blur patient’s vision, but examiner can see their eyes)
      i. If dizziness occurs, evaluate vestibular vertigo.
   f. Perform electronystagmography (ENG) to measure nystagmus precisely.

**Locating the lesion in rotational vertigo**
- Direction of hallucination of movement of environment or self is **away from side of lesion**
- Direction of fast phase of nystagmus beats **away from the side of the lesion**
- Fall **toward the side of the lesion**, particularly in darkness or with eyes closed

**Treatment**
- Acute vertigo: bed rest (1-2 days)
- Vestibular suppressant drugs (meclizine, dimenhydrinate, promethazine)
- Tranquilizers (diazepam, clonazepam)
- Steroids
- Early ambulation to promote compensatory mechanisms

**Sources**
- Case Files: Neurology, Toy, 2007
- PreTest: Neurology, Anschel, 2009
### Primary Headache Syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Migraine (16%)</th>
<th>Cluster (0.1%)</th>
<th>Tension (69%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Acute</td>
<td>Gradual</td>
</tr>
<tr>
<td>Character</td>
<td>Dull</td>
<td>Deep, stabbing</td>
<td>Wax &amp; wane</td>
</tr>
<tr>
<td>Location</td>
<td>70% unilateral</td>
<td>Unilateral</td>
<td>Bilateral</td>
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<tr>
<td>Autonomic</td>
<td>Autonomic symptoms</td>
<td>Autonomic symptoms</td>
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</tr>
<tr>
<td>N/V</td>
<td>Nausea &amp; vomiting</td>
<td>No N/V</td>
<td>No N/V</td>
</tr>
<tr>
<td>Aura</td>
<td>Aura</td>
<td>No aura</td>
<td>No aura</td>
</tr>
<tr>
<td>Abortive</td>
<td>1. NSAIDs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Triptan</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. DHE (IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic</td>
<td>Class A evidence (1st line): Propanolol, timolol, valproate, amitriptyline Others: Topiramate, imipramine, verapamil</td>
<td></td>
<td>TCA if severe/persistent to avoid NSAID overuse</td>
</tr>
</tbody>
</table>

#### Approach to the patient with acute, new-onset headache (not recurrent headaches)

1. Neurological exam
2. CT or MRI (equally sensitive) if neuro exam is abnormal or high index of suspicion
3. Identify red flags:
   - "Worst" headache ever
   - First severe headache
   - Subacute worsening over days or weeks
   - Abnormal neurologic examination
   - Pain that disturbs sleep or presents immediately upon awakening
   - Fever or unexplained systemic signs
   - Vomiting that precedes headache
   - Pain induced by bending, lifting, cough
   - Known systemic illness
   - Onset after age 55
   - Pain associated with local tenderness

#### Pathophysiology

- Two mechanisms of pain. Headache may result from either or both mechanism
  - Peripheral nociceptors activated in response to injury
  - PNS or CNS pathways are damaged or activated inappropriately
- Pain producing structures of cranium: scalp, middle meningeal artery, dural sinuses, falx cerebri, pial arteries
- Non-pain producing structures: Brain parenchyma, ventricular ependyma, choroid plexus, pial veins
- Key structures in headache: Trigeminovascular system
  - Large vessels
  - Dura mater
  - Peripheral terminals of CN V which innervate large vessels & dura mater
  - Trigeminal nucleus (caudal part) which extends into dorsal horn of spinal cord and gets C1-2 input
Migraine Headache

- Affects 15% of women and 6% of men. **2x risk of epilepsy**

**Types**
- Classic migraine (25%): migraine with preceding aura
- Basilar migraine (Bickerstaff): extremely severe. Can result in temporary quadriplegia, coma.
- Common migraine (most common): headache with no aura
- Acephalgic migraine (migraine sine hemicrania)(rare): aura only

**Signs & symptoms**
- Prodrome: nonspecific phenomenon can occur days before actual head pain
  - Depression, euphoria, irritability, increased urination
- Aura (25%): different from prodrome due to onset of frank neurologic dysfunction
  - 5 min to 1 hour prior to headache pain. Uncommon to have aura persist after headache starts
  - Visual (most common): scotoma, teichopsia (zig-zag), fortification spectra (“fortified town”), photopsias (flashes of light), distortions
  - Sensory: numbness, tingling
  - Aphasia and hemiparesis (less common)
- Cephalgia (headache pain)
  - Unilateral (65%) usually in periorbital region, but can extend to cheek and ear.
  - Can switch sides with different headaches and change place.
  - Can even occur in posterior strap muscles of cervical area.
  - Associated symptoms: nausea (87%), vomiting, photophobia (82%), phonophobia, vertigo

**Diagnosis**
- Repeated headaches 4–72 h with a normal physical examination, no other cause. >72 h = status.
- Two or more: unilateral, throbbing, aggravation by movement, moderate or severe intensity
- At least one: Nausea/vomiting, photophobia/phonophobia

**Pathogenesis**
- Cells in trigeminal nucleus release of vasoactive peptides (calcitonin gene-related peptide (CGRP)
- Synapse, then cross midline and project to thalamus, hypothalamus, and periaqueductal gray
- Serotonin (5-hydroxytryptamine): Pharmacologic evidence of involvement. 14 receptor types.
  - Triptans are agonists of 5-HT1B, 5-HT1D, and 5-HT1F. Less potent at 5-HT1A receptors.
    - H-HT1B/D receptors on blood vessels and nerve terminals are likely key to control.
- Dopamine
  - Migraine symptoms can be induced by dopaminergic stimulation.
  - Dopamine hypersensitivity in migraineurs: yawning, nausea, vomiting, hypotension
- Genetic component
  - Familial hemiplegic migraine (FHM): involvement of ion channels
    - Type 1 (50%): mutation in P/Q type voltage-gated Ca²⁺ channel
    - Type 2 (20%): mutation in Na⁺/K⁺ ATPase
    - Type 3: mutation in voltage-gated Na⁺ channel

**Treatment**
- Nonpharmacological
  - Avoidance of specific triggers. Avoid excess caffeine and alcohol. Regular sleep patterns
- Abortive therapy for acute attacks (50-75% effective)
  1. NSAIDS / Acetaminophen
  2. Triptans: selective 5-HT1B/D agonists (contraindicated with heart disease)
  3. Ergots: nonselective 5-HT agonists
- Prophylactic therapy (5+ attacks per month)
  - Propanolol, TCAs, Topiramate, Valproic acid, Gabapentin
- Adjunct therapy: antiemetics
  - Dopamine antagonists (metoclopramide) can help with headache and nausea
Status Migrainosus: intractable migraine headache for >72 hours.

1. Hydrate
2. Analgesia (non anti-migraine: opioids)
3. Anti-migraine (DHE)
4. Antiemetics (meclizine)
5. Sedation (diphenhydramine)

Tension-Type Headache
- **Signs & symptoms**
  - Bilateral, band-like dysfunction
  - Pain builds slowly, fluctuates, and may persist for many days
  - Can be episodic or chronic (>15 days/month)
  - No accompanying features like nausea, vomiting, photophobia, phonophobia (vs. migraine)
- **Pathophysiology:** Likely CNS-specific disorder (vs. migraine which is likely CNS and peripheral)
- **Treatment**
  - Analgesics: acetaminophen, NSAIDs
  - TCAs
  - Behavioral approaches
  - Triptans are not helpful
  - Botulinum toxin not helpful

Trigeminal Autonomic Cephalgia (TAC)
- Severe pain associated with cranial autonomic symptoms such as lacrimation, pupillary constriction
- May be misdiagnosed with “sinus headache” and fail treatment with nasal decongestants
- Pain occurs in periorbital or temple region
- Can occur at about the same time each day. Can spontaneously remit for years.
- Onset at night in 50%
- **Classification**
  - **Cluster headache:** named because they cluster in time.
    1-8 per day
    Extreme irritability may accompany headache
    Men > women (vs. migraine)
    Alcohol trigger (vs. other types)
    **Treatment:**
    - Acute: Oxygen and triptans
    - Prophylactic: Verapamil, TCAs, propanolol, lithium
  - **Paroxysmal hemicrania**
    1-40 per day
    **Treatment:**
    - Prophylactic: Indomethacin is effective (vs. other types)
  - **SUNCT** (short-lasting unilateral neuralgiform headache attacks with conjunctival injection + tearing)
    3-200 per day
    Less than 4 minutes in duration. Can be 5 seconds.
    Cutaneous triggers (vs. other types)
    **Treatment:**
    - Acute: Lidocaine

Tolosa-Hunt Syndrome: Nonspecific inflammation (granulomatous) in the cavernous sinus or superior orbital fissure
1. Ophthalmoplegia.
2. Retro-orbital pain, boring in nature.
3. Parasthesias, numbness in the forehead (V₁ and V₂ distribution).
Approach to the patient with chronic daily headache

- **Etiology**
  - > 4 hours: Migraine, tension-type, hemicrania continua. >72 hours = status migrainosus.
  - < 4 hours: Cluster, chronic paroxysmal hemicrania, SUNCT, haptic headache
  - Secondary: posttraumatic, inflammatory, chronic CNS infection, medication overuse headache

  **Low CSF volume headache (Spinal headache)**
  - Pain is positional. Resolves with reclining.
  - Can be following Valsalva, lifting, straining, coughing.
  - Most commonly from leak following LP, 48 hours to 12 days following.

  **High CSF pressure headache**
  - Space-occupying lesion, pseudotumor cerebri (can also see CN VI palsy)
  - Present on waking, improves as day goes on. Worse with recumbancy (vs. low CSF)
  - Visual problems are frequent. Papilledema common.
  - Imaging, then LP.
  - **Treatment:** acetazolamide, topiramate

- **Post-traumatic**
  - Can last for months-years after the event (physical trauma, infection)
    - ⅓ of patients report preceding flu-like illness with meningismus
  - Dizziness, vertigo can accompany.
  - Neurological exam and MRI normal.
  - **Treatment:** TCAs, topiramate, valproate, gabapentine, phenelzine

- **Management**
  1. Rule out underlying condition
  2. Prophylactic therapy with TCA or anticonvulsants (topiramate)
  3. If heavily medicated, attempt trial of weaning to rule out medication overuse headache

**Other primary headache syndromes**

- **Hemicrania Continua:** Moderate continuous unilateral pain
  - **Treatment:** Indomethacin

- **Primary cough headache:** begins suddenly, last for several minutes after coughing
  - Exclude “red flag” etiologies
  - Chiari malformation of CSF obstruction can be cause
  - **Treatment:** Indomethacin

- **Primary exertional headache:** Brought on with exertion. Mix of both cough and migraine features.
  - Bilateral, throbbing, 5 min - 24 hours.
  - Could be from acute venous distention (ex. weightlifters)
  - **Treatment:** Indomethacin, ergots

- **Primary Sex Headache:** Precipitated by sexual excitement
  - Important to rule out SAH, since 5-12% of SAH precipitated by sexual intercourse
  - Dull, bilateral headache which becomes intense at orgasm
  - **Treatment:** reassurance, diltiazem, ergots, indomethacin

- **Primary thunderclap headache:** Absence of known provocation
  - Differential: intracranial aneurysm, arterial dissection, cerebral venous thrombosis, drugs
  - Need imaging to rule out “red flag” cause.
  - **Treatment:** nimodipine

- **Hypnic headache:** brought on by sleep
  - Begins a few hours after sleep onset. Last 15-30 min.
  - Usually bilateral
  - Can fall back asleep only to be woken up again later.
  - Daytime naps can precipitate pain too.
  - **Treatment:** bedtime dose of lithium, verapamil, ergot, caffeine effective in ⅓
HEADACHE

Sources
- Case Files: Neurology, Toy, 2007
Sleep Disorders

Sleep stages
- Slow wave sleep (I + II) is highest in childhood and decreases through to elderly. REM increases inversely.
- Sleep cycle: 90-110 min
  - Non-REM sleep (NREM) (Stages I and II make up 50% of sleep)
    - Stage I: Transition from alpha to theta waves. Hypnic jerks (myoclonus) may occur.
    - Stage II (55%): Sleep spindles and K-complexes
    - Stage III (25%): Slow wave sleep. 20% delta waves.
    - Stage IV: 50% delta waves.
  - REM sleep (25%): nonocular muscles should be paralyzed.

Brain waves
- Alpha waves (8–13 Hz): common in the awake state
- Theta waves (4–7 Hz)
- Delta waves (0.5–2 Hz)

Sleep Disorders
- **Hypersomnia**: daytime sleepiness can be due to OSA, restless legs, narcolepsy
- **Narcolepsy**: excessive daytime somnolence plus REM sleep symptoms (“narcolepsy tetrad”)
  - REM sleep problems
    1. Cataplexy (70%): awake paralysis of muscle group or body triggered by startle or emotion.
    2. Hypnagogic hallucinations: vivid hallucinations
    3. Sleep paralysis: can’t move for a period following waking
  - Enter REM sleep early, paradoxically disrupts normal sleep, resulting in daytime sleepiness
  - Sleep attacks (less common although classically associated with the disorder”
  - Pathogenesis
    - ↓ hypocretin (lateral hypothalamus)
    - HLA types
  - PSG: enter REM before completing stages I-IV
  - Treatment:
    - Daytime sleepiness: CNS stimulants
    - Catpolxy/REM problems: TCAs, SSRIs, GHB
- **Restless Legs Syndrome (RLS)**: Irresistible urge to move legs. *Akanthia*: “inner restlessness”
  - Worse at night
  - Associated with dysthesias which are relieved by movement (vs. peripheral neuropathy)
  - Treatment: pramipexole, ropinirole. Also opioids, benzodiazipines, and gabapentin.
- **Periodic Limb Movement Disorder (PLMD)** (nocturnal myoclonus)
  - Stereotyped extensions of great toe and dorsiflexion of foot, Q 20-40 seconds during NREM
  - 17% of patients with insomnia, 11% of patients with excessive daytime somnolence
  - Treatment: dopaminergic, benzodiazipines
- **Obstructive sleep apnea**
  - Definition: AHI (apnea-hypopnea index - # per night) > 15 or > 5 with daytime sleepiness
  - Symptoms: morning headache, snoring, fatigue, erectile dysfunction
  - Associated hypertension due to: 1) hypoxic pulmonary vasoconstriction, 2) sympathetic outflow
  - Treatment: CPAP, dental devices
- **Chronic Fatigue Syndrome**: Persistent fatigue not substantially relieved by rest, unrelated to exertion > 6 mo.
- **Circadian Rhythm Sleep Disorder**: Unable to sleep/wake at times required by society. *Sleep quality normal.*
  - Extrinsic: jet lag, shift work
  - Intrinsic:
    - Delayed sleep phase syndrome (DSPS): sleep late and get up late.
    - Advanced sleep phase syndrome (ASPS): sleep early in day, get up early in night.
    - Non-24-hour sleep-wake syndrome: sleep onset later and later each day, get up later & later
    - Irregular sleep-wake rhythm: sleep multiple times/day. No main nighttime sleep. Irregular.
  - Treatment: behavioral therapy, melatonin
SLEEP DISORDERS

Approach to the patient with daytime sleepiness

1. Determine if daytime naps are intentional or unintentional
   a. Safety (while driving - 20% of serious crash injuries), affect life (while at school or work)
   b. 24 h of sleep loss is equivalent to blood alcohol level of 0.10 g/dL (0.1% BAC)
2. Differentiate tiredness & fatigue (fibromyalgia, chronic fatigue syndrome, endocrine [hypothyroid])
3. Multiple sleep latency test (MSLT) - time to onset of sleep under standardized conditions
4. Polysomnography (PSG)

Parasomnias: abnormal behaviors or experiences that arise from or occur during sleep

- **NREM sleep parasomnias**
  - **Sleepwalking** (Somnambulism)
    Automatic activities ranging from simple (urinate innappropriately) to complex (exit house)
    May be difficult to fully arouse and can respond with agitation or violence
    Occurs in stage 3 or 4 of NREM
    Most common in children and adolescence
    Cause: unknown
    Genetics: ⅓ familial
  - **Sleep Terrors** (pavor nocturnus)
    Occurs in NREM stages 3 and 4
    Screaming, autonomic arousal (diaphoresis, tachycardia, hyperventilation)
    Difficult to arouse (vs. nightmares: occur in REM sleep, cause arousal, and are remembered)
    Self-limited and benign
    Treatment: no specific therapy is indicated
  - **Sleep Bruxism**: involuntary, forceful grinding of teeth during sleep. Affects 10-20% of the population
    Age of onset: 17-20 years. Remission usually by age 40
  - **Sleep Enuresis**
    Primary: never have beencontinent
    - Before age 5 or 6, should be considered normal variant of development
    Secondary: patients who have previously been continent for 6-12 months
    - UTIs, cauda equina syndrome, epilepsy, sleep apnea, medication
    - Treatment: desmopressin (ADH), oxybutynin (anticholinergic), imipramine (TCA)

- **REM sleep parasomnias**
  - **REM Sleep Behavior Disorder (RBD)**
    Usually middle aged men with coexisting neurological disease
    50% will develop Parkinson’s disease within 10-20 years
    Agitated or violent behavior during sleep
    Injury to bed partner is common (vs. sleep walking)
    Patient retains vivid, unpleasant dream imagery (vs. sleep walking)
    **Diagnosis:** PSG to rule out seizures
    **Pathophysiology:** brainstem damage to descending motor inhibition
    - Animals with bilateral pontine tegmentum lesions exhibit similar activity
    **Treatment:** clonazepam (works in nearly 100% of patients)
  - **Nightmare disorder**
    Psychological problem
    Nightmares often portray the individual in a situation that jeopardizes their life or personal safety, usually occur during the second half of the sleeping process

Sources

- First Exposure to Neurology, Kirshner, 2007
HEAD INJURY & COMA

Concussion: Traumatically induced disturbance of neurological function and mental state.
- Grade I: No LOC. Symptoms < 15 minutes. Can return to play immediately.
- Grade II: No LOC. Symptoms > 15 minutes. Can return to play in 1 week.
- Grade III: LOC. Symptoms any duration. Can return to play in 1-2 weeks.
- Return to play after second concussion - Grade I: 1 week, Grade 2: 2 weeks, Grade 3: 1 month.

Clinical Manifestations: Signs & Symptoms
- Headache (via CN V pain fibers)
- Loss of consciousness
- Vomiting, dizziness
- CN palsies: from shearing, compression, herniation
- Papilledema: ↑ intracranial pressure (ICP)
- Ecchymosis (Battle sign, raccoon eyes)
- Cushing’s Triad: Bradycardia, respiratory depression, and hypertension

Mechanisms of injury
- Disruption of reticular activating system by movement of cerebrum with fixed brainstem results in LOC
- Contusion: petechial hemorrhage, edema, tissue destruction
  - Coup contrecoup: contusion at site of impact and contralateral side
  - CT or MRI: visible as hyperdense region
  - Plaques jaunes: hemosiderin-stained scars: main source of posttraumatic epilepsy
- Brain edema: Vasogenic (ex. meningitis) or cytotoxic (ex. ischemia, viral encephalitis)
- Torsion: Damages deep regions like basal ganglia
- Skull fractures: ⅓ of skill fractures have underlying intracranial lesions.
  - Cribiform plate: CSF rhinorrhea: target sign/ring test - CSF diffuses faster than blood on tissue paper.
  - Basilar skull fracture (4% of skull fractures): occipital, temporal, sphenoid, or ethmoid bones
    - Hemotympanum: blood behind the tympanic membrane
    - Battle sign: Ecchymosis over the mastoid process
    - Raccoon sign: peri orbital ecchymosis
  - Sella tursica fracture: radiologically occult even with severe neuroendocrine dysfunction
- Cranial nerve injuries
  - CN I: Anosmia. Particularly after fall on back of head. Shears off olfactory bulb from front.
  - Petrous bone fractures often produce facial palsy
- Seizures: uncommon immediately after injury, but very common (17%) late sequela
- Intracranial hematoma
  - Herniations: subfalcine, central & uncal transtentorial, cerebellar tonsilar, foramen magnum

Management
1. Immobilize cervical spine
2. CT without contrast if indicated
3. Consider prophylactic phenytoin in severe injury. Will not ↓ risk of late posttraumatic seizures, however.
4. Hypothermia improves long-term outcomes in traumatic brain injury
   a. ↓ metabolic demand, ↓ acidosis, ↓ changes in BBB, ↓ excitotoxic release

Indications for CT (New Orleans Criteria). Do CT if ANY are present:
- Persistent headache
- Emesis
- Age > 60
- Drug or alcohol intoxicaiton
- Anterograde amnesia
- Soft tissue/bony damage above the clavicles

Postconcussive Syndrome (30-80% of concussions)
- Within 4 weeks
- Irritability, depression, insomnia, subjective intellectual dysfunction, preoccupied with brain damage
- More common in non-sports injuries (MVAs)
- 25% have symptoms at 6 months, 10% at one year

Second impact syndrome: Diffuse swelling that occurs while a patient is still symptomatic from a previous injury
Physiology

- **Monro-Kellie Doctrine**
  - The sum of volumes of brain, CSF, and intracranial blood is constant. An increase in one causes a decrease in one or both of the remaining two.
  - CPP = MAP – ICP
    - CPP normally 50 – 70 mm Hg
    - ICP normally <20 mm Hg
  - CBF = (CAP – JVP) / CVR
    - CAP = Carotid arterial pressure

- **Autoregulation**
  - CBF is relatively constant over a wide range of CPP (40-100 mmHg)
  - In pathological state (stroke or trauma) there is a loss of autoregulation. In this setting, the brain becomes exquisitely sensitive to even minor changes in CP

**Subdural Hematoma (SDH)**
- Acute: Most are drowsy or comatose immediately (vs. epidural), but ⅔ have lucid interval.
- Subacute: drowsiness, headache, confusion, or mild hemiparesis.
  - Evolves over days to weeks following trauma
  - Minor trauma, patient may not even recall.
  - Can cause syndromes comparable to TIAs.
  - Can result in seizures
  - Elderly and alcoholics.
- CT: cresenteric (vs. lens in epidural)

**Epidural Hematoma (EDH)**
- Evolve more rapidly than subdural
- Lucid interval after injury before coma is classic, but relatively uncommon.
- 58% acute (arterial), 31% subacute, 11% chronic (venous epidural)
- ⅔ middle meningeal artery, 10% frontal or occipital
- Prognosis: non-coma: 90-100% good prognosis, coma: 10-40% mortality.
- CT: lens

**Subarachnoid hemorrhage (SAH)**
- Etiology: ruprured aneurysm, AVM, trauma
- Aneurysms: 85% in anterior circulation
  - ⅔ anterior or posterior communicating arteries. ⅔ fibromuscular dysplasia.
  - Large: >1cm may benefit from prophylactic treatment (embolization, clipping). 1%/year rupture
  - Giant: >2.5cm can cause symptoms by compressing adjacent structures. 6%/year rupture
  - Mycotic: usually more distal. Controversial whether should let heal or treat.

- **Signs & Symptoms**
  - Loss of consciousness at time of rupture (50%) thought to be from sudden ↑ in ICP
  - Severe headache (45%) (“worst headache of my life”) is usually presenting complaint
  - Meningismus: headache, nuchal rigidity, photophobia
  - Vomitting

- **Sequelae**: delayed neurologic deficits
  - Rerupture: 30% if untreated, 60% mortality
  - Vasospasm (30%): signs of ischemia appear 4-14 days (mean: 7) after SAH
    - Triple H therapy: hypotension (↑ CPP), hemodilution (↑ CBF), hypervolemia (high-normal)
  - Hyponatremia: ANF ↑, SIADH, Long QT syndrome, T-wave inversion

- Diagnosis: CT (best if 24 hrs after onset) and LP showing xanthochromia. CT is false negative in 10% (early).

**Management of Elevated ICP**
- **Treat underlying cause**
- **Avoid causing hypotension. Use pressors.**
  1. Head elevation: Reverse Trendelenberg
  2. Hyperventilation to PCO₂ of 26 to 30 mmHg
  3. Osmotic diuresis (Mannitol), goal: 300 mOsm
  4. Hypertonic saline
- **Goal**: keep ICP <20mm Hg and CPP 60-70 mmHg
  - Keep serum osmolarity 295-305
  - Sedation: ↓metabolic demand (Barbiturates)
  - Craniectomy
  - Removal of CSF (hydrocephalus)
  - LP only after CT since could precipitate herniation
Coma (from greek for “sleep”): need bihemispheric dysfunction or brainstem involvement
- Bihemispheric dysfunction: metabolic (hypoglycemia, hypothyroidism, intoxication)
- Brainstem dysfunction: reticular activating system (RAS) of pons
- Otherwise, a focal lesion will NOT cause coma.

Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eyes (4 eyes)</th>
<th>Verbal (5)</th>
<th>Motor (V-6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4: Open spontaneously</td>
<td>5: Normal conversation. Oriented.</td>
<td>6: Obey commands</td>
</tr>
<tr>
<td>3: Open to verbal stimulation</td>
<td>4: Disoriented. Words normal.</td>
<td>5: Localizes painful stimuli</td>
</tr>
<tr>
<td>2: Open to painful stimuli</td>
<td>3: Inappropriate words.</td>
<td>4: Withdraw from painful stimuli</td>
</tr>
<tr>
<td>1: Eyes do not open</td>
<td>2: Incomprehensible sounds.</td>
<td>3: Decorticate (flexion)</td>
</tr>
<tr>
<td>Scoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor: 13-15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate: 9-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe: &lt;9 (intubate), &lt;5 85% die within 24 hours</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Signs in comatose patient
- Eye deviation: look toward a hemispheral lesion and away from a brainstem lesion
- Occulocephalic reflex (“Doll’s eyes”): intact brainstem
- Occulovestibular response: Caloric stimulation (COWS)
- Corneal reflex
- Cheyne-Stokes: crescendo-decrescendo breathing followed by apnea. Signifies bihemispheric or metabolic.
- Kussmaul respirations: deep, rapid breathing. Acidosis or pontomesencephalic (pons-midbrain) lesion.
- Agonal gasps: medullary damage, terminal respiratory pattern.

Differential Diagnosis of Coma
- No focal signs and normal CSF
  - Intoxications: alcohol, sedatives, opiates
  - Metabolic: anoxia, electrolytes, DKA, HHNK, hypoglycemia, uremia, hepatic, thyroid, addisonian
  - Systemic infections: pneumonia, sepsis, Waterhouse-Friderichsen syndrome
  - Temperature: hyperthermia, hypothermia
  - Trauma: concussion, diffuse axonal injury
  - Shock
  - Postictal
  - Acute hydrocephalus
- No focal signs, positive meningismus, abnormal CSF
  - Subarachnoid hemorrhage: ruptured aneurysm, AVM, trauma
  - Infectious: bacterial, viral, fungal, parasitic
  - Emboli, carcinomatosis, lymphomatous
- Focal signs of brainstem or cerebrum
  - Hemispheric hemorrhage or infarction with brainstem compression
  - Epidural and subdural hemorrhage
  - Contusion
  - Abscess, empyema
  - Cortical vein thrombosis, HSV
  - ADEM (Acute disseminated encephalomyelitis): fever reappears, focal signs. “Monophasic MS”

Hypoxic-Ischemic Encephalopathy
- Mild pure hypoxia (high altitude): impaired judgement, inattentiveness, ataxia, euphoria. Reversible.
- Hypoxia-ischemia: full recover can occur if 3-5 min, but longer than 5 minutes permanent damage occurs.
- Blood pressure < 70 mmHg systolic or PaO2 < 40 mmHg is usually necessary
Management of the comatose patient
1. ABCS: intubate. Hyperventilate to induce hypocapnea if there is a need to reduce ICP.
   a. Secure C-spine
2. Give naloxone if narcotic overdose even remotely suspected
3. Give glucose and thiamine (vitamin B₁) if hypoglycemia is even remotely suspected.
4. Physostigmine if anticholinergic overdose.
5. Flumenazil if benzodiazepine overdose OR hepatic encephalopathy
6. Imaging study
7. CSF analysis if fever or meningismus

Brain death criteria (All conditions must be met)
1. Unresponsiveness
2. Absence of cerebral/brain stem function
   a. Absent pupillary/gag reflexes (versus vegetative state where these are present)
   b. No spontaneous respiration
3. Nature of the coma must be known
4. Reversible causes must be ruled out: E.g. hypothermia, intoxication, shock
5. Persistence of brain dysfunction
   a. 6 hours with an isoelectric EEG
   b. 12 hours without EEG
   c. An EEG is not required to diagnose brain death.

Brain Herniation: Progression from rostral-caudal deterioration of brainstem function. (Rarely observed in reality)
1. Cortical damage: Confusion apathy, drowsiness, Cheyne-Stokes respirations
   a. Pupils become small and react very little to light. VOR intact. Babinski present.
   b. Grasp reflexes and decorticate posturing appear
2. Midbrain damage: Coma, medium-sized pupils (Edinger-Wastphal nucleus CN III parasympathetic damaged)
3. Pontine damage: Loss of vestibuloocular reflex (VOR), decerebrate posturing
4. Medullary damage: irregular breathing (agonal gasps), respiratory arrest

Herniation Syndromes
- Subfalcine (#1): cingulate gyrus is pushed under the falx
  o Occlusion of ACA and frontal lobe infarction
- Transtentorial (#2): Uncal syndrome
  o Drowsiness
  o CN III compression (ipsilateral): dilation followed by paralysis
  o Compression of ipsilateral PCA
  o Rupture of basilar artery paramedian branches (Duret hemorrhages)
    Causes medullary depression and death
- Cerebellar-foramen magnum (#3) (pressure cone)
  o Respiratory arrest (compression on medulla)
  o Cerebellar fits: Episodic tonic extension and arching of the neck and back and extension of limbs
  o Cardiac irregularity (tachy or brady)
  o Loss of consciousness
  o Pain in the neck, parasthesias in the shoulders
- Kernohan-Woltman notch phenomenon (#4): severe transtentorial (uncal) herniation
  o Primary lesion on ipsilateral side causes secondary lesion on contralateral side which causes neurological findings ipsilateral to the primary lesion, “false localizing sign.”
- Transcalvarial: brain squeezes through fracture or craniotomy site.
Sources

- Evans, RW. Concussion and mild traumatic brain injury. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2011.
- American Academy of Neurology, Practice Parameters: Determining Brain Death in Adults (1994)
- Case Files: Neurology, Toy, 2009
- PreTest: Neurology, Anschel, 7th edition, 2009
CEREBROVASCULAR DISEASE

Overview:
- Third leading cause of death in USA
  - Brain is especially sensitive to ischemia since neurons lack glycogen. More than a few minutes: infarction.
  - **Transient ischemic attack (TIA):** symptoms resolve within 24 hours
    - Amaurosis fugax (“fleeting blindness”): ophthalmic artery
    - 4-10% with TIA have a frank stroke within 12 months
  - **Transient global amnesia (TGA):** antero/retrograde amnesia < 24 hours. Retain identity. No ↑ stroke risk.
- **Differential diagnosis of acute-onset neurologic symptoms**
  - Seizure
  - Intracranial tumor (Hemorrhage, seizure, hydrocephalus)
  - Migraine (especially when without headache, acephalgic migraine)
  - Metabolic encephalopathy (classically fluctuating mental status w/o focal findings, but can unmask)

Approach to the patient with acute-onset focal neurologic deficit
1. History & physical to rule out other causes of neurologic deficit. 85% ischemic stroke have hemiparesis.
2. CT of the head without contrast: (a) Rule out mass lesion and (b) Rule out hemorrhage

Ischemic stroke (80%)
1. Administer tPA if indicated.
   - Contraindications:
     - Active bleeding (hemorrhagic stroke)
     - Last known symptom-free > 4.5 hours
     - Brain cancer
     - Bleeding diathesis
     - PT > 15 (INR >1.5), platelets < 100,000
     - Stroke, head surgery within 3 months
     - LP or arterial line in last 7 days
     - Uncontrolled hypertension
     - Seizure at onset of stroke
     - Acute MI or post MI pericarditis
     - Symptoms rapidly improving
     - Blood glucose <50 or >400 mg/dl
     - Pregnant
   - Intra-arterial (local) tPA can be given < 6 hours
2. Give Aspirin (RRR > 20%): **2nd stroke prevention**
   - Heparin: no benefit in 3 month outcome
3. Treat hypertension with β-blocker if:
   - Malignant (elevated ICP)
   - → 185/110 mm Hg & tPA planned
4. Treat fever with antipyretics
5. Other treatments:
   - Surgical embolectomy
   - Endovascular cooling for metabolic slow
   - Craniotomy (especially post-acute)

Hemorrhagic stroke (20%)
1. Airway management especially important since reduction in consciousness is common
2. Assess and treat coagulopathy
   - Discontinue anticoagulants
   - Reverse Warfarin
     - Prothrombin concentrates
     - Fresh-frozen plasma
     - Vitamin K
   - Reverse thrombocytopenia: platelets
3. Surgical evacuation if cerebellar hematoma only
4. Lower ICP if elevated
   - Mannitol
   - Hyperventilation
5. Treatment of hypertension is controversial
   - Goal: MAP < 130 mm Hg
   - Use non-vasodilating drugs
     - Nicardipine, labetalol, esmolol

Treatment after the acute phase
- Search for the source of the embolus
  - Echocardiogram
  - Carotid duplex ultrasound
  - Electrocardiogram (look for A-fib)
  - MRA or CTA of brain
  - Test for hypercoagulability if suspected
- Treat cerebral edema (5-10% herniate)
  - Worse in large infarcts
  - Water restriction, IV mannitol, craniotomy

Pathophysiology of ischemic stroke

- Reduced blood flow: Need minimum 50 ml O₂/100g tissue/min to stay conscious.
  - Zero flow: infarction in 4–10 min
  - <16–18 mL/100 g tissue per min: infarction in <1 hour.
  - 18-20 mL/100 g tissue per min: ischemia without infarction unless for hours to days
- Mechanisms of cell death: ischemic cascade
  1. ↓ ATP production
  2. Loss of K⁺ from cells
  3. Membrane depolarization
  4. Build-up of glutamate
  5. Uncontrolled Ca²⁺ entry into cells
  6. Impaired mitochondrial function
  7. Activation of nitric oxide synthetase and caspases, free radical formation

Core: irreversibly damaged
Penumbra: at-risk tissue. Can be salvaged.

Etiology

- Ischemic stroke (80% of all strokes)
  - Large vessel (60% of all strokes)
    - Atheroembolic (most common)
      - Cardioembolism (20%): atrial fibrillation, MI, prosthetic valves, RHD, ischemic CM
      - Carotid atherosclerosis (10%)
    - Traumatic dissection
      - More common in younger patients
    - Vasospasm (drug-induced, migrainous, eclampsia, post-SAH)
      - Moyamoya (“puff of smoke”) disease: chronic collaterals look like smoke on CTA
    - Hyperviscosity/hypercoagulable state
  - Small vessel (20% of all strokes): pure motor, pure sensory, dysarthria
    - Leukoariosis (periventricular white matter disease): Lipohyalinosis (lacunar)
      - Chronic hypertension
    - Vasculitis (SLE, drugs)
      - CADASIL (cerebral AD arteriopathy with subcortical infarcts + leukoencephalopathy)
        - Small-vessel in striatum (60%), thalamus, pons, cerebellum.
        - 40% have migraine with aura with onset at 30-40 years
    - Hyperviscosity/hypercoagulable state

- Hemorrhagic stroke (20% of all strokes)
  - Subarachnoid hemorrhage (SAH): sudden onset of severe headache, stiff neck.
    - Rupture of berry aneurysm
  - Arteriovenous malformation (AVM)
    - Intracerebral hemorrhage (ICH): smooth or stepwise over hours (vs. SAH). 50% mortality.
      - Hypertensive (most common): Small-vessel in striatum (60%), thalamus, pons, cerebellum.
        - Evolve over 30-90 minutes. At 1-6 months, orange glial scar with hemosiderin ‘phages
        - Putamen: contralateral hemiparesis, eyes deviate toward lesion
    - Head trauma
    - Brain tumor
    - Transformation of ischemic infarction (1-6%). Usually large infarctions.
    - Drugs: Cocaine, amphetamine, phenylpropranolamine. Most common stroke in < 45 years.
    - Coagulopathy: uncommon
    - Arteriovenous malformation (AVM): Risk is 2-4%/year for bleed. Headache. 30% seizures.
    - Cavernous hemangioma
    - Amyloid angiopathy: most common cause in non-hypertensive elderly
Risk factors for ischemic stroke

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
<th>Effect of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2-5 RR</td>
<td>38% reduced with treatment</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.8-2.9 RR</td>
<td>68% reduced with treatment</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.8-6 RR</td>
<td>no reduction apparent with treatment</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.8 RR</td>
<td>50% reduced with quitting</td>
</tr>
<tr>
<td>Asymptomatic carotid stenosis</td>
<td>2.0 RR</td>
<td>Reduced risk clear only if symptomatic, &gt;70% stenosis</td>
</tr>
</tbody>
</table>

Stroke syndromes

Anterior circulation (from carotids)

- **Middle cerebral artery**
  - Complete: Hemiparesis (85% of ischemic), hemianesthesia, homonymous hemianopia, aphasia
  - Partial: any combination of above
  - Globus pallidus and putamen: parkinsonism and hemiballismus (if subthalamic nucleus infarcted)
- **Anterior cerebral artery**: proximal occlusion tolerated well because of collaterals but not distal
  - Abulia, paraparesis of lower extremities, urinary incontinence. *Sensation is spared.*
- Anterior choroidal artery (rare): contralateral hemiplegia, hemianesthesia, and homonymous hemianopia

Posterior circulation (from vertebrobasilar system)

- Posterior cerebral artery
  - **P1 syndromes** (PCA proximal to P-Comm): midbrain, subthalamic, thalamic
    - CN III palsy with contralateral ataxia (Claude’s syndrome)
    - CN III palsy with contralateral hemiplegia (Weber’s syndrome)
    - Hemibalismus if subthalamic nucleus involved
    - Decerbrate rigidity if whole midbrain infarcted
  - **P2 syndromes** (PCA distal to P-Comm): cortical temporal, occipital
    - Contralateral homonymous hemianopia with macula sparing is the usual manifestation
    - Bilateral: cortical blindness (blind with intact pupillary reflex). Can be unaware (Anton’s)
    - Peduncular hallucinosis: brightly colored hallucinations

Small vessel penetrating circulation (Lacunar infarcts): Most often in hypertensive or diabetic patients.

- Internal capsule (anterior limb): Ataxia (frontopontocerebellar tract) + hemiparesis (corticospinal tract)
- Internal capsule (posterior limb): Pure motor impairment (corticospinal). No cortical / visual dysfunction.
- Thalamus VPL nucleus infarct: Contralateral hemianesthesia/parasthesia.
  - Also can have hemihyperesthesia. (Thalamic syndrome / Dejerine-Roussy disease)
- Anterior Pons (basis pontis): Dysarthria/clumsy hand
- Mixed sensorimotor: thalamus and internal capsule infarcted.
CEREBROVASCULAR DISEASE

- Vertebral: hemiparesis does not occur, but quadraparesis can occur from total spinal infarction
  - **Lateral medullary syndrome** (Wallenberg’s) (blue): blockage of V4 (after pierces dura) of vertebral a.
    - Occlusion of one vertebral artery or PICA (would cerebellar signs too).
    - Weakness only in CNs (palate). No corticospinal weakness.
    - Vertigo (CN VIII nucleus)
    - Numbness (anaesthesia)
      - Ipsilateral face (CN V nucleus)
      - Contralateral limbs (corticospinal tract before decussation in lower medulla/cord)
    - Hoarseness, dysarthria, dysphagia (CN IX, X nucleus ambiguous)
    - Ipsilateral ataxia (inferior cerebellar peduncle)
    - Palatal myoclonus (central tegmental tract)
    - Ipsilateral Horner's syndrome (descending sympathetic tract)
  - **Medial medullary syndrome** (occlusion of anterior spinal artery
    - Weakness only in corticospinal tract. No CN weakness.
    - Contralateral hemiparesis (corticospinal tract before it decussates in low medulla/cord) of
      - Spares the face since CN VII not involved.
    - Contralateral ataxia (medial lemniscus - proprioception)
    - Ipsilateral tongue weakness (CN XII)
  - **Superior alternating hemiplegia (Weber’s syndrome)**: midbrain penetrating artery occlusion
    - Ipsilateral CN III palsy
    - Contralateral hemiparesis (corticospinal tract)
    - Contralateral parkinsonism (substantia nigra)

- Basilar
  - Complete: “locked-in syndrome”
  - Partial: vertigo, hearing loss, ataxia, dysphagia, diplopia, dysarthria, nystagmus

Sources
- Tietjen G. “Stroke” lecture notes for MS-1 Neuroscience, 2009
- PreTest: Neurology, Anschel, 2009
INFECTIONS OF THE CNS

Definitions
- Meningitis: infection of the subarachnoid space
- Encephalitis: viral infection of brain parenchyma
- Cerebritis: bacterial, fungal, parasitic infection without a capsule. Abscess if there is a capsule.
- Pachymeningitis: infection of the dura mater only

Meningitis
- **Signs & symptoms**
  - Meningismus: headache, fever, neck pain (95% sensitive). Photophobia, nausea, vomiting.
  - Decreased level of consciousness (>75%)
  - Seizures (20-40% of bacterial)
  - Elevated CSF opening pressure (90% of bacterial >180 mmHg) (vs. non bacterial)
  - Kernig's sign: supine with knee flexed: Attempts to passively extend the knee elicit pain.
  - Meningococcemia: maculopapular rash becomes petechial. On extremities, palms, soles, mucous.

Approach to the patient with headache, fever, ± nuchal rigidity.
- Empiric antibiotics/antivirals, LP, blood cultures, imaging all need to be done, but order is different.
  1. Altered mental status?
    - Yes: meningoencephalitis, ADEM, ecephalopathy, mass lesion
      - Empiric therapy
      - Blood culture
      - Head CT or MRI
      - Lumbar puncture if not mass lesion (cancer or abscess)
    - No: Papilledema or evidence of ↑ ICP?
      - No: immediate LP and blood culture
      - Yes: empiric therapy first then imaging study, then LP
- Antimicrobials (antibiotics, antivirals) do not ↓ sensitivity of CSF culture if done within 2 hours of LP.
- Look for skin rash: give steroids and antibiotics (*Neisseria meningitidis*)
- CT/MRI: give mannitol and hyperventilate if signs of ↑ ICP

Epidemiological risk
- Recent exanthem: Measles, rubella, HHV-6
- Diarrhea in infant: Rotavirus
- Hepatitis C
- Raccoon exposure: *Baylisascaris procyonis*
- Animal bite: rabies
- Cat exposure: *Bartonella henselae*
- Mouse exposure: Lymphocytic choriomeningitis Virus (LCMV)
- Cattle or unpasteurized milk: *Brucella, Coxiella*
- Pet bird: *Chlamydia psittaci* (Psittacosis)
- Mosquito or tick exposure: Colorado Tick Fever, Arbovirus, *Rickettsia, Borrelia, Ehrlichia*
- Swimming in fresh water: Amoebic meningoencephalitis (*Acanthamoeba, Naegleria fowleri*)

CSF Analysis

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Bacterial</th>
<th>TB</th>
<th>Asceptic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WBC</strong></td>
<td>&lt; 5</td>
<td>&gt; 1000</td>
<td>High</td>
<td>25-500</td>
</tr>
<tr>
<td><strong>Differential</strong></td>
<td>No PMNs</td>
<td>PMNs</td>
<td>Lymphocytes</td>
<td>Lymphocytes, can be PMN early</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>50-75 (2/3 of serum)</td>
<td>Low</td>
<td>Low</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>&lt; 60</td>
<td>High</td>
<td>Increased</td>
<td>20-80</td>
</tr>
<tr>
<td><strong>Opening pressure</strong></td>
<td>100–180 mm H₂O</td>
<td>High</td>
<td>Normal</td>
<td>High-normal</td>
</tr>
</tbody>
</table>

Hypoglycorrhachia: low glucose in CSF.
Seizures: normal CSF.
INFECTIONS OF THE CNS
Acute Bacterial Meningitis

● Etiology
  ○ *Streptococcus pneumoniae* (50% of cases): most common cause in >20 years of age.
    Risk factors: asplenia, sinusitis, otitis, alcoholism, DM, immunodeficiency (complement)
    Mortality: 20% despite antibiotic therapy. Highest mortality of all meningitides.
  ○ *Neisseria meningitidis* (25% of cases): 60% of cases between 2-20
    Presence of petechial or purpuric skin lesions
    Can be fulminant and result in death within hours of onset.
    Pathophysiology: can result after nasopharyngeal colonization
  ○ Enteric gram-negative bacilli
    Risk factors: craniotomy, DM, cirrhosis, alcoholism, UTI
  ○ *Streptococcus agalactiae* (Group B β-hemolytic): neonates and >50 years old with comorbidities
  ○ *Listeria monocytogenes*: neonates, pregnant women, >60 and immunocompromised
    Acquired from food: coleslaw, milk, soft cheese
    Can cause rhomboencephalitis (brain stem infection)
  ○ *Hemophilus influenzae*
    Declined dramatically since Hib conjugate vaccine
  ○ *Staphylococcus aureas and coagulase-negative Staphylococci (epidermidis, saprophyticus)*
    Risk factors: invasive neurosurgery, intrathecal chemotherapy
  ○ Immunosuppressed: cryptococcus (meningitis), aspergillus (abscess), mucor (diabetics)

● Pathophysiology: ↑ cytokines and chemokines (TNF and IL-1)
  ○ ↑ permeability of blood-brain barrier: vasogenic edema and leak of serum proteins
  ○ Subarachnoid exudate obstructs CSF: obstructive communicating hydrocephalus
  ○ Neutrophil degranulation: cytotoxic edema, cell injury, and cell death.

● Treatment: Ampicillin for *Listeria*. Vancomycin for *Staph*. 3rd generation cephalosporin for others.
  ○ Dexamethasone *first*: ↓ TNF by macrophages. Reduce neurologic sequelae & mortality
  ○ *CT before LP if*: ↓ consciousness, papilledema, recent trauma, immunosuppressed, focal finding
  ○ Recurrent meningitis: test for CSF leak (fluid glucose content [sensitive] β2-microglobulin [specific])

<table>
<thead>
<tr>
<th>Group</th>
<th>Antibiotic regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates, infants to 3 months</td>
<td>Ampicillin + 3rd generation cephalosporin</td>
</tr>
<tr>
<td>Immunocompetent children &gt;3 mos and adults &lt;55</td>
<td>3rd generation cephalosporin + vancomycin</td>
</tr>
<tr>
<td>Adults &gt;55 and adults of any age with comorbidities</td>
<td>Ampicillin + 3rd generation cephalosporin + vancomycin</td>
</tr>
<tr>
<td>Hospital-acquired meningitis, posttraumatic or postneurosurgery meningitis, neutropenic patients, or patients with impaired cell-mediated immunity</td>
<td>Ampicillin + 3rd generation cephalosporin + vancomycin</td>
</tr>
</tbody>
</table>

Acute Viral Meningoencephalitis (Asceptic meningitis)
Meningitis

● Enteroviruses (75%) (coxsackieviruses, echoviruses, and human enteroviruses 68–71)
  ○ Summer months
  ○ Stigmata: exanthems, hand-foot-mouth disease, herpangina, pleurodynia (CP)
● HSV-2: 25% of initial genital herpes infection
● Arthropod-borne
● HIV
● Treatment: Empiric acyclovir, gancyclovir + foscarnet for CMV.
  ○ Humoral immunodeficiency (ex. Bruton’s X-linked agammaglobulinemia): IV Ig
  ○ Supportive: analgesics, antipyretics, and antiemetics
● Prognosis:
  ○ Excellent in adults. Neonates can have permanent neurologic damage.
  ○ EEE virus: 80% have neurologic sequelae

Encephalitis: meningitis + altered mental status

● Herpesviruses (HSV-1 [HHV-1], VZV [HHV-3], EBV [HHV-8])
● Arthropod-borne (LaCrosse, West Nile, St. Louis)
  ○ WNV: Mollaret-like mononuclear cells
  ○ 40% have PMN pleocytosis
● Amebic: *Acanthamoeba, Naegleria fowleri*
  ○ Diagnosis: CSF wet mount
  ○ Prognosis: mortality approaches 100%
INFECTIONS OF THE CNS

Diagnosis
- LP: CSF culture/serology positive in 30-70%
  - ¾ of culture-negative etiologies can be identified by CSF PCR
    - PCR: Sensitivity and specificity is equivalent to or exceeds brain biopsy
- MRI, CT, EEG: done in encephalitis to rule out alternate diagnoses
  - Differentiate between focal and diffuse process
  - MRI FLAIR and EEG can have characteristic pattern with HSV

Subacute Meningitis
- Low-grade meningismus: unrelenting headache, stiff neck, low-grade fever, and lethargy for days to weeks
- Etiology:
  - Mycobacterium tuberculosis: caseating tubercles from primary infection not from lungs
    - Treatment (RIP₂E): Rifampin, Isoniazid, pyrazinamide, pyridoxine, and ethambutol
  - Fungal: Cryptococcus neoformans (most common), Histoplasma capsulatum, Coccidioides immitis
    - Inhalation of airborne spores results in self-limited pulmonary infection
    - Can see eosinophils in CSF if Coccidiodes immitis
    - Cryptococcus treatment: amphotericin B & flucytosine, then fluconazole
    - Histoplasma, Coccidioides treatment: Amphotericin B (may need intrathecal)
  - Treponema pallidum
    - Sequelae:
      - Meningitis (1-2 years): cranial mononeuropathies, hydrocephalus
      - CVA (5-7 years)
      - General paresis (10 years): ↓ cortical function, dementia, Argyll-Robertson pupil
      - Tabes dorsalis (10-20 years): Lancinating pain, ataxia, bowel dysfunction, ↓ light touch
        - Crises: abdominal, laryngeal pain. Charcot joint. ↓ DTR (Westphal sign)
      - Gummatous: any time after infection. Dependent on location.
    - Diagnosis: CSF VDRL (sensitive), FTA-AB (specific)
      - Hyporeflexia (50%), sensory impairment (48%), pupillary changes (43%) including Argyll-Robertson pupil,
      - Cranial neuropathy (36%) (CN VII and VIII most common), dementia (35%), positive Romberg (24%)
      - Nerve studies: ↓ sensory, normal motor conduction. EMG normal. H reflexes common due to damage to DRG. Neurogenic bladder.
    - Treatment: Penicillin G 4 million units Q 4 hours x 14 days

