Pathophysiology: Neuro

Functional Neuroanatomy .................................................................................................................. 2
Functional Neuroanatomy: Brainstem & Cranial Nerves ................................................................. 6
Localization ......................................................................................................................................... 12
Coma, Persistent Vegetative State & Brain Death .............................................................................. 17
Cerebrovascular Diseases .................................................................................................................. 21
Pupils & Eye Movements in Cerebrovascular Disease .................................................................... 26
CNS Infections ...................................................................................................................................... 30
Multiple Sclerosis / Demyelinating Diseases ..................................................................................... 38
Paraneoplastic Neurological Disorders (PND) ................................................................................ 42
Headache: Dangerous Secondary Causes .......................................................................................... 44
Primary Headaches (Migraine, Cluster, Tension) .............................................................................. 50
Vertigo and the Pathophysiology of Bedside Vestibular Eye Signs ...................................................... 55
Gait Disorders & Ataxia ...................................................................................................................... 62
Neuromuscular Disorders .................................................................................................................. 64
Muscular Dystrophy .......................................................................................................................... 69
Clinical Spectrum of Movement Disorders ......................................................................................... 74
Memory Loss and Alzheimer Disease ............................................................................................... 83
Clinical Features of Cognitive Disorders ............................................................................................ 87
Seizures and Epilepsy .......................................................................................................................... 94
TNDs, TIA’s, & Neuro-electrical Auras: ............................................................................................ 98
Pathogenesis of Episodic Neurologic Symptoms ............................................................................. 98
Developmental Disorders in Childhood .............................................................................................. 103
Functional Neuroanatomy

Functional anatomic system in the nervous system: population of neurons that serve a specific functional role
- Neurons linked synaptically but not always in straight chain
- **Simple**: system connects to end organ (CNS $\rightarrow$ PNS $\rightarrow$ organ, e.g. 1° motor/sense)
- **Complex**: no specific end organ (cognition, motor planning, etc)

If a functional system is damaged, the function it serves is lost or disrupted
- Sometimes disease can cause an increase in function (retinal detachment $\rightarrow$ flashes of light as detachment starts)
- **Positive symptoms** = gain of function; **negative symptoms** = loss of function

Categories of functional systems

<table>
<thead>
<tr>
<th>Input</th>
<th>Processing</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>(sensory: 6+ senses)</td>
<td>(consciousness / cognition: 2 genres)</td>
<td>(motor: 3 classes)</td>
</tr>
<tr>
<td><strong>General</strong> (touch/sense position, feel pain/temp)</td>
<td><strong>Consciousness</strong> (sleep/wake, pay attention, enjoy)</td>
<td><strong>Voluntary</strong> (initiate / move face, head, arms, legs)</td>
</tr>
<tr>
<td><strong>Special</strong> (smell, see, taste, hear, balance)</td>
<td><strong>Cognition</strong> (communicate, remember, interpret, plan)</td>
<td><strong>Special</strong> (look, chew/swallow/speak, breathe, coordinate)</td>
</tr>
</tbody>
</table>

Organization of functional systems (simple = linear, complex = non-linear)

<table>
<thead>
<tr>
<th>Simple (linear)</th>
<th>Sensory</th>
<th>3-neuron chain: primary, secondary, tertiary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>2-neuron chain: upper &amp; lower motor neurons</td>
<td></td>
</tr>
<tr>
<td>Autonomic</td>
<td>3 neuron chain: 1st, 2nd, 3rd order</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Complex (non-linear)</th>
<th>Diffusely projecting</th>
<th>One-to-many</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reciprocal circuits</td>
<td>Feed-forward &amp; feed-back loops</td>
<td></td>
</tr>
<tr>
<td>Distributed networks</td>
<td>Many-to-many, often with a hub</td>
<td></td>
</tr>
</tbody>
</table>

**Simple systems (linear)**

Basic sensory systems
E.g. vision, hearing, touch
- **General senses** (epicritic = light touch / proprioception, protopathic = pain / temp)
- **Special senses** (vision, taste, hearing balance)

Example (eye)

<table>
<thead>
<tr>
<th>0. Receptor (specialized end organ)</th>
<th>Example (eye)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transduction apparatus: Cornea / lens</td>
<td>Specialized receptors: Rods / cones</td>
</tr>
<tr>
<td>1° neuron (receptor to relay nucleus*)</td>
<td>Bipolar cell body (inner nuclear layer of retina) &amp; axon (inner plexiform layer of retina)</td>
</tr>
<tr>
<td>2° neuron (relay nucleus* to thalamus)</td>
<td>Ganglion cell body (ganglion cell layer of retina), axon (optic nerve / tract)</td>
</tr>
<tr>
<td>3° neuron (thalamus to cerebral cortex)</td>
<td>Geniculate cell body (lateral geniculate nucleus), axon (optic radiations) $\rightarrow$ primary visual (striate) cortex cell body</td>
</tr>
</tbody>
</table>

* the relay nucleus has different names in different systems:
  - retina (eye), vestibular nucleus (balance), nucleus gracilis / cuneatus (light touch), dorsal horn (pain)

Thalamus: way-station for virtually all sensory information headed to cerebral cortex
- has cell bodies of all third order sensory neurons whose axons terminate on sensation-specific regions of cerebral cortex
- Exception: **smell** (goes straight back to 1° olfactory cortex $\rightarrow$ thalamus $\rightarrow$ other brain regions
  - Evolutionarily older, no separate receptor, 2 neurons instead of 3
• Each neuron chain attached to only a very small part of receptor (e.g. one cone photoreceptor)
  • chains **bundled together** in groups of different sizes
    o Given different names: **retina, optic nerve, optic radiations**, etc; some packed more tightly or loosely

**Nomenclature:**

<table>
<thead>
<tr>
<th>Gray matter (cell bodies)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral nervous system</strong></td>
</tr>
<tr>
<td><strong>Spinal cord, brainstem</strong></td>
</tr>
<tr>
<td><strong>Cerebral, cerebellar hemispheres</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>White matter (axons)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral nervous system</strong></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
</tr>
</tbody>
</table>

**Basic motor systems**
E.g. face, limb movement

2-neuron chain

1. **Upper motor neuron**: Primary motor cortex to
   a. **Brainstem** *(cranial nerve nuclei)* via **corticobulbar tract**
   b. **Spinal cord** *(ventral horn)* via **corticospinal tract**

2. **Lower motor neuron**:
   a. **Cranial nerve nuclei** to **muscles of head and neck**
   b. **Spinal cord ventral horn** to **muscles of arm, legs, trunk**

**Corticobulbar tract**: connects primary motor cortex (pre-central gyrus) to brainstem (bulb)

• control **voluntary muscles of face, tongue, neck** & specialized mm for chewing, swallowing speaking
• 2 UMN innervate 1 LMN *(different from basic motor paradigm) – redundancy*
  o **Unilateral UMN** inactivation **doesn’t** cause clinical deficit here
• LMN in **brainstem cranial nerve nuclei** → head and neck
  o Cranial nerve **fascicles within brainstem**
  o **Cranial nerves** *(PNS)* after exiting brainstem

**Corticospinal tract**: connects primary motor cortex (pre-central gyrus) to spinal cord (ventral horn)

• Control **voluntary muscles of limbs, trunk** & special midline muscles for truncal postural control
• **Redundant innervation** typically here too
  o unilateral UMN inactivation doesn’t cause deficit in redundantly innervated muscles
• **Spinal cord** = CNS, **spinal nerves** *(PNS)* once they exit
  o **PNS names**: root, plexus, trunk, division, cord, nerve, branch *(depends on surface appearance)*
• **No synapses** between **ventral horn** and **neuromuscular junction**
• **NMJ**: converts electrical signal into one that can be received by muscle
• **Motor unit** = **NMJ** & **muscle**

**Basic autonomic systems**
E.g. papillary motor control

3-neuron chain *(first, second, third-order)*

1. **1st order neuron** *(hypothalamus to brainstem or SC gray matter)*
2. **2nd order neuron** *(brainstem / SC to autonomic ganglion)*
3. **3rd order neuron** *(autonomic ganglion to NMJ → smooth muscle in specialized end organ)*
3 major visceral motor systems follow this paradigm:
   1. Pupillomotor system
   2. Exocrine motor system (tears & saliva)
   3. Vasomotor system

   - bowel, bladder, sexual control are similar but slightly more complex
   - solid-organ innervation is less well defined anatomically

Autonomic functions: symps & parasymps (dual innervation, including blood vessels)
   - mostly happening at unconscious level
   - Simplistic view: HYPOTHALAMUS is the “COMMAND AND CONTROL CENTER” for autonomic nervous system
     o Most signals for symps / parasymps begin here

Pupillomotor system is most important clinically
   - Unique anatomy → well recognized bedside syndromes
     o Pupillary paralysis / anisocoria (= asymmetric pupils)

Pupillomotor system: parasympathetic
   1. Hypothalamic cell body (hypothalamus) → axon →
   2. Brainstem cell body (Edinger-Westphal nucleus in midbrain) → axon (3rd fascicle / nerve) →
   3. Ganglion cell body (ciliary ganglion) → axon (short ciliary nerves) →
   4. Iris sphincter muscle (papillary constriction) + ciliary muscle (lens accommodation)

Pupillomotor system: sympathetic
   1. Hypothalamic cell body (hypothalamus) → axon (lateral brainstem sympathetic tract) →
   2. Spinal cord cell body (cervical cord) → axon (ventral root, rami communicantes, sympathetic chain/trunk) →
   3. Ganglion cell body (stellate ganglion) → axon (long / short ciliary nerves)
   4. Iris dilator muscle (papillary dilation)

Note the long path over the lung taken by sympathetic system: upper chest lesions can result in dysfunction!

---

Complex systems (non-linear)

3 types, in order of increasing complexity

<table>
<thead>
<tr>
<th>Diffusely projecting systems</th>
<th>One-to-many, originate from single nucleus</th>
<th>Brainstem reticular activating system, dopaminergic “reward” pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reciprocal circuits</td>
<td>Semi-distributed, reciprocally-innervated parallel loops</td>
<td>Basal ganglia circuitry, memory circuitry</td>
</tr>
<tr>
<td>Distributed networks</td>
<td>Diffusely interconnected networks with regional “hubs”</td>
<td>Language area, prefrontal motor cortex, parietal association cortex</td>
</tr>
</tbody>
</table>

Diffusely projecting
   - “shotgun approach” – system tightly packed at origin but projects widely (diffuse / dispersed system at target)
   - Small lesion at origin can cause devastating widespread neuro dysfunction (e.g. coma)
     o May also be potential target for therapy (restore simple region?)
Reciprocal circuits
E.g. basal ganglia: starting, speed, smoothness, synchrony, stopping of voluntary movements
- Reciprocally-innervated parallel loops with on and off (excitation / inhibition) signals sent
  - Diseases that affect different parts of loop can have opposite effects
    - Huntington's chorea (too much movement), Parkinson's disease (too little)
    - Therapy: selectively stimulate / inhibit correct part of circuit (deep brain stim in Parkinson's)

Distributed Networks
E.g. language, motor planning, sensory integration
- Neurons in many locations but regional specialization into hubs (certain information coalesces)
- Wernicke's area: major regional hub for language
  - Language not stored here but rather in diffuse neural networks
  - Wernicke's area is like a network router; destroy the router and access to network is lost!
    - Global aphasia results

The brain (to a first approximation)

<table>
<thead>
<tr>
<th>Part of brain:</th>
<th>Front</th>
<th>Back</th>
</tr>
</thead>
<tbody>
<tr>
<td>General function</td>
<td>Output</td>
<td>Input</td>
</tr>
<tr>
<td>Heteromodal association cortices</td>
<td>Frontal</td>
<td>Temporal / Parietal</td>
</tr>
<tr>
<td>Role of association cortices</td>
<td>Plan</td>
<td>Interpret</td>
</tr>
<tr>
<td>Lesion to this integrative area</td>
<td>Apraxia, Abulia</td>
<td>Agnosia, Neglect</td>
</tr>
</tbody>
</table>
Functional Neuroanatomy: Brainstem & Cranial Nerves

**Basic Structure / Introduction**

**Midbrain:** rostral
- On **top:** stuff here linked to basal ganglia & thalamus
- **Substantia nigra:** motor, tone / speed
- Peri-aqueductal gray matter: sensory, pain/pleasure

**Pons:** middle
- Heavily connected with cerebellum
- Cerebro-ponto-cerebellar circuit: learning (esp motor)

**Medulla:** caudal
- On **bottom:** linked to spinal cord / body
- Respiratory / cardiovascular centers, etc.

**Cranial nerves:** nerves to/from hands/face/neck
- Part of **PNS** (optic nerve clinically & anatomically PNS although immunologically / embryologically CNS)

**Cardinal Sections of the Brainstem**
(look at an atlas) →

**What’s the point of the brainstem?**

**Conduit (‘long tracts’)**
- **Motor** (out) to body
- **Sensory** (in) from body
- **Autonomic** (bowel/bladder)

**Cranial (CN 3-12)**
- **Motor** (out) to head
- **Sensory** (in) from head

**Control**
- EOM control centers
- Arousal/sleep, mood, pain/pleasure
- HR, BP, Resps, etc.

**Long Tracts (conduit functions)**

<table>
<thead>
<tr>
<th>Tract</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticospinal</td>
<td>Motor</td>
<td>Voluntary motor to limbs / trunk</td>
</tr>
<tr>
<td>Dorsal column – medial lemniscus</td>
<td>Sensory (epicritic)</td>
<td>Light touch, vibration, proprioception</td>
</tr>
<tr>
<td>Spino-thalamic (a.k.a. anterolateral)</td>
<td>Sensory (protopathic)</td>
<td>Pain, temperature</td>
</tr>
</tbody>
</table>

**Other tracts too:** (wouldn’t worry about the course of these – but they pass through the brainstem)
- **Corticobulbar** (voluntary motor to head/neck)
- Cerebro-ponto-cerebellar (descending motor learning circuit)
- Reticulo-, rubro-, tecto-, vestibule-spinal (accessory motor / postural control)
- **Autonomic tracts** (sympathetic / parasympathetic bladder pathway)
- **Spino-cerebellar, dentate-rubro-thalamic** tracts (cerebellar in/output)
Cranial Nerves / Functions

- Damage: varied symptoms (diplopia, gaze palsy, etc.)
  - Damage to spinal nerves generally just produces weakness (motor) and/or numbness/tingling/pain (sensory)

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Olfactory</td>
<td>Smell</td>
</tr>
<tr>
<td>II. Optic</td>
<td>Vision</td>
</tr>
<tr>
<td>III. Oculomotor</td>
<td>Motor (eye movements) &amp; parasympathetic (constrict pupil)</td>
</tr>
<tr>
<td>IV. Trochlear</td>
<td>Motor (eye: superior oblique)</td>
</tr>
<tr>
<td>V. Trigeminal</td>
<td>V1 (ophthalmic) – sensory only (forehead, eye, etc.)</td>
</tr>
<tr>
<td></td>
<td>V2 (maxillary) – sensory only (middle of face, nasopharynx, etc)</td>
</tr>
<tr>
<td></td>
<td>V3 (mandibular) – motor (mm of mastication) &amp; sensory (lower jaw, floor of mouth, anterior 2/3 tongue)</td>
</tr>
<tr>
<td>VI. Abducens</td>
<td>Motor (eye: lateral rectus)</td>
</tr>
<tr>
<td>VII. Facial</td>
<td>Sensory (auricle; taste in ant. 2/3 of tongue)</td>
</tr>
<tr>
<td></td>
<td>Motor (muscles of facial expression)</td>
</tr>
<tr>
<td></td>
<td>Parasympathetic (secretomotor to nasal mucosa, lacrimal, salivary glands).</td>
</tr>
<tr>
<td>VIII. Vestibulocochlear</td>
<td>Hearing / Balance</td>
</tr>
<tr>
<td>IX. Glossopharyngeal</td>
<td>Taste &amp; general sense: post. 1/3 of tongue, pharynx)</td>
</tr>
<tr>
<td></td>
<td>Motor (stylopharyngeus), Parasympathetic (parotid gland)</td>
</tr>
<tr>
<td>X. Vagus</td>
<td>Motor (larynx, pharynx, palate)</td>
</tr>
<tr>
<td></td>
<td>Parasympathetic (visceral mucosa to left colic flexure)</td>
</tr>
<tr>
<td>XI. Accessory</td>
<td>Motor (trapezius / sternocleidomastoid mm.)</td>
</tr>
<tr>
<td>XII. Hypoglossal</td>
<td>Motor (tongue muscles)</td>
</tr>
</tbody>
</table>

Brainstem Control Centers

- Serve semi-autonomous functions: eye movements, extrapyramidal / accessory motor control, “visceral” fxns

<table>
<thead>
<tr>
<th>Location</th>
<th>Centers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midbrain</td>
<td>Eye movements: vertical gaze &amp; vergence centers</td>
</tr>
<tr>
<td></td>
<td>Visceral: periaqueductal gray (pain, pleasure)</td>
</tr>
<tr>
<td></td>
<td>Motor: substantia nigra (extrapyramidal motor)</td>
</tr>
<tr>
<td>Pons</td>
<td>Eye movements: horizontal gaze center</td>
</tr>
<tr>
<td></td>
<td>Visceral: locus ceruleus, raphe nuclei (arousal, mood)</td>
</tr>
<tr>
<td>Medulla</td>
<td>Eye movements: horizontal gaze-holding center</td>
</tr>
<tr>
<td></td>
<td>Visceral: respiratory &amp; cardiovascular centers</td>
</tr>
</tbody>
</table>

Pain/pleasure sensing structures (lots of opiate receptors) – esp. periaqueductal gray of midbrain
- Pain transmission / modulation

Substantia nigra, pars compacta (niagro-striatal): part of basal ganglia circuitry; lose neurons → bradykinesia (Parkinson’s)
Reticular activating system (pons, midbrain) → diffusely protejecting; responsible for arousal (look like net)
Respiratory / CV control in medulla

Brainstem Organization: Front-to-back (ventro-dorsal)

<table>
<thead>
<tr>
<th>Ventral (front)</th>
<th>Middle (“tegmentum”)</th>
<th>Dorsal (back: “tectum” or “velum”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long tracts (motor)</td>
<td>Long tracts (sensory)</td>
<td>CSF space – aqueduct, 4th, open subarach space</td>
</tr>
<tr>
<td></td>
<td>Cranial nerve nuclei</td>
<td>Tectum – quadrigeminal plate (’colliculi’=’hills’)</td>
</tr>
<tr>
<td></td>
<td>Visceral (HR, BP, resps) &amp; special (EOM...) centers</td>
<td></td>
</tr>
</tbody>
</table>

Brainstem Organization: Front-to-back (ventro-dorsal)
MOTOR TRACTS are ANTERIOR (ventral)

- **Corticospinal tract**: from cortex to spinal cord
  - Decussates @ cervico-medullary junction

- **Cerebral peduncles → basis pontis → olives & pyramids**
  (names of surface landmarks)

2/3 of descending motor info is **NOT** destined for SC / limbs

- Fronto-pontine (1/3), parieto-pontine (1/3) projections destined for **cerebellum** (motor cortex → pons → cerebellum → basal ganglia → motor cortex circuit; important for learning) – damage produces **very few deficits**

CSF SPACES (in back)

- **Lateral ventricles** (choroid plexus → (foramen of Monroe) →
- **3rd ventricle** (diencephalon, sandwiched between 2 halves of thalamus / hypothalamus)
- **Cerebral (Sylvian) aqueduct** (midbrain) →
- **4th ventricle** (pons, cerebellum) → (foramina of Lushka, lateral, and foramen of Magendie, median) →
- **Subarachnoid space** → around SC, etc. → reabsorbed via arachnoid granulations → superior sagittal sinus