Chronic Encephalitis
- Subacute Sclerosing Panencephalitis (SSPE) (Measles virus)
  - Primary infection at early age, latent for 6-8 years, then progressive neurologic disorder
  - 85% are between 5-15 at diagnosis
  - Signs & symptoms
    - Initial manifestations: mood and personality changes
    - Fever, headache do NOT occur
    - Intellectual deterioration, seizures, myoclonus, ataxia, and visual disturbances
    - Late: unresponsive, quadriplegic, spastic, ↑ DTR
  - Diagnosis:
    - MRI: ↑ T2 signal in white matter of brain and brainstem
    - EEG: nonspecific slowing, then high-voltage sharp slow waves every 3-8 seconds, then flat
    - CSF: acellular, mildly ↑ protein. ↑↑ gamma globulin, ↑ measles antibodies
  - Treatment: no good treatment available. Isoprinosine or IFN-α
- Progressive Rubella Panencephalitis (Extremely rare)
  - Affects males with congenital rubella syndrome after a latent period of 8-19 years
  - Signs & symptoms
    - Progressive neurologic deterioration, similar to SSPE
  - Diagnosis:
    - CSF: lymphocytic pleocytosis, ↑ protein, ↑ gamma globulin, ↑ rubella oligoclonal bands
  - Treatment: no therapy available
INFECTIONS OF THE CNS
Brain Abscess
- Risk factors: otitis media, mastoiditis, sinusitis, pyogenic infection, penetrating trauma, neurosurgery
  - Cryptogenic: abscess with no underlying indentifiable source
- Etiology (healthy): *Streptococcus* (40%), Enterobacteriaceae (25%), anaerobes (30%), *Staphylococci* (10%)
- Etiology (immunocompromised): *Nocardia*, *Toxoplasma*, *Aspergillus*, *Candida*, *Cryptococcus*
  - Latin america: Neurocystercercosis, India: Tuberculoma
- Route of infection: 1) spread from contiguous site (33%), 2) hematogenous (25%), 3) remote site
- Pathogenesis: Likely need focal weakening (ischemia, necrosis, hypoxia) for infection to occur
  - Cerebritis (day 1-3): perivascular infiltration which surround core of coagulative necrosis.
  - Late cerebritis (day 4-9): pus formation leads to enlargement of necrosis. Fibroblasts surround.
  - Early capsule formation (day 10-13): stronger on cortical side than ventricular side. Ring-enhancing.
  - Late capsule formation (day 14+): well formed necrotic center surrounded by dense collagen capsule.
- Signs & symptoms
  - Depends on location and level of ICP
    - Frontal lobe: Hemiparesis, temporal lobe: dysphasia, cerebellar: ataxia
    - Elevated ICP: papilledema, nausea and vomiting, drowsiness
  - Meningismus is not present unless the abscess has ruptured
- Diagnosis: Imaging studies
  - MRI is better than CT especially in early (cerebritis stages, <10 days): low-intensity signal on T1
  - Ring-enhancement of capsule
    - May be altered by treatment with steroids.
- Treatment
  - Antimicrobial therapy for minimum 6-8 weeks
  - Prophylactic anticonvulsant therapy since 35% develop seizures
  - Do not give steroids unless elevated ICP
  - Neurosurgical drainage mandatory, unless cerebritis, small (<2cm), inaccessible
  - Immunosuppressed who don’t respond to antimicrobials need brain biopsy to rule out lymphoma
Subdural empyema: collection of pus between dura mater and arachnoid mater
- Risk factors: sinusitis, male gender (3:1)
- Can have an extremely rapid course since the space has few barriers
- Often comorbid with epidural empyema (40%), cortical thrombophlebitis (35%), and abscess (>25%)
- Signs & symptoms
  - Fever and a progressively worsening headache (most common presentation)
  - Progresses to focal neurologic deficits, seizures, nuchal rigidity, and signs of ↑ ICP
- Diagnosis: MRI > CT for all intracranial infections
- Treatment
  - Neurosurgical drainage with burr hole or craniotomy
  - Antimicrobial therapy
- Prognosis: Long term sequelae (ex. seizures) occur in 50% of cases
Epidural abscess: Rare. <2% of intracranial infections.
- Signs & symptoms: fever (60%), headache (40%), nuchal rigidity (35%), seizures (10%), and focal deficits (5%)
- Etiology: Periorbital edema and Potts puffy tumor (frontal bone osteomyelitis) in 40%.
  - Potts puffy tumor: swelling of the forehead from underlying osteomyelitis and abscess
- Prognosis: Mortality < 5%
- Risk factors: IVDA
Suppurative Thrombophlebitis: Septic venous thrombosis of cortical veins and sinuses

- **Etiology:** complication of bacterial meningitis, abscess, infection of skin of the face, sinusitis, mastoiditis
- **Pathophysiology:** cerebral veins/sinuses have no valves, retrograde flow occurs.
  - CN III, CN IV, CN VI, CNS V₂ & V₃, and ICA all pass through the cavernous sinus
  - Septic cavernous sinus thrombosis
    - fever, headache, frontal and retroorbital pain, and diplopia
    - EOM: ptosis, proptosis, chemosis (conjunctival edema), and extraocular dysmotility
    - CN V: hyperesthesia of face and decreased corneal reflex
- **Signs & symptoms:** headache, fever, nausea and vomiting, confusion, seizures, hemiparesis
- **Diagnosis:** MRI and MR venography showing ↓ flow
  - MRI > CT for all intracranial infections
- **Treatment:**
  - antibiotics, hydration, removal of infected tissue.
  - Heparin. Small intracerebral hemorrhage is not a contraindication since infection is so virulent.
  - tPA, but studies are limited

Chronic and Recurrent Meningitis

- **Definition:** Meningismus for > 4 weeks and associated with persistent inflammation of CSF (WBC > 5)
- **Etiology:** 1) infections, 2) malignancy, 3) inflammatory 4) chemical, and 5) parameningeal infections
- **Signs & symptoms:** chronic headache, hydrocephalus, CNeuropathy, radiculopathy, cognitive decline
  - Intracranial: ↑ ICP, vomiting, apathy, drowsiness, gait instability, impaired upgaze, CNeuropathy
  - Spinal: multiple radiculopathies, myelopathy. Do electrophysiologic testing
- **Diagnosis:** Imaging showing *dural enhancement* (always abnormal except post-LP)
- **Approach to the patient**
  1. CSF analysis
    - PMN-predominant: Nocardia, Actinomyces, Brucella, TB, fungi, noninfectious (SLE, chemical)
    - Eosinophil-associated: parasites, fungal, neoplasia, inflammatory (sarcoid, hypereos syn)
  2. Search for underlying systemic cause
  3. Biopsy of meninges
    - Successfully identifies pathology in 80% of enhancing lesions, but only 9% of non-enhancing
    - Sarcoid (31%) and metastatic cancer(25%) were the most common conditions identified

Sources:

- Roos Karen L, Tyler Kenneth L, "Chapter 376. Meningitis, Encephalitis, Brain Abscess, and Empyema" (Chapter).
- Case Files: Neurology, Toy, 2007
Seizures: Latin sacire, “to take possession of.” Excessive, hypersynchronous discharges from CNS neurons.

Epilepsy: 2+ unprovoked seizures.

Approach to the patient with a seizure

1. Verify that it was truly a seizure
   a. Exclude syncope, migraine, TIA, psychosis, nonepileptic seizure (eyes often closed. Open in epileptic)
      i. Syncope (<15s) can have convulsion if remain in upright posture and reduce brain perfusion.
   b. Rule out nonconvulsive status epilepticus (NCSE) with EEG if the patient is still confused/postictal

2. Determine cause: identify risk factors and precipitating events
   a. CBC, electrolytes, serum glucose, liver & renal function, urinalysis, tox screen, sleep deprived?
   b. Risk factors: head trauma, family history, history of meningitis
   c. Look for structural abnormality: CT or MRI
      i. New onset seizure in an adult is tumor or stroke until proven otherwise
   d. History of seizures: test for serum levels of antiepileptics
   e. Febrile: CT, LP (looking for meningoencephalitis)
   f. EEG
      i. Focal abnormality: do CT/MRI to look for mass lesion, degenerative disease
      ii. Intercital abnormality in 40% with epilepsy

3. Determine AED medication is indicated. 1st seizure: 75% never seize again. 2nd seizure: 70% WILL seize again
   a. Recurrent seizures of unknown etiology
   b. Known cause that cannot be reversed
   c. Present with status epilepticus
   d. Family history of seizures
   e. Abnormal interctal EEG
   f. Job depends on no seizures (ex. driver)

Selection of antiepileptic drugs

- Begin with monotherapy. Add a second drug with a different mechanism of action if poorly controlled
- Surgery is an option in focal epilepsy with poor control on medications.
  - Lesionectomy, temporal lobectomy, amygdalohippocampectomy, corpos collostomy
- Efficacy of all drugs is roughly equivalent. Select a drug based on patient comorbidities.
  - Migraine: Topiramate, Overweight: Topiramate or Zonisamide, Multiple interactions: Levitiracetam

Partial (includes 2nd generalization)  Generalized  Absence  Atypical Absence
   Phenytin  Lamotrigine  Vaproaic acid  Lamotrigine
   Lamotrigine  Topiramate  2. Lamotrigine  Topiramate
   Oxcarbazepine  Zonisamide  Clonazepam  Clonazepam
2. Levitiracetam  Phenytoin  Phenytoin  Carbamazapine
   Tiagabine  Oxcarbazepine  Carbamazapine
   Zonisamide  Phenobarbital
   Gabapentin  Primidone
   Phenobarbital  Felbamate
   Primadone  Felbamate
   Felbamate

Discontinue antiepileptic therapy if ALL are true:
1. Complete medical control of seizures for 1–5 years
2. Single seizure type, either partial or generalized
3. Normal neurologic examination, including intelligence
4. Normal EEG

Status epilepticus: continuous or repetitive seizures for >5 minutes. Convulsive (GCSE) or nonconvulsive (NCSE).

1. ABCs
2. Lorazepam 0.1 mg/kg
3. Fosphenytoin 20mg/kg, Repeat fosphenytoin 10 mg/kg. Too fast infusion can cause cardiac arrhythmia.
4. Phenobarbital 20mg/kg, Repeat phenobarbital 10mg/kg
5. General anesthesia with propofol, midazolam, or pentobarbital
Seizures: Latin sacire, “to take possession of.” Excessive, hypersynchronous discharges from CNS neurons.

Epilepsy: 2+ unprovoked seizures.

- 5-10% of people will have a seizure in their lifetime
- Partial seizures (80% of seizures)
  - **Simple partial:** consciousness preserved, originates from focus
    - Clonic movements can be explained by focus. Hand/face nearby in homunculus.
    - Jacksonian march: spread of activity along contiguous areas homunculus
    - Ictal EEG shows focal activity.
    - May experience Todd’s paralysis in the involved region.
    - Epilepsia partialis continua: focal seizure for hours to days. Refractory to medication.
    - May experience aura: strange smell (“uncinate fits,” source = uncus/limbic system)
  - **Complex partial:** consciousness impaired but not lost. (35% of epilepsy)
    - Automatisms: lip smacking, picking
    - Visual or auditory hallucinations, feelings of familiarity (déjà vu) or strangeness (jamais vu).
    - Postictal confusion. Can have anterograde amnesia or aphasis for seconds to an hour.
    - Interictal EEG may show intermittent epileptiform spikes, or sharp waves.
  - **Partial with secondary generalization**
    - Often only determined to be partial during EEG since partial symptoms overlooked.
- Generalized seizures: originate from both cerebral hemispheres simultaneously.
  - **Absence (petit mal)**
    - No loss of postural control. No postictal confusion. Usually only a few seconds.
    - Begins in childhood (ages 4-8).
    - EEG: 3 Hz spike-and-wave
      - 60-70% remit during adolescence
      - Atypical variant: last longer, <2.5 Hz, can be associated with mental retardation (LGS)
  - **Tonic-clonic** (grand mal): 10% of all epilepsy + most common metabolic seizure
    - Tonic phase: 10-20 seconds. Often started by “ictal cry,” contraction of expiratory mm.
    - Clonic phase: intermittent relaxation periods which get progressively longer. (~1 min)
    - Postictal: unresponsive, flacid, excessive salivation, headache, fatigue.
    - EEG: Spike & wave: Low-voltage fast activity, then high-amplitude, polyspike discharges
  - **Tonic:** Lennox-Gastaut syndrome
  - **Atonic:** sudden loss of postural muscle tone lasting 1-2 s. No postictal confusion.
  - **Myoclonic**
    - Don’t confuse with benign myoclonus which occurs during sleep-wake transition.
    - Most common in metabolic disorders, cerebral anoxia, and CNS diseases
- Unclassified seizures: Neonatal seizures, Infantile spasms

Seizures: pathophysiology

1. Endogenous factors: some experience febrile seizures, but only a small subset. Most be a predisposition.
2. Epileptogenic factors: Penetrating head trauma has 50% risk of chronic seizure disorder.
3. Precipitating factors: Epileptics can be normal for months to years between seizures.

- **Causes of seizures**
  - **Neonate** (<1 month): Hypoxia, CNS infection, metabolic, drug withdrawal, developmental disorder
  - **Children** (<12 years): Febrile, genetic, CNS infection, trauma
    - Febrile seizures: 6 months - 6 years. Usually GTC.
- **Epilepsy syndromes present.**
  - **Adolescent** (18-35): Trauma, alcohol withdrawal, drugs, tumor, idiopathic
  - **Older adults** (>35): Cerebrovascular disease (50%), tumor, alcohol withdrawal, metabolic.

- **Mechanisms of epileptogenesis**
  - Initiation phase: High-frequency bursts of action potentials and Hypersynchronization
  - Propagation phase: Recruitment of adjacent neurons

- **Cryptogenic seizure:** specific etiology unknown but evident that one exists (ex. MR with dysmorphic facies)
**Idiopathic Epilepsy Syndromes** (genetic cause): remit as adult (febrile, benign childhood, absence), don’t remit (JME)

- **Benign Childhood Epilepsy** with Centrotemporal Spikes (Rolandic, Sylvian Epilepsy) and with Occipital Spikes
  - Autosomal Dominant. *Most common epilepsy syndrome of childhood (10-20%).*
  - Begins at age 5-9. **Sleep-precipitated** tonic-clonic seizure with **focal onset**. Remits by 20s
  - Most seizure activity is during sleep
  - **Interictal EEG:** spikes in the contralateral rolandic (motor strip) or centrotemporal area
  - **Treatment:** Oxcarbazepine, gabapentin, vaproic acid

- **Juvenile Myoclonic Epilepsy** (4% of epilepsy): Onset: 5-15 years. Polygenetic.
  - Multiple seizures types:
    - Waking: myoclonic jerks (vs. physiologic sleep myoclonus which occurs at onset of sleep)
    - Sleep-deprived: Generalized tonic-clonic.
    - Occasionally: absence (⅓)
  - Consciousness is preserved unless the myoclonus is especially severe.
  - Not associated with other cognitive abnormalities (vs. Lennox-Gastaut)
  - **Treatment:** Responds well to Valproic acid (but doesn’t remit)

- **Febrile seizure**
  - Onset: 6 months - 2 years. Family history of febrile seizures (25-40%) 
  - 5% of all children. Only 1.5% of them eventually develop epilepsy.
  - Complex if last >15 minutes, recurs in 24 hours, or if focal onset.

- **Childhood/Juvenile absence epilepsy**
  - Mutations in T-type calcium channels.
  - Provoked by hyperventilation or carbamazepine.
  - Can go on to develop JME.
  - **Treatment:** ethosuxamide or valproic acid

- **Benign neonatal convulsions**: potassium channel mutations

**Symptomatic Epilepsy Syndromes** (cause unknown)

- **Infantile spasms** (West syndrome): Onset <1 year.
  - Recurrent, single episodes of gross flexion movements of the trunk/limbs. Associated with colic.
  - Especially common in Tuberous Sclerosis
  - EEG: hypsarrhythmia (“mountainous arrhythmia”), multifocal spikes + waves (nonspecific)
  - Responds well to ACTH, steroids, benzodiazepines
  - Disappear by 4-5 years old, or progresses to Lennox-Gastaut Syndrome (25%).

- **Landau-Kleffner syndrome (LKS)**(Epileptic aphasia): Onset: 3-6 years old
  - Become progressively aphasic.
  - EEG shows focal epileptiform activity in language center. **Non-REM sleep: 80% epileptiform.**

- **Lennox-Gastaut Syndrome**: Onset 1-7 years.
  - Occurs in children and is defined by the following triad:
    1. Multiple seizure types (GTC, atonic, and atypical absence seizures)
    2. EEG showing slow 1-2 Hz (<3 Hz) spike-and-wave discharges
    3. **Impaired cognitive function** (mental retardation) in most cases (vs. JME no MR)
  - Associated with perinatal hypoxia/ischemia, trauma, infection, and other acquired lesions.
  - Secondary generalized seizures.
  - Poor prognosis

- **Mesial Temporal Lobe Epilepsy Syndrome (TLE)**: *Most common cause of epilepsy in adults*
  - Most common syndrome associated with complex partial seizures
  - History: Febrile seizures. Family history of epilepsy.
  - Aura: rising epigastric sensation, memory deficits
  - MRI: hippocampal sclerosis
  - **Single proton emission CT (SPECT)**: bilateral hypoperfusion of frontal/parietal association cortex
  - Refractory to medical therapy but responds well to surgery (80% become seizure free)

- **Early myoclonic encephalopathy**: occurs a few hours after birth.

- **Epilepsy partialis continua**: seizures remain localized to the part of the body where originate. Can last days.
Management issues

- Depression in 20%
- Todd’s palsy: residual neurological deficit lasting < 48 hours.
- Mortality 2-3x matched controls
  - Tumors, accidents, status epilepticus
  - Sudden unexpected death in epileptic patients (SUDEP): cause unknown. Young pts, night seizure
- Driving: laws vary, but generally cannot drive for 3 months - 2 years after seizure (on or off medications)
- Female issues
  - Catamenial epilepsy: ↑ frequency during menses. Might be Δ in metabolism. Tx: Acetazolamide
  - Pregnancy
    - Phenytoin, Valproate, Carbamazepine: cleft + palate, cardiac defects, digital hypoplasia
  - Breastfeeding: generally okay if no apparent problem with the infant

Sources

- Case Files: Neurology, 2008, Toy, Lange
- PreTest: Neurology, Anschel, 2009
### Antiepileptics

<table>
<thead>
<tr>
<th>Group/Mech</th>
<th>Drugs</th>
<th>Adverse Effects</th>
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<tbody>
<tr>
<td>Sodium channel Blockers</td>
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<td>- Prevent repetitive AP propagation</td>
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<td>- Stabilizes inactive state</td>
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<td>- Due to inhibiting high-frequency neurons</td>
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<td>o Nystagmus</td>
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<td>o Cognitive slowing</td>
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<td>- Peripheral neuropathy</td>
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<td>- Blood: Anemia (megaloblastic)</td>
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<td>- Teratogenic</td>
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<td>- Purple glove syndrome (Phenytoin only)</td>
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<td>- Gingival hyperplasia</td>
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<td>- Vitamin D deficiency - Osteopenia: Ca^2+ ↓</td>
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<td>- “Fat, shaky, bald, yellow”</td>
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<td>- Weight gain, tremor, alopecia, hepatotoxicity</td>
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<td>- Blood: Neutropenia, thrombocytopenia, aplastic anemia</td>
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<td>- Asceptic meningitis</td>
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<td>- GABA transmission</td>
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<td>- Chan: BZs, Barbs, Topiramate</td>
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<td>- Synthesis: Gabapentin</td>
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<td>- GABA metab: Valproaic ac.</td>
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<td>- Confusion, Memory probs</td>
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<td>- Somnolence</td>
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| ↑ GABA transmission | | |
|↑ chan: BZs, Barbs, Topiramate | | |
|↓ GABA metab: Valproaic ac. | | |

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<th>Somnolence</th>
<th>Confusion, Memory probs</th>
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| T-type Ca channel agents | | |
| - Stabilize inactive state | | |
| - Prevent rhythmic firing | | |

| Inhibition of excitatory amino acid synaptic release | | |
| - Prevent rhythmic firing | | |

| Slow inact. of Na⁺ chan. | | |
|--------------------------|-----------------|

| Stab. inactive Na⁺ chan. | | |
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<tr>
<th>phenobarbital</th>
<th>- Sedation: Cognitive slowing, respiratory ↓</th>
<th>- Pediatric: Hyperactivity (paradoxical)</th>
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<tr>
<td>Barbiturates:</td>
<td>↑ P₄₅₀</td>
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<td>Ethosuximide (Zarontin™)</td>
<td>- Nausea / vomiting</td>
<td>- Headache</td>
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<td>- Renal excretion</td>
<td>- Hiccups</td>
<td>- ↓ concentration</td>
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<td>- Hepatic excretion</td>
<td>- Aggressiveness</td>
<td>- Blood: Leukopenia, agranulocytosis</td>
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<tr>
<th>Gabapentin (Neurontin™)</th>
<th>- Dizziness</th>
<th>- Pedestrians: aggressive behavior</th>
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<tbody>
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<td>- Renal excretion</td>
<td>- Weight gain</td>
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<th>Pregabalin (Lyrica™)</th>
<th>- Sedation, cognitive impairment</th>
<th>- Dry mouth</th>
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<tbody>
<tr>
<td>- Blurred vision</td>
<td>- Peripheral edema</td>
<td>- Blood: Thrombocytopenia</td>
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<td>- Weight gain</td>
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<th>Levitiracetam (Keppra™)</th>
<th>- Sedation, dizziness</th>
<th>- Psychosis</th>
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<td>- Ataxia</td>
<td>- anemia, neutropenia</td>
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<th>Lacosamide (Vimgat™)</th>
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| Rufinamide (Banzel™) | - Lennoux Gastaut (MR, multiple seizure types) |  |
Side effects (by effect):

- **Rash:** Stevens-Johnson Syndrome
  - Phenytoin (*Dilantin™*), Carbamazepine (*Tegretol™*), Oxcarbazepine (*Trileptal™*), Zonisamide (*Zonegran™*)
  - Valproic Acid (*Depakote™*), Ethosuximide (*Zarontin™*), Pregabalin (*Lyrica™*), Levatiracetam (*Keppra™*)
- **Blood problems**
  - Phenytoin (*Dilantin™*), Carbamazepine (*Tegretol™*), Oxcarbazepine (*Trileptal™*), Zonisamide (*Zonegran™*)
- **Hepatotoxicity**
  - Phenytoin (*Dilantin™*), Valproic Acid (*Depakote™*), Zonisamide (*Zonegran™*)
- **Pediatric problems**
  - Phenobarbital, Gabapentin (*Neurontin™*), Lamotrigine (*Lamictal™*)
- **Kidney stones**
  - Carbamazepine (*Tegretol™*), Oxcarbazepine (*Trileptal™*), Valproic Acid (*Depakote™*)
- **Osteopenia**
  - Carbamazepine (*Tegretol™*), Oxcarbazepine (*Trileptal™*), Valproic Acid (*Depakote™*)
- **Weight gain**
  - Valproic Acid (*Depakote™*), Gabapentin (*Neurontin™*), Pregabalin (*Lyrica™*)
- **Weight loss**
  - Topiramate (*Topamax™*), Zonisamide (*Zonegran™*)

### Antiepileptics

<table>
<thead>
<tr>
<th>Antiepileptics</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Partial</td>
<td>Generalized</td>
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<td><strong>Phenytoin (Dilantin™)</strong></td>
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<td><strong>Fosphenytoin (Cerebyx™)</strong></td>
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<td><strong>Valproic Acid (Depakote™)</strong></td>
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<td><strong>Lamotrigine (Lamictal™)</strong></td>
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<td><strong>Topiramate (Topamax™)</strong></td>
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<td><strong>Zonisamide (Zonegran™)</strong></td>
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<td><strong>Clonazepam (Klonopin™)</strong></td>
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<td><strong>Lorazepam (Ativan™)</strong></td>
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<td><strong>Phenobarbital</strong></td>
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<td><strong>Ethosuximide (Zarontin™)</strong></td>
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**Side Effects**

- **Rash**
- **Cardiac conduction**
- **Blood**
- **Hepatotoxicity**
- **Pediatric problems**
- **Kidney Stones**
- **Osteopenia**
- **Weight gain**
- **Weight loss**

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<th>Rash</th>
<th>Cardiac conduction</th>
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**Determine if medication is indicated:**

- Recurrent seizures of unknown etiology
- Known cause that cannot be reversed
- Present with status epilepticus
- Family history of seizures
- Abnormal interictal EEG
- Job depends on no seizures (ex. driver)

**Selection of antiepileptic drugs**

- Begin with monotherapy. Add a second drug with a different mechanism of action if poorly controlled
- Surgery is an option in focal epilepsy with poor control on medications.

**Discontinue antiepileptic therapy if:**

1. Control of seizures for 1–5 years
2. Single seizure type
3. Normal neuro exam including intelligence
4. Normal EEG

**Status epilepticus:** continuous or repetitive seizures for >5 minutes

1. ABCs
2. Lorazepam 0.1 mg/kg
3. Fosphenytoin 20mg/kg
4. Phenobarbital 20mg/kg
5. General anesthesia with propofol, midazolam, or pentobarbital

**Sources**

- UTCOM MS-2 Antiepileptics lecture handout by Dr. Greenfield
- UTCOM MS-3 Neurology Clerkship Antiepileptics table by Dr. Ali
DEMENTIA

Overview
- Acquired deterioration in cognitive ability that impairs performance of activities of daily living.
  - Normal aging memory loss does not interfere with activities of daily living.
  - Pseudodementia is depression masquerading as a true dementia.
  - Differentiated from delirium by normal level of consciousness, attention, and chronic course.
- Usually progressive, but some forms are static.
- Cognitive abilities lost:
  - Memory (most common)
  - Language
  - Visuospatial
  - Calculation
  - Judgment
  - Problem solving
- Neuropsychiatric deficits:
  - Depression
  - Withdrawal
  - Hallucinations
  - Agitation
  - Insomnia
  - Disinhibition
- Most common reversible comorbidities:
  1. Depression
  2. Hydrocephalus
  3. Alcohol dependence

Major causes of dementia
1. Alzheimer’s Disease (>50%)
2. Vascular disease (10-20%)
3. Parkinson’s Disease with dementia (often with underlying Lewy Body Dementia)
- Frontotemporal Dementia is nearly as common as Alzheimer’s in dementia patients under 60.

Histological deposits of common dementias
- β-amyloid (Aβ) Amyloid plaques (AD)
- α-synuclein Lewy bodies (DLB, Parkinson’s)
- Tau Pick bodies (Pick’s Disease), Neurofibrillary tangles (AD)

Clinical Differentiation of the Major Dementias (Harrison’s)

<table>
<thead>
<tr>
<th>Disease</th>
<th>First Symptom</th>
<th>Mental Status</th>
<th>Neuropsychiatry</th>
<th>Neurology</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease (AD)</td>
<td>Memory loss</td>
<td>Episode memory loss</td>
<td>Initially normal</td>
<td>Initially normal</td>
<td>Entorhinal cortex and hippocampal atrophy</td>
</tr>
<tr>
<td>Frontotemporal Dementia (FTD)</td>
<td>Apathy; poor judgment/insight, speech/language; hyperorality</td>
<td>Frontal/executive, language; spares drawing</td>
<td>Apathy, disinhibition, hyperorality, euphoria, depression</td>
<td>Due to PSP/CBD overlap; vertical gaze palsy, axial rigidity, dystonia, alien hand</td>
<td>Frontal and/or temporal atrophy; spares posterior parietal lobe</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies (DLB)</td>
<td>Visual hallucinations, REM sleep disorder, delirium, Capgras, parkinsonism</td>
<td>Drawing and frontal/executive; spares memory; delirium prone</td>
<td>Visual hallucinations, depression, sleep disorder, delusions</td>
<td>Parkinsonism</td>
<td>Posterior parietal atrophy; hippocampi larger than in AD</td>
</tr>
<tr>
<td>Creutzfeld-Jakob Disease (CJD)</td>
<td>Dementia, mood, anxiety, movement disorders</td>
<td>Variable, frontal/executive, focal cortical, memory</td>
<td>Depression, anxiety</td>
<td>Myoclonus, rigidity, parkinsonism</td>
<td>Cortical ribboning and basal ganglia hyperintensity on DWI/flare MRI</td>
</tr>
<tr>
<td>Vascular</td>
<td>Stepwise decline; apathy, falls, focal weakness</td>
<td>Frontal/executive, cognitive slowing; can spare memory</td>
<td>Apathy, delusions, anxiety</td>
<td>Motor slowing, spasticity; can be normal</td>
<td>Infarctions, confluent white matter disease</td>
</tr>
</tbody>
</table>

38
- **Anterior**: FTD (loss of social graces)
- **Posterior**: AD (intellectual ↓)
- Others: Pick, semantic (verbal & nonverbal), progressive nonfluent aphasia (verbal only)

- Much more treatable than cortical dementias
- PD, HD, PSP, MSA, hydrocephalus, Binswanger, CADASIL, DLB, environmental, neurosyphilis

Mild Cognitive Impairment (MCI)
- Memory loss begins to affect day-to-day activities or falls below 1.5 standard deviations from normal.
- 50% of MCI individuals will progress to Alzheimer’s Disease within 5 years

Alzheimer’s Disease: Typical course is 8-10 years. 4th most common cause of death in USA.

**Symptoms**
- Begins with memory impairment and spreads to language and visuospatial deficits.
  - 20% present with nonmemory complaints (word-finding, organizational, or navigational difficulty.)
- Some experience anosognosia (unaware of deficit)
- Frequently lose olfaction early (anosmia)
- Progress to losing track of finances, problems driving and shopping. Changes of environment are confusing.
- Language becomes impaired
  - 1) Naming, 2) Comprehension, and ultimately 3) Fluency
- Many remain ambulatory, but wander aimlessly and get lost.
- Loss of judgment and reason are next.
- Many develop delusions, such as theft, infidelity, or misidentification.
  - Capgras’ syndrome (10%), believing caregivers are impostors, can develop late (early in DLB)
- Can look Parkinsonian, but rarely have resting tremors

**Risk Factors**
- Advanced age (20-40% of 85+)
- Genetics
  - Down syndrome: Nearly all develop AD. Amyloid precursor protein (APP) is on chromosome 21.
  - Apo ε on chromosome 19 is implicated in sporadic, late onset Alzheimer’s.
- Diabetes (3x risk increase)
- Low educational attainment
- Vascular disease
- Aluminum, mercury, viruses have *not* been demonstrated to be risk factors.

**Treatment**
- Acetylcholine esterase inhibitors: Donepezil, rivastigmine, galantamine
- NMDA receptor antagonists: Memantine
- Ginko biloba showed improvement but study was limited.
- Aβ vaccine worked well in mice but led to meningoencephalitis in human trials.

**Anatomic lesions**: Nucleus basalis of Meynert (acetylcholine-rich), hippocampus, temporal cortex.
Vascular Dementia

Subtypes
- Multi-infarct dementia
- Diffuse white matter disease (leukoaraiosis, Binswanger’s, or subcortical arteriosclerotic encephalopathy)

Symptoms
- Discrete episodes of sudden neurologic deterioration. Often stepwise progression of disease.
- Focal neurological deficits.
  - Pseudobulbar palsy: Lesion in the corticobulbar pathway, motor neurons to cranial nerves.
- Risk factors: Same as those for atherosclerosis, ie. HTN, DM, coronary artery disease.
- Early symptoms: mild confusion, apathy, changes in personality, depression, memory, and spatial
- Marked difficulties in judgment and orientation and dependence on others for daily activities develop later.
- Euphoria, elation, depression, or aggressive behaviors are common as the disease progresses.
- Both pyramidal and cerebellar signs may be present in the same patient. Gait disorder present in > 50%

Non-atherosclerotic causes of vascular dementia
- Adult metachromatic leukodystrophy (arylsulfatase A deficiency)
  - Autosomal recessive
  - No conversion of sulfatide to cerebroside (a major component of myelin). Sulfatide accumulates.
  - Onset in age 1-4. Progressive impairment of motor (gait disorder, spasticity), speech, regression.
  - Peripheral nerves become involved later and lose DTRs.
  - Diagnosis: MRI, deficiency of arylsulfatase in WBCs, ↓ sulfatide in urine, elevated CSF protein
- Progressive multifocal leukoencephalopathy (PML) (JC papovavirus infection).
  - 5% of AIDS patients get PML. (75% of PML cases are in AIDS patients). 14% cancer. 5% transplant.
  - CSF: normal cytology, but can PCR for JC virus
  - MRI: focal well-defined white matter lesions that do not enhance or have mass effect
  - Personality changes and intellectual impairment herald the onset (38%)
  - Later: hemiparesis, quadriplegia, a visual field defects (45%), aphasia, ataxia, confusion, coma.
  - Death in 3-6 months.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).
  - Autosomal dominant
  - Develops in the fifth to seventh decades in multiple family members who may also have a history of migraine and recurrent stroke without hypertension.
  - Skin biopsy may show characteristic dense bodies in the media of arterioles.
- Mitochondrial diseases
  - Can selectively injure basal ganglia or cortical structures
  - Ophthalmoplegia, retinal degeneration, deafness, myopathy, neuropathy, or diabetes.

Treatment: Treat underlying cause.

Frontotemporal Dementia (FTD) (Pick’s disease)
- Usually begins age 40-60 and in this age subset is nearly as common as Alzheimer’s
  - Unlike AD, behavioral symptoms predominate in the early stages of FTD.
- Usually begins with spared memory, but deficits in planning, judgment, and language.
- Common behavioral deficits: apathy, disinhibition, weight gain, food fetishes, compulsions, and euphoria.
- Variable mixtures of disinhibition, dementia, PSP, CBD, and motor neuron disease.
  - Can reflect variable anatomic locations of lesions
    - Left predominant lesions: Primary progressive aphasia.
    - Right predominant lesions: antisocial, loss of empathy, disinhibition
- Imaging: marked lobar atrophy of temporal and/or frontal lobes
- Genetics
  - Autosomal dominant mutation in tau.
  - Autosomal dominant mutation in progranulin (rare)

Treatment: Symptomatic. SSRIs and SNRIs can help with depression, hyperorality, compulsions, and irritability.
Progressive Supranuclear Palsy (PSP)

- Onset in 60s to 70s.
- Involves deposition of tau protein in the brainstem, basal ganglia, and neocortex.
- Early: motor. Late: dementia with worsening motor.
- Motor deficits: Begins with falls and downward supranuclear gaze paresis.
  - Parkinsonism: bradykinesia, shuffling gait.
  - Tremor is uncommon
  - Loss of down gaze is specific to PSP and differentiates from Parkinson’s upgaze deficit
  - Intact oculocephalic reflexes (doll’s head maneuver).
  - “Supranuclear”: reflex arc is intact, thus the lesion is above the level of the brainstem.
  - Stiff, unstable posture with hyperextension of the neck
- Progresses to symmetrical rigidity and dementia.
  - Dementia similar to FTD: apathy, frontal/executive dysfunction, poor judgment
- MRI: atrophy of superior colliculus

Treatment & Prognosis

- L-Dopa is limited effect
- Death occurs within 5-10 years of onset

Corticobasalar Degeneration (CBD): Parkinsonism, alien hand, myoclonus, intention tremor.

- Onset in 60s to 70s.
- Pathology:
  - Deposition of tau protein and severe gliosis (proliferation of astrocytes leading to glial scar) and neuronal loss in both the neocortex and basal ganglia (substantia nigra and striatum)
- Symptoms
  - Bradykinesia, rigidity, dystonia, myoclonus, and apraxia of one arm/hand (alien hand) (~asymmetric)
  - 2-5 years: becomes bilateral, dysarthria, slow gait, action tremor, and dementia.

Parkinson’s with Dementia: if Parkinson’s precedes the dementia by > 2 years (vs. DLB where dementia is first)

Dementia with Lewy Bodies (DLB): executive dysfunction + Parkinsonism

- Core features (at least 2 for diagnosis)
  1. Visual hallucinations
  2. Fluctuating alertness, falls, and often REM sleep behavior disorder.
  3. Parkinsonism (tremor, hypokinesia, rigidity, and postural instability). Follows dementia (vs. P w/D)
- Highly susceptible to metabolic problems
  - Some: First manifestation of illness is a delirium, precipitated by an infection or systemic disturbance
  - Delirium induced by L-dopa, prescribed for parkinsonian symptoms attributed to PD, may be the initial clue that the correct diagnosis is DLB
- Not much anterograde amnesia (vs. AD).
- Visuospatial deficits worse than AD: construction apraxia (draw pentagons) severely impaired
- Fluctuations: confusion intermixed with lucid intervals.
- Pathology: Lewy bodies (ubiquitin + α-synuclein) in cortex, amygdala, cingulate cortex, and substantia nigra.
  - Lewy bodies also in substantia nigra of idiopathic Parkinson’s Disease

Treatment: Anticholinesterases can be helpful

Prion Disorders (ex. Creutzfeld-Jakob)

- Rapidly progressive dementia: progression to akinetic mutism (don’t speak or move) or coma in months
- Psychiatric symptoms: anxiety, euphoria, depression, labile affect, delusions, hallucinations, and changes in personality or behavior may be prominent.
- Myoclonus (often induced by a startle), extrapyramidal signs (rigidity, bradykinesia, tremor, dystonia, chorea, or athetosis), cerebellar signs
- EEG: periodic sharp waves or spikes. MRI: cortical ribboning. CSF: elevated protein
Huntington’s Disease: Chorea, dementia, psychosis
- Autosomal Dominant trinucleotide (CAG) on chromosome 4
- Onset 30-40
- Chorea, behavioral disturbance, and frontal executive disorder.
  - Chorea: brief, quasi-purposeful, irregular contractions that are not repetitive or rhythmic, but appear to flow from one muscle to the next.
- Memory not impaired until late.
- Disease duration: usually 15 years.

Treatment: None specific, but movements may respond to antipsychotics

Normal Pressure Hydrocephalus
- Signs & symptoms: Triad: wet (incontinent), wacky (dementia), wobbly (gait disturbance)
  - Evans' index >0.3. (maximal width of frontal horns of lateral ventricles/maximal width of inner skull)
  - CSF pressure in high-normal 150-200 mm H₂O. (Normal is 70-200 mm H₂O)
    Normal CSF parameters - volume: 150ml, production: 500 ml/day, turnover: 3.3/day
- Pathophysiology
  - A communicating hydrocephalus with patent aqueduct of Sylvius
  - Stretches long motor tracts of lower extremities and bladder with expanding ventricles.
  - Impaired absorption of CSF and reabsorption into venous system
  - Some patients have a history of conditions producing scarring of the basilar meninges (blocking upward flow of CSF) such as previous meningitis, subarachnoid hemorrhage, or head trauma.
    Others have longstanding asymptomatic congenital hydrocephalus with adult-onset decompensation
    In most cases, the cause cannot be established, so an asymptomatic fibrosing meningitis is presumed
- Treatment: 30-50% improve with ventricular shunt.

Dementia pugilistica: dementia following head trauma
<table>
<thead>
<tr>
<th>Disease</th>
<th>Early</th>
<th>Late</th>
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<tbody>
<tr>
<td>Alzheimer’s</td>
<td>Cognitive: Memory, language, spacial</td>
<td>Motor (less common)</td>
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<tr>
<td>Vascular</td>
<td>Cognitive: Memory, apathy, spacial</td>
<td>Cognitive: Judgment and orientation</td>
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<td>Motor: Focal deficit in cerebellar and pyramidal</td>
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<tr>
<td>Frontotemporal</td>
<td>Cognitive: Behavioral symptoms predominate</td>
<td>Cognitive: memory</td>
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<td>Motor: Supranuclear gaze palsy, axial rigidity</td>
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<tr>
<td>Lewy Body</td>
<td>Motor: new onset Parkinsonism</td>
<td>Cognitive can follow or coincide</td>
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<tr>
<td>Corticobasilar</td>
<td>Motor: dystonia, myoclonus, extrapyramidal</td>
<td>Cognitive: dementia</td>
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<tr>
<td>PSP</td>
<td>Motor: downward gaze deficit, axial rigidity</td>
<td>Cognitive: dementia</td>
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<tr>
<td>Parkinson’s</td>
<td>Motor: upward gaze deficit</td>
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<tr>
<td>Huntington’s</td>
<td>Cognitive: behavioral, loss of executive function</td>
<td>Cognitive: memory</td>
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<td>Motor: chorea</td>
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<tr>
<td>Prions</td>
<td>Motor: diffuse rigidity, akinesia, myoclonus</td>
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**Sources**
EXTRAPYRAMIDAL MOVEMENT DISORDERS

Extrapyramidal system
- As opposed to the motor tracts traveling in the pyramids of the medulla (corticospinal + corticobulbar) and directly innervating targets, extrapyramidal motor tracts are more involved in reflexes, locomotion, complex movements, and postural control.
- Examples
  - Parkinsonism: lead-pipe rigidity, bradykinesia/akinesia, resting tremor, and postural instability
  - Tremor
  - Dystonia
  - Tardive dyskinesia

Parkinson's Disease
- Parkinsonism: bradykinesia, resting tremor, muscular rigidity, shuffling gait, and flexed posture.
- Epidemiology
  - 1 million individuals in the United States
  - Peak age of onset: early 60s (range 35–85 years). Course: 10-25 years.
  - Parkinson's disease represents 75% of all cases of parkinsonism
    - Other causes: neurodegenerative disorders, cerebrovascular disease, and drugs.
  - Familial forms: AD and AR forms of PD comprise 5% of cases. Earlier onset, <45 years. parkin gene.
- Diagnosis: 2 of 3 cardinal signs (resting tremor [85%], rigidity, and bradykinesia)
- Clinical features
  - Motor
    - Bradykinesia
      - Resting tremor (4-6 Hz) “pill-rolling” supinate/pronate, spares head/neck. Often asymmetric.
      - Cogwheel sensation (subclinical tremor), and ↑ tone.
    - Dystonia: in early-onset Parkinsons and as a result of dopaminergic therapy
    - Festinating gait: combination of flexed posture & loss of postural reflexes. Falls problematic.
      - Upward gaze palsy (vs. PSP downward gaze palsy)
  - Non-motor
    - Depression, anxiety, cognitive impairment, sleep disturbances, sensory abnormalities and pain,
      loss of smell (anosmia), and dysautonomia
    - Akathisia: “inner restlessness.” Restless legs can precede development of motor PD sx.
  - Neuropsychiatric
    - Depression in 50%
    - Dementia: 6x more common than age-matched control
    - Psychotic symptoms (40%): visual illusions + hallucinations, but insight retained. Can be drugs
- Pathology
  - Loss of dark melanin pigment in midbrain.
  - Substantia nigra pars compacta (SNpc): ↓ dopaminergic cells, presence of Lewy bodies
  - Lewy bodies: α-synuclein buildup in SNpc, temporal, limbic, frontal cortex.
    - α-synuclein mutation: Familial Parkinsons
- Pathophysiology
  1. Striatal dopamine denervation: ↑ indirect (striatum → GPe → STN → GPi), ↓ direct (striatum → GPi)
  2. ↓ activity in striatal outflow stemming from the ↑ activity of STN and thus GPi/SNr neurons.
  3. Striatal outflow is inhibitory to the thalamus (GABA): ↓ thalamic activation of cortex.
- Differential Diagnosis
  - Wilson’s Disease if under 40, Chédiak-Hagashi, Fragile X, Vascular PD (if sudden onset)
  - Multiple System Atrophy, Tauopathies (FTD, PSP, CBD), Dementia with Lewy Bodies (DLB)
  - High frequency (8-10 Hz) symmetric tremor
  - Secondary parkinsonism
    - Neurotoxin exposure: manganese, carbon monoxide, MPTP (meperidine home synthesis)
    - Drugs: antipsychotics, antiemetics, lithium, valproate, α-methylldopa. (symmetric, vs. PD)
    - Infectious: Postencephalitic, Neurosyphilis
EXTRAPYRAMIAL MOVEMENT DISORDERS

- **Treatment**: only symptoms are treatable. Nothing slows the progression of the disease.
  - Treatable early: Bradykinesia, tremor, rigidity, and abnormal posture
  - Not as treatable: cognitive symptoms, hypophonia, autonomic dysfunction, and imbalance.
  - Common misconceptions: initiating treatment too early will result in dyskinesias and not last long
  1. Get an MRI to rule out other causes of parkinsonism.
  2. Dopamine agonist (bromocriptine, pramipexole, ropinirole, rotigotine) (or levadopa-carbidopa)
  3. Add levadopa-carbidopa (Sinemet™)
  4. Increase dose, or dose more frequently
     - a. Tremor: Add anticholinergic
     - b. Drug-induced dyskinesias: Add amantadine
     - c. Freezing episodes: Add apomorphine (nonselective dopamine agonist)
  5. Add COMT (entacapone) or MAO-B inhibitor (selegiline)(no hypertensive crisis w/tyramine).
     - a. Indications: intractable tremor and drug-induced motor fluctuations or dyskinesias
  - Depression: treat with TCAs or SSRIs
  - Psychosis: discontinue anticholinergics and amantadine

Multiple System Atrophy (parkinson’s α-synucleinopathies)

- **Overview**
  - Parkinsonism with cerebellar (ataxia), corticospinal, and autonomic dysfunction
  - α-synuclein mutations
  - Earlier onset than parkinsons (50 versus 65)
  - Symptoms are determined by the distribution of Lewy Bodies
    - Striatum only: Parkinson’s Disease
    - Striatum and cortex: Dementia with Lewy Bodies
    - Striatum and Cerebellum: Multiple System Atrophy
  - Autonomic failure: orthostatic hypotension, odd sweating, and autonomic storms (flushing + sweat)

- **Classification**
  - MSA-p: prominent parkinsonism at onset
    - Present with pure form of akinetic rigid parkinsonism and a limited response to levodopa
  - MSA-c: prominent cerebellar involvement at onset
    - Ataxia, UMN and corticobulbar involvement, myoclonus, peripheral neuropathy, deafness

- **Pathological classification**: Where Lewy Bodies and atrophy are found
  - Striatonigral degeneration (SND)
    - Shy-Drager syndrome: Parkinsons + dysautonomia (usually orthostatic hypotension)
  - Olivopontocerebellar atrophy (OPCA): Prominent ataxia
  - Progressive autonomic failure (PAF)

- **Treatment**: Try dopamine agonists but may precipitate hypotension

Parkinson’s plus tauopathies (see Dementias)

- Progressive supranuclear palsy
- Corticobasilar Degeneration

Sources

HYPERKINETIC MOVEMENT DISORDERS

All can be psychogenic (most common: tremor). 2-3%, more common in women. Disappears when not observed.

Definitions
- **Athetosis**: Slow, distal, writhing, involuntary movements with a propensity to affect the arms and hands.
- **Tremor**: Rhythmic oscillation of a body part due to intermittent muscle contractions.
- **Dystonia**: Involuntary sustained/repeated muscle contractions. Twisting movements and abnormal posture.
- **Chorea**: Rapid, semipurposeful, graceful, dancelike, nonpatterned involving distal or proximal muscles.
- **Tics**: Brief, repeated, stereotyped muscle contractions (often suppressible).
- **Myoclonus**: Sudden, brief (<100 ms), shocklike, arrhythmic muscle twitches.

**Essential Tremor (ET)**: High-frequency tremor (up to 11Hz) (vs. Parkinson’s 3-4 Hz). Mostly upper extremities.
- Autosomal dominant (50%) or sporadic. Improves with alcohol. Worse with stress.
- Presents in childhood and progresses with age.
- Postural and kinetic. No tremor at rest (vs. Parkinson’s)
- Tremor often involves the head (vs. Parkinson’s which almost never does)
- **Treatment**: 1) propranolol (20–80 mg/d), 2) primidone (25–1000 mg/d) or ↓ amplitude but not frequency.
  - Deep brain stimulation of VIN nucleus of thalamus: ↓ amplitude and ↓ frequency.