TECTUM / VELUM

**Tectum**: “Roof” over cerebral aqueduct (midbrain only)

- Four **colliculi** (“quadrigeminal plate”)
  - **Superior colliculi**:
    - **saccades** (fast eye movements)
    - turn head to **novel/threatening sights**
  - **Inferior colliculi**:
    - **auditory processing** (turn head to novel/threatening sounds)

**Velum**: medulla; anatomic structure, not of much clinical relevance

TEGMENTUM (middle: the “beef”)

- Everything between CSF space & motor parts up front
- **Cranial nerve nuclei & visceral / special centers** live here
- **Sensory long tracts** pass through here

Much has a “reticulated” appearance (mixed white/gray matter)

See next page for more descriptions
**Tegmentum: Sensory long tracts**

<table>
<thead>
<tr>
<th>Pain / temp</th>
<th>(spinothalamic/anterolateral)</th>
<th>more lateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touch / vibration</td>
<td>(dorsal column / medial lemniscus)</td>
<td>more medial</td>
</tr>
</tbody>
</table>

**Tegmentum CN Nuclei**
- See top-bottom organization below (2-2-4-4 rule)
- Recognize that CN nuclei are in tegmentum

**Cerebellar Peduncles**
- Just think of where they are and figure out where they’re going

<table>
<thead>
<tr>
<th>Inferior</th>
<th>Input to cerebellum</th>
<th>From spinal cord</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle</td>
<td>Input to cerebellum</td>
<td>From cerebrum (via cerebral peduncles &amp; pontine nuclei)</td>
</tr>
<tr>
<td>Superior</td>
<td>Output to cerebrum</td>
<td>(red nucl. → basal ganglia → ctx)</td>
</tr>
</tbody>
</table>

**Stuff Around the Top of the Brainstem**

**Pineal gland:** circadian rhythms (melatonin)
- Masses → compress dorsal midbrain (cause upgaze, failure of papillary light reflexes, convergence-retraction nystagmus, eyelid retraction, potentially life-threatening obstructive hydrocephalus)

**Diencephalon = thalamus, mamillary bodies, hypothalamus**

**Thalamus:** major sensory way-station
(almost all sensory input passes through here)
- **Lateral geniculate bodies** = relay for visual sensory information, hang down off sides

**Mamillary Bodies:**
- part of memory circuitry
  (w/ hippocampus, medial thalamus)
- right next to 3rd ventricle
- affected by thiamine deficiency
- major site of memory-disturbing pathology in Wernicke – Korsakoff syndrome (acute confusional + post-confusional / amnestic)

**Hypothalamus:**
the “command center” for most autonomic functions

Cell bodies here include:
- **Neuroendocrine functions** (hypothal-pituitary-adrenal axis; thyroid/other releasing hormones)
- **1st order symp neurons** (headed for SC → head/body via sympathetic chain)
- **Pre-motor neurons** (descend to control 1st parasymp neurons in brainstem)
Brainstem Organization: Top-to-bottom (rostro-caudal)

Cranial Nerves: 2-2-4-4 rule
(cerebrum 2, midbrain 2, pons 4, medulla 4)

Cranial Nerves: remember that nuclei all in tegmentum

Gaze center locations are logical:
- **Vertical gaze:**
  - CN III, IV are involved; *vertical gaze center & CN III/IV nuclei* located *together* in midbrain
- Same with *horizontal gaze* and CN VI (lateral rectus)
  - Signal for *horizontal movements* needs to get to CN III (nucleus in *midbrain*; innervates *medial rectus*)
  - Travels up *MLF* (medial longitudinal fasciculus) to midbrain

Gaze holding: *sustaining eye* in eccentric position of gaze (e.g. look to side & hold eyes there)
- Need *sustained signal*
  - (orbital tissues, mm are elastic; tend to return eyes to center)
- **Medulla** has gaze-holding center
  - does OK job on own but great when *calibrated* by inferior *cerebellum* (nearby)

**Medial Longitudinal Fasiculus**
- superhighway of axons that connects eye-movement-related sections
Brainstem Organization: Middle-to-Side (Medio-Lateral)

<table>
<thead>
<tr>
<th>Medial (Motor)</th>
<th>Intermediate (Visceral)</th>
<th>Lateral (Sensory)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Somatic motor CN nuclei</td>
<td>- Special motor nuclei (e.g. for swallowing)</td>
<td>- Somatic sensory CN nuclei</td>
</tr>
<tr>
<td></td>
<td>- Parasympathetic CN nuclei</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Sympathetic tracts</td>
<td></td>
</tr>
</tbody>
</table>

“Motor” is Medial
- Somatic motor = purely voluntary (arms/legs/eyes/tongue) - medial
- Special motor ("branchiomotor" – moving face / jaw - intermediate

Note that only eye (3/4/6) and tongue (12) CN motor nuclei are medial; other CN motor nuclei are intermediate

Selective lesions (e.g. strokes) can affect lateral brainstem only (or medial)
- Medulla (Wallenberg syndrome) or pons

How? Vascular supply to lateral brainstem is different from medial brainstem

LATERAL BRAINSTEM STROKE = MOTOR (MEDIAL) SPARED
- Stroke with NO HEMIPARESIS (weakness) / HEMIPLEGIA (paralysis)
- Corticospinal tract fibers SPARED
- Dx: dizziness, nausea, vomiting, gait unsteadiness: looks like benign inner ear problems but stroke!
Localization

**Functional Segregation**

- If function is only segregated in one place along a chain, selective loss of one function means lesion is there
- **Corollary:** More “abstract” functions lost means lesion is more likely to be near cerebral cortex

**Examples:**
- **Night blindness:** selective visual loss, can only happen at photoreceptor / retina (cones = day, rods = night)
- **Loss of stereognosis:** selective tactile sensory loss – only separated at cerebral cortex
  - Loss of 2-point discrimination is the same – has to be at cortex

---

**“Trophic Influences” (UMN vs LMN)**

- Identify UMN vs LMN (BOTH present with weakness)

<table>
<thead>
<tr>
<th>LMN</th>
<th>UMN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weakness</strong> plus...</td>
<td><strong>Weakness</strong> plus...</td>
</tr>
<tr>
<td>Fasciculation (ACUTE) – irritability of mm fibers</td>
<td>Upgoing toe (Babinski)</td>
</tr>
<tr>
<td>Atrophy (chronic)</td>
<td>No atrophy*</td>
</tr>
<tr>
<td>Aberrant regeneration (chronic)</td>
<td>Spasticity (chronic)</td>
</tr>
<tr>
<td>Normal to low tone</td>
<td>Clonus (chronic)</td>
</tr>
<tr>
<td>Loss of reflexes</td>
<td>Hyperreflexia (chronic)</td>
</tr>
</tbody>
</table>

* mild atrophy can develop in UMN lesions (disuse); more profound in LMN

Note: **flaccid weakness** occurs in acute UMN lesions!
- Don’t use flaccid weakness to Dx LMN lesion unless atrophy / fasciculation present

**Acute Lesions: HARD**
- **BABINSKI** is ONLY reliable sign to indicate ACUTE UMN LESION
- **FASCICULATIONS** are ONLY reliable sign to indicate ACUTE LMN LESION

**Chronic lesions: easier**
- Spasticity, hyperreflexia, clonus = chronic UMN lesions

**Redundancy**

- If there’s redundancy, then unilateral UMN (cortical) lesions produce no deficits (brainstem / CN)
  - Unilateral LMN lesions will produce deficits (ipsilateral to lesion – LMNs on same side!)
  - If there’s partial redundancy (e.g. 7th n), then cortical lesions produce partial deficits!

Due to either:
- unilateral BRAINSTEM (LMN) or
- unilateral CEREBRAL (UMN) dz

<table>
<thead>
<tr>
<th>CN</th>
<th>Can only be caused by:</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/6</td>
<td>unilateral 3rd, 4th, or 6th nerve palsy,</td>
</tr>
<tr>
<td>5</td>
<td>unilateral paralysis of chewing muscles</td>
</tr>
<tr>
<td>9</td>
<td>unilateral complete facial paralysis</td>
</tr>
<tr>
<td>11</td>
<td>unilateral loss of taste</td>
</tr>
<tr>
<td>12</td>
<td>unilateral hearing loss</td>
</tr>
<tr>
<td>3/4/6</td>
<td>unilateral paralysis of soft palate or vocal cords</td>
</tr>
<tr>
<td>7</td>
<td>unilateral weakness of head turning (SCM)</td>
</tr>
</tbody>
</table>

*(CNs / end organs could be damaged too, just not cerebral lesions – but think of these as brainstem symptoms / signs*
Redundancy example: Facial Nerve weakness
- note: most “lower” (5, 7, 9-11) CN nuclei are redundantly innervated by both hemispheres
- CN 7: only gets partially redundant innervations

Top part of forehead ONLY is redundantly innervated (red in pic)

Paralysis of left lower face & sparing of left brow movement:
- RIGHT (contralateral) UMN CN 7 lesion!
- Left brow is redundantly innervated (Left CN 7 UMN supplying; preserves movement
- See right pic →

Bell’s Palsy: LMN CN 7 lesion
- Ipsilateral CN 7 LMN affected (L. Bell’s palsy = L. CN 7 LMN)
- Total hemifacial weakness without brow sparing
- Bell’s phenomenon: pt. attempts to close eyes, affected side doesn’t close, affected side’s eye rolls up in orbit (means pt is making a good effort at eye closure)

Density
- Small lesions in densely packed bundles produce big deficits (e.g. L. internal capsule → R. hemiparesis)
- If lesion is in loosely-packed “bundle” and produces big deficit, it must be large (e.g. motor cortex)

Mangification
Cortical representations are magnified to importance (lips & hands)
- Think homunculus
  - lesions in important areas produce smaller deficits (in terms of body zone affected)
  - lesions in less important areas produce larger deficits

Proximity
- If chains converge / diverge, patterns of loss indicate particular localization
- If chains from different body regions close to each other, can get discontiguous defects

Example: Visual System
- Monocular = pre-chiasmal lesion
- Binocular = post-chiasmal lesion
- Review the picture to the right & understand it

Example: Cortical stroke → face/hand without arm
- See homunculus above
- Face & hand are next to each other; arm is farther away
- Cortical stroke can produce face/hand deficits
  - But SPARE arm (seems weird!)
Orientation (Long Tracts vs Segmental Systems)

- **Long tracts**: up and down the neuroaxis, rostro-caudally
  - **Symptoms** only localize lesion if they fit a pattern
- **Segmented**: in and out of neuroaxis; ventro-dorsally
  - Cognitive circuitry, cranial nerves & spinal nerves
  - **Symptoms** define narrow level that can be affected

<table>
<thead>
<tr>
<th>Function</th>
<th>Long tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Spino-thalamo-cortical</td>
</tr>
<tr>
<td>Motor</td>
<td>Cortico-spinal</td>
</tr>
<tr>
<td>Coordination</td>
<td>BG-vestibulo-cerebello-spinal</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Cortico-hypothalamo-spinal</td>
</tr>
</tbody>
</table>

Example: Arm / Leg weakness

- Distal lesion can only cause leg weakness (not arms)
- Proximal lesion can cause either arm + leg weakness or leg weakness only (partial lesion!)
- **Key point**: if arms affected, lesion must be proximal. If legs only, you can’t tell

Adjacency (what runs near what?)

- Lesions produce **dissociated** loss of functions when pathways are not adjacent
- Have to know **levels of crossing** to be able to localize!

Example: Lateral medullary syndrome

- Touch / vibration = dorsal column – medial lemniscus
- Pain/temperature = antero-lateral, a.k.a. spinothalamic

These pathways are far apart in medulla but right next to each other in midbrain
- Lateral medullary syndrome: take out pain/temp but spare touch/vibration (pic)
- Midbrain lesion: really hard to take one out without the other

Example: “crossed” brainstem syndrome

**Symptoms:**
- ipsilateral face affected
- contralateral body affected

Brainstem lesion: take out one side of brainstem (e.g. midbrain infarction)
- **CST** hasn’t crossed yet, so LMNs to **contralateral body** affected!
  - CST still in cerebral peduncle; won’t decussate until cervico-medullary junction
- Cranial nerve LMNs innervating same side of face are affected!

Reflexes

- **Reflexes** = direct connections between motor / sensory systems; bypass processing steps
- If a function is lost:
  - reflex integrity means lesion is inside brain (beyond reflex arc!)
  - reflex loss means lesion is causing segmental dysfunction (cut reflex arc!)
    - For example, deep tendon reflexes lost means there’s dysfunction at that segment level!

Common reflexes

<table>
<thead>
<tr>
<th>Pupillary light</th>
<th>CN 2 → 3</th>
<th>Vestibulo-ocular</th>
<th>CN 8 → 3/4/6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pupillary near</td>
<td>CN (2) → 3</td>
<td>Gag</td>
<td>CN 9 → 10</td>
</tr>
<tr>
<td>Blink</td>
<td>CN 5 → 7</td>
<td>Jaw jerk</td>
<td>CN 5 → 5</td>
</tr>
</tbody>
</table>

Deep tendon (UE/LE) 1st order sensory neurons → spinal LMNs

Example: Blindness with intact pupillary light reflex

- If patient is **blind** but has **intact pupillary light reflex**, that means lesion **can’t be in optic nerve**!
- **Must** be in occipital lobe (or somewhere “behind reflex” like that!)
Major concepts of localization

Parsimony: simpler explanation is usually better

3 major questions:

1. What’s the level?
   a. **Supratentorial** = cerebrum, CN 1-2
   b. **Infratentorial** = brainstem, cerebellum, CN 3-12
   c. **Spinal** (cord or nerves)

2. Inside or out?
   a. Intra-axial or Extra-axial (CNs extraaxial)

3. More than one lesion?
   a. If more than one: territory / tissue specific or non-specific?

Where’s the level?

Symptom Quality

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Mnemonic</th>
<th>Attic As</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CORTEX:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- aphasia-amnesia-agnosia,</td>
<td>- Aphasia</td>
<td>- Abulia</td>
</tr>
<tr>
<td>- apraxia, dementia-delirium, seizure</td>
<td>- Amnesia</td>
<td>- Anosmia</td>
</tr>
<tr>
<td><strong>BASAL GANGLIA:</strong></td>
<td></td>
<td>- ‘Anopsia’ (blindness)</td>
</tr>
<tr>
<td>- rigidity-bradykinesia-freezing, dystonia</td>
<td>- Agnosia</td>
<td></td>
</tr>
<tr>
<td><strong>CN 1-2:</strong></td>
<td>- Apraxia</td>
<td></td>
</tr>
<tr>
<td>- anosmia, visual loss, photopsia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supratentorial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- stupor-coma</td>
<td>- Diplopia</td>
<td></td>
</tr>
<tr>
<td>- hearing loss, dizziness,</td>
<td>- Dysarthria</td>
<td></td>
</tr>
<tr>
<td>- nausea/vomit</td>
<td>- Dysphagia</td>
<td></td>
</tr>
<tr>
<td>- anisocoria, diplopia, nystagmus</td>
<td>- Dysphonia</td>
<td></td>
</tr>
<tr>
<td>- dysmetria, dyssynergy, ataxia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- jaw/tongue/palate/vocal weakness</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infratentorial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- <strong>respiratory (diaphragmatic) failure</strong></td>
<td>- Breathing</td>
<td>- Broken reflexes</td>
</tr>
<tr>
<td>- loss of deep tendon reflexes, limbs</td>
<td>- Bowel/bladder</td>
<td></td>
</tr>
<tr>
<td>- bowel &amp; bladder dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supratentorial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Face &amp; hand, but <strong>not leg</strong> (think homunculus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- (If motor, top ½ face spared)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infratentorial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Crossed syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Head on one side, body on other</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spinal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Sensory “level” (dermatome)</td>
<td>- Distal symmetric numb feet ± hands</td>
<td></td>
</tr>
<tr>
<td>- Both legs only (paraparesis/plegia)</td>
<td>- Myotome / dermatome pattern loss</td>
<td></td>
</tr>
<tr>
<td>- Four limbs but awake</td>
<td>- Individual nerve root problem</td>
<td></td>
</tr>
</tbody>
</table>

Pattern of Symptoms

<table>
<thead>
<tr>
<th>Quality of symptoms</th>
<th>Pattern of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intra-axial (∼CNS)</strong></td>
<td><strong>Extra-axial (∼PNS)</strong></td>
</tr>
<tr>
<td>Cerebrum, brainstem / cerebellum, SC</td>
<td>Cerebral, sensory organs, skin receptors, NMJ, mm</td>
</tr>
<tr>
<td>- <strong>Cognitive</strong> or <strong>affective</strong> dysfunction, <strong>stupor-coma</strong></td>
<td>- <strong>Hearing</strong> loss</td>
</tr>
<tr>
<td>- <strong>Complex motor</strong> (rigidity-dystonia-chorea, ataxia...)</td>
<td>- Monocular visual loss</td>
</tr>
<tr>
<td>- <strong>UMN signs</strong> (spasticity, hyperreflexia, Babinski...)</td>
<td>- Root, plexus, nerve distribution of weakness and/or sensory change</td>
</tr>
<tr>
<td><strong>Intra-axial</strong></td>
<td><strong>Extra-axial</strong></td>
</tr>
<tr>
<td>- Homonymous field cut</td>
<td>- Bilateral motor structures involved without sensory</td>
</tr>
<tr>
<td>- 'UMN' facial weakness</td>
<td>- Single cranial nerve</td>
</tr>
<tr>
<td>- Crossed brainstem syndromes</td>
<td></td>
</tr>
</tbody>
</table>
Notes:
- **Tenderness** almost always from 1st muscle disease (e.g. inflammatory myopathies)
  - Exception: transverse myelitis (sensitization of central pain neurons)
- **Bilateral motor w/o sensory chain** almost always extra axial
  - ALS / motor neuron disease is exception
- **UMN** is intra-axial, but **LMN** doesn't have to be extra-axial
  - Lower motor neuron **CELL BODIES** are intra-axial

---

**More than One Lesion?**

### Linked to vascular territory
- **Anterior circulation**
  - R. hemiparesis & aphasia with L. eye blindness: ICA (ophthalmic & MCA)
  - Proximal arm & proximal leg: ICA borderzone
- **Posterior circulation**
  - Vertigo, nausea, vomiting with visual field defect: vertebral (PICA & PCA)

### Linked to Physiologic State
**Example: ↑ intracranial pressure**
- Characteristic “constellation” of signs / symptoms (but appear to be “all over the place”)
- **Sx**: Headache, blurred / transiently obscured vision, diplopia
- **Signs**: papilledema, esophoria / esoptropia or frank uni/bilateral 6th n palsies

### Linked to Tissue Type

<table>
<thead>
<tr>
<th>Classification</th>
<th>Affected tissue</th>
<th>Example</th>
<th>Signs / Sx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gross Tissue</strong></td>
<td>Meninges</td>
<td>Meningitis</td>
<td>• Headache, ‘stretch signs’</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Multiple cranial-spinal nn.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Isolated reflexes lost</td>
</tr>
<tr>
<td>Blood vessels</td>
<td>Vasculitis</td>
<td></td>
<td>• Blindness, jaw pain, HA, anemia, weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mononeuritis multiplex</td>
</tr>
<tr>
<td><strong>Cell type</strong></td>
<td>Motor neurons</td>
<td>ALS-SMA</td>
<td></td>
</tr>
<tr>
<td><strong>Subcellular</strong></td>
<td>Mitochondria</td>
<td></td>
<td>• Visual, auditory, weakness, cardiac arrhythmia</td>
</tr>
<tr>
<td><strong>compartment</strong></td>
<td>Myelin</td>
<td>Demyelinating dz</td>
<td>• Diplopia, visual loss, sensory</td>
</tr>
<tr>
<td></td>
<td>NMJ</td>
<td>MG / botulism</td>
<td>• Ascending weakness, reflexes</td>
</tr>
<tr>
<td></td>
<td>Channels</td>
<td>Migraine, seizures</td>
<td></td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Serotonin</td>
<td>Depression</td>
<td></td>
</tr>
</tbody>
</table>

**Multifocal: no linkage to lesions**
- Think: what could be causing this?

**Examples:**
1. Multiple cancer mets to brain / cord
2. Multiple stokes (e.g. A-fib)
3. Multiple petechial hemorrhages (e.g. trauma)
Coma, Persistent Vegetative State & Brain Death

Epidemiology of Coma
- Cardiac arrest survivors (150k), severe TBI (100k) represent majority of coma pts
- 30K in “minimally conscious state” (partial response), 6k in vegetative state (can be aroused, but response cut off)

“Coma is like CHF or kidney failure, but with the brain”
- Cardiac arrest survivors: 80-90% initially comatose, 5-30% comatose at discharge
- Critically ill pts with mechanical ventilation: 15-20% comatose at some point
- Elderly admitted to ICU: 1/3 comatose

Coma is an independent predictor of death, functional outcome
- after ischemic stroke, intracerebral hemorrhage, TBI, cardiac arrest
- along with length of mechanical ventilation, length of stay

Glasgow Coma Scale (GCS) – one of the most commonly used ways to evaluate coma

Arousal & Consciousness

<table>
<thead>
<tr>
<th>Domains of consciousness</th>
<th>Wakefulness</th>
<th>Awareness</th>
</tr>
</thead>
</table>
| Comprises:                | Alertness, arousal, vigilance | Content of consciousness:  
  • attention, executive function, memory, perception |
| Areas involved…           | Subcortical: brainstem arousal centers | Cortical |

Lots of redundancy in these systems (important!)
- Loss of consciousness: usually problem with
  - brainstem arousal system (ascending reticular system) or
  - diffuse bilateral cortical injury

Anatomy & Function (via fMRI)

<table>
<thead>
<tr>
<th>Awareness</th>
<th>Arousal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forebrain, cortex</td>
<td>Midbrain / thalamic junction (triggers awareness)</td>
</tr>
</tbody>
</table>

Self-awareness & external awareness are separate
- Comatose: can’t respond to internal stimuli (not self-aware)
  - Hyperglycemia, bladder obstruction & rupture can result!
- External awareness: cerebellum, parietal areas, etc.