**Dystonia**
- Sustained or repetitive involuntary muscle contractions. Twisting movements with abnormal postures.
- Starts as action dystonia (brought on by voluntary movement), and can later become sustained and extend.
- Aggravated by stress and fatigue and relieved by relaxation and sensory tricks (touch the body part)
- Cocontracting bursts in agonist and antagonist muscle groups. Likely basal ganglia lesion.
- **Primary Dystonias**:
  - Idiopathic torsion dystonia (ITD), or Oppenheim's dystonia
    - Autosomal dominant. Predominantly Ashkenazi Jews
    - Onset <26 years
    - Mutation in DYT1 gene: single codon deletion (GAG in torsin A)
  - Dopa responsive dystonia (DRD) or the Segawa variant (DYT5)
    - Autosomal dominant
    - Early onset: 1-12 years
    - Foot dystonia which interferes with walking
    - Some response to levadopa
- **Focal Dystonias**: 30s to 50s. Affect women > men. Hypertrophy of muscle groups can occur.
  - **Blepharospasm**: ↑ blinking that can interfere with reading, watching TV, and driving.
  - **Oromandibular dystonia (OMD)**: Lower face, lips, tongue, and jaw (opening or closing).
    - Meige's syndrome is a combination of OMD and blepharospasm. Women > 60. **Tx**: BoTox.
  - **Spasmodic dysphonia**: Vocal cords during phonation, causing impaired speech.
  - **Cervical dystonia**: Neck muscles, causing the head to deviate
    - To one side (torticollis), forward (anterocollis), backward (retrocollis)
  - **Limb dystonias**: these can be present in either arms or legs and often task-specific such as handwriting (writer's cramp), playing an instrument (musician's cramp), or putting in golf (the yips).
- **Secondary dystonias**: Most commonly with antipsychotics or chronic levadopa therapy.
- **Dystonia plus syndromes**: Dystonia is not the prominent feature, but is present.
  - Huntington's disease (HD)
  - Parkinson's Disease, Corticobasal degeneration, Progressive supranuclear palsy
  - Wilson's disease
  - Lubag form of dystonia-parkinsonism (DYT3)
  - Mitochondrial encephalopathies
- **Treatment**: Symptomatic, unless underlying disorder can be treated
  - Levadopa, Anticholinergics (Trihexyphenidyl [Artane]), Baclofen
  - Botulism toxin for focal dystonia
HYPERKINETIC MOVEMENT DISORDERS

Chorea: Rapid, semipurposeful, graceful, dancelike, nonpatterned involving distal or proximal muscles.
- Huntington’s Chorea: Onset 25-45
  - Autosomal Dominant. CAG trinucleotide repeat on chromosome 4. (Disease if > 40 repeats)
  - Neurological: Dysarthria, gait disturbance, and oculomotor abnormalities
  - Behavioral: Depression, aggressive behavior, and psychosis
  - Westphal variant: chorea with parkinsons or akinetic-rigid
  - Advanced disease: dystonia, rigidity, bradykinesia, myoclonus, and spasticity
  - Imaging: atrophy of head of caudate nucleus (hydrocephalus ex vacuo)
  - Treatment: none good. Atypical antipsychotics can help with psychosis.
- Huntington’s Chorea: Onset 25-45
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  - Treatment: none good. Atypical antipsychotics can help with psychosis.
- Sydenham’s chorea: children, 5-15. Associated with Streptococcus pyogenes
- Chorea gravidarum: Associated with pregnancy or sex hormones
- Neuroacanthocytosis: Chorea and acanthocytes (spiked RBC). Autosomal recessive.
- Paroxysmal kinesigenic dyskinesia: Associated with voluntary movement
- Systemic lupus erythmatosus: most common systemic disorder causing chorea
  - Imaging: atrophy of head of caudate nucleus (hydrocephalus ex vacuo)
  - Treatment: neuroleptics, dopamine-blocking agents, propranolol, clonazepam, and baclofen

Hemiballismus
- Violent movements of one side of the body. Can cause exhaustion, local injury, death.
- Most common cause is local lesion (infarct or hemorrhage) in the Subthalamic nucleus (STN)
- Treatment: haloperidol, propranolol, phenytoin, clonazepam, and baclofen

Tics: brief, rapid, recurrent, and seemingly purposeless stereotyped motor contraction
- Tourette Syndrome
  - Presents between 2-15, and often lessen or disappear in adulthood.
  - Associated: anxiety, depression, ADHD, self destructive behavior
  - Complex inheritance. Thought to be dopamine-related.
  - Overwhelming urge to express tics, but can voluntarily suppress them for short time.
  - Motor tic
    - Simple: individual muscle group. Complex: multiple muscle groups
    - Vocal tic
      - Simple: grunting. Complex: echolalia (repeat others), palalia (self), coprolalia (obscene)
  - Sensory tic: Unpleasant sensations in face, head, neck
  - Treatment:
    1. $\alpha_2$ agonists: Clonidine, guanfacine
    2. Antipsychotics: Risperidone, olanzapine

Myoclonus: brief, rapid (<100 ms), shocklike, jerky movement consisting of single or repetitive muscle discharges
- Focal, multifocal, segmental, or generalized. Can be physiologic (hypnic jerks)
- Action myoclonus, startle myoclonus, negative myoclonus (asterixis)
- Can be brought on by hypoxic damage (especially after cardiac arrest), encephalopathy, neurodegenerative
diseases
- Commonly observed in people when waking up or falling asleep.
- Treatment: GABA. Valproate, piracetam, (levetiracetam), clonazepam, or primidone

Tardive Syndromes: develop months to years after initiation of neuroleptic treatment. “Tardive” = late onset
- Tardive Dyskinesia: choreiform movements involving the mouth, lips, and tongue
  - ½ remit after stopping offending drug
  - For those that don’t: valproic acid, anticholinergics, or botulinum toxin injections.
  - Atypical antipsychotics have much lower risk
- Tardive Akathisia (restless legs)
- Tardive Tourette syndrome
- Neuroleptic malignant syndrome:
  - Rigidity, ↑ temperature, altered mental status, tachycardia, labile blood pressure, and renal failure
  - Treatment: stop drug, start dopaminergic, dantrolene, benzodiazipine. Cooling blanket
- Serotonin syndrome: MDMA, meperidine. Confusion, hyperthermia, tachycardia, myoclonus (vs. NMS)
HYPERKINETIC MOVEMENT DISORDERS

Enhanced physiologic tremor: 10-12 Hz
- Drugs: beta-agonists, theophylline, caffeine, TCAs, SSRIs, lithium,
- ↑ sympathetic outflow: anxiety, hypoglycemia, opiate/alcohol withdrawal, fever
- Endocrine: thyrotoxicosis, pheochromocytoma

Approach to the patient with tremor/movement disorder
1. Determine if the tremor is present at rest, with posture, and/or with goal-directed movement.
2. Look for associated neurological signs (stroke, ataxia, cerebellar disease)
3. Occurs during sleep? Movement disorders of the basal ganglia (PD, HD, Wilson’s) disappear during sleep.
4. Assess for history of brain trauma
5. Labs: thyroid function, Ceruloplasmin (Wilson’s), heavy metals (mercury, arsenic)

Resting  Postural-action  Intention
- PD, parkinsonism  ● Enhanced physiologic  ● Cerebellar disease
- Palatal myoclonus  ● Essential Tremor  ● Multiple Sclerosis
- Midbrain (rubral) tremor  ● Primary writing  ● Midbrain (rubral) tremor
- Wilson’s Disease  ● PD, Wilson’s  ● Occasionally ET
- Severe Essential Tremor  ● Dystonia  ● Cerebellar disease
-  ● Peripheral neuropathy
-  ● Psychogenic

Pathophysiology of tremor
- Oscillators: systems able to produce rhythmic activity.
- Mechanisms:
  - Mechanical tremor of the extremity (physiological)
    - Muscle fibers firing in resonance to hold up limb against gravity
      - 25 Hz fingers, 6–8 Hz hand, 3–4 Hz elbow, and 0.5–2 Hz shoulder
    - Frequency ↓ with ↑load, by the equation
      \[ \text{frequency} \approx \sqrt{K / \text{inertia}} \]
  - Reflex activation in the CNS leading to oscillatory activity
    - Any movement in one direction activates afferent stretch of the antagonist.
  - Central oscillators
    - Pacemakers in the inferior olive and the thalamus have two modes of discharging.
      - Summation of excitatory action potentials at the membrane and firing of a regular action potential when the firing threshold is reached.
      - Oscillatory mode: prolonged AP and prolonged repolarization
    - Instability of feedforward or feedback systems. (Especially the cerebellum in intention tremors)
      - Delayed antagonist activity, insufficient braking of ballistic movement and overshoot.

Miscellaneous Tremors
- Holmes (Rubral) Tremor: “wing-beating” combination of resting, postural, and intention tremors of 2-5 Hz.
  - Always associated with cerebellar and/or midbrain (central tegmental tract) damage.
- Palatal tremor: myoclonus of palatal muscles. Lesion of central tegmental tract (red nucleus to ipsilateral inferior olive). Results in clicking noise which does not subside when the patient sleeps.
- Orthostatic tremor: present when standing 14-18 Hz, suppressed by walking.

Sources
- PreTest: Neurology, Anschel, 7th edition, 2009
- GUNTHER DEUSCHL, MD, JAN RAETHJEN, MD, MICHAEL LINDEMANN, MSc, and PAUL KRACK, MD. Department of Neurology, Christian-Albrechts-Universitat, Niemannsweg 147, D-24105 Kiel, Germany. THE PATHOPHYSIOLOGY OF TREMOR. MUSCLE & NERVE. June 2001
DEMYELINATING DISEASES

Multiple Sclerosis

● Overview
  ○ Triad: 1) inflammation, 2) demyelination, 3) scarring (gliosis)
  ○ “Lesions separated by time and space”: varying locations of lesions and at different times
  ○ Demyelination occurs in CNS ONLY (no LMN signs)
  ○ No evidence of systemic disease
  ○ Variable course: can be totally benign or rapidly evolving and incapacitating
  ○ Risk factors: female gender (3x), high latitude, maybe infectious (EBV, HHV6, Chlamydia pneumonia)
    Genetics: twin concordance, clusters in families.

● Pathogenesis
  ○ Possibly Vitamin D related (immunoregulatory). Lower latitudes get more sun and are at lower risk.
  ○ Plaques vary from 1mm to several cm in size
  ○ Variability: 1) antibodies or not, 2) damage in myelin or oligodendrocyte cell body 3) axonal damage
    Axonal damage is major predictor of prognosis since it is irreversible (vs. remyelination)
    ● May be via microglia release of NO, glutamate
  ○ Axon conduction: myelinated (70 m/s), unmyelinated (1 m/s)
  1. Acute: perivenular cuffing with T-cells and macrophages. Inflammation disrupts blood-brain barrier
  2. Macrophages and microglia (CNS ‘phages from marrow) scavenge free myelin. May be antibodies too.
  3. Gliosis: astrocytic proliferation
  4. Surviving oligodendrocytes or new ones attempt to remyelinate (shadow plaques), but often fail.
  ○ Immunology
    T-cells: react to myelin basic protein (MBP)
    Humoral antibodies: anti-myelin, anti-myelin oligodendrocyte specific glycoprotein (MOG)
    Cytokines: IL-2, TNF-α, IFN-γ. (TNF-α & IFN-γ may directly injure ologodendrocytes or myelin)

● Signs & symptoms
  ○ Sensory loss (37%), optic neuritis (36%), weakness (35%), paraesthesia (24%), diplopia (15%),
    ataxia (11%), tremor, Lhermitte sign (3%) - electrical sensation running down back w/movement
  ○ Optic neuritis: ↓ acuity, dimness, ↓ color perception (desaturation). Eye pain (92%).
    Marcus Gunn pupil: afferent pupillary defect. ⅔ normal fundoscopic exam. ⅓ disk swelling.
  ○ Internuclear ophthalmoplegia: ↓ adduction of affected eye due to ipsilateral MLF demyelination
    MLF connects the paramedian pontine reticular formation (PPRF)-abducens nucleus (CN VI)
    (abduct) of contralateral eye to the oculomotor nucleus (CN III) of the affected (adduct)
    Convergence is preserved
  ○ Bladder dysfunction (90%): spastic (UMN) not usually atonic, constipation.
    Treatment (symptomatic): TCA’s (via anti-ACh), oxybutynin (anti-ACh)
  ○ Fatigue (90%)
  ○ Pseudoexacerbation: Heat, infection, PMS triggering symptoms (ex. vision loss while in hot shower)
  ○ Paroxysmal symptoms: can occur for 10s-2m up to several times per day, with remission
  ○ Trigeminal neuralgia, hemifacial spasm, and glossopharyngeal neuralgia

● Course
  ○ Relapsing/remitting (85%): onset usually 20s
  ○ Secondary progressive: begins as relapsing/remitting
  ○ Primary progressive (10%): do not experience attacks but instead a steady decline. Older age: 40.
  ○ Progressive/remitting (5%): progressive, but also experience attacks

● Diagnosis: clinical. Two white matter lesions separated by space and time.
  ○ Definite: 2 or more lesions of white matter, evidence of 2 or more anatomic locations > 3 mo apart.
    Symptoms present for > 24 hours. At least one present upon neurological examination.
  ○ 2+ subjective attacks with 1 lesion on exam + MRI evidence
  ○ 1 subjective attack with 1 lesion on exam + MRI evidence AND CSF evidence
  ○ CSF: oligoclonal bands (85%), ↑ protein, pleocytosis (<75 cells), ↑ IgG:Albumin (90%)
DEMYELINATING DISEASES

- **Treatment**
  - Acute exacerbations: **steroids, plasmapheresis**
  - Disease-modifying: IFN-1α, IFN-1β, glatiramer (myelin-like AAs), and natalizumab (anti-α4 integrin)
    - Natalizumab thought to work by preventing WBCs from crossing BBB or intestines (Crohn's)
    - None work for primary progressive MS
  - Pseudoexacerbation: treat underlying cause. No steroids

- **Variants**
  - Neuromyelitis optica (NMO) (Devic's syndrome): separate attacks of acute optic neuritis and myelitis
    - Anti-aquaporin-4 antibodies. Probably a variant of ADEM.
  - Acute MS (Marburg's variant): fulminant disease, progresses to death within 1–2 years

**Acute Disseminated Encephalomyelitis (ADEM)**

- Monophasic course (vs. multiple sclerosis)
- Widely scattered foci of perivenular inflammation and demyelination
- Acute hemorrhagic leukoencephalitis: severe variant. Vascular hemorrhaging. Devastating course
- **Trigger**: immunization (postvaccinal) or infection (postinfectious)
  - Postvaccinal: live measles or varicella
  - Postinfectious: rubella, mumps, influenza, parainfluenza, EBV, mycoplasma.
- **Pathogenesis**: cross-reactive immune response to infectious agent which triggers demyelinaiton
  - Antibodies to myelin basic protein (MBP, and other myelin components
  - Unlikely to be frank invasion of CNS

- **Signs and symptoms**
  - Fever reappears (postinfectious). Neurological symptoms appear late.
  - Headache, meningismus
  - Lethargy progressing to coma.
  - Seizures are common
  - Hemiparesis, quadriparesis, + Babisky
  - CSF
    - Protein modestly elevated: 50-150 mg/dl
    - Pleocytosis: 200 cells/L (80%)
  - **No oligoclonal bands (vs. multiple sclerosis)**
    - MRI: gadolinium enhancement of white matter in brain and spinal cord

- **Diagnosis**: Meningismus, drowsiness, coma, seizures suggest ADEM vs. MS
- **Prognosis**
  - Measles: mortality rate is 5-20%
  - Even those who recover may have persistent seizures and learning disorders
- **Treatment**
  - High dose steroids
  - Plasmapheresis
  - IV IgG

**Sources**

- PreTest: Neurology, Anschel, 2007
Guillain-Barre Syndrome (GBS): Acute areflexic motor paralysis with or without sensory disturbance + dysautonomia

- Clinical manifestations: Respiratory support required in 30%
  - Usually ascending paralysis first noticed as “rubbery legs”, progresses over the next few days.
  - Fever and constitutional symptoms are absent. If present, likely the diagnosis is something else.
  - Pain in the neck, shoulder, back, over the spine common in the early stages (50%)
  - Bulbar weakness common: 50% experience facial diparesis
  - Bladder dysfunction is rare, but may occur late in a severe course. If early, spinal cord etiology likely.
  - Dysautonomia: loss of vasomotor control, labile blood pressure, postural hypotension, arrhythmias.
  - Sensory loss (vs. myopathy)

- Subtypes
  - Acute inflammatory demyelinating polyneuropathy (AIDP): 90% of GBS cases in western world
    - Adults > children, rapid recovery
    - Demyelinating. Anti-GM1 (ganglioside) antibodies
  - Acute motor axonal neuropathy (AMAN): Pure motor. Prevalent in China and Mexico
    - Children and young adults.
    - Axonal. Anti-GD1a (ganglioside?) antibodies
  - Acute motor sensory axonal neuropathy (AMSAN)
    - Adults; uncommon, recovery slow, often incomplete. Severe.
    - Axonal.
  - Miller Fisher syndrome (MFS)
    - Descending paralysis: Ophthalmoplegia, ataxia, and areflexia.
    - Demyelinating. Anti-GQ1b antibodies (90%)

- Pathogenesis
  - Begins 1-3 weeks following infection, usually gastrointestinal or respiratory.
    - Campylobacter jejuni (30%), Herpesvirus (CMV, EBV)(20-30%), lymphoma, HIV, SLE.
  - Misdirection immune response to foreign antigens on host tissues via epitope (molecular mimicry).
    - Gangliosides are present in large quantity on Schwann cells, particularly Nodes of Ranvier.
    - Polyclonal IgG antibodies, cytokines, and complement all play a role.
  - Primarily demyelinating, but axonal damage in severe cases secondary to extensive demyelination
  - Elevated CSF protein without pleocytosis beginning 48 hours after onset

- Diagnosis: clinical
  - Required
    1. Progressive weakness of 2+ limbs from neuropathy
    2. Areflexia
    3. Disease course <4 weeks
    4. Exclusion of other causes:
      - Vasculitis, toxins, botulism, diphtheria, porphyria, localized spinal cord or cauda equina syndrome
  - Supportive
    - Relatively symmetric weakness
    - Mild sensory involvement
    - Facial nerve or other CN involvement
    - Absence of fever
    - Typical CSF profile: acellular, ↑ protein
      - Albuminocytologic dissociation
    - Electrophys: demyelination (↓ velocity)

- Treatment
  - IV immune globulin (IVIg) or plasmapheresis, but after 2 weeks of motor symptoms is ineffective
  - ***Gluocorticoids are not effective***
  - 85% resolve fully. Some may have minor residual deficits (areflexia)

- Management
  1. Get FVC (should be >15-20 ml/kg) and max. inspiratory pressure (should be >30 cm H₂O) or intubate
  2. LP: CSF shows ↑ protein, no pleocytosis, normal glucose, pi
  3. Nerve conduction velocity studies (NCV) to demonstrate demyelination (velocity ↓ > amplitude)
  4. Imaging of spinal cord

- Differential diagnosis
  - Botulism (also has GI symptoms & is descending). NMJ ↓
    - Remove the tick and symptoms abate.
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): weakness, sensory deficit > 4 wk (vs. AIDP). Older men

- **Overview.** Similar features as GBS: ↑ CSF protein, demyelination: ↓ conduction velocity
  - Can be chronic and progressive or relapsing and remitting.
  - Serum protein electrophoresis. Monoclonal gammopathy (MGUS) is concomitant in 25%
  - Onion-bulb changes (demyelination and remyelination)

- **Diagnosis:** EMG & NCV, CSF, nerve biopsy (definitive diagnosis shows segmental demyelination)

- **Treatment**
  - Usually only indicated when severe or walking is impaired. Mild cases can have expectant mgmt.
  - IVIg, plasmaphoresis, and glucocorticoids are all more effective than placebo. (steroids not in GBS)

Vasculitic Neuropathy: Ischemic neuropathy of vasa nervorum

- Consider when mononeuropathy multiplex is associated with constitutional symptoms.
  - ⅓ of cases are nonsystemic vasculitic neuropathies (no systemic symptoms)

- Polyarteritis Nodosa (PAN): 50% of patients clinically and 100% at autopsy. Axonal. Infarction.


- Symmetric with dysesthesias (unpleasant sensation) and sensory loss progresses to all limbs, the torso, face.
- Ataxia, pseudoathetosis: abnormal writhing movements occur when eyes closed only (vs. true athetosis)
- Antibodies against RNA-binding proteins (HuD, HuC, and Hel-N1) normally only expressed in nerve tissue
  - Small cell lung cancer expresses these and alloimmunizes against them
- Encephalomyelitis can develop
- Usually precedes the identification of SCLC by 6 months.
- **Course:** rapid over a few weeks and then stabilizes with patient disabled.
- **Treatment:** none effective. IVIg, PE, glucocorticoids don’t work.

Myasthenia Gravis

- **Clinical manifestations**
  - Weakness and fatigability, starting with predominantly bulbar distribution: ocular and pharyngeal
  - Deep tendon reflexes are preserved
  - Other conditions can make MG worse and precipitate myasthenic crises (respiratory compromise)
    - Treatment: plasmapheresis and intubation
  - 85% of patients have generalized weakness following bulbar
    - Ocular MG: don’t develop generalized weakness after 3 years, unlikely ever will.

- **Pathogenesis:** antibody and T-cell damage to AChR’s and/or muscle-specific kinase (MuSK)(subtype)
  1. ↑ turnover of AChRs by cross-linking and rapid endocytosis of the receptors
  2. Blockade of the active site of the AChR
  3. Damage to the postsynaptic muscle membrane by the antibody in collaboration with complement.
    - In MuSK subtype, loss of MuSK results in inefficient clustering of AChR’s
    - 75% of patients have abnormal thymus: 65% have hyperplastic thymus, 10% have thymoma.
      - Probably myoid (muscle-like) cells in thymous auto-immunizing
      - Thymectomy indications: thymoma, generalized MG without thymoma. Remission in 80%.

- **Diagnosis**
  - Serum anti-AChR antibody: 85% sensitive, 40% in ocular MG
  - Electrical stimulation (3-4 Hz): In normal individuals, amplitude of action potentials does not ↓
    - Anticholinesterase test: Edrophonium administratin gives improvement

- **Differential Diagnosis**
  - **Lambert-Eaton Myasthenic Syndrome (LEMS)**
    - Distinguished by ↓ DTR, autonomic symptoms, and ↑ response to repetitive stimulation
    - Antibodies to P/Q type calcium channels in NMJ in 85%
    - Often underlying SCLC
      - Treatment: Plasmapheresis, immunosuppression, AChE’s
  - **Botulism:** DTR preserved early. Toxic detected in serum. Treatment: antitoxin.
  - **Neurasthenia:** Not organic
  - **Progressive external ophthalmoplegia:** Mitochondrial disorder
  - **Congenital myasthenic syndromes:** mutation in AChR subunit. Suspect when early onset + no ABs.
IMMUNE-MEDIATED NEUROPATHY

Sources

Trigeminal Neuralgia (Tic Douloureux)

- 60% occur in women of middle age or elderly
- **Signs & symptoms**
  - excruciating paroxysms of pain in the lips, gums, cheek, or chin and V_1 (very rare) of CN V
  - Lasts a few seconds to a minute, but may be so intense that the patient winces (tic) (vs. cluster)
  - Paroxysmal, occurring frequently both day and night for weeks at a time.
  - Can occur with chewing, speaking, smiling.
  - Trigger zones: on face, lips, tongue that provoke attacks
    - Tactile stimuli (ex. washing face, brushing teeth) can bring on attack (like SUNCT)
  - No sensory loss (or weakness)
- **Pathophysiology**
  - Ectopic generation of action potentials in pain fibers of CN V at nerve root.
  - Compression or disease leads to demyelination of large fibers, but pain fibers get hyperexcitable
    - Reason why tactile stimuli (via myelinated fibers) can trigger pain fibers
    - Compression by blood vessel (SCA) in many patients
- **Differential diagnosis**
  - Dental pain
  - Migraine pain: deep-seated and steady, unlike superficial quality of trigeminal neuralgia
  - Cluster-tic (rare): Cluster headache associated with trigeminal neuralgia
  - Temporal arteritis: facial pain is present but is not shock-like, and other symptoms are present.
  - Younger patient: suspect multiple sclerosis
  - Focal neurologic deficits: suspect mass lesion (aneurysm, neurofibroma, schwannoma, meningioma)
- **Diagnosis:**
  - ESR if temporal arteritis is suspected
  - MRI only necessary if multiple sclerosis or aneurysm is under consideration
- **Treatment:**
  1. Carbemazepine: successful in 50-75%, titrated from 100 mg daily up to 200 mg QID
  2. Phenytoin, other anticonvulsants
  4. Surgery: radioablation of trigeminal ganglion (short-term relief in 95%, recurs in ⅓)
  5. Microvascular decompression via suboccipital craniotomy: 70% effective, low recurrence, but invasive.

**Atypical facial pain:** Constant deep pain. Not lancinating (vs. trigeminal neuralgia). Treatment: TCAs
- Sometimes post-dental procedure. High suspicion for nasopharyngeal carcinoma or apical lung tumor.

**Trigeminal Neuropathy**
- Frequently presents with sensory loss and/or weakness of jaw muscles (vs. trigeminal neuralgia)
- Deviated jaw opening indicates weakness of pterygoid muscle on the side to which the jaw deviates
- Differential: Trismus (tetany of masticatory mm.) occurs in tetanus and phenothiazine (neuroleptic) drugs
- **Etiology**
  - Systemic: Sjögren's syndrome, SLE, scleroderma, or mixed connective tissue disease
  - Infectious: herpes zoster (VZV), *Mycobacterium leprae*
  - Tumors: meningioma, schwannoma, metastasis
  - Thrombosis of cavernous sinus can affect V_1 and V_2 (sparing V_3)
- **Prognosis:** gradual recovery.

**Facial weakness: Anatomy of cranial nerve VII**
- Sensory component small (nervus intermedius): taste from anterior ⅔ of tongue, external auditory canal
- Motor nucleus: anterior and lateral to abducens (CN VI) nucleus.
  - Pontine lesions here often affect CN VI as well as corticospinal tract (crossed)
- Joins vestibulocochlear nerve (CN VIII)
Lesion here: stapedius is interrupted results in hyperacusis (sensitivity to loud sounds)

- Can also cause “neighborhood sign” of hearing loss, tinnitus, dizziness

- Gives off chorda tympani to taste buds of mouth
- Courses in bony facial canal, and exits via stylomastoid foramen
- Passes through parotid gland (without innervating it - CN IX does that)
- Subdivides and supplies facial muscles

Forehead muscles are bilaterally innervated from cortex, cheek and chin muscles are not

- Synkinesis: long time paralysis can result in reinervation by smaller subset or by wrong fibers.
  - Attempted closure of orbicularis occuli only may result in contraction of whole side of face.
  - Can also anomalously innervate lacrimal gland, causing “crocodile tears”

Bell’s Palsy: most common form of facial paralysis

- Signs & symptoms: Abrupt onset (48 hours) (vs. tumors which are insidious)
  - Pain behind the ear may precede paralysis by a day or two
  - Taste sensation may be lost and hyperacusis (sounds are louder) may be present

- Labs
  - CSF: lymphocytosis
  - MRI: swelling and enhancement of geniculate ganglion, facial nerve, and entrapment of nerve
  - Electromyography (EMG): denervation after 10 days is poor prognostic indicator.