Clinical Syndromes

Taxonomy: like shades of gray (blend together); better to quantify

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnolence</td>
<td>Really sleepy</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Slight ↓ in alertness, clouding of consciousness</td>
</tr>
<tr>
<td>Obtundation</td>
<td>↓ alertness, ↓ interest in environment, psychomotor slowing</td>
</tr>
<tr>
<td>Stupor</td>
<td>Behavioral unresponsiveness (can only arouse with vigorous, continuous stimulation)</td>
</tr>
<tr>
<td>Coma</td>
<td></td>
</tr>
</tbody>
</table>

Approach to the unresponsive patient

Level of Consciousness
- Assess arousal: establish best response with least stimulation (least pain)
- Assess awareness / content (alert / awake / oriented? Simple → complex)
- Use standard questions & establish a trend over time
Motor system
- Look for spontaneous movements & meaningful activity
- Record response over time – what is best response to least stimulus
- Stimulate in midline trunk, face/head: use least noxious stimulus possible
  - Name → tap → shake → midline stimulus
  - Purposeful or posturing? Tone / reflexes?
  - Grasp is reflexive, letting go is voluntary

The Eye
Pupillary response: CN III → lose parasymps → unopposed symps → BLOWN PUPIL on one side = neuro STEMI
- CN III stretched from midbrain herniation – bad! Need to decompress!

Ocular motility: need to move pt’s head if comatose! Pt can’t move it
- Check for spontaneous movements, EOM integrity, conjugate/disconjugate gaze
  - Doll’s eye (oculocephalic reflex) in response to movement, caloric response (vestibular)

Fundoscopy (optic disc, etc.) can be useful too

Other cranial Nerves
- More difficult, but CN’s can be tested with a comatose pt!

Autonomic functions
- Often overlooked!
- HR, BP, resps, temp

Cushing’s reflex (brain herniation syndrome)
- Hypertension, bradycardia, tachypnea
- Means pt is in extremis
  - If crushing brain, BP ↑, HR ↓, hyperventilate, vasoconstrict (trying to fill heart better, perfuse brain)

Coma
State of unarousable responsiveness with no voluntary /purposeful motor function
- Can be a transitional state (< 4 wks usually)
- Quantify with Glasgow Coma Scale (GCS) or Full Outline of UnResponsiveness (FOUR)

Results from:
- Bilateral / paramedian hemispheric (more diffuse) injury
- Diencephalic or brainstem (more specific) injury

Spectrum: Coma → arousal → awareness → consciousness

Glasgow Coma Scale
- Score motor (1-6), verbal (1-5), eye (1-4) responses
- Lowest score is 3 (no motor/verbal/eye response)

Limitations:
- No direct assessment of brainstem function (no CNs)
- No evaluation of resp pattern alterations
- Can’t test verbal component if comatose / intubation
- Limited prognostic value for verbal / eye components
Full Outline of UnResponsiveness (FOUR)

- Grade eye response, motor response, brainstem reflexes, respiration on 0-4 scales
  - Minimum = zero, max = 16

**Brain Death**

Complete, irreversible loss of all brain activity
- Both necessary and sufficient to diagnose death of organism; prerequisite for cadaveric organ donation

Results from extensive hemispheric / brainstem injury

<table>
<thead>
<tr>
<th>Cardinal findings in brain death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. coma / unresponsiveness</td>
</tr>
<tr>
<td>2. absence of brainstem reflexes</td>
</tr>
<tr>
<td>3. apnea</td>
</tr>
</tbody>
</table>

Diagnosis: exclude physiologic, metabolic, endocrine, pharm confounders
- Clinical / neuroimaging evidence of acute CNS catastrophe
- Exclusion of complicating medical conditions, no drug intoxication / poisoning
- Core temp ≥ 32° C

**Vegetative State**

- Signs of arousal (open eyes) but lack awareness of self or environment
  - Sleep/wake cycles restored
- Persistent vegetative state if > 1 mo (non-traumatic usually > 3 mo; traumatic usually > 12 mo)

Usually from bilateral cortical / thalamic injury with relative sparing of hypothalamus / brainstem

**Minimally Conscious State**

- Arousal mechanisms present & rudimentary elements of awareness
- Transient, inconsistent but unequivocal behaviors suggesting awareness of self / environment
  - Follow commands, verbalize in appropriate context, attend to stimuli, visual tracking

Usually from cortical and/or thalamic injury

**Delirium**

Acute confusional state; acute onset of altered mental status with impaired attention
- Fluctuating course
- Disorganized thinking, psychomotor agitation or withdrawal

From physiologic, metabolic, endocrine, pharm disturbances; can also be from frontal or right parietal injury

**Locked-in syndrome**

Not a consciousness disorder: wakefulness & awareness preserved
- Quadriplegia, anarthria; classically preserve ability to blink & look upwards

From injury to pons or midbrain
- destruction of CST & caudal corticobulbar tracts with sparing of tegmental arousal systems
- cortical areas still working, but cut off from everything else

**Other Disruptions of Consciousness**

Seizures can disrupt consciousness (generalized tonic/clonic, absence, complex partial seizures)
- nonconvulsive seizure status (status epilepticus) detected in up to 20% critically ill pts w/ altered mental status

General anesthesia too!
Arousal, awareness, and various states of consciousness

Coma, anesthesia: arousal, awareness both decreased
Vegetative state: arousal preserved, not aware
Minimally conscious: arousal, some awareness preserved
Locked in syndrome: both arousal & awareness preserved

Parietal association areas involved with awareness
(note that there’s some activity in minimally conscious state, but not in vegetative state)

Wakefulness vs awareness:
- At some point (brain death), this damage becomes irreversible – to the left of that line, can’t recover (to the right, you can)

Wakefulness over time: note that there’s a continuum of responses
- Best progression: from coma → vegetative state → MCS → conscious wakefulness, but can have death from coma or permanent VS / MCS at any point along the recovery

Causes of Coma / Unconsciousness

<table>
<thead>
<tr>
<th>Structural</th>
<th>Bilateral / diffuse hemispheric injury</th>
<th>Bilateral / paramedian brainstem injury</th>
<th>Toxic</th>
<th>Metabolic</th>
<th>Endocrine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trauma, Stroke</td>
<td>Hemorrhage, infarction, tumor, trauma, CPM</td>
<td>Medication overdose</td>
<td>Sepsis</td>
<td>Myxedema coma, hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Hypoxic ischemic encephalopathy</td>
<td>Compression by posterior fossa mass</td>
<td>Drugs of abuse</td>
<td>Electrolyte imbalance</td>
<td>Adrenal failure</td>
</tr>
<tr>
<td></td>
<td>Tumor, CNS infections</td>
<td></td>
<td>Environmental exposures</td>
<td>Organ failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammatory/immune encephalitides</td>
<td></td>
<td></td>
<td>Wernicke’s encephalopathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrocephalus</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Ethical Implications

- Poor compliance with AAN guidelines – need to ↑ education of providers!
- PVS: 1% prognosis of moderate disability, good recovery < 3 mo: but 0% at 6 mo
- Need good prognostic ability to be able to recommend whether to withdraw care or not!
Cerebrovascular Diseases

See Cerebrovascular Diseases in Neuro: Pathology for more complete description of anatomy

**Definitions**

<table>
<thead>
<tr>
<th>Ischemic stroke</th>
<th>Cerebral infarction caused by interruption of blood supply to a portion of the brain, with focal neurological deficit lasting &gt; 24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Ischemic Attack (TIA)</td>
<td>Neurologic deficit due to ischemia that completely reverses within 24 hrs and does not produce an infarct on imaging studies</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td><strong>Bleeding</strong> into:</td>
</tr>
<tr>
<td></td>
<td>brain parenchyma</td>
</tr>
<tr>
<td></td>
<td>ventricles</td>
</tr>
<tr>
<td></td>
<td>Intracerebral hemorrhage</td>
</tr>
<tr>
<td></td>
<td>Intraventricular hemorrhage</td>
</tr>
<tr>
<td></td>
<td>CSF / subarachnoid space</td>
</tr>
<tr>
<td></td>
<td>Subarachnoid hemorrhage</td>
</tr>
</tbody>
</table>

**Approach to stroke diagnosis**

- **Where is it?** (neuro exam, brain imaging studies to confirm – diagnosis is based on neuro exam)
- **What is the vascular anatomy / pathology?** (vascular imaging)
- **What is the cause?**
  - Large vessel atherosclerosis
  - Cardiac embolism
  - Small vessel disease (lacunes)

**Anatomy: Overview**

**Anterior circulation**

- **Carotids → MCA, ACA**
  - **Contralateral** motor, sensory, vision
  - Aphasia, neglect

**Posterior circulation**

- **Vertebrals → basilar, PCA**
  - **Bilateral** motor, visual
  - Dizziness, ataxia, nystagmus
  - Crossed syndromes

**Territory** | **Symptoms** | **Picture**
--- | --- | ---
**MCA** Lateral frontal, parietal, temporal lobes | • Contralateral motor and sensory loss (primarily face + arm)  
• Dysarthria, aphasia (dominant)  
• Neglect (non-dominant)  
• Contralateral visual loss  
• Gaze deviation towards lesion | ![MCA Symptoms](image1)

**ACA** Medial frontal, parietal lobes | • Contralateral weakness of foot and leg  
• Sensory loss of foot  
• Frontal lobe signs (apathy, cognitive slowing) | ![ACA Symptoms](image2)

**PCA** Occipital, medial temporal lobes | • Contralateral hemianopia  
• Cognitive impairment (medial temporal lobe) | ![PCA Symptoms](image3)

*Emboli, etc. tend to head to the MCA*
**Vertebrobasilar System**

**Basilar** gives off:
- **PICA** (just where vertebrals join), **AICA**, pontine branches
- **SCA** (sup. cerebellar), **PCA** (posterior cerebral)
- **P-com** to join anterior circulation

<table>
<thead>
<tr>
<th>Cerebellar infarct (PICA)</th>
<th>Basilar artery infarct</th>
<th>Basilar artery thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertigo, nystagmus</td>
<td>Pontine, midbrain</td>
<td>Bilateral pontine ischemia</td>
</tr>
<tr>
<td>Gait, limb ataxia</td>
<td>ischemia</td>
<td>Coma, quadriaparesis</td>
</tr>
<tr>
<td>Falling towards side</td>
<td>Hemipontine pure</td>
<td>Can lose all voluntary</td>
</tr>
<tr>
<td>of lesion</td>
<td>motor hemiparesis</td>
<td>movement but eyes – locked in!</td>
</tr>
</tbody>
</table>

**Etiology of Ischemic Stroke**

**Large artery atherosclerosis**

**Common sites:**
- Extracranial (ICA)
- Vertebrobasilar atherosclerosis

**Large vessel TIA:** usually from atherosclerosis
- **Repetitive** (often have Hx of prior TIA)
- **Stereotyped** (same vessels as previous TIAs – fixed lesions)
- Can be **blood pressure related** (orthostatic symptoms)

**Carotid Artery TIA**
- **Numbness, weakness of contralateral face / arm** (whole MCA territory affected)
- **Aphasia** if in dominant hemisphere
- **Ipsilateral amaurosis fugax**
  - (sudden clouding → loss of vision in one eye b/c blood flow ↓ to retina)

**Risk of recurrence:** % stenosis and symptoms are predictive

**Carotid Endarterectomy** (remove plaque on inside of artery)
- **Standard of care for symptomatic carotid stenosis**
  - NNT = 6 in 2 yrs vs. best medical therapy (usually aspirin) ofr pts with minor stroke, ≥ 70% stenosis by angiography
- **Less valuable for asymptomatic carotid stenosis**
  - NNT = 67 in 2 yrs; use CEA if you have **good surgeons** (need low complication rate to be worth it)

**Treatment of Carotid Stenosis: Summary**

<table>
<thead>
<tr>
<th>Stenosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30%</td>
<td>medical treatment (aspirin)</td>
</tr>
<tr>
<td>&gt; 70%</td>
<td>significant benefit of CEA over medical therapy</td>
</tr>
<tr>
<td>&gt; 60%</td>
<td>modest benefit of CEA; tailor to pt and surgeon</td>
</tr>
<tr>
<td>High risk for CEA complications</td>
<td>can use <strong>carotid artery stenting</strong> (in trials for 1st line)</td>
</tr>
</tbody>
</table>
### Intracranial Large Artery Atherosclerosis

- Intracranial carotid artery, circle of Willis, vertebrobasilar atherosclerosis
- Treatment: ANTIPLATELET therapy with ASPIRIN
  - Equivalent to anticoagulation with warfarin but fewer serious bleeding complications
  - Intracranial angioplasty, stenting being investigated

### Cardioembolic Stroke

- Atrial fibrillation (LA mural thrombus, esp. in older pts)
- LV thrombus (acute MI, DCM)
- Bacterial, non-bacterial endocarditis
- Valvular disorder (mitral stenosis, prosthetic valve)
- Cardiac tumor (e.g. cardiac myxoma)
- Aortic arch atheroma

### Presentation

- **Sudden onset**, **maximal** deficit at **onset**
- **MCA territory** is most common (straight shot)
- **Multiple cortical strokes** in **differing vascular territories** suggests **cardioembolic stroke**

### Treatment:

- Balance risk of recurrent embolism vs risk of bleeding
  - **Anticoagulate** for high risk conditions (warfarin) for 2º prevention of recurrent stroke
  - **Don’t anticoagulate** BACTERIAL ENDOCARDITIS (can cause aneurysms, can rupture with anticoagulation)
  - No benefit from immediate anticoagulation with IV heparin acutely

### Lacunar Stroke

**Small infarcts** in territory of penetratng arteries

### Lacunar Syndromes

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Lacunae in...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pure motor hemiparesis</strong></td>
<td></td>
</tr>
<tr>
<td>- Weakness of face, arm, leg (often equally affected)</td>
<td></td>
</tr>
<tr>
<td>- Absence of objective sensory loss, visual field defect, aphasia (MOTOR ONLY)</td>
<td></td>
</tr>
<tr>
<td>Internal capsule (or pons)</td>
<td></td>
</tr>
<tr>
<td><strong>Pure sensory stroke</strong></td>
<td></td>
</tr>
<tr>
<td>- Hemibody sensory loss</td>
<td></td>
</tr>
<tr>
<td>- <strong>No</strong> weakness, visual loss, aphasia (can have sensory hemiataxia)</td>
<td></td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
</tr>
</tbody>
</table>
Treatment of lacunar stroke
- **Antiplatelet** therapy: aspirin, clopidogrel (Plavix), aspirin + dipyridamol
- **Risk factor control** (BP is #1, also cholesterol, DM?)

### Management of Acute Stroke

- **Supportive care**
- **BP, glucose, fever** control
- **Acute pharmacotherapy**
  - **Thrombolytic** therapy
  - **Endovascular** therapy

### In Inpatient Setting
- Admit to **stroke care unit** (certified, better adherence to guidelines)
- Telemetry for 24 hrs, then prn (check for a-fib)
- BP, vital signs q4h, neuro checks q4h, swallowing evaluation, glucose checks, DVT prophylaxis

### Glucose and Stroke
- **Diabetics, acute hyperglycemia** at time of infarct have **worse outcome** after stroke
- Mechanism unclear (↑ lactate around ischemia? Gene induction?), **uncertain benefit** to fixing hyperglycemia

### Temperature
- Fever worsens outcome (↑ 1° C, risk of poor outcome doubles); greatest effect in 1st 24 hrs
- Treatment: aggressive acetaminophen or physical means; search for **underlying cause**
  - Hypothermia under investigation (hard to do – people shiver!)

### Blood Pressure
Normally **autoregulated** (constant blood flow to brain across wide range of BP)
- **Autoregulation impaired / lost** in area of infarction, so **ischemic tissues** are **perfusion-pressure dependent**!
- Hx of **HTN**: autoregulation shifted to **higher pressures**! (bad)

**Treatment:** no proven optimum range of BP in acute stroke
- avoid hypotension
- treat **hypertension** only if SBP > 220, DBP > 120, or signs of end organ damage (”permissive hypertension”)

### Antithrombotic therapy
- Rule out **intracranial hemorrhage** (CT/MRI); tailor Rx to suspected etiology

### Acute stroke:
- **Give aspirin 325 mg PO** (small beneficial effect w/in 24 hrs)
- **Acute anticoagulation** (heparin, warfarin) **discouraged** (↑ bleeding)

### Secondary prevention
- Do use antithrombotic therapy later (with aggressive HTN, DM, hyperlipidemia, cig smoking management)
- **Aspirin** and **statins** are most powerful to prevent stroke
- **Warfarin** in pts with A-fib (prevent mural thrombi)
# Pharm Review: Role of Antithrombotics in Stroke

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Notes</th>
</tr>
</thead>
</table>
| **Aspirin** | irreversible platelet inactivator (COX inhibitor) | • ↓ 1 yr mortality in acute stroke – works!  
• Gastritis / GI side effects |
| **Clopidogrel (Plavix)** | Selective irreversible inhibitor of ADP-induced platelet aggregation | • Equivalent to aspirin for prevention of recurrent stroke but  
• ↑ bleeding (bad) |
| **Dipyridamole** | Phosphodiesterase inhibitor (↓ aggregation) | • Ineffective as monotherapy  
• Maybe slightly better than aspirin alone if in combo  
• Major side effect: 30% get severe headaches |
| **Statins** | HMG CoA-reductase inhibitors (block rate-limiting step in cholesterol biosynthesis) | • Significant reduction in stroke risk  
(even if “normal” chol values)  
• Try to get LDL < 70 mg/dL |
| **AntiHTN** | Various | • ↓ stroke risk, ↓ intracerebral hemorrhage risk  
• ACEi / ARB may be particularly useful (even in pts with relatively normal BP) |

### Thrombolytic Therapy (rTPA)

Tissue plasminogen activator:
- serine protease, converts plasminogen → plasmin in presence of fibrin, leads to thrombolysis

**rTPA (Alteplase) = recombinant TPA**
- **Major risk:** intracranial bleeding (but no ↑ risk death)  
- Only FDA-approved therapy for acute stroke

### Endovascular therapy

**Various options available:**
- Intra-arterial thrombolysis (thrombolytics directly to clot)  
- Intracranial angioplasty, stenting  
- Intra-arterial mechanical embolectomy  
- Intra-arterial ultrasound combined with thrombolysis
Pupils & Eye Movements in Cerebrovascular Disease

Oculomotor Systems

<table>
<thead>
<tr>
<th>Shift Gaze / Attention (Fast movements)</th>
<th>Stabilize Gaze / Attention (Stop / slow movement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Voluntary / volitional saccade / Vergence</td>
<td>• Fixation, VOR suppression</td>
</tr>
<tr>
<td>• Reflexive saccade</td>
<td>• Vestibular pursuit (VOR / OTR)</td>
</tr>
<tr>
<td>• Nystagmus quick phase (VOR / OKN)</td>
<td>• (Conjugate) visual pursuit / vergence pursuit</td>
</tr>
<tr>
<td></td>
<td>• Gaze holding</td>
</tr>
</tbody>
</table>

Remember the basics of extraocular muscle movement
- Vertical, horizontal, torsional (extort: top out; intort: top in)
- 4: intort; 6: abduct (lateralize); 3: everything else

Basic scheme

<table>
<thead>
<tr>
<th>Voluntary EOMs</th>
<th>Reflexive EOMs</th>
<th>Primary machinery*</th>
<th>Tuning</th>
</tr>
</thead>
<tbody>
<tr>
<td>front of brain</td>
<td>back of brain</td>
<td>brainstem</td>
<td>cerebellum</td>
</tr>
</tbody>
</table>

* (CN 3/4/6 nuclei, α-motor neurons for EOM)

Brainstem Machinery

<table>
<thead>
<tr>
<th>Midbrain</th>
<th>Vertical / Torsional Gaze &amp; Holding; Vergence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pons</td>
<td>Horizontal Gaze</td>
</tr>
<tr>
<td>Medulla</td>
<td>Horizontal Holding</td>
</tr>
</tbody>
</table>

Horizontal section: note that:
- medial longitudinal fasciculus (MLF) runs along the back of everything; connects CN 6 & 3 for horizontal gaze
- Cerebellum (accuracy center) is right near everything
- Cranial nerve nuclei are in logical places (see previous lectures)

Supranuclear control systems determine / shape inputs to eye system

Saccades

Eye-only vs. eye-head shifts
- When eye moves alone: shift, then hold
- When head moves too (real life)
  - Lead with eyes → head turns; eyes correct back

Eyes only  Eyes + head
Pulse-step physiology
- Move eyes (burst)
- Hold eyes there (sustained ↑ tonic impulse)

Machinery (how does this happen?)
- **Parapontine Reticular Formation (PPRF) – horizontal gaze center**
  - Initiates saccades; ipsilateral
- Reciprocal innervations with local inhibitory loops
- Complicated anatomy: one part is “gas” (burst), one part is “clutch” (terminate burst), one part is brake (hold; “integrator”)

**Horizontal Leftward Voluntary Saccade**: “Look to the left”
1. R. frontal eye field
2. R. saccade center
3. L. horizontal gaze center
4. L. 6th nucleus (L eye out)
5. R. MLF
6. R. 3rd nucleus (R eye in)

**KNOW THIS LEVEL OF DETAIL!!**
- Think of anatomy: where is the lesion?
- Lesion in R FEF, for example, knocks out the contralateral 6 & ipsilateral 3, so you won’t be able to look away from the lesion and you’ll tend to look towards it

**Cerebral gaze palsy (“preference”)**
60 year-old woman presents with sudden-onset left hemiplegia. She is confused and neglecting the left side, but able to follow commands. Her eye movement exam reveals eye deviation to the right, and an inability to make voluntary eye movements to the left in response to verbal commands.
- Both eyes affected, voluntary saccades knocked out
- **Lesion here in right frontal eye field** (knock out L 6, R 3: can’t look left!)
- Right MCA ischemic stroke or something like that

**INO (Intranuclear opthalmoplegia)**
45 year-old man presents with sudden-onset diplopia. He feels a little unsteady on his feet, but has no other symptoms. His eye movement exam reveals an exotropia (wall-eyed) and an adduction (medialization) failure in the right eye on attempted leftward gaze. The deficit is overcome by convergence.
- Can’t bring right eye in towards nose voluntarily, but can follow finger heading towards nose (convergence)
- **Lesion in right MLF** (“intranuclear” = between 3 and 6 nuclei)
  - e.g. right brainstem stroke
  - Look left: L. CN 6 ok (L. eye out), but R. CN 3 not connected (R. eye doesn’t go in)

**Convergence Pursuit**
“watch my finger” as I move it towards your nose
- **Bilateral** (both eyes need to move in)

Machinery:
1. **Bilateral motion perception areas** (MST)
2. **Bilateral frontal eye fields**
3. **Bilateral vergence centers**
4. **Bilateral 3rd nuclei** (both eyes in)

*Note that MLF is nowhere near pathway* (convergence preserved in INO)
**Pupils: Efferent Pathway**

**Efferent (Motor) pathway**
- EFFERENT problems with one pupil cause **ANISOCORIA** (asymmetric SIZED pupils)

<table>
<thead>
<tr>
<th>Role</th>
<th>Parasympathetics</th>
<th>Sympathetics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Constrict pupil in light</td>
<td>Dilates pupil in darkness</td>
</tr>
<tr>
<td><strong>Anatomy</strong></td>
<td>Inside skull</td>
<td>Outside skull</td>
</tr>
<tr>
<td></td>
<td>- CN II → Edinger-Westphal nucleus →</td>
<td>- Hypothalamus → exit in thoracic SC →</td>
</tr>
<tr>
<td></td>
<td>- parasympathetics out on CN III →</td>
<td>- sympathetic trunk → over lung, under</td>
</tr>
<tr>
<td></td>
<td>- ciliary ganglion → short ciliary nerves →</td>
<td>subclavian →</td>
</tr>
<tr>
<td></td>
<td>- constrict pupil</td>
<td>- up ICA → trigeminal ganglion →</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- out on CN V roots → dilate pupil</td>
</tr>
</tbody>
</table>

- **Defect causes...**
  - BIG, POORLY REACTIVE pupil, with anisocoria maximal in **BRIGHT** light
  - SMALL pupil that **DILATES POORLY** in darkness, with anisocoria maximal in **DIM** or **NO** light

| Ptosis | BIG ptosis on side of BIG PUPIL (3rd nerve affected too – levator palpebrae m.) | SMALL ptosis on side of SMALL PUPIL (“Horner’s”) (Sympathetics: superior, inferior tarsal mm.) |

---

**Right 3rd nerve palsy**

42 year-old man presents with sudden-onset diplopia and a severe **headache**. His eye movement exam reveals a moderate right ptosis, an exotropia (wall-eyed), and a dilated, non-reactive right pupil. His left eye moves **normally**, but the right has **limited** movement other than **normal abduction** (lateralization).

- CN III affected (6 ok: can still abduct)
- Big ptosis, extropia, dilated pupil = 3rd nerve palsy
- Berry aneurysm (compresses CN III – little white circles in picture)

---

**Left Horner Syndrome**

48 year-old woman presents with a 10-minute episode of **word-finding difficulty**. She has had a left frontal headache for the past two weeks that came on after a fall. Her exam reveals slight left ptosis and subtle anisocoria, with the left eye pupil smaller. The left pupil **dilates slowly** when the lights are **turned off**, and **anisocoria** is more obvious in **darkness**. Ocular motility is **normal**.

- Baby ptosis, anisocoria in **dark** → sympathetic (can’t dilate in dark)
- **Left carotid dissection** (prior to stroke)
  - Sympathetics in wall of carotid
  - THERAPEUTIC EMERGENCY
    - (anticoagulate – unlike A0 dxn, can have thrombotic sequelae!)
Pupils: Afferent Pathway

Left Relative Afferent Pupillary Defect (RAPD)

77 year-old man presents with a month of bitemporal headaches and one day of acute vision loss in the left eye. His exam reveals hand motions vision in the left eye. The left pupil responds to light, but there is a left relative afferent pupillary defect on the swinging flashlight test. The left optic disc is pale, swollen.

“swinging flashlight sign” – penlight in R, then L eye; Affected eye appears to dilate paradoxically when you light on it.

- **Double decussation** in afferent light reflex: CN II has synaptic outputs to EW nucleus on BOTH SIDES
- **NO ANISOCORIA** in AFFECTED DEFECT (both eyes respond the same)
  - But when you shine light in bad eye (CN II damaged, etc), both pupils “dilate” (don’t constrict)

<table>
<thead>
<tr>
<th>Shine light in...</th>
<th>Response</th>
<th>Explanation</th>
</tr>
</thead>
</table>
| Good eye          | ![Good Eye](image) | Good Eye
|                   | ![Bad Eye](image) | Bad Eye
|                   | **Both constricting maximally**
|                   | (plenty of light to trigger constriction) |
|                   | **Light “seen” by EW nucleus: 100%** |
| Bad eye           | ![Good Eye](image) | Good Eye
|                   | ![Bad Eye](image) | Bad Eye
|                   | **Both eyes “dilate”**
|                   | (less light getting in to trigger constriction) |
|                   | **Light “seen” by EW nucleus: ≈ 50%**
|                   | (depends on extent of defect) |

**Giant Cell arteritis** (ischemic optic neuropathy), etc. – affect optic nerve

- Pale, swollen disc from ischemic optic neuropathy
CNS Infections

**Anatomical Considerations**

Key features of CNS:
- **sequestered** from systemic compartment (BBB)
- **limited regenerative potential** (neurons) – almost irreplaceable (gial cells: low turnover, promote scarring)
- **little extracellular space** (easy cell-cell spread)
- **specialized receptors** (e.g., Ach receptor for rabies, heparan sulfate for herpes)

Bony protection: calvarium; dura tightly bound together
- **Epidural infections**: usually from bone infection (osteomyelitis); remain localized
- If bacteria get into subdural space, infection spreads rapidly over hemisphere

BBB: good & bad
- Excludes most **microorganisms** but also most inflammatory cells / Abx / Ab (hampers clearance)
- Limited endogenous defenses in CSF, low C' levels, low Ab levels, few phagocytic cells, etc.

CSF:
- **Subarachnoid space**: pathogens can undergo rapid growth here; spread through CNS
- **Lumbar puncture** is KEY in evaluating / treating CNS infections

---

**Meningitis**

18 year old male, military recruit presents with CC of intense headache, fever and stiff neck.

Meningitis = inflammation of the meninges (diffuse CNS infection)
- bacterial / fungal / parasitic growth in subarachnoid CSF space or
- intracellular growth of bacteria / viruses in arachnoid, ependymal cells

**Causes of meningitis**

**Bacterial meningitis:** 20k cases /yr, most deaths in neonates (even though only 10% total cases)

<table>
<thead>
<tr>
<th>Neonates (&lt; 28d)</th>
<th>Children</th>
<th>Adults</th>
<th>Older (&gt;60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>enteric bacilli (esp. <em>E. coli</em>)</td>
<td>Strep pneumo</td>
<td>Neisseria meningitidis*</td>
<td>Strep pneumo</td>
</tr>
<tr>
<td>Group B Strep</td>
<td><em>N. meningitidis</em></td>
<td>Strep pneumo</td>
<td>Listeria</td>
</tr>
<tr>
<td><em>Listeria</em></td>
<td><em>H. influenza</em> (vaccine)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*most cases of pyogenic meningitis are sporadic, but *N. meningitidis also causes epidemic disease (Africa)*

**Meningococcal meningitis (N. meningitidis):** typically **young adults** living in barracks / dorms; preventable by **vax**

**Viral meningitis**
- Frequent (75k/yr); VIRAL >> bacterial meningitis
- Enteroviruses (late summer, early fall); West Nile (more encephalitis), others – think mosquitos, travel

**Pathogenesis of Meningitis**
- Bacteria / virus invades CNS from blood (↑ risk with ↑ magnitude, duration of bacteremia/viremia)
  - **Capsid polysaccharides**: resistant to phagocytosis, better chance of invasion
  - **Intracellular bacteria** often elude this clearance too
- **Rapid multiplication in subarachnoid space** (lack of immune defenses) → Release of bacterial cell wall components → inflammation, proinflammatory cytokines → Brain, blood vessel inflammation

*Pathology:* Cloudy, purulent meninges filled with bacteria (purple – right)
Clinical Manifestations of meningitis

- Headache, fever, nuchal rigidity are classic
- Obtundation, seizures common; lethargy, nausea/vomiting, rash, ataxia

**Signs** on physical exam (basic idea: stretching inflamed meninges is painful)

If not treated:
- collection of pus at base of brain forms: **CN palsies (VI, VII, VIII especially), CSF obstruction → hydrocephalus**
- Infection of vessels: can produce **septic occlusion → infarction** of brain, **multifocal neuro deficits**

Rash: May progress to **purpura fulminans**, associated with **multiorgan failure**
- *(Waterhouse-Friderichsen syndrome – N. meningitidis → adrenal gland infection → hemorrhage, DIC, etc.)*

### Diagnosis of meningitis

**CSF is KEY:**

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pressure</th>
<th>Cells</th>
<th>Protein</th>
<th>Sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral meningitis</td>
<td>Normal</td>
<td>mononuclear (10-1000)</td>
<td>↑</td>
<td>Normal</td>
</tr>
<tr>
<td>Bacterial meningitis</td>
<td>Normal or ↑</td>
<td>PMNs (&gt;100)*</td>
<td>↑↑</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>Subacute meningitis (e.g. TB)</td>
<td>Normal</td>
<td>mononuclear</td>
<td>↑↑</td>
<td>Normal to ↓</td>
</tr>
</tbody>
</table>

* WBC > 2000, PMN > 1180 is 99% predictive of bacterial meningitis

**Other Techniques**
- **Bacterial**: culture / Gram stain; immunoelectrophoresis (capsular polysaccharides)
- **Viral**: usually can’t culture, use PCR

### Management of meningitis

- **LP (ASAP!)**
- **High risk of herniation**: > 60 yo, immunocompromised. Hx of CNS disease, seizures w/in 1 wk, abnormal consciousness, focal findings (if none of these symptoms, 97% of time there’s no mass effect)

**Pharmacotherapy**: start ABX IMMEDIATELY

- **Empiric antibiotics: ASAP!** (during or right after LP!)
  - Cefotaxime + vancomycin for community acquired meningitis
  - + Ampicillin for immunocompromised (to cover *Listeria*)
- **Acyclovir** if pleocytosis is mononuclear (think viral)
  - Herpes simplex encephalitis is only viral one to distinguish urgently: others often self-limited
- **Corticosteroids** in acute bacterial meningitis in children w/o HiB vax or adults with ↑ ICP, high bacterial cell ct
  - Otherwise ↑ risk of serious gastrointestinal bleeding, not worth it
Clinical course of meningitis
- 15-30% die even with prompt treatment (highest with pneumococcal meningitis)
- Venous thrombosis, cerebral edema possible with bacterial meningitis
- Neuro sequelae: seizures, hydrocephalus, cranial nerve deficits common
  - Kids: deafness, hearing loss
  - Adults: facial nerve palsies

Chronic Meningitis
Meningo-encephalitis syndrome lasting 4+ weeks; Less than 10% of all cases of meningitis
- Fever, headache, meningismus, alterned mentation, seizures, dementia, other neuropsych presentations
- CSF: Mononuclear pleocytosis + elevated protein
- Consider infectious, neoplastic, non-infectious causes
  - TB meningitis (immunocompromised, immigrants) – can cause meningitis, abscesses, epidural infections affecting spine (Pott’s disease) in HIV pts

Bacterial Brain Abscesses
38 year old male presents with CC of new onset focal seizures while on skiing trip. No preceding sx, headache, focal weakness, or CVA risk factors. Recently had a root canal performed. Exam: mild left hemiparesis.

Abscess: foci of purulent infection developing from either:
- Spread of contiguous focus of infection (ears, nasal/mastoid sinuses, TEETH – dental work!)
- Hematogenous spread (lung / heart, e.g. purulent pulmonary disease, subacute bacterial endocarditis, etc.)
Invasive procedures too: vascular catheters, other instrumentation → bacterial seeding → abscess

Etiology: mostly mixed flora of aerobic & anaerobic bacteria
- Streptococci (60-70%), also S. aureus, enterobacteriaciae, bacteroides
- Fungi / parasites too (see later)

Appearance:
- Ring-like lesions on T1 w/contrast
  - Walled off, rim is vascular / edematous & enhances with contrast, pus doesn’t

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>TB</th>
<th>Toxo</th>
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<tr>
<td>Liquefactive necrosis</td>
<td>Caseating necrosis</td>
<td>Solid necrosis</td>
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Clinical Manifestations
- “Classic triad” – headache, focal signs, seizure
  - But the triad occurs in FEWER THAN 50%
- CSF is usually sterile (would need to aspirate cavity!)

Treatment:
- Multiple abx to cover common organisms
  - Ceftriaxone, metronidazole (anaerobes), Nafcillin (S. aureus), Ceftazidime (P. aeurg), Vanc (MRSA)
- Anticonvulsants may be helpful
- Surgical DRAINAGE to determine specific flora, help abx penetrate, prevent rupture
- Avoid STEROIDS (decreases CNS penetration!)

Spinal epidural abscesses
- Diabetics, pts on hemodialysis, IV drug users
- Local pain & tenderness → rapid course
  - Segmental pain along nerve roots, paresthesias below level → irreversible paraplegia!
- Surgical emergency (Dx & drain!)
  - Use spinal MRI (compressive lesion involving disk space, anterior to cord)
**Encephalitis**

28 year old female secretary presents with a 3 day hx of 102 fever, mild confusion and headache. Family says she’s had brief episodes of “left arm twitching uncontrollably, being out of it, with lip-smacking”. Exam shows disorientation, mild hemiparesis.