- Prognosis: 80% recover within weeks-months
- Pathophysiology: HSV-1 DNA in endoneurial fluid and posterior auricular muscle, but unproven.
- Differential diagnosis: first differentiate from supranuclear CN VII palsy by forehead involvement.
  - Lyme disease: can be bilateral
  - Ramsay Hunt syndrome: reactivation of herpes zoster (VZV). Vesicular eruption in auditory canal
    - Herpes Zoster Oticus: otalgia, vertigo, hearing loss, tinnitus
  - Sarcoidosis: often bilateral
  - Guillain-Barré syndrome
  - Leprosy
  - Diabetes mellitus
  - Connective tissue disease: Sjögren’s syndrome and amyloidosis
  - Acoustic neuroma
  - Infarcts, demyelinating lesions (MS): other signs of brainstem involvement are present
  - Tumor compression (cholesteatoma, dermoid): onset is insidious and progressive (vs. Bell’s)

- Diagnosis: Clinical diagnosis with ALL the following present
  1. Typical presentation
  2. No risk factors or preexisting conditions for other causes of facial paralysis
  3. Absence of VZV vesicles in auditory canal (Ramsay Hunt syndrome ruled out)
  4. Normal neurologic exam (outside of CN VII)
- Treatment: steroids shorten recovery period and improve functional outcome. No benefit of acyclovir.
  - Tape eye shut during sleep to prevent corenal drying
  - Massage weakened muscles

Hemifacial spasm: painless irregular involuntary contractions on one side of the face

- Etiology:
  - Idiopathic (most common)
  - Sequela of Bell’s palsy
  - Irritative lesion of facial nerve (CN VII) (ex. acoustic neuroma or aneurysm)
- Treatment: Carbamazepine, gabapentin, or baclofin. Botulinum toxin can help for 3-4 months.

Blepharospasm: involuntary recurrent spasm of both eyelids.
CRANIAL NERVE DISORDERS

- Usually occurs in elderly persons as an isolated phenomenon or with other facial muscle spasms
- Treatment: Botulinum toxin if severe

**Facial myokymia:** rippling activity of the facial muscles
- Etiology: Multiple sclerosis or Guillain-Barré syndrome

**Facial hemiatrophy:** disappearance of fat in the dermal and subcutaneous tissues on one side of the face.
- Occurs mainly in women. Begins in adolescence and is slowly progressive.
- Dermal appendages (hair, sebaceous glands) disappear. Bilateral involvement can occur
- Treatment: cosmetic, skin grafts etc

**Glossopharyngeal Neuralgia & Vagus Neuralgia**
- CN IX supplies taste to posterior ⅓ of tongue and (with vagus) sensation to posterior pharynx
- **Signs & symptoms:** resembles trigeminal neuralgia but is much less common
  - Intense paroxysmal pain from one side of the throat, usually in the tonsillar fossa
  - Can radiate to the ear (tympanic branch of glossopharyngeal nerve)
  - Can be triggered by swallowing or coughing
  - No motor or sensory loss
  - Autonomic dysfunction: bradycardia, asystole, hypotension, syncope
- **Etiology**
  - Herpes zoster (VSV) (very rare)
  - Tumor of jugular foramen: jugular foramen syndrome (vocal paralysis, deviation of palate, weak SCMs)
- **Treatment**
  - Similar to trigeminal neuralgia: carbamazepine, baclofen, surgery (rhizotomy - sever nerve roots)

**Dysphagia and Dysphonia**
- Diphtheria: can affect pharyngeal branches of CN X. Nasal voice, regurgitaiton of liquids.
- Tumors, infections, vascular lesions can affect CN X at meningeal or brainstem level
- Polymyositis/dermatomyositis cause horiness by direct involvement of laryngeal muscles (not CN X)
- Recurrent laryngeal nerve damage: intrathoracic disease, aortic aneurism, large left atrium, surgery.
  - Intramedullary: also ipsilateral cerebellar, ↓ of sensation ipsilateral face & contralateral arm. Horner’s
  - Extramedullary: CN IX and XI are frequently affected (jugular foramen syndrome)
  - Extracranial: can have palsy of CNs IX, X, XI, XII and Horner’s syndrome
  - If no sensory loss of palate, lesion is below departure of pharyngeal branches. Usually mediastinal

**Tongue paralysis**
- Motor neuron disease (most often), intramedullary lesion, poliomyelitis
- Compression at hypoglossal canal by platybasia, Paget’s disease, tumors.

**Multiple Cranial Nerve Palsies**
- Determine whether the lesion is in the brainstem or outside it
  - Surface of brainstem (Compression): adjacent cranial nerves, late involvement of corticospinal tract
  - Intramedullary: corticospinal tract early - “crossed paralysis”: ipsilateral CN, contralateral body
  - Outside the brainstem: diabetes, trauma, herpes zoster, meningitis, granulomatous disease, Behçet’s disease, enlarging saccular aneurysms, or tumors (nasopharyngeal, lymphoma, neurofibroma, meningioma, chordoma, cholesteatoma)
- Purely motor deficit without atrophy: Myasthenia gravis
- Guillain-Barré syndrome, Fisher variant: oculomotor paresis, ataxia, areflexia of limbs
- Cavernous sinus syndrome: orbital, facial pain, swelling (chemosis), fever, oculomotor neuropathy (CNs III, IV, VI only) and trigeminal neuropathy (V1 and V2 only)
  - Usually thrombosis from infection with *Staphylococcus aureus* from face cellulitis
  - Carotid aneurysm
CRANIAL NERVE DISORDERS

- Carotid-cavernous fistula (orbital bruit present)
- Idiopathic granulomatous (Tolosa-Hunt syndrome)

Sources

AUTONOMIC NERVOUS SYSTEM DISEASE

Anatomy
- Parasympathetic preganglionic: CNs III, VII, IX, X and S2-3
- Sympathetic preganglionic: T1-L2
- ACh is preganglionic neurotransmitter of both divisions (ganglia have nicotinic AChR’s)
  - Parasympathetic postganglionic: ACh
  - Sympathetic postganglionic: NE (except eccrine sweat glands, ACh)

Symptoms of Autonomic Dysfunction
- **Classification**
  - Loss of function: impaired baroreflex
  - Overactivity: hyperhidrosis, hypertension, tachycardia
  - Loss of regulation: autonomic storm, autonomic dysreflexia
- **Orthostatic hypotension**
  - Definition: sustained drop in systolic (20 mmHg) or diastolic (10 mmHg) BP within 3 min of standing
  - Dimming or loss of vision, lightheadedness, diaphoresis, ↓ hearing, pallor, weakness and syncope.
  - Constant HR whether supine or standing
  - Etiology: aging (20%), DM (10%), other neuropathy (rare), MSA (rare), pure autonomic failure (rare)
- **Approach to the patient**
  1. Rule out reversible causes
     a. Medications: diuretics, antihypertensives, antidepressants, ethanol, narcotics, insulin
  2. Relationship to meals (splanchnic pooling)
  3. Standing on awakening in AM (intravascular voume depletion)
  4. Ambient warming (vasodilation)
  5. Exercise (muscle arteriolar vasodilation)
    o Determine pattern
      - Systemic (BP, HR, sleep, temperature)
      - Organ systems (pupils, bladder, sexual)
- **Testing**
  - Cardiovagal function: Heart rate response to deep breathing (HRDB)
    - Normal variation: young (15-20), old (5-8)
  - Postganglionic sudomotor function: Quantitative sudomotor axon-reflex test (QSART)
    - ACH-induced sweating
  - Adrenergic function: beat-to-beat blood pressure response to valsalva (BPBB)
  - Adrenergic and cardiovagal response: head-up tilt (HUT)
  - Pharmacological
    - Tyramine (releases NE from postganglionic)
    - Phenylephrine (α₁ agonist)
    - Trimethaphan (ganglionic blockade)
    - Arginine vasopressin (afferent central pathways)

Specific syndromes of autonomic dysfunction

Multiple System Atrophy
- Autonomic failure: orthostatic hypotension and/or neurogenic bladder required for diagnosis
- Striatonigral degeneration (parkinsonism) (Shy-Drager/MSA-p) or olivopontocerebellar atrophy (MSA-c)
- Differentiate from PD: innervation of heart (MIBG - radiolabeled NE) impaired in PD but normal in MSA
- Prognosis: death in 7-10 years
  - Treatment: does NOT respond to carbidopa-levadopa

Dementia with Lewy Bodies (DLB): less severe dysautonomia than PD or MSA

Spinal cord lesions
- Autonomic hyperreflexia: affects bowels, bladder, sexual, temperature, cardiovascular
  - Bladder: increased autonomic discharge from stimulating bladder, skin or muscles (85% of spinal cord)
- Dysregulation of temperature due to inability to sense temperature in extremities
- Quadriplegic: supine hypertension, orthostatic hypotension - no sympathetic innervation of BVs
Peripheral nerve and NMJ Disorders associated with autonomic neuropathy

- Most common cause of chronic autonomic insufficiency
- Neuropathy: DM, amyloidosis, chronic alcoholism, porphyria, Guillain-Barré syndrome
- NMJ disorders: botulism, Lambert-Eaton Syndrome
- **Diabetes Mellitus**
  - Begins 10 years after onset of DM
  - Early: vagal disturbances (↓ HR variation with deep breathing)
  - Late: gastroparesis, N/V, bowel/urinary incontinence, pupillary, orthostatic hypotension, Long QT
  - Sympathetic neuropathy may mask the warming signs of hypoglycemia (tachycardia)
- **Amyloidosis**
  - Primary (sporadic and multiple myeloma) and familial (transthyretin - most common)
  - Associated painful distal neuropathy
  - Diagnosis: protein electrophoresis of blood and urine
- **Alcoholic neuropathy**
  - Mild autonomic neuropathy: impotence.
  - Orthostatic hypotension is due to brainstem involvement
  - Severe autonomic symptoms are associated with Wernicke’s encephalopathy.
- **Porphyria**
  - Most pronounced in acute intermittent type
  - Autonomic symptoms: tachycardia, sweating, urinary retention, hypertension
  - Other symptoms: anxiety, abdominal pain, nausea, vomiting
- **Guillain-Barre Syndrome**
  - Blood pressure fluctuations and arrhythmias can be severe. 2-10% with GBS suffer cardiac arrest.
  - GI involvement, sphincter disturbances, abnormal sweating, pupillary dysfunction
  - Degree if autonomic involvement is independent of severity of motor / sensory neuropathy.

Autoimmune Autonomic Neuropathy (AAN)

- Subacute autonomic failure with orthostatic hypotension, enteric neuropathy, cholinergic failure
  - ACh failure: loss of sweating, sicca complex (dry eyes, mouth, vagina), tonic pupil
- **Pathophysiology**: Antibodies against AChR A_3_ (ganglionic)
- **Etiology**
  - Follows viral infection in 50%
  - Paraneoplastic syndrome

**Botulism**

- Botulinum toxin binds to presynaptic ACH nerve terminals, taken into cytosol, block ACh release
- **Signs & symptoms**: motor paralysis and autonomic dysfunction. Blurred vision, dry mouth, constipation
Pure Autonomic Failure (PAF): Postural hypotension, impotence, bladder dysfunction, defective sweating
- Sporadic. Does not shorten life span
- Onset: middle aged women
- Signs & symptoms: motor paralysis and autonomic dysfunction. Blurred vision, dry mouth, constipation
- Pathophysiology: primary disorder of postganglionic sympathetic neurons
  - Low supine plasma NE levels and noradrenergic supersensitivity (↑ regulate receptors)
- 10-15% evolve into MSA.

Postural Orthostatic Tachycardia Syndrome (POTS)
- Orthostatic intolerance, not orthostatic hypotension. Normal when lying down, but tachycardic standing.
- 5x more common in women. Occurs ages 15-50.
- 50% report antecedent viral infection
- 80% of patients improve but only 25% eventually resume normal daily activities (ex. sports)
- Signs & symptoms: orthostatic intolerance, syncope, palpitations, tremulousness, dysautonomia, fatigue.
- Treatment: expand fluid volume, postural training. Midodrine, fludrocortisone, phenobarbital, β-blocker.

Inherited Disorders: 5 types of hereditary sensory and autonomic neuropathy (HSAN I - V)
- HSAN I: autosomal dominant. SPTLC mutation (ceramide pump). Presents as distal small-fiber (burning feet).
  - ↓ tears, ↑ sweat, ↓ sensitivity to pain, areflexia, no fungiform papillae on tongue, and labile BP
  - Episodic abdominal crises and fever.
  - IKBKAP gene mutated, a transcription factor in neural development

Primary Hyperhidrosis
- Affects 1% of the population. Not dangerous, but can be embarassing (ex. shaking hands)
- Onset: adolescence
- Signs & symptoms: ↑ sweating on palms and soles
- Treatment
  1. Topical antiperspirants
  2. Anticholinergic drugs (glycopyrrolate)
  3. T2 ganglionectomy or sympathectomy (90% successful with palmar)
     a. Complications: recurrent hyperhidrosis (16%), Horner’s (<2%), gustatory sweating
  4. Botulinum toxin injection

Holmes-Adie Pupil (Tonic Pupil): Unilateral tonic pupils, ↓ corneal sensation, ↓ DTR in legs
- If both pupils are tonic in a young patient, suspect drug use (amphetamines, cocaine, psilocybin)
- Slow constriction on accommodation and slow relaxation
- Parasympathetic pathway: Miosis (constriction)
  - Edinger-Westphal Nucleus in midbrain
  - Fibers run in epineurium of CN III to orbit (subject to compressive injury)
  - Synapse in Ciliary Ganglion and postganglionic fibers innervate the eye and lacrimal glands
- Sympathetic pathway: Mydriasis (dilation)
  - Ipsilateral postorolateral hypothalamus
  - Cilospinal cortex of Budge-Waller: C8-T2 (within interomediolateral spinal cord gray matter: T1-L2)
  - Fibers run with internal carotid until the cavernous sinus
  - Nasociliary nerve → Long ciliary nerve.
- Diagnosis: Apply 1% pilocarpine. If constricts normally, diagnosis is confirmed.
Acute Autonomic Syndromes (AAN): Acute autonomic failure (↓ autonomic) and autonomic storm (↑ autonomic)

- **Acute autonomic failure**
  - **Etiology**
    - Autoimmune autonomic neuropathy (most common)
    - Organophosphate poisoning
    - Hypothalamic disorder (abnormalities in temperature, satiety, sex, circadian rhythm)
    - Infections

- **Autonomic storm**
  - **Etiology**: brain, spinal cord injury, toxins, drugs, autonomic neuropathy, chemodectomas (ex. pheo)
    - Brain injury (most common)
      - Following severe head injury (with diffuse axonal injury)
      - Postresuscitation encephalopathy following anoxic-ischemic insult
    - Acute intracranial lesions: hemorrhage, infarction, tumor, hydrocephalus
      - Diencephalon lesions are more pronounced
    - Acute spinal cord lesion (less common cause)
    - Drugs & toxins: sympathomimetics, cocaine, TCAs, tetanus, botulinum toxin (less often)
    - Guillain-Barré syndrome
  - **Signs & symptoms**
    - Fever, tachycardia, hypertension, tachypnea, hyperhidrosis, pupillary dilation, flushing.
    - Seizures
    - Neurogenic pulmonary edema
  - **Treatment**
    1. Rule out other causes (malignant hyperthermia, porphyria, epilepsy, sepsis, encephalitis)
      - MRI of brain and spine
    2. Admit to ICU
    3. Morphine sulfate, labetalol

Complex regional pain syndrome (CRPS) types I and II: Reflex Sympathetic Dystrophy and Causalgia

- **Diagnosis**: Pain is primary clinical feature
  - Vasomotor dysfunction, sudomotor abnormalities, edema must be present for diagnosis
- **Complex regional pain syndrome (CRPS) type I**: Reflex Sympathetic Dystrophy (RSD)
  - Usually develops after tissue trauma (MI, shoulder injury, stroke), but absence of nerve injury.
  - Allodynia (from nonpainful stimulus), hyperpathia (exaggerated response), and spontaneous pain.
  - Renamed due to unclear relationship to autonomic nervous system.
  - Phases
    - Phase I (<3 weeks): pain (burning, aching) and swelling in distal extremities. Hair growth.
    - Phase II (3-6 months): thin, shiny, cool skin appears.
    - Phase III (6-9 months): atrophy of skin and flexion contractures.
- **Complex regional pain syndrome (CRPS) type II**: Causalgia. Aberrant reinnervation following nerve injury
  - Develops after injury to peripheral nerve (vs. CRPS type I)
  - Sponatenous pain occurs within that distribution but may spread

Sources
- Case Files: Neurology, Toy, 2007
- First Exposure to Neurology, Kirschner, 2007
Types of peripheral nerve Injury

- **Class 1 Injury (Neurapraxia):** conduction block but without Wallerian degeneration
  - Transient sensation of numbness in an extremity, as occurs after lying or sitting in a certain position.
- **Class 2 injury:** interrupts the axon’s continuity and results in Wallerian degeneration.
  - **Axonotmesis (mild):** endoneurium is preserved. Return of function expected.
  - **Neurotmesis (severe):** endoneurium is destroyed. Return of function not expected.

### Classification

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Demyelinating</th>
<th>Axonal</th>
<th>Neuronal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Rapid</td>
<td>Slow</td>
<td>Rapid</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Paresthesia and weakness</td>
<td>Dysestheasias and distal weakness</td>
<td>Paresthesias, gait ataxia</td>
</tr>
<tr>
<td>Sensory signs</td>
<td>Proprioception &gt; pain</td>
<td>Pain &gt; proprioception</td>
<td>Proprioception &gt; pain</td>
</tr>
<tr>
<td>Nerve biopsy</td>
<td>De- and re-myelination</td>
<td>Axonal de- and regeneration</td>
<td>No regeneration</td>
</tr>
<tr>
<td>Nerve conduction</td>
<td>Velocity ↓ &gt; amplitude</td>
<td>Amplitude ↓ &gt; velocity</td>
<td>Sensory amplitudes</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Rapid recovery</td>
<td>Slow recovery</td>
<td>Poor recovery</td>
</tr>
<tr>
<td>Causes</td>
<td>GBS, diptheria, CIDP, DM, MMN</td>
<td>Toxic, metabolic, HIV, CMT2, DM</td>
<td>Sjögren's, cisplatin, B&lt;sub&gt;6&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

### Approach to the patient

1. Is this a peripheral neuropathy?
   - a. Sensory symptoms (parasthesias, numbness) usually before motor (gait, weakness)
2. What is the distribution?
   - a. Neuronal (mononeuropathy), dermatomal (radiculopathy), myotomal, sclerotomal (conn. tissue)
   - b. Polyneuropathy: diffuse symmetric dysfunction of peripheral nerves
   - c. Mononeuropathy: single peripheral nerve. Compression, trauma, or vascular causes.
     - i. Multiple mononeuropathy: multiple individual peripheral nerves
   - d. Mononeuropathy multiplex: multiple entrapments, infiltration, or vasculitis.
   - f. Plexopathies (brachial or lumbosacral): multiple peripheral nerves, asymmetrically.
3. Which fibers are affected? (small or large-fiber sensory, motor, and/or autonomic)
   - a. Small sensory fibers (C-fibers): stabbing, shooting, allodynia
     - i. Leprosy, diabetes, amyloidosis, Tangier disease, Fabry disease, Dysautonomia, HIV
   - b. Large sensory fibers: Tingling, “pins and needles,” ↓ vibration sense + proprioception (ataxia)
     - i. Sjögren's, Vitamin B<sub>12</sub> deficiency, cisplatin, pyridoxine, Friedrich’s, DM
   - c. Motor: cramps, weakness, foot/wrist-drop, hyporeflexia
     - i. Immune neuropathy (Guillain-Barré), Acute intermittent porphyria, lead, brachial, DM
   - d. Autonomic: Orthostasis, change in sweating or salivation, presyncope
     - i. Acute: Acute pandysautonomic neuropathy, botulism, porphyria, GBS, amiodarone
     - ii. Chronic: Amyloid, DM, Sjögren's, HSAN I and III (Riley-Day), Chagas, paraneoplastic
4. What tests are indicated?
   - a. Impaired glucose tolerance test is found in >50% of idiopathic sensory neuropathy
   - b. Electrodiagnosis (EEG, nerve stimulation), nerve biopsy, muscle biopsy

### LMN vs UMN

<table>
<thead>
<tr>
<th>Weakness</th>
<th>UMN</th>
<th>LMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>Weak</td>
<td>Weak</td>
</tr>
<tr>
<td>Tone</td>
<td>↓ (flaccid)</td>
<td>↑ (spastic)</td>
</tr>
<tr>
<td>Reflexes</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Babinsky</td>
<td>Downgoing</td>
<td>Upgoing</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Atrophic</td>
<td>Not atrophic</td>
</tr>
<tr>
<td>Fasciculations</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Mononeuropathy: single peripheral nerve - both motor + sensory loss. Compression, trauma, or vascular causes.

- **Carpal tunnel syndrome** (median nerve mononeuropathy): tingling, numbness in fingers worse at night.
  - Phalen’s sign: flex wrist reproduces sx. Tinel’s sign: tap wrist reproduces sx (any mononeuropathy)
  - Treatment: 1) NSAIDs, 2) diuretics, 3) steroids, 4) lidocaine, 5) splint, 6) surgery (decompression)
- **Ulnar nerve entrapment**: numbness, paraesthesia in ulnar hand, worse at night or elbow flexion.
  - Ulnar claw: 4th and 5th fingers will not straighten. (vs. median: 4th and 5th are only ones to flex)
  - If at wrist (vs. elbow), sensory loss spares dorsum of hand
- **Radial**: Saturday night palsy (radial nerve at spiral groove). Wrist drop (wrist extensors paralyzed). Elbow OK.
- **Lower Limb** (Sciatic n): Fibular n (L4-5, dorsiflexion & eversion), Tibial n. (S1-2, plantarflexion & inversion)
  - Sciatica: L4-S3. Flail foot + numbness/parasthesias. Weak hamstring, Injection injury, fracture.
  - Tarsal Tunnel Syndrome: Pain and paraesthesia worse at end of day. Sensory loss in sole.

Mononeuropathy multiplex: multifocal involvement of individual peripheral nerves

- Usually is due to an inflammatory cause. Rarely can be independent compressive neuropathies.
  - **Mononeuritis multiplex**: systemic (67%) and non-systemic (33%) vasculitis can present.
    - Systemic (w/constitutional sx): PAN, RA, SLE, Churg-Strauss, Wegener’s, and hypersensitivity vasculitis
    - Common fibular nerve is affected (foot drop) in 75% of patients with vasculitic neuropathy
    - Leptospira neuritis: cooler body areas, mainly unmyelinated fibers, patch of anesthetic reddened skin
    - Sacroiliitis: anywhere. Heerfordt’s syndrome: bilateral facial paralysis, parotiditis, and uveitis
    - Treatment: Steroids and cyclophosphamide

Polyneuropathy: distal, symmetric sensorimotor

- Length-dependent pattern. Sensory symptoms tend to be more prominent than motor symptoms.
- Glove-and-stocking: Rarely extends above knees or proximal to forearms.
- Endocrine: diabetes (most common), hyperthyroidism, hypothyroidism, acromegaly
- Hematalogic: Paraproteinemia (2nd most common): MGUS, amyloidosis, lymphma, POEMS syndrome
- Vasculitis: PAN, SLE, RA, Sjogren, Scleroderma
- Symmetric diabetic neuropathy (Diabetic sensoriomotor polyneuropathy [DSPN])
  - Stocking-glove, length-dependent (hand paraesthesia appear once leg paraesthesia reaches knee.)
  - GLUT-3 insulin-independent uptake of glucose into neurons.
    - Theory 1: conversion to sorbitol depletes second messengers and ↓ Na/K ATPase. Swelling.
    - Theory 2: conversion to sorbitol depletes NADPH, NO causing constriction in vasa nervorum.
  - Treatment: Glucose control, Aldose reductase (aldose --> sorbitol) inhibitors (in trials - inconsistent)
- Asymmetric diabetic neuropathy
  - CN III paralysis. Not blown pupil since pupillomotor fibers are on the outer layers. (vs. compression)
  - Limb nerves: more susceptible to entrapment, perhaps due to endoneurial edema.
  - Truncal radiculopathy: pain in thoracic spine or abdomen. Sudden onset, probably vascular cause.
  - Amyotrophy: Pain and wasting in thighs, hard climbing stairs. Weight loss is invariably present.