**Encephalitis:** inflammation of the brain
- most commonly caused by viruses

**Etiology**
- **common:** HSV, Arboviruses, Enteroviruses, Mumps, CMV, EBV, VZV, HIV, Measles
- **less common:** Adenovirus, Colorado tick fever, Influenza, LCM, Parainfluenza, Rabies, Poliomyelitis, Rubella

**Life threatening encephalitis:** usually due to:
- HSV (sporadic)
- Arboviruses (epidemic; mosquito-borne; e.g. West Nile encephalitis, others)
- Rabies: uniformly fatal encephalitis; < 5 cases in USA / yr

**Pathogenesis**

**Herpes simplex encephalitis (HSE)**
- HSV-1 usually; **localized infection** in brain
  - acquired in childhood, latent in trigeminal ganglia, reactivates (cold sores,)
  - can spread along nerve fibers, uniquely localized to **orbital frontal & medial temporal lobes**
- Host has pre-existing immunity (needs to spread continuously to avoid blood) – **neurons & glia** affected

**Arboviruses:**
- Spread from **blood** to **brain** following **arthropod bite** (mosquito or tick)
- Few / no sx during **systemic infection**; 1:20-1:1000 spread to CNS
- **Diffuse infection, neurons only** affected
- **Case-fatality rates** range (50% for Eastern equine, 5-15% for West Nile, <1% for LaCrosse)

**Clinical manifestations of encephalitis**
- **NEUROLOGICAL DEFICITS** (vs meningitis: no neuro deficits!)
- Fever, headache, nausea, vomiting, altered mentation, seizures, hyper-reflexia, meningismus

<table>
<thead>
<tr>
<th>HSE</th>
<th>Arbovirus encephalitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal signs</strong> (rare in other forms) – hallucinations, bizarre behavior, focal seizures, hemiparesis, aphasia</td>
<td><strong>More diffuse disease</strong> (rapid depression of consciousness, frequent generalized seizures) – but can be indistinguishable from HSE</td>
</tr>
<tr>
<td>Evolve over <strong>days to weeks</strong></td>
<td><strong>Very rapid progression</strong></td>
</tr>
</tbody>
</table>

**Diagnosis**
- CSF: ↑ pressure, **mononuclear cells** (lymphocytes), protein ↑, glucose normal
- Culture usually negative

**Arboviruses:** **virus-specific IgM** in CSF (rapid diagnosis)

**HSV:** CSF PCR sensitive, specific (empiric tx without brain biopsy)
- MRI: can see **frontal & temporal lobe hemorrhage & necrosis** (see pics)

**Treatment**
- **HSV:** **ACYCLOVIR** REDUCES MORTALITY (70% w/o tx, <25% with tx)
  - Need **rapid diagnosis & treatment of HSE**!
- Otherwise: **supportive care**
Lyme Disease
25 year old male med student presents with CC of “Bell’s facial palsy”. He has had fevers and arthralgias for 2 weeks.
Exam: 6 cm “target” rash on arm. Left ‘peripheral pattern’ facial palsy

Etiology: *Borrelia burgdorferi*
- carried by *Dermacentor variabilis* (American dog tick) and *Ixodes scapularis* (black-legged “deer” tick) – NE USA

Signs / symptoms
- Cranial nerve VII palsies
- “Bull’s eye rash”
- Meningitis / encephalitis / radiculoneuritis, can **mimic** lots of other diseases
- MRI: can mimic MS or ischemia

Course: rash, neuro symptoms: later neuro symptoms (?)
Diagnosis: ELISA (false positives possible; confirm with Western)
Treatment:
- If chronic neuro symptoms + (Hx Lyme dz, + lyme serology, or CSF abnormalities): give **antibiotics**
  - 4 week course of IV ceftriaxone or 60 days PO doxycycline
- No evidence for abx in “Post-Lyme syndrome”

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**Neurologic Infections in Immunocompromised Hosts**

Need to be **precise** about what type of immunocompromise the patient has

<table>
<thead>
<tr>
<th>Example</th>
<th>Susceptible to</th>
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<tbody>
<tr>
<td>Humoral (antibody) deficit</td>
<td>Mult. myeloma, splenectomy</td>
</tr>
<tr>
<td><strong>Encapsulated bacteria</strong> (H. flu, S. pneumo, enteroviruses)</td>
<td></td>
</tr>
<tr>
<td>Cellular (T-cells) deficit</td>
<td>AIDS</td>
</tr>
<tr>
<td>Toxo, cryptococcus, CMV / JCV</td>
<td></td>
</tr>
<tr>
<td>Granulocytes deficit</td>
<td>After chemo</td>
</tr>
<tr>
<td>Fungal (Aspergillus, C. albicans, Mucor), Gram negs</td>
<td></td>
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</tbody>
</table>

**Opportunistic** infections: exposure to ubiquitous organisms that are normally of low pathogenicity

**Reactivated** infections: remote Asx primary infection, become reactivated from latency if immune deficiency acquired

**Neuro complications** in HIV (can have combo):
- directly HIV-related
- from complications of immune deficiency

---

**Opportunistic Infections in Advanced HIV**
- Occur with CD4 < 200; may be **multiple** in 15%
- May require **lifelong maintenance therapy** until immune system recovers (HAART)
- **CSF PCR** helpful for some infections
- Imaging characteristics **very helpful**
- **Biopsy** 90% sensitive, but 7% morbidity ~ so avoid unless absolutely necessary
Cryptococcal meningitis

**Etiology:** Ubiquitous yeast; CNS infection in 5% AIDs pts

**Presentation:** Headache, altered mentation, cranial neuropathies, fever, vomiting
- **NECK STIFFNESS UNCOMMON** (limited CSF inflammatory response!)

**Pathology:** Extensive meningial invasion, tons of budding yeast forms
- Form *cryptococcomas* frequently, esp. basal ganglia
- Prominent jelly-like capsule

**Course:** Complication: obstruction of CSF outflow $\rightarrow$ ↑ ICP

**Diagnosis:** Cryptococcal Ag in CSF or Cx (*Normal CSF cells / protein in 50%*)

**Treatment:** Amphotericin B x 14 d (induction); follow with fluconazole x 10 wks
- *Remember liposomal ampho is a little better if renal impairment*

Cerebral toxoplasmosis

**Etiology:** *Toxoplasmosis gondii*, obligate intracellular protozoan; toxoplasmosis in 5-10% AIDs pts

**Presentation:** Fever, altered mentation, seizures, focal neuro signs that develop *subacutely* (days – wks)

**Pathology:** Multifocal necrotic abscesses
- scattered throughout hemispheres (esp basal ganglia)

**Pathogenesis:** *Reactivation* of latent organisms
- *encysted* in brain

**Course:** Reactivation common, need lifelong suppressive therapy (pyrimethamine)

**Diagnosis:** CT/MRI: RING-ENHANCING mass lesions
- *not specific: CNS lymphoma, abscesses similar*

**Treatment:** Pyrimethamine & sulfadiazine + folinic acid (prevent bone marrow suppression)
- leads to clinical, radiological improvement in ~80% pts in 10 days
  - RELs in HIV: treat for toxo & see if it gets better; if not, lymphoma?
- *Steroids* only if large lesion, mass effect

Primary CNS lymphoma (PCNSL)

- 2% AIDs pts develop primary CNS lymphoma
- B-cell origin, associated with EBV infection
- Multicentric, aggressive: progressive neuro deterioration with encephalopathy, focal signs, seizures

Progressive Multifocal Leukoencephalopathy (PML)

**Etiology:** Reactivation of *latent JC Virus* (a papovavirus) infection with immunodeficiency (HIV or natalizumab)
- *Natalizumab*: MS therapy, blocks alpha 4 integrin / vascular cell adhesion; ↓ immune response

**Presentation:** Primary JCV infection usually asymptomatic; PML in 5% AIDs pts
- Progressive hemiparesis, hemianopsia, aphasia, ataxia
- NO HEADACHE

**Pathogenesis:** JCV infects oligodendroglia $\rightarrow$ patchy white matter foci of demyelination

**Pathology:** inclusion bodies in deformed oligodendroglia, demyelination, bizarre giant astrocytes

**Course:** Before HAART: death in wks / months
Diagnosis: MRI virtually pathognomonic (Bx not usually required)
- Multiple, asymmetric areas within subcortical white matter
- no prominent enhancement or mass effect

Treatment: HAART (alpha-interferon or mirtazapine (antidepressant) as adjunct)

Listeria monocytogenes
- Common cause of bacterial CNS infection in immunodeficiency (cancer chemo, renal transplant, corticosteroids)

Risks: GI colonization, ↓ T-lymphocytes, Mφ

Presentation: subacute fever, altered mental status, focal neuro signs in setting of bacteremia

Diagnosis: CSF: PMN pleocytosis; Cx: + for blood, CSF

Treatment: Ampicillin (erythromycin, chloramphenicol if allergic to PCN)

CMV Encephalitis
- Important cause of CNS infection in transplant recipients & HIV pts

Presentation: headache, fever, altered mental status
- focal neuro signs, meningismus uncommon
- Can infect lumbosacral nerve roots (subacute cauda equine syndrome)

Pathology: necrotizing infection of subependymal region or brainstem
- Inflammation, necrosis, CMV “OWL’s EYE” inclusions

Diagnosis: CSF CMV PCR is useful (esp. in AIDS)
- difficult (CSF cx usually (-); viral blood cultures may be (+))

Treatment: ganciclovir (esp. CMV retinitis)

Slow and Chronic Infections of the Nervous System

Chronic CNS infections (e.g. syphilis): run course over many years; unpredictable appearance of varied complications
Slow CNS infections (e.g. CJD): more predictable incubation with progressive buildup, predictable course
- need to differentiate both from static sequelae of acute bacterial meningitis, viral encephalitis

Syphilis
- a spirochete; causes varied neuro disease

Presentations:
- Secondary syphilis (6wks – 3mo post infection): may see benign, mild meningitis (CNS involvement in 25% w/o Tx)
- Ocular manifestations (uveitis, neuroretinitis, episcleritis)
- Late-stage syphilis:

<table>
<thead>
<tr>
<th>Time after 1st infection</th>
<th>Possible manifestation</th>
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<tbody>
<tr>
<td>3-5 years</td>
<td>Meningovascular syphilis → stroke</td>
</tr>
<tr>
<td>8-10 years</td>
<td>Progressive dementia (“general paresis”)</td>
</tr>
<tr>
<td>10-20 years</td>
<td>Chronic arachnoiditis (“tabes dorsalis”) – primarily posterior SC roots involved</td>
</tr>
</tbody>
</table>

Diagnosis: syphilis serology (VDRL+ / RPR↑, etc. even if pt immunosuppressed)

Treatment: high dose IV PCN (not consistently effective in neurosyphilis / with HIV – reexamine at 6 mo)

Direct HIV-1 involvement of nervous system
- Neuro sx in HIV: 50% from opportunistic infections, 50% from HIV-1 effects itself
- Pathogenesis not entirely understood
HIV-associated dementia

- A chronic viral encephalitis in 15-20% AIDS pts

Presentation: Progressive subcortical dementia with CD4 < 500
- ↓ cognition, behavioral changes, motor dysfunction
- impaired short-term memory, imbalance, slower reaction times
- apathy & social withdrawal
- psychomotor slowing with sparing of language

Diagnosis: Clinical mostly (see above)
- FLAIR: deep white matter hyperintensities & central atrophy

Pathogenesis:
- perivascular Mφ are major target of HIV infection in brain; NOT NEURONS
- reactive astrocytosis, microglial nodules, multinucleated giant cells (Mφ fuse)

Treatment: HAART (aggressive) – can ↓ sx in a few weeks

Prion Diseases

Prion diseases: transmissible spongiform encephalopathies (TSEs)
- caused by infectious agents without nucleic acids
- spongiform: post-mortem brain has large vacuoles in cortex and cerebellum
- beta-sheet formation (PrP) characteristic

Prions = misfolded proteins ("small proteinaceous infectious particles which resist inactivation by procedures that modify nucleic acids")

Kuru and Creutzfeld-Jacob Disease are two human prion diseases
- Kuru = ritual cannibalism in Fore tribe of Papua New Guinea

CJD
- Presenile dementia with progressive course and death in < 6 mo
- Presents at 50-60 yo with triad of progressive dementia, myoclonus, characteristic EEG findings

Rare (1/million worldwide, 85-95% sporadic; 5-15% familial)
- Iatrogenic: corneal transplants, dural grafts, contaminated growth hormone

Diagnosis: Specific marker protein (14-3-3) >90% specificity, sensitivity
Pathology: pathognomonic: neuronal loss, gliosis, spongiform appearance

Animal TSE

BSE: England, 80s, changes in food processing system
- Prion-contaminated nervous tissue into food chain

New-variant CJD: unusual CJD-like cases in young adults
- Early behavioral disturbances, paresthesias, ataxia, slower progression
- Extensive amyloid plaque formation in brain

MRI in sCJD

BSE Bovine spongiform encephalopathy: cows
Scrapie Sheep
TME Transmissible mink encephalopathy
CWD Chronic wasting disease: mule deer, elk

MRI in nvCJD
Multiple Sclerosis / Demyelinating Diseases

**Demyelinating Diseases**

Destruction of previously normal myelin sheath in CNS with accompanying inflammatory response
- *myelinoclastic* process

Contrast to dysmyelinating disorders, when myelin doesn’t form / delayed / arrested / maintenance disturbed
- e.g. leukodystrophies (myelin deficient in CNS / PNS), lipid storage diseases, aminoacidopathies
- Adrenoleukodystrophy (ALD): X-linked disorder with combined demyelination / dysmyelination

**Multiple Sclerosis: overview**
- Inflammatory demyelinating disease of the brain and spinal cord that usually presents at 20-45 yo
- Genetic predisposition with environmental trigger
  - **Pathogenesis**: precipitating *microbial infection* that through molecular mimicry or release of sequestered antigens results in chronic autoimmunity in genetically predisposed host
  - HLA-DR2, IL-2 receptor alpha, and IL-7 receptor gene polymorphisms associated with MS
- MRI and spinal fluid aid diagnosis
- Partly effective treatments exist to prevent immune cell activation and migration
  - interferon beta, glatiramer acetate, and natalizumab

**Epidemiology of MS**
- Far and away most common demyelinating disease
- Most common cause of disability in young adults, annual cost in US $6.8-11.9B
- 250-300k in US; 2/3 FEMALE, ↑ in Northern Europeans; onset: 15-50 yrs
- ↑ in temperate higher latitudes of both hemispheres

**Immunopathogenesis of MS**
- Polygenic disease: inheritance confers susceptibility to autoimmunity
- Inflammatory response genes implicated: HLA-DR2, IL-2 receptor-α, IL-7 receptor-α

**Environmental trigger(s)**: virus, toxin, etc. provoke through molecular mimicry or release of sequestered antigens
- Autoreactive T-cells activated, traffic into CNS, release proinflammatory cytokines
- ↑ adhesion molecules on brain vascular endothelial cells
- ↑ BBB permeability, non-specific immune cell recruitment
- Demyelination → attempts at remyelination
- eventually scarring / gliosis / axonal degeneration

**What does myelin do?**
1. rapid conduction of nerve impulses
2. protection of nerve fibers
3. trophic support

**Clinical Features of MS**

**Clinical Courses**

<table>
<thead>
<tr>
<th>Clinical Course</th>
<th>Details</th>
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<tbody>
<tr>
<td>Relapsing and Remitting (RR)</td>
<td>85-90% at onset</td>
</tr>
<tr>
<td>Secondary Progressive (SP)</td>
<td>RR pts can convert to SP: 50% after 10 years, 80% after 30-40 yrs</td>
</tr>
<tr>
<td>Primary Progressive (PP)</td>
<td>10-15% are progressive from onset</td>
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</table>

Course is highly variable
- Some: **malignant, disseminated, fulminating** (5-10% pts, esp. younger)
- Some: RR/SP with **benign course**, few symptoms
Even RR can progress stepwise (see top picture to right)
- MRI shows continuing inflammation / demyelination even during clinical remissions!
  - MS is a chronically active disease

### Symptoms:
- Visual
- Sensory
- Fatigue
- Dizziness (vertigo, dysequilibrium)
- Impaired coordination, balance
- Heat sensitivity
- Burning/electrical pains
- Motor
- Bowel, bladder
- Sexual
- Cognitive
- Psychiatric (depression)

### Signs:
- Sensory loss
- Weakness, spasticity, hyperreflexia, Babinski's
- Impaired coordination (limbs and gait), action tremor
- Nystagmus, impaired eye movements, or monocular visual loss
- Incontinence, abnormal sphincter function
- Depression and memory loss
- Fluctuation with temperature

Later signs / symptoms: para/quadriplegia, urinary incontinence, constipation, impotence, cognitive impairment, etc.

### Diagnosis of MS

**Dissemination in space and time**
- 2 or more episodes of neurologic dysfunction with associated signs referable to CNS, or
- Chronic progression for more than 6 mo without other definable cause

**Clinical** diagnosis; need exclusion of other conditions
- MRI can be used to establish dissemination in time & space after 1st clinical episode

### Aids to MS Dx

**MRI of brain / spinal cord**
- Surpasses all previous diagnostic tests; can use to follow pt (serial imaging)
- New lesions are Gadolinium enhancing
  - Paramagnetic substance; injected IV; indicates BBB is “open” (active inflammation)

**Features:**
- High signal T2-weighted lesions that are:
  - Perpendicular to ventricles (Dawson's fingers)
  - Pericallosal, juxtacortical, in posterior fossa, spinal cord
- Low-signal T1 lesions ("black holes") – axonal loss
- Contrast-enhancing lesions,
- Lesions changing size, lesions coming / going / accumulating

---

**Dawson's Fingers** (perpendicular to ventricle)
Can also use to measure disease activity (Serial MRI)
- most lesions occur in periventricular white matter
  - (but can’t follow clinically - redundancy of pathways; small lesions have no good clinical correlates)

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<tr>
<th>Finding</th>
<th>Indicates...</th>
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<tbody>
<tr>
<td>Accumulation of T2 periventricular lesions</td>
<td>Ongoing disease activity (bad prognosis)</td>
</tr>
<tr>
<td>Contrast enhancement</td>
<td>BBB breakdown (disease activity)</td>
</tr>
<tr>
<td>T1 low signal lesions (“black holes”)</td>
<td>Tissue loss (disability, poor prognosis)</td>
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</table>

**CSF**
- Oligoclonal bands (IgG) – 2 or more in CSF but not paired serum sample
- Seen in 85% of MS
- **Lacks specificity:** can also see in other inflammatory dz, CNS infection

**Exclusionary too:** infections (culture, ↓ glucose), malignancy (cytology, ↑ protein)

**Evoked potentials**
- Can see slowed conduction (optic nerves, brainstem, SC pathways)
- Lacks specificity and sensitivity; supplanted by MRI

**Lab tests to exclude other diseases**
- Need to exclude other better explanations that can mimic MS
- **The full workup:** a lot of stuff! ESR/ANA (Lupus), SSA (Sjogren’s), B12, Lyme titer, RPR (Syphilis), EBV, CMV, HIV, HTLV-I (HAM/TSP), ACE, CXR (sarcoidosis), VLCFA (adrenoleukodystrophy), biopsy (rarely – tumor, etc)

**Pathology of MS**

**Gross Findings**
- Multiple, irregularly-shaped, sharp-edged plaques
  - Slightly pink / swollen → gray, retracted, opalescent with age
- More severe cases: Atrophy (anterior horns of lateral ventricles, cortical atrophy too)

**Microscopy**
- Loss of myelin (perivenous at first, with monocytes / lymphocytes around)
  - Areas of myelin loss **enlarge with time**
- Loss of oligodendroglia (make myelin); ↑ astrocytes & lipid-laden Mφ (foamy – eating myelin)