Nutritional neuropathies

- B1 (thiamine) deficiency (Dry Beriberi): axonal degeneration
  - Acute or subacute onset of paresthesias, dysesthesias, and mild weakness in the legs.
  - Erythrocyte transketolase activity is reduced.
  - Treatment: replace thiamine, 100mg/day
- B6 (pyridoxine) deficiency or overdose: axonal degeneration.
  - Usually not due to nutritional deficit. More commonly due to isoniazid or penicillamine
- B12 (cobalamine) deficiency: peripheral less prominent than subacute combined degeneration (cord)
  - Lhermitte’s sign: shooting electrical sensation down the spine after neck flexion / extension
  - Similar symptoms occur in Friedrich’s Ataxia
**PERIPHERAL NEUROPATHY & RADICULOPATHY**

**Inherited Polyneuropathy**

- **Hereditary Motor and Sensory Neuropathy (HMSN) (Charcot-Marie-Tooth Disease)**
  - Chronic distal sensory and motor. Most common inherited neuropathy. Onset < 20 years old.
  - Longstanding gait difficulty, followed by difficulty with handling keys and opening jars
  - Wasting and weakness of the distal muscles of the legs. Can’t walk on heels or do tandem gait.
  - Get “Charcot Foot”: atrophic, high arch, and claw toes
  - Nerve conduction indicates *demyelinating process* (velocity affected more than AP amplitude)
  - Normal life expectancy
  - Proliferation of Schwann cells thicken nerves in continual attempt to remyelinate. Visible CNs.
    - Roussy-Lévy Syndrome: CMT-1 with postural and action tremor
  - CMT-2: Autosomal dominant. Predominantly axonal damage with ↓ amplitude (vs. CMT-1)

- **Hereditary neuropathy with liability to pressure palsy (HNPP)(Tomaculous neuropathy)**
  - Autosomal dominant. Inherited predisposition for entrapment neuropathies.
  - Tomaculae are bulbs of demyelination provoked by pressure or trauma

- **Hereditary motor neuropathy:** Wasting and distal weakness

- **Hereditary sensory and autonomic neuropathy:**
  - Type 3 (Riley-Day syndrome): Familial dysautonomia. Autosomal recessive. ~exclusively Ashkenazi
  - Sensitivity to pain, inability to produce tears, poor growth, and labile blood pressure.

- **HMSN Type 4 (Refsum Disease):** Autosomal recessive ↓ oxidation of phytanic acid, a branched-chain FA
  - Retinitis pigmentosa presenting as night blindness often precedes the onset of neuropathy
  - Thickened skin (ichthyosis), sclerodactyly, cardiomyopathy, and cataracts.

- **Familial Amyloid Neuropathy:** Autosomal dominant extracellular deposition of amyloid
  - Painful sensory neuropathy with early autonomic involvement and cardiomyopathy.

- **Familial Alpha-lipoprotein deficiency (Tangier Disease):** severe deficiency of high-density lipoproteins (HDL)
  - Autosomal recessive.
  - Deposition of cholesterol esters in skin and organs, most commonly tonsils + mucous membranes.
  - *Syringomyelic presentation* includes wasting of hand muscles, loss of pain + temperature sensation

- **Acute intermittent porphyria**
  - Triad (in order): 1) abdominal crisis, 2) psychosis (hysteria), 3) acute neuropathy (usually motor)
  - Asymptomatic between attacks. No skin lesions (vs. porphyria cutanea tarda)
  - Acute attacks: ↑ urine aminolevulinic acid and/or porphobilinogen (between attacks, too)

**Radiculopathy** (nerve roots)

- Suggested if axial spine pain associated with radiating pattern in the limb.
  - Axial predominant pain suggests degenerative spondylosis (vertebral osteoarthritis) or myofascial
- **Red flags**. 3% of of disk hernation/spondylosis have serious underlying cause. Need workup (MRI or CT)
  - Incontinence: cauda equina syndrome (LMN), conus medullaris syndrome (UMN + LMN), myelopathy
  - Progressive
  - Immunosuppression: infectious radiculopathy, viral myoradiculitis, neoplasm
  - Fevers, chills, constitutional symptoms: infections radiculopathy
  - Recent surgery: epidural abscess, hematoma, spine instability
  - Pain during sleep, while supine, > 50 years old, history of cancer: suspect cancer
  - Osteoporosis: vertebral fracture

**Cauda equina syndrome**

- Asymmetrical
- Lower motor neuron
- Reflexes: ↓
- Babinsky absent

**Conus medullaris syndrome**

- Symmetrical
- Mixed UMN and LMN
- Reflexes: quadriceps (L3) ↑, Achilles (S1) ↓
- Babinsky present

**Myelopathy**

- Local pain
- Upper motor neuron
- Babinsky present
PERIPHERAL NEUROPATHY & RADICULOPATHY

● Cervical spondylosis (cervical vertebral osteoarthritis) C6 & C7 most common: weak arm flexors.

<table>
<thead>
<tr>
<th>Motor</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5: shoulder abduct</td>
<td>C5: shoulder</td>
</tr>
<tr>
<td>C6: arm pronation</td>
<td>C6: lateral forearm, digit 1-2</td>
</tr>
<tr>
<td>C7: elbow/wrist extend</td>
<td>C7: digit 3</td>
</tr>
<tr>
<td>C8/T1: finger movements</td>
<td>C8: digit 4/5</td>
</tr>
<tr>
<td>T1: medial arm</td>
<td></td>
</tr>
</tbody>
</table>

○ Seen in elderly women (vs. ankylosing spondylitis, young men)
○ Pathophysiology: hypertrophic degenerative changes and/or disk herniation impinge on roots.
○ Signs & symptoms:
  - Reduced range of motion of neck (most common finding)
  - Neck pain and associated occipital headache.
  - Spurling sign: ↑ radicular pain on neck extension and lateral bending ipsilateral to lesion
  - Lhermitte sign: electrical sensation running down the back (like MS)
○ Diagnosis: X-ray of head/neck showing osteophytes, osteoporosis is diagnostic.
○ MRI only if red flag signs or hasn’t resolved in 4-6 weeks
○ Electrodiagnosis: good at localizing lesion once it is diagnosed.
  ○ Sensory nerve conduction should be normal (otherwise neuropathy is likely)
○ Treatment: gabapentin, pregabalin, SSRI, TCA, topiramate while natural healing occurs.

● Lumbar disc herniation (4% of mechanical lower back pain)

○ Signs & symptoms:
  - Sciatica: saddle distribution of pain (burning, shooting) associated with back pain.
  - Can impinge on same-level or level below depending on location of herniation.

<table>
<thead>
<tr>
<th>Root</th>
<th>Myotome</th>
<th>Dermatome</th>
</tr>
</thead>
<tbody>
<tr>
<td>L2</td>
<td>Hip flexors (iliopsoas)</td>
<td>Upper medial thigh</td>
</tr>
<tr>
<td>L3</td>
<td>Knee extensors (quadriceps)</td>
<td>Thigh, medial knee, leg</td>
</tr>
<tr>
<td>L4</td>
<td>Ankle dorsiflexors (peroneal n.)</td>
<td>Thigh, medial knee, leg</td>
</tr>
<tr>
<td>L5 (most common)</td>
<td>Extensor hallucis longus</td>
<td>Lateral leg, dorsal foot</td>
</tr>
<tr>
<td>S1</td>
<td>Ankle plantarflexors (tibial n.)</td>
<td>Posterior leg, sole and lateral foot</td>
</tr>
</tbody>
</table>

○ Diagnosis:
  - Straight-leg raising (SLR)(Laségue maneuver): stretches the root. 90% sensitive, 50% specific.
  - Crossed SLR: pain in symptomatic limb reproduced. 90% specific if combined with SLR.
  - Achilles reflex lost on affected side.
○ Treatment: Conservative: NSAIDs etc (90% improve), unless red flags present (see below)

● Spinal stenosis (3% of mechanical lower back pain)

○ Hypertrophic and spondylothisic degenerative process most common in older adults
○ Risk factors: trauma, osteoporosis, hyperparathyroidism, renal osteodystrophy, Paget’s disease
○ Signs & symptoms:
  - Pain, numbness, tingling in one or both legs relieved by spinal flexion (vs. lumbar disk)
  - Straight leg test often negative (vs. lumbar disk herniation)
  - Pseudoclaudication: pain brought on by exercise and relieved by rest but not arterial.
  - Symptoms are often diffuse, bilateral, because the disease usually involves several vertbrae.
○ Diagnosis: MRI if indicated (red flags)
○ Treatment: conservative unless red flags are present (see: approach to the patient, below)
○ Prognosis: usually stay stable (70%) or get worse (15%) (vs. lumbar disk, usually gets better [90%])

Polyradiculopathy: Proximal and distal nerves affected in symmetric or asymmetric and patchy distribution

● Weakness in proximal and sometimes cranial muscles differentiates from polyneuropathy.

● Etiology:
  ○ Immune: Guillain-Barre (AIDP, Miller-Fisher), CIDP, AMAN
  ○ Infectious: HIV, Lyme disease, CMV, diptheria, Hepatitis C
  ○ Medical: DM, sarcoidosis, paraprotein (MGUS, POEMS, Waldernstrom’s, amyloidosis), porphyria
  ○ CT disease: SLE, Sjogren, PAN
PERIPHERAL NEUROPATHY & RADICULOPATHY

Plexopathy

- **Brachial plexopathy (C5-T1)**
  - Causes: birth injury, trauma (70%), cancer, radiation (s/p mastectomy), familial, immune-mediated
  - Often follows MVA neck hyperextension (whiplash)
  - Brachial neuritis (2nd most common): sudden onset of pain, followed by weakness & atrophy
  - **Signs & symptoms:**
    - Upper (C5-7): weakness & atrophy of shoulder girdle and upper arm muscles.
      - Anterior humeral dislocation (90%): forced external rotation and abduction
      - Posterior humeral dislocation (4%): forced internal rotation. Suspect in seizure.
      - Inferior dislocation (Luxatio erecta) (uncommon): downward dislocation
      - Erb-Duchenne (C5-C6): internally rotated, adducted arm w/finger flexion (waiter’s)
    - Lower (C8-T1): Distal arm weakness, atrophy, focal sensory deficits in hand.
      - Arm jerked upward.
      - Kumpke’s Palsy (C8-T1): elbow flexion, claw hand (↓ extension of fingers)
  - **Thoracic outlet syndrome**
    - Compression of structures above 1st rib and behind clavicle in the interscalene triangle
    - Often tenderness in supraclavicular fossa
    - **Structures compressed**
      - Brachial plexus (95%)
        - C8 + T1 (most common): Pain/paresthesia in medial arm and digits 4 & 5
      - Subclavian vein (4%)
      - Subclavian artery (1%)
        - Five P’s: pain, paresthesia, paralysis, pulselessness, pallor, poikylothermia,
    - **Diagnosis**
      - Duplex ultrasonography, MRA, during provocative maneuvers
      - Diminished radial pulse with provocation (92% sensitive)
      - Chest X-ray showing cervical rib if congenital
    - **Treatment**
      - Medical: Avoid provocative positions. Shoulder girdle exercises.
      - Surgery: resection of first rib or scalene m. (if signs of ischemia or intractable pain)

- **Lumbar plexopathy (L1-S4)**
  - Causes: trauma, surgery, pregnancy, retroperitoneal hemorrhage, radiation, cancer, DM, AAA
  - **Signs & symptoms:** pain, sensory deficits, weakness in lower limbs in asymmetric distribution

Approach to the patient with low back pain

1. Identify any red flags, which are indications for urgent imaging, surgery
   - a. Progressive weakness
   - b. Signs of cord compression (conus medullaris syndrome, cauda equina syndrome)
   - c. Incapacitating pain despite medical treatment
   - d. Recurrent pain
2. Identify constitutional symptoms (fever, weight loss) that could suggest systemic/neoplastic disease
3. **Physical examination**
   - a. Straight leg raise test, cross leg raise test
   - b. Identify any pseudoclaudication
4. If no red flags, trial of conservative therapy (NSAIDs, muscle relaxants) for 4-6 weeks
   - a. Need imaging/surgery if persists beyond 4-6 weeks
   - b. Avoid triggers of back pain but bed rest not recommended. Exercise helps recovery.
PERIPHERAL NEUROPATHY & RADICULOPATHY

Etiology of low back pain

Mechanical spinal (97%)
- Lumbar strain (70%)
- Degenerative changes (10%)
- Herniated disk (4%)
- Spinal stenosis (3%)
- Compression fracture (4%)
- Spondylolisthesis (2%)
  (slipped disk)
- Spondyloysis
  (vertebral structural defect)

Nonmechanical spinal (1%)
- Neoplasia (0.7%)
- Infection (0.01%)
- Inflammation (0.3%)
  Ex. Ankylosing spondylitis

Visceral (2%)
- Pelvic organs
  (prostatitis, endometriosis)
- Renal disease
  (pyelonephritis, stone)
- Abdominal aortic aneurysm
- Gastrointestinal organs
  (pancreatitis, cholecystitis)

Sources
- Case Files: Neurology, Toy, 2007
- PreTest: Neurology, Anschel, 2009
MYOPATHY

Overview
- Proximal, symmetric limb weakness (arms or legs) with preserved reflexes and sensation.
- Anterior horn cell disease, NMJ disease can mimic

Electromyography
- **Myopathy:** ↓ amplitude & duration of response. **Neuropathy:** ↑ amplitude & duration of response.

Diagnostic evaluation
- **Intermittent weakness**
  - Myoglobinuria: do muscle biopsy
    - ↓ lactic acid during exercise: **Glycolytic pathway defect**
      Normal lactic acid during exercise: **CPT defect** (transports FAs into mitochondria for oxidation)
  - No myoglobinuria: do DNA test
    - Paradoxical myotonia: worse with exercise (vs. myotonia congenita: better with exercise)
      - ↓ K+: **Hypokalemic Periodic Paralysis**
      - Normal/↑ K+: **Paramyotonia Congenita**
- **Persistent weakness:** many possible diagnoses
  - EMG: confirms diagnosis and rules out ALS
  - Repetitive nerve stimulation: rules out MG
  - Creatine kinase ↑ supports diagnosis
- **Muscle pain without weakness** (Serum CK, EMG, and muscle biopsy are normal)
  - Fibromyalgia
  - Polymyalgia Rheumatica: ↑ ESR. Many have associated temporal arteritis. Steroids treat both.

Other muscle-related symptoms
- **Cramp** (spasm): EMG shows firing of motor units. Can occur in neuropathies but not muscle disease.
- **Contracture:** EMG is silent - inability to relax.
- **Myokymia:** groups of fasciculations associated with continuous undulations of muscle. ↑ sweating.
- **Myotonia:** prolonged contraction followed by slow relaxation. Often channelopathies.

Inherited myopathies (muscular dystrophies: mutation in structural proteins)
- **Duchenne muscular dystrophy** (X-linked): dystrophin gene mutation
  - Onset between 3-5. Gower maneuver is often the first sign. See pseudohypertrophy of calves.
  - Contractures occur and result in kyphoscoliosis, which can result in pulmonary problems.
  - By age 12, usually confined to wheelchair. Death usually by 18 by pulmonary complication.
    - **Cardiomyopathy in nearly all patients** but it rarely causes death.
      - Intellectual impairment common (IQ 1 STD below mean)
      - Female carriers can have mild ↑ CK and mild calf pseudohypertrophy.
      - Lab tests
        - Serum CK: ↑↑ 20-200x (10,000 IU or higher) normal
        - Biopsy shows fat infiltration (pseudohypertrophy)
        - Treatment: steroids slow progression for up to 3 years, immunosuppressants
- **Becker muscular dystrophy** (X-linked). Less severe due to “in-frame” mutation (vs. Duchenne)
  - Weakness appears in first decade, but may not become significant until 40s.
  - CK elevations are elevated but not as dramatically as DMD
  - Cardiomyopathy may be more disabling than the skeletal muscle weakness.
- **Congenital Muscular Dystrophy** (Autosomal Recessive): presents at birth. Hypotonia. ↑ Serum CK.
- **Myotonic Dystrophy** (Autosomal dominant): prolonged contraction followed by slow relaxation.
  - “Hatchet-face” due to temoralsis, SCM wasting. Frontal balding prominent.
  - Cardiomyopathy/arrhythmia, gonadal atrophy, cataracts, insulin resistance, mental retardation
  - **Type 1:** CTG trinucleotide repeat. Distally weak. **Type 2:** tetranucleotide repeat. Proximally weak.
  - Lab tests
    - CK: can be normal. EMG shows myotonia.
    - Biopsy shows selective atrophy of type 1 (slow twitch) muscle fibers.
Limb-girdle dystrophy (LGMD): clinical presentation similar to DMD/BMD. Proximal involved more than distal mm.

- Type 1: autosomal dominant
- Type 2: autosomal recessive (more common)

Congenital Myopathy: presence of specific histochemical and structural abnormalities (vs. Hereditary myopathy)

- All are autosomal recessive.
- Adult onset diseases
  - Central core disease (AD): ↓ oxidative enzymes in central sarcomere. Childhood proximal weakness.
  - Nemaline (“threadlike”) Myopathy: Delayed motor milestones

Mitochondrial myopathy: >50% of all have constant extracellular weakness (vs. myasthenia gravis intermittent)

- mtDNA: circular dsDNA, 16,569 bp. Codes for 22 tRNAs, 2 rRNAs, and 13 polypeptides of the respiratory chain
  - Inherited from the cytoplasm of gametes. Almost exclusively mother-inheritance.
- Biopsy shows ragged red fibers
- Chronic progressive external ophthalmoplegia (CPEO)
  - Kearns-Sayre Syndrome (KSS): sporadic
    - Triad: onset before age 20, CPEO, and pigmentary retinopathy
    - Complete heart block, CSF protein >100 mg/dL, or cerebellar ataxia
  - Progressive External Ophthalmoplegia (CEO): mendelian inheritance since somatic gene modify mito.
    - Ophthalmoplegia, sensorineural hearing loss. Onset after puberty.
    - CSF protein: normal.
  - Autosomal Recessive Cardiomyopathy and Ophthalmoplegia (ARCO)
  - Skeletal muscle–CNS syndromes
    - Mtc. myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) (most common)
      - Onset before age 20. Seizures, hemiparesis, hearing loss, DM
    - Myoclonic epilepsy with ragged red fibers (MERFF): Myoclonic epilepsy, cerebellar ataxia, weakness.
  - Pure myopathy (simulates muscular dystrophy or metabolic myopathy)
    - Mitochondrial DNA depletion myopathy: Autosomal recessive. Looks like Duchenne

Channelopathies: All are autosomal dominant. Heart is also often involved: arrythmias.

- Hyperkalemic periodic paralysis (Na+ channel abnormality): weakness provoked by K+ exposure
  - Onset in childhood. Weakness develops rapidly. Exercise early in attack may abort.
- Familial hypokalemic periodic paralysis (FHPP) (Ca2+ channel abnormality)
  - Attacks: heavy legs, proximal weakness, serum K+ may fall to 1.5 mEq/L. Last for hours.
  - Secondary hypokalemic paralysis: thyrotoxicosis, renal/adrenal failure, diuretics.
  - Carbohydrate load can precipitate an attack.
  - Treatment: Acetozolamide for prophylaxis
- Paramyotonia congenita (Na+ channel abnormality)
  - Combination of hyperkalemic periodic paralysis and myotonia of the face, eyes, tongue, and hands.
- Myotonia congenita (Cl- channel abnormality)
  - Weakness is better with exercise (not paradoxical myotonia)
  - Worse when sitting or cold.
  - All muscles are involved. Muscle hypertrophy may be pronounced (“little hercules”)

Sources

- First Exposure to Neurology, Kirschner, 2007
Benign fasciculations
- Most common in eyelids, arms, legs
- Any intentional movement causes fasciculations to cease immediately (vs. pathological fasciculations)

**Stiff person syndrome:** resembles tetanus
- Waxing & waning muscle rigidity
- Autoimmune: Anti glutamic acid decarboxylase (GAD)
  - Anti-GAD AB’s also seen in DM type 1, celiac disease
  - Glutamic acid decarboxylase ↓, GABA ↓, spinal interneuron inhibition of motor neurons ↓
- **Treatment:** baclofen, benzodiazepine, PE, IVIg

### Amyotrophic lateral sclerosis (ALS):
- Upper and lower motor neuron signs
  - **Upper and lower motor neuron death.** Without both, alternate diagnosis likely.
  - **No sensory involvement**
  - Other motor neuron disorders, affect only a subset of motor neurons. ALS is the only one to affect all.
  - Usually spares: bowel/bladder sphincters, eye movement
  - Normal cognitively (except 5% FTD)
  - Median survival: 3-5 years, death by respiratory arrest
  - Almost all sporadic. 5-10% autosomal dominant mutation of superoxide dismutase
  - **Pathology:**
    - Accumulation of lipofuscin in neurons and glia
    - Amyotrophy: muscle atrophy after denervation
    - Lateral sclerosis: loss of fibers in corticospinal tracts and remaining firm fibrillary gliosis.
    - Remarkable selectivity: motor neurons only. Cognitive neurons intact.
  - **Signs & symptoms:**
    - Asymmetric weakness in legs or trouble chewing as first symptom
    - Dysarthria
    - Pseudobulbar affect: exaggeration of motor expressions of emotion - excessive laughing, crying
  - **Diagnosis:** definite (3+), probable (2), possible (1)
    - Bulbar, cervical, thoracic, and lumbosacral motor neurons
  - **Treatment:** **Riluzole**

### Lower motor neuron disorders:
- exclusively lower motor neuron signs
  - **X-Linked Spinobulbar Muscular Atrophy (Kennedy's Disease)**
    - X-linked, CAG repeat in X chromosome
    - Onset: mid-life
    - Progressive weakness of limb and bulbar muscles
    - NO UMN signs
    - Androgen insensitivity: gynecomastia, infertility
  - **Adult Tay-Sach's Disease**
    - Deficiency of hexosaminindase A
  - **Multifocal motor neuropathy with conduction block (MMCB)**
    - Focal blocks in conduction
    - Many have elevated titers of antibodies to ganglioside GM1 (seen in AIDP)
    - Thought to produce focal demyelination of motor neurons
    - **Treatment:** IV immunoglobulin or chemotherapy.
  - **ALS juvenile variant (Fazio-Londe syndrome):** atrophy is limited to the corticobulbar tract.
  - **Machado-Joseph Disease** (olivopontocerebellar degenerations)
**Spinal Muscular Atrophy (Werdnig-Hoffman Disease):** LMN signs only. *No UMN signs.*

- SMN1 gene on chromosome 5 is mutated – normally an anti-apoptotic gene
- Death of anterior horn cells - LMN signs only.
  - Damage pattern in spinal cord identical to poliomyelitis.
- Muscle denervated, especially type II (fast twitch) muscle fibers (*Muscle biopsy is diagnostic*)
  - Versus myotonic dystrophy: selective atrophy of type I (slow twitch) fibers
- Pseudohypertrophy (fatty change) like in Duchenne Muscular Dystrophy can occur
- Clinical course
  - Type I presents at birth the other types present later in life
  - Restrictive progressive respiratory muscle weakness
  - Patients generally die of respiratory failure secondary to diaphragm denervation

- Genetics
  - All forms have association with 5q13 locus of Survival Motor Neuron 1 gene (SMN1)
  - Type 1 is most severe (“Type 0” is fatal in utero) and each subsequent type is less severe and presents later in life
  - Autosomal recessive in Type 1

- Diagnosis
  - Electromyography showing fasciculations
  - Muscle biopsy showing atrophy of type I + II with hypertrophy of remaining type I fibers

- Treatment
  - Supportive
  - Valproate (?) has demonstrated an ↑ in expression of positive modulator of SMN in vitro

**Upper Motor Neuron Diseases:** exclusively upper motor neuron signs

- **Primary lateral sclerosis (PLS)**
  - Progressive spastic weakness
  - Spastic dysarthria and dysphagia
  - No fasciculations, amyotrophy, or sensory changes
  - EMG nor biopsy shows denervation (there is none)
  - Degeneration of corticospinal and corticobulbar projections
  - Course: Variable, can be 3 years

- **Familial Spastic Paraplegia (FSP)**
  - Degeneration of corticospinal tracts
  - Autosomal dominant type
    - Onset: 20-30
      - Progressive spastic weakness beginning in lower extremities
      - Course: long survival, because *respiratory function is spared*
  - Autosomal recessive type
    - Accompanied by posterior column sensory loss and bladder/bowel dysfunction
  - X-linked type
    - Mutation in myelin proteolipid

**Sources**

- Migita R. Etiology and evaluation of the child with muscle weakness. In: UpToDate, Basow, DS (Ed), UpToDate, Waltham, MA, 2011.
Anatomy

- Cord growth lags behind body growth in development. Ends at L1 in adults with filum terminal to coccyx.
- Farther down you go, ↑ disparity between vertebral and cord level. T12-L1 vertebrae compresses sacral cord.
- Localizing the lesion
  - Sensory: damage is 1-2 segments below where pain sensation is lost (ascent & decussation @ level)
  - Upper end of lesion: Segmental signs. Hyperalgesia or hyperpathia. Fasiculations & atrophy @ level
  - Cervical cord: quadriplegia, weakness of diaphragm, Horner’s syndrome
  - Thoracic cord: Beevor’s sign - upward movement of umbilicus when abdominal muscles contract
  - Lumbar cord: legs paralyzed
  - Sacral cord: Conus medullaris and Cauda equina syndromes

Spinal Cord Syndromes

- **Conus medullaris** (UMN + LMN): Saddle anesthesia (S3-5), bladder dysfunction and impotence. Muscles okay
- **Cauda equina syndrome** (LMN only): Low back and radicular pain, asymmetric leg weakness and sensory loss, variable areflexia in the lower extremities, and relative sparing of bowel and bladder function.
- **Brown-Squard Hemicord Syndrome**
  - Ipsilateral weakness (corticospinal) and loss of position sense (posterior column)
  - Contralateral loss of pain and temperature (spinothalamic) 1-2 levels below the lesion
  - Segmental signs (radicular pain, atrophy, loss of DTR) are unilateral
- **Central Cord Syndrome**
  - Damage to crossing spinothalamic tracts: cape distribution loss of pain (if cervical)
  - Damage to gray matter (LMN): weakness predominantly in arms vs. legs (if cervical)
  - Sacral sparing
  - Causes: Trauma, synringomyelia, tumors, anterior spinal artery ischemia
- **Anterior Spinal Artery Syndrome**
  - Bilateral tissue destruction which spares the posterior columns
  - All functions are lost below except the striking retained vibration + position sense
- **Foramen Magnum Syndrome**
  - Disrupt decussating pyramidal tract fibers destined for legs (cross lower than arm pyramidal fibers)
  - Cural paresis: weakness in legs
  - “Around the clock” pattern: weakness in ipsilateral arm, then leg, then contralateral leg, arm
  - Suboccipital pain spreading to shoulders
- **Intramedullary vs. Extramedullary Syndromes**
  - Extramedullary: compression or ischemia. Radicular pain, early sacral sensory and pain loss
    - Extradural: usually malignant, usually acute
    - Intradural: usually benign (neurofibroma), so often chronic
  - Intramedullary: Poorly localized burning. Sacral sparing.

**NEUROLOGY CLERKSHIP STUDY GUIDE**
Acute and subacute diseases (hours-days): focal neck / back pain, paresthesias, sensory loss, motor weakness
- Can mimic Guillain-Barre Syndrome
- First step: MRI with gadolinium at suspected level to exclude a treatable extrinsic compression
- Spinal shock: initially shows LMN signs (areflexia) which progress to UMN signs. Give steroids.
  - Initial loss of reflexes over days may progress to hyperreflexia over weeks to months
- Compressive myelopathy
  - Neoplastic: Most are epidural metastases
    - Prostate and ovarian: via Batson’s plexus of veins to lumbar and sacral spine
    - Intradural: Meningioma, neurofibroma. Treatment is resection.
    - Primary intramedullary (rare): ependymomas, hemangioblastomas, or low-grade astrocytomas
      - Usually present as central cord or hemicord syndrome
    - Pain is usually the presenting symptom, sharp and radiating
    - MRI is test of choice. X-ray and radionucleotide scans are not very sensitive.
  - Treatment: steroids, local radiation, surgery
- Epidural abscess
  - Triad: 1) Midline dorsal pain, 2) Fever, 3) Progressive limb weakness
  - Pain usually 2 weeks prior to presentation
  - Fever, ↑ WBC, ↑ ESR
  - Can be sterile granulomatous abscess which occurs after treatment of epidural infection
  - Risk factors: impaired immune status (DM, CKD, alcoholism, cancer), IVDA, current infection
  - Etiology: Staphylococcus aureas, gram-negative bacilli, Streptococcus, anaerobes, fungi
    - ¾ Hematogenous bacteria from skin, soft tissue, or viscera (endocarditis).
    - ¼ Direct extension of local infection: osteomyelitis, decubitus ulcer, LP, surgery
  - Diagnosis: MRI. LP CSF analysis is only required if questionable associated meningitis (25%)
    - Blood culture positive in <25% of cases
  - Treatment: decompressive laminectomy with debridement + long-term (4+ wks) antibiotics
- Spinal Epidural Hematoma
  - Acute focal radicular pain
  - Risk factors: anticoagulation, trauma, tumor, blood dyscrasia, (LP, epidural anaesthesia)
  - Diagnosis: MRI and/or CT
  - Treatment: reverse coagulopathy, surgical decompression
- Hematomyelia: hemorrhage into the substance of the cord (rare)
  - Trauma, intraparenchymal vascular formation, vasculitis (PAN, SLE), coagulopathy, cancer
  - Acute painful transverse myelopathy
  - Diagnosis: MRI and/or CT
  - Treatment: supportive. Angiography/surgery for vascular malformation

Acute Transverse Myelitis (ATM)
- Demyelination of entire cross section of a segment of cord. 80% of lesions are in the thoracic cord.
- Can occur in isolation or part of ADEM, neuromyelitis optica, multiple sclerosis
- Meningismus may be present.
- Incidence is bimodal, peaks at 10-19 and 30-39. May have preceding viral illness.
- Diagnosis:
  - Sensory, motor, autonomic deficit attributable to spinal cord.
  - Bilateral signs & symptoms
  - Clearly defined rostral border of lesion (sensory level)
  - CSF: pleocytosis, IgG index ↑
  - Onset to nadir: 4-21 days
  - Imaging: Normal brain MRI (vs MS & ADEM), spinal lesion not more than 2 segments
SPINAL CORD DISEASES

Definitions
- **Transverse myelitis**: entire cross-section of the spinal cord is affected at a given section.
- **Diffuse or disseminated transverse myelitis**: multiple lesions or lesion extending vertically.
- **Longitudinally extensive myelitis**: special form of necrotic myelopathy
- **Pachymeningitis**: inflammation of spinal dura only

Noncompressive myelopathies - Acute Transverse Myelopathy (ATM)
- **Spinal Cord Infarction**
  - Three arteries supply cord (1 anterior, 2 posterior)
    - Anterior fed by vertebral arteries, radicular vessels (C6), T1, and T11 (artery of Ademkiewicz)
      - Supply anterior ⅔ of cross section of spinal cord
      - Watershed zone between T1 and artery of Ademkiewicz
    - Systemic hypotension causes cord infarction in watershed zone (T3-T4)
    - Anterior spinal artery causes Anterior Cord Syndrome: loss of everything but spared vibration sense
      - Progressive over a few hours, unlike hemispheric stroke
      - Spinal shock: areflexia, hyperreflexia, spasticity
  - Etiology: aortic atherosclerosis, aortic dissection, vertebral occlusion, profound hypotension

Inflammatory and Immune Myelopathies (Myelitis)
- **Systemic inflammatory disorders**
  - CSF: normal or mild lymphocytic pleocytosis. Possible oligoclonal bands
  - **Treatment**: steroids and/or cyclophosphamide
  - Sarcoïd myelopathy: edematous cord mimics tumor. Gadolinium enhancement
    - Slit-lamp test to assess for uveitis, X-ray for medastinal lymphadenopathy
- **Demyelinating Myelopathies**
  - Multiple sclerosis (rarely transverse myelopathy - bilateral signs)
  - Neuromyelitis optica (NMO): optic neuritis and myelopathy. **Diagnosis**: serum anti-aquaporin 4 AB’s
  - **Treatment**: steroids. Anti-CD20 antibodies for NMO
- **Postinfectious Myelitis**: Acute disseminated encephalomyelitis (ADEM)
  - Follow infection or vaccination
  - Recovering from acute febrile infection. Fever reappears. Focal signs. “Monophasic MS”
  - EBV, CMV, mycoplasma, influenza, measles, varicella, rubeola, mumps
  - **Treatment**: steroids, plasmapheresis
- **Acute Infectious Myelitis**
  - Herpes zoster, HSV 1 & 2, EBV, CMV, rabies
  - HSV-2: recurrent sacral myelitis associated with recurrences of genital herpes
  - Poliomyelitis: restricted to gray matter of cord
  - Bacteria are less likely cause (usually abscess), but Listeria, Borrelia, Treponema, Mycoplasma can.
  - Schistosomiasis: inflammatory and granulomatous
  - **Treatment**: acyclovir for suspected viral, ganciclovir + foscarnet if suspect CMV

NEUROLOGY CLERKSHIP STUDY GUIDE
SPINAL CORD DISEASES

Chronic Myelopathies

- **Spondylitic Myelopathy**
  - One of most common causes of gait difficulty in the elderly: Romberg sign, diminished vibratory
  - Neck and shoulder pain with stiffness
  - Impingement of bone and soft tissue overgrowth on nerve roots associated with radicular pain
  - Most common in C5 or C6
  - Compression of the cord (⅓ of cases) produces spastic paraparesis
  - **Diagnosis**: MRI or myelography
  - **Treatment**: Cervical collar, surgical decompression by laminectomy

- **Vascular Malformations**
  - Most occur at or below midthoracic level
  - Typical presentation: middle aged man with progressive myelopathy, remits, recurs (resemble MS)
  - Acute exacerbations are due to hemorrhage into the cord
  - Stepwise saltatory progression from recurrent hemorrhages
  - Incomplete sensory, motor, bladder disturbances. Mixed upper and lower motor neuron signs
  - Pain over dorsal spine, dyesthesia, radicular pain
  - Foix-Alajouanine syndrome: subacute progression of paraparesis from hyalinized vessels
  - **Diagnosis**: spinal bruit, MRI with contrast, CT myelography, spinal angiography
  - **Treatment**: endovascular embolization

- **Retrovirus-associated Myelopathy**
  - Human T-cell Lymphotropic Virus (HTLV-1) (tropical spastic paraparesis)
    - Slowly progressive asymmetric spastic, variable sensory and bladder disturbance
    - ⅓ have mild back or leg pain
    - Unable to walk within 10 years
    - **Diagnosis**: HTLV-1 antibody in serum by ELISA, western blot
    - **Treatment**: symptomatic
  - HIV: vacuolar degeneration of posterior and lateral tracts resembling subacute combined degen.

- **Syringomyelia**: Cavitary expansion of the cervical cord
  - Begin insidiously in adolescence or early adulthood, progress, can arrest and reappear
  - ⅓ are associated with Chiari type 1 malformation (cerebellar tonsils herniate)
  - Can be acquired: trauma, myelitis, necrotic tumor, arachnoiditis
  - Central cord syndrome: areflexic weakness in upper limbs, sparing of touch hand vibration
  - LMN syndrome in upper limbs (damages anterior horn cells) and UMN in lower limbs
  - Syringobulbi (extension into brainstem): palatal or vocal cord paralysis, dysarthria, nystagmus
  - **Diagnosis**: MRI
  - **Treatment**: Shunt. Decompression, laminectomy, dural graft. Morbidity is common.

- **Subacute Combined Degeneration** (Vitamin B₁₂ deficiency)
  1. Loss of vibration, touch, and position sense in hands & feet. Parasthesias. (dorsal column damage)
  2. Ataxia (spinocerebellar tract damage)
  3. Spastic paralysis. Positive Babinsky signs (corticospinal tract damage)
    - Flaccid paralysis can follow this because peripheral motor neurons are involved late.
  - Optic atrophy. Irritability or other mental status changes
  - **Diagnosis**: blood smear (macroovalocytes, hypersegmented PMNs), ↓ serum B₁₂ level, ↑ homocysteine and methylmalonic acid
  - **Treatment**: 1000g of IM B₁₂ repeated, or switched to oral

- **Hypocupric Myelopathy**
  - Virtually identical to subacute combined degeneration, but normal serum B₁₂
  - Low serum copper and low serum ceruloplasmin
  - **Treatment**: oral supplementation
SPINAL CORD DISEASES

- **Tabes Dorsalis** ("dorsal wasting")
  - Cardinal signs:
    - **Argyll Robertson pupil (>90%)**
    - ↓ DTR legs
    - Impaired position sense (leading to ataxia of legs and gait)
    - Romberg’s sign
    - Fleeting and repetitive lancinating pains in legs
    - Parasthesia, bladder disturbances
    - Visceral crisis: Acute abdominal pain with vomiting (15-30%)

- **Familial Spastic Paraplegia**
  - Variable inheritance patterns (autosomal dominant, autosomal recessive, x-linked forms)
  - Progressive spasticity and weakness in legs, usually symmetrical
  - Sensory symptoms are absent or mild
  - Can have nystagmus, ataxia, optic atrophy
  - Onset can be first year of life to middle adulthood
  - Treatment: symptomatic

- **Adrenomyeloneuropathy** (X-linked)
  - Variant of adrenoleukodystrophy
  - Adrenal insufficiency beginning in childhood
  - Progressive spastic or ataxic paraparesis beginning in early adulthood
  - Mild peripheral neuropathy
  - Femal heterozygotes: slower, insidious spastic myelopathy beginning in adulthood. No adrenal sx.
  - Mutation in peroxisome membrane transporter
  - Diagnosis: ↑ VLCFA in plasma (very long chain fatty acids)

**Rare causes of myelopathy**
- Lathyrisn: ingestion of chick peas with B-N-oxalyalinoalanine (BOAA) excitotoxin
- Sjögren’s syndrome, sarcoidosis, cancer

**Workup of a Transverse Myelopathy**
1. MRI of spinal cord with and without contrast to exclude compressive causes.
2. CSF: Cytology, protein, glucose, IgG index, serology, gram stain, culture
3. Serum serology: HIV, syphilis, enterovirus, mumps, measles, rubella, etc.
4. Autoimmune: ESR, ANA, rheumatoid factor, Sjögren’s, complement levels, ANCA
5. Sarcoidosis: Serum ACE, Ca²⁺, 24 hour urine Ca²⁺, Chest X-ray, CT, lymph node biopsy.
6. Demyelinating: Brain MRI, evoked potentials, CSF elecrohoresis, neuromyelitis optica AB (aquaporin-4).
7. Vascular causes: CT myelogram, spinal angiogram.

**Rehabilitation**: Prospects for recovery fade after 6 months
- Symptomatic treatment
  - Bladder problems
  - Spasticity: stretching exercises, baclofen, diazepam
- Paroxysmal autonomic hyperreflexia can occur following lesions above T6
  - Headache, diaphoresis, flushing
  - Trigger: noxious stimuli
  - Treatment: ganglionic blocking agents (mecamylamine)

**Sources**
- PreTest: Neurology, Anschel, 2009
NEUROCUTANEOUS SYNDROMES

Overview: Also known as phakomatoses
- Developmental abnormalities of the skin and nervous system tumors.
- Autosomal dominant with variable penetrance.
- True neuroectodermoses: Tuberous sclerosis, Neurofibromatosis (types 1 & 2)
- Cutaneous angiomatics (not ectodermal) with CNS abnormalities
  - Sturge-Weber, Osler-Weber-Rendu disease, von Hippel-Lindau, Ataxia-telangiectasia, Fabry

Neurofibromatosis Type 1 (Von Recklinghausen's Disease) (Peripheral NF)
- Signs & symptoms
  - Cutaneous neurofibromas: benign tumors of Schwann cells and fibroblasts
  - Café au lait spots: pigmented skin lesions (also in NF-2)
  - Freckling in non-sun-exposed areas like the axilla
  - Lisch nodules: hamartomas of the iris (vs. retinal hamartomas in NF-2)
- Complications
  - Acqueductal stenosis with hydrocephalus
  - Bony problems: scoliosis, short stature
  - Hypertension
  - Epilepsy
  - Mental retardation
- Associated nervous system neoplasms
  - Plexiform neurofibromas
  - Optic glioma
  - Ependymoma
  - Meningioma
  - Astrocytoma
  - Pheochromocytoma

- Genetics: Mutation in NF1 gene (neurofibromin tumor suppressor) on chromosome 17

Neurofibromatosis Type 2 (Central NF)
- Signs & symptoms
  - Cataract: juvenile posterior subcapsular lenticular opacity
  - Café au lait spots (rare): pigmented skin lesions
- Complications
  - Progressive unilateral deafness in 20s
  - Bilateral “acoustic neuromas” (vestibular schwannomas) on MRI
    - Need surgery
  - Associated nervous system neoplasms
    - Vestibular schwannoma (90%)
    - Meningioma
    - Glioma
    - Schwannoma of cranial and spinal nerves
- Genetics: Mutation in NF2 gene (neurofibromin 2/schwannomin/merlin) on chromosome 22

Tuberous Sclerosis (Bourneville's Disease)
- Signs & symptoms
  - Cutaneous lesions: Hypopigmentation (vs. neurofibromatosis hyperpigmentation)
    - Adenoma sebaceum (facial angiofibromas). Ungual fibromas.
    - Ash leaf spots: hypipigmented macules - best seen with Wood’s lamp
    - Shagreen patches: yellowish thickening of skin over lumbosacral region
    - Depigmented nevi
  - Paraventricular “tubers” (95%): supependymal nodules (can be calcified) seen on MRI
  - Retinal hamartoma (vs. NF-1 iris) (40-50%): no treatment necessary
  - Seizures: ex. infantile spasms (West syn.) with hyspsarrhythmia (high-voltage spikes and slow waves)
  - Mental retardation
- Complications
  - Rhabdomyomas (30-50%): myocardium
  - Angiomyomas
    - Kidney, liver, adrenals, pancreas
  - Lymphangiomatosisis (LAM)
    - Proliferation of sm. muscle in lungs
- Associated nervous system neoplasms
  - Ependymomas: paraventricular “tubers”
  - Childhood astrocytomas
    - 90% supependymal giant cell type
    - Can obstruct foramen of Monro - hydrocephalus
- Genetics: Mutation in TSC-1/2 gene (tuberins) on chromosome 16. 70% sporadic. 30% autosomal dominant.
  - ACTH helps control infantile spasms
NEUROCUTANEOUS SYNDROMES

Von Hippel–Lindau Syndrome

- **Complications**
  - Cysts
    - Kidney
    - Pancreas
    - Epididymis
    - Liver
  - Polycythemia secondary to erythropoietin made by hemangioblastomas

- **Associated neoplasms**
  - Hemangioblastomas (cavernous)
    - Retina
    - Cerebellar: need surgery
    - Spinal
  - Hypernephroma (tubular cell)
  - Renal cell carcinoma
  - Pheochromocytoma

- **Genetics**: Mutation in VHL (tumor-suppressor) on chromosome 3
  - One function of VHL is modulation of response to cellular hypoxia.

Sturge-Weber Syndrome

- **Signs & symptoms**
  - Seizures - focal or generalized. Focus is ipsilateral to port wine stain.
  - Contralateral homonymous hemianopia
  - Hemiparesis & hemisensory disturbance contralateral to port wine stain
  - Ipsilateral glaucoma
  - Mental retardation
  - Skull X-ray: gyriform (“tramline”) intracranial calcification, usually at parieto-occipital junction

- **Associated neoplasms**
  - Capillary angioma (“port wine stain”)
    - Upper face - in V1 distribution
      - Eyelid involvement indicates CNS involvement (vs. benign strawberry angioma)
    - Leptomeningial angiomatosis - usually occur on same side as facial lesion
      - Leptomeninges: pia or arachnoid mater
    - Choroidal

- **Treatment**
  - Anticonvulsants
  - Surgery, ophthalmologic advice about choroidal angioma due to increased intraocular pressure

Hereditary Hemorrhagic Telangiectasia (Osler-Rendu-Weber Disease)

- **Signs & symptoms**
  - AVMs of skin, mucous membranes, GI, GU, lungs, occasionally nervous system
    - Probably a defect in the vessel wall leading to fragility and bleeding
    - Enlarge through lifetime and may resemble spider angioma of liver disease in adulthood
    - Blanch with pressure

- **Complications**
  - Severe epistaxis, GI, GU bleeding
  - Iron deficiency anemia
  - Intracranial hemorrhage
  - Pulmonary fistulas
  - Brain abscesses

Dermatomal Hemangiomas with Spinal Vascular Malformations

- Hemangioma of the spinal cord may have vascular nevus in the corresponding dermatome
- Retinal-diencephalic arteriovenous malformation (AVM) with a nevus of the trunk or face

Epidermal Nevus Syndrome

- Epidermal nevus or linear sebaceous nevus associated with ipsilateral hemicranial abnormalities
  - One-sided thickening of skull
  - Unilateral cerebral atrophy, porencephalic cyst, leptomeningial hemangioma, AVN, artery atresia
- MR, seizures, hemiparesis
Sources

INTRACRANIAL TUMORS

Overview
- ⅔ are primary, ⅓ are metastatic
  - Metastatic sources: lung (35%), breast (17%), GI tract (6%), melanoma (6%), kidney (5%)
  - Metastases usually appear at the gray-white junction, getting stuck in watershed microvasculature
- ⅓ glial, ⅔ non-glial

Approach to the patient with a brain tumor
- Usually present with one of three syndromes:
  1. Subacute focal neurological deficit. Can be acute onset with high-grade glioma.
  2. Nonfocal neurological disorder: headache (↑ ICP), dementia, personality Δ(frontal), gait Δ, N/V
  3. Seizure: tumors which compress cortex (vs. subcortical)
- Do not result in serologic abnormalities such as ↑ ESR or tumor-specific antigens
- Lumbar puncture CSF analysis is generally not helpful except ruling out other causes of symptoms
  - No malignant cells except in: leptomeningeal metastases, primary lymphoma, medulloblastoma
- Treatment
  - Symptomatic: dexamethasone decreases vasogenic edema and lacks mineralcorticoid effects.
  - Radiation
  - Chemotherapy less likely to work
  - Metastases: usually appear at gray-white junction
    - Single: surgical excision
    - Multiple: radiation

Glial tumors
- **Astrocytic**: tumors of astrocytes (form blood-brain barrier, regulate electrolytes, form scars in inflammation)
  - **Pilocytic astrocytoma**
    - WHO grade I 93.5 months median survival
    - Most common childhood brain tumor
    - Subependymal giant cell astrocytoma: associated with Tuberous sclerosis
  - **Astrocytoma**
    - WHO grade II 93.5 months median survival
  - **Anaplastic astrocytoma**
    - WHO grade III 12.4 months median survival
  - **Glioblastoma multiforme**
    - WHO grade IV 5.1 months median survival
- **Oligodendrogial**: tumors of myelin-producing cells.
  - **Oligodendroglioma**
  - **Anaplastic oligodendroglioma**
    - WHO grade III
    - 30% have “eggshell” calcifications
- **Ependymal cell**: tumors of cells which line the ventricles. Choroid plexus is made of ependymal cells.
  - **Subependymoma**
  - **Ependymoma**

Other brain tumors
- **Medulloblastoma**
  - Second-most common brain tumor of children
  - Primitive neuroectodermal tumor (PNET), but can occur in adults.
  - Frequently metastasize along neuroaxis. Can cause cauda equina syndrome.
- **Primary CNS Lymphoma**
  - Diffusely enhancing. Ring-enhancing if immunosuppressed.
  - Treatment: methotrexate
- **Meningioma**: Arise from mesoderm, arachnoid granulations
  - Treatment: resection (curative)
- **Schwannomas**
  - Bilateral accoustic neuromas are pathognomonic for NF-2
- **Colloid cyst**
  - Occur in 3rd ventricle and obstruct CSF flow
- **Craniopharyngioma**
  - Benign epithelial tumor of oral ectoderm (odontogenic origin - tooth forming)
  - Uni or multi-cystic, viscous yellow fluid content, heavy calcifications (tooth-forming)
INTRACRANIAL TUMORS

Tumors by location

- Supratentorial
  - Germinoma
  - Meningioma
  - Glioblastoma multiforme
  - Astrocytoma
  - Oligodendroglioma
  - Ependymoma

- Infratentorial
  - Cerebellar astrocytoma
  - Medulloblastoma
  - Hemangioblastoma
  - Ependymoma
  - Craniopharyngioma
  - Pituitary adenoma
  - Schwannoma

Sources

Prions
- **Definition:** proteinacious infection
- **Pathophysiology**
  - $\text{PrP}^\text{C}$ (high $\alpha$-helix content) $\rightarrow$ $\text{PrP}^\text{Sc}$ (high $\beta$-sheet content)
  - PRNP: gene for PrP on chromosome 20

Creutzfeld-Jackob Disease
- **1/1,000,000**
- **Onset @ 60. 90% die in 1 year**
- **Signs & symptoms**
  - **Myoclonus (90%) & dementia**
    - Persists during sleep. Can be precipitated by startling.
    - Can also be seen with AD, DLB, cryprococcal encephalitis, and Unverricht-Lundborg disease.
  - Fatigue, sleep disturbance, weight loss, headache, malaise, and ill-defined pain
  - Visual (diplopia), cerebellar (ataxia) dysfunction
  - Extrapyramidal dysfunction: rigidity, mask-like facies, chorea
  - Seizures
  - Hypoesthesia
  - Supranuclear gaze palsy, optic atrophy
  - Akinetic mutism
- **Course:** Variable incubation period.
  - Once it begins, progress over weeks-months to profound dementia, death in 6-12 months usually
- **Differential Diagnosis**
  - AD, DLB, FTD, PSP, ceroid lipofuscinosis
    - FLAIR MRI: no abnormalities (vs. CJD)
  - Hashimoto’s encephalopathy
    - EEG: periodic triphasic complexes on the EEG
    - High titers of antithyroglobulin, antithyroid peroxidase
    - Improves with steroid therapy.
  - Infectious: AIDS dementia, neurosyphilis, PML
- **Types**
  - **Sporadic (sCJD) (85%)**
  - **Hereditary (15%)**
    - Gerstmann–Sträussler–Scheinker syndrome (GSS)
  - **Acquired (1%)**
    - Iatrogenic CJD (iCJD): from dura mater grafts and GH therapy
    - Variant CJD (vCJD): psych symptoms, younger patients. Likely BSE (mad cow) but unproven
    - Kuru: from ritual cannibalism
    - Panencephalic CJD (pCJD): Japan. Longer course
- **Diagnosis**
  - **EEG:** periodic sharp wave complexes (1-2 Hz) (80% of cases)
  - **MRI - FLAIR:** “cortical ribboning.” T2: increased signal in basal ganglia (in some cases)
  - Pathology: spongiform degeneration and astrocytic gliosis. Lack of inflammation. Vacuoles
    - GSS has amyloid plaques distinct from Kuru
    - vCJD has “florid plaques”
- **Treatment:** symptomatic. Opiates, valproate help with myoclonus.

Sources:
- Case Files: Neurology, Toy, 2007
- PreTest: Neurology, Anschel, 2009