**Mimics of MS on MRI**
- ADEM (Acute disseminated encephalomyelitis)
- HTN/small vessel dz
- CADASIL
- Sarcoidosis
- Vasculitis
- Migraine
- Aging-related changes
- Organic aciduria
- Histiocytosis
- HTLV-1
- Lyme disease
- Leukodystrophies
- Mitochondrial disease
- Lupus
- Behcet’s disease
- HIV
## Treatment of MS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
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</table>
| Interferon β 1a *(Avonex & Rebif)* | Naturally-occurring cytokine  
• may suppress interferon gamma (proinflammatory cytokine) &  
• block migration of activated T-cells into CNS |
| Interferon β 1b *(Betaseron & Extavia)* | Copolymer of 4 AA that are highly represented in myelin basic protein (major constituent of myelin)  
Maybe an immunological “decoy”?  
• block immune attack on natural myelin (?) or  
• ↑ formation of glatiramer acetate reactive T-cell (Th2 regulatory effect?) |
| Glatiramer acetate *(Copaxone)* | Copolymer of 4 AA that are highly represented in myelin basic protein (major constituent of myelin)  
Maybe an immunological “decoy”?  
• block immune attack on natural myelin (?) or  
• ↑ formation of glatiramer acetate reactive T-cell (Th2 regulatory effect?) |
| Mitoxantrone *(Novatron)* | Type II topoisomerase inhibitor  
• Associated with cardiotoxicity, leukemias (use with caution!) |
| Natalizumab *(Tysabri)* | mAb against adhesion molecule for cell migration across endothelial barriers  
• blocks T and B-cell migration into CNS; maybe Mø too but not PMNs  
• 1/1000 pts → progressive multifocal leukocencephalopathy (PML)  
  • JC virus in brain, immune system can’t respond like it normally does |

- “ABC” drugs (interferons & glatiramer acetate): shown to reduce exacerbation by 1/3  
- Interferon betas: decrease active MRI lesions by 70-80%  

Other treatments:  
- Immunosuppression (azathioprine, methotrexate, cyclophosphamide, IVIG, plasma exchange)  
- Symptomatic therapies (for bladder dysfunction, spasticity, pain, fatigue, depression)

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### Sample case: Optic Neuritis & MS

27 yo Caucasian woman w/ CC double vision; pharyngitis, anorexia, myalgia, rigors →3 days later **unilateral L. visual loss with pain over eyebrow and L. afferent papillary defect (APD – indicates loss of II transmission)**

- **Swinging Flashlight test:** when you shine into affected eye, dilates (both eyes actually)  
  • Helps dx vs MLF lesion (INO), which could also cause blurred vision

- **Optic neuritis** on MRI (enhancement of L. optic nerve); other enhancing lesions too

- **Labs:** negative for ANA (Lupus), SSA, SSB (Sjogren’s), Lyme, ESR nL, ANCA nL (vasculitis), Rheumatoid factor negative, ACE normal (Sarcoid), Glucose / HbA1C nL (diabetes)  
  • Oligocolonal bands present in CSF

**Dx:** optic neuritis with high risk for MS  
- Pts with optic neuritis & normal brain MRI: 25% chance of developing MS in 15 yrs  
- Pts with optic neuritis & one or more brain MRI lesions: 75% chance of developing MS in 15 yrs

**Tx:** Cortocosteroids IV x 5 days, h/a & vision get better

**Course:**  
- 6 mo later: numbness from neck down; ↓ pinprick / vibration on exam & hyperreflexia w/ Babinskis  
- MRI: old lesions became smaller; several new lesions + spinal cord lesion

**Definitive dx:** MS *(RR)*; started on interferon-β (or glatiramer acetate)  
- Flu like side effects; does well for 4 years, then presents with ataxia & dysmetria (tremor) on finger-nose testing  
- New cerebellar peduncle lesion, black holes on MRI, mild brain atrophy  
- Switched to natalizumab mAb infusions
Paraneoplastic Neurological Disorders (PND)

**Mechanisms** (generally speaking)
- immune system attacks cancer → “crossfire” / collateral damage against nervous system
- Secretion of hormones or proteins by tumor → secondary remote effects

**Direct invasion** too (metastasis to brain / SC, etc) – not the subject of this lecture

**Paraneoplastic syndromes**: sx / signs resulting from damage to tissues / organs remote from the site of malignancy
- Cancer calchexia, hypercalcemia, Cushing’s syndrome, Trouseau’s syndrome, etc.
- Associated with secreted substances (e.g. hormones / proteins) from tumor or immune-mediated rxns against tumor

**Epidemiology**
- Symptomatic PND are rare (=0.001% cancer pts)
- Certain conditions have ↑ risk of PND
  - Small cell lung cancer → lambert-Eaton myasthenic syndrome in 3% pts
  - Thymomas → Myasthenia gravis in 15% pts

### Examples of PND by Target

<table>
<thead>
<tr>
<th>CNS</th>
<th>PNS</th>
<th>Neuromuscular junction, muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbic encephalitis</td>
<td>Subacute sensory neuropathy (numbness &amp; tingling, CSF negative, no DM, etc.)</td>
<td>Lambert-Eaton myasthenic syndrome (fatigue, mm weakness; #1 frequent PND)</td>
</tr>
<tr>
<td>Subacute cerebellar degeneration</td>
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</tbody>
</table>

**Limbic Encephalitis**

Features:
- **Subacute cognitive decline** (esp in setting of malignancy)
- EEG, CSF negative
- **Hippocampal abnormalities** on MRI
- Ab against tumors **cross to brain; specific** for hippocampus!

*Sample case: 74 yo man with recent onset cognitive dysfunction; subacute abnormal behavior, speech disturbances*
- EEG normal, CSF cultures, viral PCR (look for HSV encephalitis) normal
- See **lung mass** on CT → **small cell lung cancer**
- MRI: damaged grey / white matter in hippocampus (memory problems)
- Dx: **Limbic encephalitis**

**Subacute Cerebellar Degeneration**

- **Cerebellar signs** (ataxia, dysmetria, gaze-induced nystagmus)
- Associated with **anti-Yo, anti-Hu, anti-CV2 Ab**
- May have normal brain MRI, no detectable tumor on presentation

*Sample case: 36 yo woman w/ 3 mo Hx of diplopia, unsteadiness: ataxia, dysmetria, gaze-induced nystagmus on exam*
- Brain MRI normal, CSF normal, etc.; FDG-PET shows breast cancer
- **Anti-Yo** ab found
**Mechanism of PND**

Mostly from immune-mediated responses against tumor cells

- **Tumor → dendritic cell** recognizes, presents Ag to lymph nodes
- **Immune response:** activation of specific T / B cells, specific CD8+ T-cells produced, specific Ab produced
- **This is all good & normal! Helps keep tumor under control**

In PND:

- **Ab produced** against onconural antigens (common epitopes between tumor & nervous system)
- Can have **Ab against any point** of nervous system (neuronal soma, axon, NMJ, etc)

---

**Paraneoplastic antibodies**

Certain **Ab** have been **well characterized:** produced by **certain tumors** & result in **certain syndromes**

- E.g. **Anti-Hu** (comes from SCLC, produces limbic encephalitis, cerebellar degeneration, encephalomyelitis)
- Others (think PND if you see these): Anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, anti-amphiphysin

If you suspect **PND:** look for **Abs** (ask lab to check for PNDs; they will run whole panel) & search for **mets**

---

**PND Antibody Targets**

- **NMDA receptor** (cognitive dysfunction)
- **voltage-gated Ca channels** (L-E syndrome)
- **voltage-gated K channels** (limbic encephalitis)
- **AChR** (myasthenia gravis)
- **Neuronal AChR** (autonomic neuropathy)

---

**Cancers associated with PND**

- Small cell lung cancer
- Testis tumors
- Ovarian tumors
- **Thymomas** (esp. encephalomyelitis, L-E myasthenia gravis)
- **Breast cancer**

---

**Assessment / management of PND**

Suspect **PND:** pt may or may not have **known history of cancer**

- **PND could be at 1st presentation of cancer!**
- **Look for PND** (Ab; imaging) & **look for cancer** (imaging / Bx)

---

**Treatment of PND**

<table>
<thead>
<tr>
<th>Treatment of...</th>
<th>Via...</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The primary malignancy</strong></td>
<td>Surgical resection/chemotherapy or radiation therapy</td>
</tr>
<tr>
<td><strong>The immune-mediated mechanisms of disease</strong></td>
<td>Steroids, Plasma exchange, IVlg, Immunosupression (e.g. cyclophosphamide), Anti-B cell treatment (e.g. Rituximab)</td>
</tr>
<tr>
<td><strong>The secondary problems</strong></td>
<td>Antiepileptics, cognitive therapy, PT and OT.</td>
</tr>
</tbody>
</table>

*Note the problem: immunosuppression → control of tumor growth!*
Headache: Dangerous Secondary Causes

Introduction

Phenomenology

Cephalalgias: usually episodic pains in the head, face, eyes, ears, nose, mouth, throat, neck, etc.
- Usually divided into several clinical groups (headaches, facial pain, eye pain, etc)
- Lots of overlap between groups
- Use OPQRST to characterize in history

Physiology

Pain in the head: either...

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disease other than headache</td>
<td>Caused by something else</td>
</tr>
<tr>
<td>Migraine, tension-type, cluster...</td>
<td>Meningitis, brain tumor, aneurysm</td>
</tr>
<tr>
<td>Central pain systems</td>
<td>Peripheral pain receptors</td>
</tr>
<tr>
<td>Neurons; Trigeminal nucleus – sensory from head, etc.,</td>
<td>(nociceptors – end organs)</td>
</tr>
<tr>
<td>PAG: relays nociceptive signals; thalamus</td>
<td></td>
</tr>
</tbody>
</table>

The brain parenchyma is generally the only thing that doesn’t hurt in the head
- no pain receptors (nociceptors) on neurons / glia
- central pain centers (5th nucleus, PAG, hypo-/thalamus) are few things in brain that do hurt

Where the head hurts doesn’t correspond in a 1:1 way with where problem is
- pain patterns (see picture): pain can be referred to different areas
- Can’t just use localization of pain to tell you where pathology is

Axiology

Epidemiology: Headaches are COMMON
- #1 neuro sx in primary care; lifetime prevalence 96%
- 50% women, 40% men with disabling headache at some point in time in life
- > 50% have more than 1 type of HA
- 20% of work absenteeism; > 1000 missed workdays per 1000 pop / yr

Most headaches are benign
- 97% episodic (<72 hrs)
- 60-80% tension-type, 10-30% migraine, 1-5% cluster / other “trigeminal autonomic cephalalgias” (TACs)

Diseases causing headaches can KILL

| Arterial dissection | Leading IDable cause of stroke in young adults (18-44 yrs) |
| Giant cell arteritis | Most common vasculitis; permanent blindness in 30-60% untreated |
| Dural thrombosis | Intracerebral hemorrhage in young women, sometimes just post-partum |
| SAH from intercranial aneurysms | 22k/yr in US, 50% dead / seriously disabled |
Clinical approach

100k+ causes of headache - what are dangerous headaches?

SNOOP (the patient at greater risk for dangerous headache)
- **Systemic disease** (malignancy, AIDS, systemic symptoms / signs)
- **Neurologic symptoms / signs** (especially **diplopia**, **confusion**, **optic nerve edema**; anything except visual aura)
- **Onset sudden** (thunderclap HA, time to peak ≤ 5 min)
- **Older** (>50 yrs)
- **Pattern change**

5 rules of thumb
- **Persistent** headaches (>72h) may be bad
- **Abrupt-onset** headaches are **often** bad
- H/A with fever are **usually** bad (intercranial infection, etc)
- H/A with diplopia are **almost always** bad
- H/A with change in mental status are **always** bad

**Evaluation of Headache**

**Clinical**
- **Pattern**: Episodic, Persistent, Punctuated, New-First
- **Timing**: Abrupt v. Gradual Onset; By Duration
- **Site**: Head, Face, Eye, Ear, Tooth, Jaw, Throat, Neck
- **Special Features**: coital, postural, cough, diurnal

**Etiopathogenetic**
- **Etiology**: ‘Primary’ v. ‘Secondary’; ‘Dangerous’ v. ‘Not’
- **Pathophysiology**: Neural, Vascular, Inflammatory, Serotonergic, Muscle-Tension, Rebound... other???

**Headache + DIPLOPIA ≠ migraine!** Just about always bad!
- Elevated ICP
- Aneurysms
- Pituitary apoplexy
- Cavernous sinus infections
- Meningitis (esp. Tb, crypto)
- Brainstem encephalitis
- Giant cell arteritis
- Brainstem stroke/hemorrhage

Brain tumors & headaches
- At Dx, 31% brain tumor pts have headache, but only 8% have isolated headache (seizure, etc.)
- “Classic” morning (↑ ICP) H/A is uncommon!
- ↑ ICP is the big problem, not H/A
- Even in pts with high risk (systemic cancer patients) with H/A: only 32% have mets
  - Lesion predictors: new pattern or new H/A < 10 wks, Pain not “tension-type”, Vomiting
- **Exception**: Kids with occipital H/A – worry about posterior fossa tumors

What can’t we miss? Things that are threatening, time-dependent, treatable, and tricky!

DANGEROUS HEADACHES

DATA C²A²N save lives
1. **Dissection** (carotid or vertebral)
2. **Arteritis** (giant cell)
3. **Thrombosis** (dural venous)
4. **Aneurysm** (leak or expansion)
5. **Carbon monoxide & Colloid cyst**
6. **Angle closure & Angina**
7. **Norepi neoplasm** (pheochromocytoma)

Note: DAT are chronic, ACAN are episodic
Dissection of carotid / vertebral arteries
- Any age, mostly < 65 yo (younger!); 50% with h/o trauma (fall, minor MVA, etc.)

Clinical features
- Sx: Frontal headache (C>V) or neck pain (V>C)
- Carotid: Horner’s syndrome (= 50% - sympathetic on carotid), occasional CN 9-12 palsy
- Vertebral: no findings but TIAs (dizzy – ischemic cerebellum) & pain (= 50%)

PGx: 50% have stroke < 90 days without Rx
Dx: angiography (CTA / MRA / DSA)
Rx: anticoagulation (counterintuitive: unlike Ao Dxn; end-process is thrombus → stroke here)

Pictures:
Left: false lumen; occluded blood vessel above
Right: MRI T1
- (bright: fat, melanin, contrast, extravasated blood)
- T1 fat-saturated axial images – remove other stuff, see right vertebral dissection as bright crescent in wall of vessel

Arteritis (Giant Cell, a.k.a. temporal arteritis)
- Age > 50 years (older!), most > 65

Clinical findings (no pt has all of these!)
- Gradual onset H/A, scalp / TA tender
- 30-40% fatigue, fever, wt loss, arthralgias, myalgias
- Jaw claudication (34%, very specific), transient monocular blindness

PGx: 30-60% risk permanent visual loss
- 10-30% risk of 2nd eye blindness < 3 wks if untreated
Dx: ESR / CRP, temporal artery biopsy
Rx: corticosteroids (oral / IV if neuro sx)

Thrombosis of dural venous sinuses
- Any age patient

Clinical findings
- Gradual / abrupt onset, worse in AM / lying flat, ± pulsatile tinnitus
- Loss of venous pulsations (↑ venous pressure) ± papilledema (>40%)
- Hypercoagulable (>1/3) or postpartum (12%)

PGx: >50% stroke < 1 month w/o Rx
Dx: LP, venography (CTV-DSA), coagulation studies
- MRV is not adequate (MR – venogram – see pic)
Rx: Anticoagulation
**Aneurysm** (leak [sentinel bleed] or expansion)

- Any age, more common > 40 yo

**Clinical findings**

- Rapid onset (<30m, usually < 5m) after exertion / Valsalva
- ± neck stiffness, photophobia
- Diplopia / 3rd n. palsy
- Often no neuro findings (especially A-com)

**Most common sites**: Pcom, PCA, basilar, SCA, ICA

- A-COM RUPTURE CAN BE ASYMPTOMATIC

**PGx**: > 20% mortality in 1st 2 weeks

**Dx**: CT (good for blood, bone, bullets) then LP (look for blood) then angiography (MRA-CTA-DSA)

**Rx**: Surgical clip or endovascular occlusion

---

**Carbon Monoxide** (intermittent exposure)

- Any age, #1 cause of poisoning death in US

**Clinical findings**

- Linked to location (goes away on vacation)
- *Car, furnace, heater, gas stove* – poor ventilation
- Headache plus… dizzy/lightheaded (80%), lethargic/confused
- Co-habitants symptomatic (incl. pets)

**PGx**: Death with no Rx

**Dx**: CO detectors (home), COHb levels (blood)

**Rx**: Avoid exposure (fix appliances, ventilate)

---

**Colloid Cyst of 3rd ventricle**

- Any age, peak in middle age (40 ± 15 yo)

**Clinical findings**

- Intermittent, severe, abrupt-onset, brief H/As
- Usually bifrontal, can be relieved by lying down (ball valve effect)
  - Intermittent obstructive hydrocephalus
- Syncope or brief loss of consciousness often

**PGx**: Sudden death / herniation w/o Rx

**Dx**: CT / MRI

**Rx**: Surgical resection
Angle closure glaucoma (episodic → permanent)
- Any age; more common > 40, Eskimo, Chinese

Clinical findings
- Brought on by darkness (e.g. theatre)
- Can be asx if blurred vision in one eye only
- Red eye common; can miss if it resolves

PGx: blindness w/o Rx
Dx: gonioscopy
Rx: iridotomy

Angina
- > 40, vasculopathic risk factors (DM/HTN/chol/smoking)

Clinical findings
- Episodic, often exercise-induced
- Can be severe (10/10)
- Usually bifrontal / vertex (referred chest pain!)
- May be no associated chest pain!

PGx: MI/death w/o Rx
Dx: EKG, stress test, coronary angiography
Rx: CABG

Norepinephrine neoplasm (pheochromocytoma)
- Any age, peak middle age (40 ± 15 yo)

Clinical findings
- Episodic headaches, often abrupt onset
- Brief (minutes) to long (hours/days)
- Palpations, sweating, anxiety, dizziness
- Unexplained HTN & tremors

PGx: MI, stroke, death
Dx: Plasma free metanephrines
Rx: Surgical resection

Diagnostic Note: DATA CAN...

Note that ONLY THE COLLOID CYST is excluded by normal CT or standard unenhanced MRI
- Others are not excluded (normal tests are falsely reassuring)
**Extras: the “I’s” have it** (things that present to ED instead of primary care)

<table>
<thead>
<tr>
<th>Infections</th>
<th>ICP (H^3)</th>
<th>Infarcted Pituitary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cavernous sinus +/- sphenoid sinus infection</td>
<td>1. Hydrocephalus</td>
<td>(pituitary apoplexy)</td>
</tr>
<tr>
<td>2. Orbital cellulitis +/- ethmoid sinusitis</td>
<td>2. High altitude</td>
<td></td>
</tr>
<tr>
<td>3. Meningitis +/- mastoiditis</td>
<td>3. Hypertension (arterial or venous, pregnant [eclampsia] or not)</td>
<td></td>
</tr>
<tr>
<td>4. Encephalitis (esp. Herpes/Listeria): Treatment often not applied! Could be Rx’d but coverage not adequate!</td>
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### Headaches: Clinical Approach

Of those you’ll see in practice:

- **Most headaches are episodic**
  - Most of these are **migraines** (OK)
  - Watch out for rare bad actors ("ACAN" esp. aneurysms)

- **Less commonly, continuous headaches**
  - Most of these are BAD (meningitis, “DAT”)
  - Some can be OK (med overuse)

**Episodic (<24h)**
- Aneurysm* (leak)
- CO*
- Colloid cyst*
- Angle closure
- Angina
- Norepi neoplasm (phea)

**Continuous (>24-72h)**
- Dissection (C/V)*
- Arteritis (GCA)
- Thrombosis (DVST)
- Infections
- ICP (H^3)
- Infarcted pituitary (pituitary apoplexy)

* = can cross the “time divide”

---

### Benign Headaches

- Often misdiagnosed: some things aren’t actually common causes of headache
  - E.g. sinus headache, HTN, arthritis, flu/viral, TMJ syndrome, eyestrain, depression
- Overdiagnosed: migraine, tension headache
- Underdiagnosed: migraine, cluster, med overuse

---

### Medication Overuse Headaches (MOH)

- “around the clock” headache with Q4-6h med self-dosing; severe H/A w/o meds
- Daily, worse in AM (haven’t had meds), severity ↑ with time
  - Analgesic rebound cycle kicks in, eventually can’t get same effect with meds
  - Can even have basal level of pain develop

**Dx:** clinical trend, polypharmacy, exclude original pain cause!
**Rx:** Detox over several weeks
Primary Headaches (Migraine, Cluster, Tension)

<table>
<thead>
<tr>
<th>Tension</th>
<th>Cluster</th>
<th>Migraine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common, least disabling</td>
<td>Rare but extremely disabling</td>
<td>Highest disease burden (prevalence x disability)</td>
</tr>
</tbody>
</table>

Primary headaches: idiopathic syndromes
- Disorders of brain function rather than brain pathology – neurochemical problem, not lesion
- Common: tension, migraine, cluster (trigeminal autonomic cephalalgia = TAC family)
- More rare: primary stabbing, hypnic (alarm clock), cough, exertional, sexual activity – related, 1st thunderclap, etc.
- Continuous: hemicranias continua, new daily persistent headache
- “Benign” but cost a lot of money and cause a lot of suffering

Headache Pattern:
- Acute recurring is reassuring
  - Can’t tell if it’s the 1st headache (1st or worst – worry!)
- Chronic progressive is worrisome!

Migraine

Epidemiology:
- #1 referral to neurologists: prevalence: more than (asthma+diabetes) or (alz+stroke+Parkinson+epilepsy+MS) combined!
  - High prevalence of bed-ridden days / yr; $13-20B/yr in lost revenue, as disabling as quadriplegia
  - Lots of comorbidities: depression, stroke, MI, SLE, tons more; may escalate if untreated
- 13% adult pop at any given time; 43% F, 18% M lifetime
  - Up to 3.2% kids by age 7, 11% by age 15
- Adults: 3:1 F:M (prepubertal ≈ 1:1 F:M); 90% have first H/A by age 40
- Peak onset: 12-14 yo; peak prevalence: 25-55 yo
- Misdiagnosed & mismanaged!

Pearls
1. In a primary care setting, 90%+ of patients with chief complaint of intermittent headache have migraine
  - Prevalent & severe enough to make an appointment!
2. Migraine is actual disease responsible for almost all “sinus” headaches
3. Migraine is most common cause of thunderclap headache (way more prevalent than aneurysm)

What is it?
A syndrome: a chronic disorder of hyperexictable brain function, the primary Sx are recurring “sick” headaches
- Chronic disease with episodic manifestations
- Think of it as “asthma of the brain”
  - Preventative, maintenance care plus acute management

SULTANS
5+ headaches, 4-72 hrs with...

- Severity - Moderate or worse
- Unilateral
- Throbbing
- Activity causes worsening
- Nausea
- Sensitivity to light / sound

Clinical practice: 2/3 of nausea, light sensitivity, exacerbation with activity will be migraine
**Course & Model of a Migraine Attack**

**Course:**
- some kind of dopamine signaling involved before aura (pts can tell that they’re going to get it)
- Headache follows, series of attacks
- Hypersensitive on the way down; postdrome (like hangover) at end

**Model:** we know that there are triggers; H/A produce certain symptoms
- How the headache’s generated is still a bit of a mystery – “black box”

---

**Pathophysiology**

**Vascular theory** dominated for a long time
- *Spasm → aura; dilation → pain;* so tx with vasoconstrictors (triptans / ergotamines)
- Probably not true (constriction/dilation happens all the time, no measurable constraction / excitation, triptans / ergotamines work on neurons; now have drugs that stop migraine w/o affecting vasculature)

*Animal models:* used now to mimic and study

**Human studies**
- Interictal studies: epidemiology, genetics (between migraines)
- Ictal studies: harder, try to catch during attack
  - can do all kinds of studies during attack

**Headache Generator: Trigeminocervical (TGC) complex**
- Efferent & afferent loops, blood flow to brainstem involved
- Reflex innervations between TGC & areas of brain responsible for:
  - nausea / vomiting
  - response to noxious stimuli (photophobia, phonophobia, etc)

**Hyperexcitable brain:** migraine sufferers ↑ carsickness, chemical induced H/A, etc.

**Genetics:**
- FHx confers 2-3x risk (1 parent: 45% risk, 2 parents: 70%)
- Caucasian > AA; Lower SES doubles risk vs highest SES
- Polygenic; single gene mutations for migraine syndromes only
  - Neuroexcitatory channelopathies, others

---

**Aura**
- Transient, reversible, focal neurological deficits related to migraine
  - (not seizure, hypoglycemia, TIA, etc)
- Usually stereotyped for single patient
  - Visual / scintillating scotoma
  - Unilateral sensory or dysphasia
- Gradual, creeping over 5 min, ≤ 60m
- Single individual can have migraine w/o aura, migraine with aura, aura w/o migraine
- Only ¼ migraneurs ever have aura

**Cortical Spreading Depression:** the mechanism of aura
- Electrical phenomenon – *spread of electrical*, then *blood flow* disturbance
- Marches across brain at 2-3mm/min (reflected in size of spread of aura)
- Easiest to induce in occipital lobe (visual); burn out at central sulcus (usually no motor sx)
  - Opens BBB, activates trigeminovascular system in models: does it cause migraine?
  - Can we stop migraines by stopping CSD?

**Gene mutations:** hyperexcitable channelopathies → ↑ CSD → ↑ auras → ↑ headaches
Pathogenesis

Initiation:
- **Triggers** act on hyperexcitable brain
- Cortical spreading depression (can perceive as aura)
- Activates trigemino-cervico-vascular system and brainstem
  - Sterile neurogenic inflammation (TGC neurons act on meningeal blood vessels → inflammation)
  - Mast cells involved, CGRP, substance P, kinins released
  - Neurons get revved up further → feedback loop

Peripheral sensitization:
- Trigeminal nociceptors → irritated by inflammation
- Send pain responses to brainstem trigeminal nucleus caudalis (TNC)
  - TNC signals thalamus, cortex (pain perceived)
  - Over time, trigeminal system becomes peripherally sensitized (pounding, worse when bending)
    - **Pounding**: blood vessel nociceptors now sensitized, responding to normally non-noxious stimuli (pulse = throbbing, distension on bending)

Central sensitization
- Prolonged sensitization; TNC starts firing regardless of input
- Cutaneous allodynia (everything hurts)

Spread: Other brainstem centers activated (nausea, GI stasis, photo/phonophobia)

Sensitization hypothesis
- Migraine is a process of sequential sensitization of neurons from periphery to CNS

<table>
<thead>
<tr>
<th>1(^\circ) Nociceptor (TG neuron)</th>
<th>2(^\circ) (TNC) neuron</th>
<th>3(^\circ) (Thalamic) neuron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation</td>
<td>Nociception with minimal or no input</td>
<td>Enlarged receptive fields</td>
</tr>
<tr>
<td>Throbbing</td>
<td>Cutaneous allodynia (non-painful stimuli become painful)</td>
<td>Spread of pain and alldynia</td>
</tr>
<tr>
<td>pain, eye movement pain,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pain on bending over</td>
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</tr>
</tbody>
</table>

Headache imaging
- Trigeminal nucleus (dorsolateral pons), PAG (midbrain) light up

Triggers
- Common: menstruation, alcohol, disrupted sleep, change in stress (well documented)
- More “aggravators” than “triggers” (often add up)
  - A few can be reliable in given individuals (ID & avoid – keep a diary)
  - Most are low potency / loosely correlated / only responsible for small % of migraines
- Could give pretty much anybody a migraine with enough stress
  - Some people have lower thresholds / higher tendency towards migraine
  - To determine if Rx needed, ask: would you take a pill every day to prevent these?
    - Meds: raise threshold
    - Behavior: lower / avoid triggers (counseling, etc.)
Treatment of Migraine

NOTE: Pain doesn’t show up until well into the process!

- Prevention is crucial! Avoid triggers if possible
  - regular sleep, don’t skip meals, don’t get dehydrated, exercise, weight control, stress management
- Give acute treatment early (stop the process!)
- Need to use preventative meds for > 1 mo
- Use migraine cocktails to hit thalamus, other areas of these loops

Preventative meds taken daily: the three “antis” (all work by ↑ threshold)
  - Antihypertensive (β-blockers, others)
  - Antidepressants (TCAs, venlafaxine)
  - Anticonvulsants (topiramate, valproate)

Triptans

5HT agonists (serotonin = 5HT, works but not well tolerated)
  - Designer drugs aimed specifically at migraine
Block / reverse vasodilation but also block neurogenic inflammation (nerve terminals, centrally too?)
Most effective migraine meds available; very safe (unless vasculopath)

CGRP: Calcitonin gene related peptide: vasodilator, mast cell activator, released from trigem nerve terminals
  - Can block it (triptans or experimental agents) & treat migraine w/o affecting vessels!

Halting an aura
  - Most drugs will be too slow
  - Unpublished: try to zap brain with transcranial magnetic stimulation – blast brain to disrupt CSD!

Cluster Headache

Rapid (<15m onset), horrible, acute, terrible pain syndromes
Shorter than migraines (< 90m)
Need to rule out underlying cause (pituitary, carotid, post. fossa lesions can mimic)
  - Get MRI/A

Timing:
  - Multiple attacks in single day (up to 8)
  - Attack frequency: builds up over few days, stays for few weeks, fades / remits (“cluster period”)
  - Circadian & circannual (same time of day, same season of year)
  - Can become chronic over time w/o remissions

Pathophysiology: hypothalamus (ipsi post inf hypothal) may be generator
  - Area tied to biological clock and autonomic nervous system!
  - Also: trigeminovascular / CGRP (like migraine), cranial parasymps, ICA swells → sympathetic outflow affected → partial Horner’s

Features: AUTONOMIC ACTIVITY
  - Lacrimation (90%), conjunctival injection
  - nasal stuffiness, rhinorrhea, ptosis, eyelid edema
  - ± nausea, phono/photophobia, v. rare auras

Epidemiology of cluster headaches
  - 4:1 M:F, onset teens to 30s
  - Prevalence 0.1%
  - Smoking is risk factor
  - Get individual H/A w/in 3hrs of EtOH consumption during cluster period
**Presentation:** the “suicide headache”

- REALLY BAD. Migraine sufferers sit in bed, these people are hitting themselves, rocking back and forth, etc.
- Screen all pts for suicidal behaviors! Excruciating pain + sympathetic arousal → can do stupid things

**Treatment:**

- Acute: Oxygen, rapid-acting 5HT₁ agonists (nasal / injectable)
- Preventative: mostly bad studies; verapamil, anticonvulsants, lithium, melatonin; steroids?
- Invasive procedures if really bad
  - trigeminal nerve / ganglion destruction, deep brain stimulation, occipital nerve stimulation

---

**Tension-type headaches**

**High prevalence** (80% lifetime)

**Recurring primary headache** defined by relative lack of other features

- 10+ episodes; last 30min-7days
- 2/4 of pressing/tightening (non-pulsating) quality, mild/moderate intensity, not aggravated by physical activity
- No nausea/vomiting, can have either photo or phonophobia but not both
- Not attributed to another disorder

**Features:**

- NO MEASURABLE MUSCLE TENSION (tension-type is misnomer)
- Bilateral, pressing, rarely activity sensitive
- Not usually disabling

Rx: NSAIDs, acetaminophen, etc. are usually effective

**Episodic H/A can become CHRONIC or CONTINUOUS**

Attacks of pain → more frequent

- Chronic daily headache (Migraine, tension: pain becomes constant with exacerbations superimposed)
  - CDH: H/A > 15days/month
- Cluster: remissions can stop!

May represent progression of accumulating brain pathology

- “burn out” pain systems, end up with baseline pain
- Can represent medication overuse (treat, but may still have chronic daily headache!)

---

**Recap:** the 3 primary headaches (from notes)

Idiopathic syndromes of recurring, stereotyped cranial pain

<table>
<thead>
<tr>
<th>Migraine (remember SULTANS)</th>
<th>Cluster</th>
<th>Tension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest disease burden (prevalence x disability)</td>
<td>Rare but terribly severe</td>
<td>Most common, least disabling</td>
</tr>
<tr>
<td>Pain, polymodal hypersensitivity, nausea</td>
<td>Sudden severe unilateral pain, peculiar circadian and circannual characteristics, prominent autonomic involvement</td>
<td>Usually just pain</td>
</tr>
<tr>
<td>Hypersensitive brain, CSD, brainstem generator (TNC, PAG), neurogenic inflammation, trigeminal-vascular system</td>
<td>Posterior-inferior hypothalamus</td>
<td>Pathophysiology poorly understood</td>
</tr>
<tr>
<td>Serotonin, CGRP involved</td>
<td>VIP (vasointestinal peptide) involved</td>
<td></td>
</tr>
</tbody>
</table>

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Vertigo and the Pathophysiology of Bedside Vestibular Eye Signs

Normal Vestibular Function

Vestibular system: the “sixth sense”
- Balance organ in inner ear + connection in brainstem & cerebellum
- Substrate for “sixth sense” of balance; usually operates quietly in background
- Sends signals to cerebrum & SC for walking and EOMs (to keep vision stable)

Goals of vestibular system
- Keep us (un)aware of which way is up
- Keep us from crumpling to the ground
- Keep vision steady when moving head

VOR = vestibular-ocular reflex
- Connection between balance organs & eye movement structures
- Keeps vision steady as we move: instantaneously rolls eyes in direction opposite any head movement

If you lose VOR: head movement makes visible world appear to move
- Use cortical vision processing to track movement, keep eyes on target during slow head movements
- Vision takes ~100ms to process (too slow to keep up with rapid, transient head movements during walking / jogging)

Anatomy of vestibular section

Inner ear: labyrinth = balance organ (semi-circular canals + utricle / saccule)

<table>
<thead>
<tr>
<th>Organ</th>
<th>Measures</th>
<th>Subserves</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semicircular canals x 3</td>
<td>angular rotations of head</td>
<td>A-VOR (angular VOR)</td>
</tr>
<tr>
<td>Utricle / saccule (otolith)</td>
<td>linear accelerations of head</td>
<td>L-VOR (linear VOR)</td>
</tr>
</tbody>
</table>

Labyrinth sits in petrous temporal bone, 8th n. exits to brainstem (8th n. nuclei)

- Goes to vestibular nuclei in brainstem (pons), then connected to:
  - Vestibulocerebellum (nearby anatomically)
    o The inferior part: has floccus, parafloccus, nodulus
  - Bidirectional connections: cerebellum & vestibular nuclei;
    o also direct connections from labyrinth to cerebellum
      (bypassing 8th n nucleus)
  - Gaze-holding center in brainstem is nearby too
  - Note: 8th n enter near low pons but 8th n nuclei are long
    o Extend into medulla; can be damaged by acute stroke of the lateral medulla

Vestibular nuclei (8th) connected to oculomotor nuclei (midbrain)
- 3rd & 4th – vertical/torsional
- 6th and 3rd – horizontal

Remember: (2-2-4-4)
- CN 3,4 in midbrain
- CN 6 in pons
How does aVOR work?

- Turning towards the canal(s) is ON
- Tonic firing at rest; rate changes with head motion
- Neural signal stimulates eyes to move in plane of canal (VOR) opposite head rotation

Towards is “ON”

- Head rotation = canal rotation (part of skull)
- Endolymph usually doesn’t move (inertia)
- “Disconnect” between endolymph & canal motion causes firing (hair cells displaced, stimulated)
- Endolymph eventually catches up, signal off again

Canal planes

- Anterior canal
- Posterior canal
- Horizontal canal (30° displacement / tilted up but just think of it as horizontal)

Tonic firing changes with rotation

- Turning head to right: R 8th n firing rate ↑; L. 8th n. firing rate normal
- Cerebrum interprets the asymmetry in firing as normal head rotation

So what needs to happen?

- Need to activate the correct oculomotor signals to produce the correct movements!
- Just think of how eyes need to move and figure out which muscles will be activated

Testing the VOR: Head Impulse Test

- HIT = bedside test of vestibular function
- Pt: look at doc’s nose; rapid head rotation to elicit a VOR response (firing rate)
  - If VOR is intact, eyes stay on target despite rotation
  - If NOT intact, they slip off the target (go with head; see refixation saccade)
Otolith-Ocular Reflexes

Vestibular system: designed to control vertical & torsional eye position in response to lateral head tilts
- Used to be lateral-eyed animals (tilting head pointed one eye at floor), now our eyes point straight ahead

Vestigial otolith-ocular reflexes are suppressed by the “modern” cerebellum & brainstem (lateral medulla / midbrain)
- Come back out in disease states! See later part

Gaze-holding

Natural resting position of eyeballs is straight out
- Need to apply EOM force to sustain eyes in eccentric position
- Force generated by gaze-holding center in medulla
  - calibrated by cerebellum
  - different neurons calibrate gaze-holding than those cerebellar neurons calibrating VOR, but both groups are right next to each other in the vestibulocerebellum

Abnormal Vestibular Function

Key idea: how can we tell benign from bad?

What happens when balance system is broken?

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness/vertigo, motion</td>
<td>Abnormal VOR response</td>
</tr>
<tr>
<td>Intolerance, nausea/vomit</td>
<td>Nystagmus +/- ocular misalignment</td>
</tr>
<tr>
<td>Oscillopsia (bouncing/jumping vision) +/- Diplopia</td>
<td>Ataxic gait and tendency to fall (lateropulsion)</td>
</tr>
<tr>
<td>Unsteady walking and standing balance</td>
<td></td>
</tr>
</tbody>
</table>

Dizziness

What it feels like when balance system is broken (ears telling you one thing, rest of brain something else)

Four “types” of dizziness (don’t apply well clinically)
- Vertigo (spinning / motion)
- Presyncope (near faint)

Disequilibrium (unsteady walking)
Other vague lightheadedness (nonspecific)

Causes of dizziness

<table>
<thead>
<tr>
<th>“Non-vestibular”</th>
<th>“Vestibular” (less common)</th>
</tr>
</thead>
<tbody>
<tr>
<td>orthostatic dizziness (esp. anti-HTN, volume loss)</td>
<td>BPPV (benign paroxysmal positioning vertigo)</td>
</tr>
<tr>
<td>cardiac dizziness (esp. arrhythmias, vasovagal)</td>
<td>migraine &amp; Meniere disease</td>
</tr>
<tr>
<td>intoxication (esp. EtOH, anticonvulsants, illicits)</td>
<td>bilateral vestibulopathy (idiopathic/hereditary, ototoxic)</td>
</tr>
<tr>
<td>post-concussive syndrome (after head injury)</td>
<td>vestibular neuritis (a.k.a. labyrinthitis, “APV”)</td>
</tr>
<tr>
<td>presbylibrium (a.k.a. multisensory dizziness)</td>
<td>brainstem/cerebellar stroke &amp; transient ischemic attack</td>
</tr>
<tr>
<td>panic attack +/- hyperventilation</td>
<td>other central lesions (MS, cerebellar degeneration)</td>
</tr>
</tbody>
</table>

Epidemiology

- Common (one of top 10 complaints in outpatients: 25%; >50% elderly)
- Tricky (DDx complex, H&P confusing)
- High-stakes (rarely serious in OPD, but up to 25% pts > 50yo in new, isolated vertigo have cerebellar stroke)
Vertigo
- **Hallucination** of (angular) motion when there is none
- **Head is not moving, but you feel like it is**
- Can be described as **spinning**, **rocking**, **swaying** (e.g. like a pendulum), etc.
- Implies **asymmetry** (e.g. right vs left) in vestibular inputs (can be CNS or PNS)

Nystagmus

<table>
<thead>
<tr>
<th>Pendular nystagmus (slow-slow type, rare)</th>
<th>Jerk nystagmus (slow-fast type, rare in general pop; common in dizzy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Associated sx: usually <strong>oscillopsia</strong></td>
<td>• Associated sx: usually <strong>dizziness / balance probs</strong></td>
</tr>
<tr>
<td>• Usually <strong>brainstem lesions</strong> (MS/stroke)</td>
<td>• Results from <strong>vestibular lesions</strong> (peripheral or central) or <strong>gaze-holding deficits</strong> (central)</td>
</tr>
<tr>
<td>• Can be associated with <strong>jaw/palate motion</strong></td>
<td></td>
</tr>
</tbody>
</table>

Jerk nystagmus (nystagmus: from Gr. Nystagmos, drowsiness – like head nodding when dozing off)
- This is more common; rest of discussion focuses on this one

Vestibular / spontaneous nystagmus
- Lesion-related asymmetry in vestibular system produces **spontaneous eye jerking**
- Sslow movement in one direction (from asymmetry) then **jerk back** ("quick phase correction") the other way
  - Slow phase = pathologic manifestation of vestibular asymmetry (drives eyes like normal VOR)
  - Quick phase = same as normal voluntary saccades (cerebrum wants to “reset” to straight ahead)
- By convention, nystagmus is **named** for quick phase direction

Failure of gaze-holding mechanism
- Produces eye jerking with **sustained gaze**
- Slow movement in towards the natural eye position with a **jerk back** (quick-phase correction) the other way
  - Slow phase: gaze holding failure (medulla’s gaze holding center or cerebellar calibration)
  - Quick phase: reset using saccade machinery (cerebrum wants to look at something!)
- Nystagmus still **named** for quick phase direction

<table>
<thead>
<tr>
<th>Vestibular / spontaneous</th>
<th>Gaze-holding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion</td>
<td>Tonic asymmetric activation of vestibular signals</td>
</tr>
<tr>
<td>Eyes drift (slow phase) because...</td>
<td>VOR (e.g. R HC &gt; L HC, head thinks it’s turning to right, VOR turns eye to left)</td>
</tr>
<tr>
<td>Eyes correct (quick phase)</td>
<td>Saccade machinery (cerebrum wants to be looking straight ahead)</td>
</tr>
<tr>
<td>See nystagmus</td>
<td>Looking straight ahead</td>
</tr>
</tbody>
</table>

**Clinical Approach**

Textbook approach not good (vertigo = vestibular, send to ENT, presyncope – CV, send to cardio, etc.)
Timing approach (how long did it last) – hard; can use clinically.

Neuritis vs Stroke
- High stakes (35% strokes / TIAs missed in ED dizzy pts, vs 4% those with motor sx)
- Probably missing 35k/yr dizzy strokes in ED

“Acute Vestibular Syndrome”: clinical presentation of pts with either **vestibular neuritis** or **stroke**
- Sick, dizzy, puking, nystagmus
- Is it **vestibular neuritis** (peripheral) or **stroke** (central)?
**Vestibular neuritis**: vestibular nerve affected; **labyrinthitis**: labyrinth affected

- Clinically: usually can’t distinguish vestibular neuritis from labyrinthitis
- Either see stroke on MRI or we think it’s something more peripherally (one of these two)

**Strokes**:
- **Brainstem** (eg lateral medulla) strokes
- **Cerebellar stroke** (e.g. PICA; can swell up, crush brainstem, etc.)
- Lesions in **any of these locations** (vestibulocerebellum, vestibular nuclei, 8th n) produce **similar symptoms** (acute vestibular syndrome)
  - All close together too!
- **AICA** or **PICA** are generally involved (lateral brainstem and/or cerebellar infarcts)

---

**So how can we tell these things apart?**

<table>
<thead>
<tr>
<th>Symptoms can give a clue</th>
<th>Vestibular neuritis</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger</td>
<td>Worse if moves</td>
<td></td>
</tr>
<tr>
<td>Duration</td>
<td>Days – wks</td>
<td></td>
</tr>
<tr>
<td>N/V</td>
<td>Prominent nausea / vomiting</td>
<td></td>
</tr>
<tr>
<td>Auditory</td>
<td>± HL/tinnitus</td>
<td></td>
</tr>
<tr>
<td>Neuro</td>
<td>Mild unsteadiness</td>
<td>Severe unsteadiness</td>
</tr>
<tr>
<td>PE</td>
<td>Unidirectional nystagmus HIT abnormal</td>
<td>± skew, directional change nystagmus HIT normal</td>
</tr>
<tr>
<td>Onset</td>
<td>Monophasic</td>
<td>Pain nausea/vomiting &gt; dizziness</td>
</tr>
</tbody>
</table>

---

**The “Eyes” have it**

3 vestibulo-ocular signs (distinguish “peripheral” (neuritis) from “central” (stroke) causes of acute vestibular syndrome)

<table>
<thead>
<tr>
<th>Vestibular neuritis</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head impulse test</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Skew deviation</td>
<td>Absent</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Direction-fixed, horizontal</td>
</tr>
<tr>
<td></td>
<td>Vertical, torsional or with directional change</td>
</tr>
</tbody>
</table>

**Head Impulse Test**

If VOR intact, then eyes stay on target; if not slip off and see correction

- **Vestibular neuritis**: pathway interrupted; response abnormal
- **Cerebellar stroke**: pathway intact (skips cerebellum), response normal
  - **Brainstem stroke**: abnormal HIT but would see other sx too

Remember to be unpredictable during this test (brainstem can figure out what’s up and start saccading ahead of time; sign will diminish)
Skew Deviation

- Remember that vestigial otolith-ocular reflexes are suppressed by “modern”:
  - cerebellum &
  - brainstem (lateral medulla & midbrain)

If you damage the cerebellum or brainstem, vestigial reflexes take over & cause skew deviation
- eyes misaligned vertically
- Test: cover eye, uncover: positive if eye comes in & up (was down & out)

Nystagmus

3 types of jerk nystagmus relevant here:

<table>
<thead>
<tr>
<th>Nystagmus:</th>
<th>Spontaneous vestibular</th>
<th>Gaze-holding</th>
<th>Mixed vestibular / gaze-holding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Damage:</td>
<td>Unilateral vestibular</td>
<td>Bilateral or unilateral gaze-holding</td>
<td>Damage to both pathways</td>
</tr>
</tbody>
</table>

Spontaneous Vestibular Nystagmus

Can be caused by: (usually PERIPHERAL, e.g. neuritis)
- medial cerebellar stroke
- lateral pontine stroke
- vestibular neuritis

Characteristics
- Persistently present (incl. look straight ahead)
- Horizontal > torsional
- Damps when looking towards slow phase & vice-versa
  - “Alexander’s law” – worse if look to fast phase
- Never changes direction (always leftward, never rightward, or vice-versa.)

Why worse if looking to fast phase (Alexander’s Law)?
Left-beating as example:
- Lesion always says “look right slowly”
- If doctor / cerebrum says “look right”, everybody’s in agreement: look right
- If doctor / cerebrum says “look straight”, there’s a mild conflict (lesion wants to look right) – mild nystagmus
- If doctor / cerebrum says “look left”, there’s a big conflict (lesion really wants to look right) – big nystagmus

Gaze-holding Nystagmus

Can be caused by: (ALWAYS CENTRAL)
- Lateral cerebellar stroke or cerebellar degeneration
- medial medulla stroke
- other damage to gaze-holding structures
- note: NOT VESTIBULAR in nature

Characteristics
- Absent when looking straight ahead
- Horizontal
- Worse when looking laterally (eye eccentric)
  - Eye drifting back to middle
- Changes direction (beats left looking left, right looking right)
- Note that cerebellum normally calibrates EOM force in gaze holding, so see this if cerebellum damaged
Mixed Vestibular / Gaze-holding Nystagmus

- Can be tricky: may present as if it were vestibular

Can be caused by: (CENTRAL)

- Med/lateral cerebellar stroke WITH
- Med/lateral medullary stroke

Features: mixture of vestibular & gaze-holding
- KEY FEATURE: CHANGES DIRECTION
  (if you look away from straight-ahead beating direction)

Clinical take-home message

If you see acute vestibular syndrome; check those three subtle eye signs

“Safe to Go” Triad of Subtle Eye Signs (pt OK if all 3 true, probably vestibular neuritis or something peripheral)

1. Direction-fixed, horizontal nystagmus
   a. not vertical or torsional
   b. obeys Alexander’s law (worse in direction of fast phase, better in direction of slow phase)
   c. no direction change in different gaze positions
2. Normal vertical misalignment (i.e., no skew)
3. Impaired VOR function (ABNORMAL h-HIT)
Gait Disorders & Ataxia

I have no idea what was going on in this lecture. Good luck.

Gait is like handwriting: everybody has a unique gait

Abnormality: from:

- neuro, muscular, orthopedic problem (very few neuro disorders don’t compromise balance/gait)
- voluntary / unconscious compensatory response to real or perceived deficit
  - Compensatory strategy can be maladaptive

Falls are a big problem, interventions can help

Physics of balance & gait

Equilibrium = maintain center of gravity (COG) over base of support (BOS)
- Walking = controlled fall
  - COG displaced forwards beyond BOS
  - Step required to keep BOS under displaced COG
  - Tripping: don’t get step to get BOS under COG

Gait cycle
- Look at a pt walking to assess!

Where could things go wrong?
- Muscle, NMJ, peripheral nerve
- Sensory (vestibular, visual, somatosensory)
- Spinal cord
- Cerebellum/brainstem
- Cerebrum (cautious / psychiatric / reckless)?

How to examine pt
- General gestalt
- Observe symmetry & presence of arm swing, posture of any fixed limbs
- Signs of pain or discomfort?
- Base (distance between medial malleoloi)
- Deviation towards examiner rather than fixed direction (is the direction consistent?)

Upper motor neuron dysfunction: cervical myelopathy
- Sx: stiffness, heaviness, slowness; neck pain, incontinence, sensory loss, flexor spasms
- Signs: spasticity, hyperreflexia, jaw jerk not involved (cervical, not higher), ↓ cervical range of motion

Myelopathic gait
- Both legs circumduct; hip adduction with knees crossing (“runway model”)
- Steps short, step height reduced (scuffling)
- ↑ tone may be needed for weight bearing given paraparesis (can’t just ↓ tone: using ↑ tone to support weak legs!)
### Hemiplegic gait
- Sort of like half of a myelopathic gait (e.g. L. sided stroke)
- Leg swings outward, in semi-circle from hip (circumduction)
  - Swinging out (ankle plantarflexed, knee extended → don’t want to hit ground)
- Knee may hyperextend, ankle may excessively plantar-flex & invert
- With ↓ paresis, may only lose arm swing and drag/scrape foot

### Neuropathic gait
- ↑ knee flexion for clearance; Hyperextension during stance
- ↑ step height (steppage gait) (trying to avoid tripping)
- Feet dropped rather than placed, initial contact with front of foot (foot slap)
  - Weakness – can’t flex well
- Need visual feedback for foot placement

### Normal pressure hydrocephalus (NPH)
**Classical triad:** Gait disorder + Subcortical dementia + Urinary incontinence

- Imaging shows enlarged ventricles out of proportion to atrophy
- Response to CSF drainage is best predictor of improvement with shunting procedure

---

### Ataxia

**Definition:**
- Incoordination of limbs, imbalance, dysarthria / dysphagia, sensory ataxia (vestibular / proprioceptive)

**Cerebellar ataxia:** huge list of possible disease mechanisms
- Inborn errors of metabolism, paraneoplastic problems, nutritional (thiamine – Wernicke’s encephalopathy)
- Channelopathies, ataxia telangiectasia (DNA repair) – really rare

**Workup of cerebellar ataxia**
- Screen for reversible causes (vitamin E, gluten? Thyroid, PNP, etc)
- Establish molecular diagnosis (?)
- Treatment: not good options, amantadine (?) / bupropion

**Workup of ataxia in general**
- Thyroid function tests, B₁₂, vitamin E, thiamine, ceruloplasm
- Ab testing for gluten sensitivity
- Hashimoto’s thyroiditis
- Paraneoplastic syndrome
- Whipple / Wilson dz
- Nucleotide repeats, other genetic stuff

**Autosomal dominant spinocerebellar atrophy** (apparently exists)
- Related to repeats in SCA genes (earlier onset with ↑ # repeats)
- SCA7: can see pontine, cerebellar atrophy

**Ca-channel subunit gene on chr 19**
- 3 overlapping syndromes with different alleles
  - Familial hemiplegic migraine, episodic ataxia type 2 can tx with acetazolamide, spinocerebellar ataxia type 6
Neuromuscular Disorders

Anatomy of the Motor Unit

<table>
<thead>
<tr>
<th>Neuronopathy</th>
<th>disease of motor neuron body itself</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiculopathy</td>
<td>disease of nerve root as it exits vertebral body</td>
</tr>
<tr>
<td>Motor Nerve</td>
<td>affects motor nerve itself</td>
</tr>
<tr>
<td>Neuromuscular Junction diseases</td>
<td>NMJ</td>
</tr>
<tr>
<td>Myopathy</td>
<td>broad spectrum of muscle disorders</td>
</tr>
</tbody>
</table>

Motor unit = Motor neuron, axon, NMJ, and all fibers associated with it

Approach to Neuromuscular Disorders

- Where is it?
- Atrophy?
- Sensory findings?
- Reflexes?

<table>
<thead>
<tr>
<th>Motor Neuronopathy</th>
<th>Radiculopathy</th>
<th>Motor nerve</th>
<th>NM junction</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>Asymmetric</td>
<td>Focal</td>
<td>Focal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal&gt;Prox</td>
<td>Root</td>
<td>Multifocal</td>
<td>Prox&gt;Distal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generalized</td>
<td></td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td>Bulbar</td>
<td>Respiratory</td>
<td>Respiratory</td>
<td>Bulbar muscles</td>
</tr>
<tr>
<td></td>
<td>Respiratory</td>
<td>involved (i.e. deltoid C5)</td>
<td>Facial</td>
<td>Bulbar muscles</td>
</tr>
<tr>
<td></td>
<td>Limbs</td>
<td></td>
<td>Limb</td>
<td>Ocular muscles</td>
</tr>
<tr>
<td><strong>Atrophy</strong></td>
<td>Marked &amp; Early</td>
<td>Mild</td>
<td>Moderate</td>
<td>Eye muscles spared</td>
</tr>
<tr>
<td><strong>Sensory</strong></td>
<td>None</td>
<td>None</td>
<td>Rare</td>
<td>Limbs</td>
</tr>
<tr>
<td><strong>Reflexes</strong></td>
<td>Variable (UMN and/or LMNs may be affected)</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

- Bulbar muscles are innervated by cranial nerves; e.g. muscles of face

Amyotrophic Lateral Sclerosis (ALS)

37 year old athletic man who notes that 2 years ago he noted that he was falling more frequently when ice skating with his wife. He was a baseball player at that time and relays a story in which he came to bat 4 times with runners on base and failed to get a hit. On that same day he muffed a routine out on a ball tossed from the pitcher to his position at first base. His batting average was down....

ALS = PROTOTYPIC MOTOR NEURON DISEASE (motor neuron itself)
- Also Poliomyelitis & spinal muscular atrophy

ALS: 90% spontaneous, 10% familial

Both upper and lower motor neuron signs present in ALS (disease of motor neuron itself)

Upper motor neuron signs
- Brisk jaw reflex (open jaw loosely, tap)
- Brisk gag reflex
- Pseudobulbar features (inability to suppress emotions)
  - emotional lability with easy laughter, crying

  Note that you wouldn't see these with a cervical myelopathy (UMN not affected)
- Hyperreflexia (brisk deep tendon reflexes)
- Extensor plantar response (Babkinsi sign)
- Spasticity
**Lower motor neuron signs**

- **Weakness** (often asymmetric, e.g. 1 hand very weak, other normal)
- **Atrophy** (often asymmetric, e.g. mm of hand atrophic on exam)
- **Fasciculations** (spontaneous discharge of an axon causing contraction of muscle fibers in rippling unit)
  - “Twitches” as described by pt
  - Only worrisome in setting of atrophy

**Criteria inconsistent** with diagnosis

- Sensory loss (no numbness, tingling, etc) – sensation is normal
- Autonomic dysfunction
- Visual system abnormalities
- Polyradiculopathy / myelopathy (= spinal cord disease, e.g. cervical myelopathy)

**Electromyography (EMG/NCS):** a diagnostic measure to see LMN function

Looking for **combination** of:

- **acute denervation** (fibrillations, positive waves)
- **chronic denervation** (large, polyphasic motor units with delayed recruitment pattern) – neurons trying to grow back

*Note that in polio, would only see chronic denervation – not acute*

---

**Poliomyelitis**

- follows **polio virus infection** (acute: fever, malaise, GI upset)
- 50% with clinical manifestations → **paralysis**
- **Postpolio syndrome:** progressive weakness in a limb previously affected by polio (years after stable disease)

---

**Spinal Muscular Atrophy**

Associated with **SMN1** gene (RNA SPLICING GENE)

**Clinical features:**

- Usually associated with infant weakness (**floppy baby** – Werdnig-Hoffman)
  - One of various causes of infant hypotonia (here losing muscle neurons)
- **Diffuse & severe weakness** (poor feeding, resp. insufficiency – paradox. resp.)
  - **facial & oculomotor spared**
- Hypotonia, tendon reflexes reduced or absent; Normal, alert faces

**Prognosis:** Resp failure and death (50% by 7 mo, 95% by 17 mo); chronic course in 5%
Radiculopathy

Radiculopathy: disk pressing on nerve root; often described as “slipped disk”, “ruptured disk”, “sciatica”

Pathogenesis: compression of nerve root by herniated disk
- Inner core (nucleus pulposus) of disk bulges out through outer layer of ligaments that surrounds disc (annulus fibrosis)
  - Usually affects single root: think about what muscles are involved!
  - S1 = plantarflexion weakness (gastroc); ↓ ankle jerk

Most common:
- Cervical: C7/6
- Lumbosacral: L4-L5, L5-S1

Disorders of the Peripheral Nerve

What can be affected?
- Axons
- Demyelination (GBS, CIDP = chronic inflammatory demyelinating polyneuropathy)
- Sensory neuropathy
  - DRG: death/dysfunction
  - Paraneoplastic (anti-Hu, with SCLC, etc.)
  - Sjogrens’, HSV (localized), idiopathic

<table>
<thead>
<tr>
<th>Fiber type</th>
<th>Sensory Neuropathy</th>
<th>Demyelinating Neuropathy</th>
<th>Sensory Neuronopathy (Dorsal root ganglia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Distal&gt;Motor</td>
<td>Proximal&gt;Distal</td>
<td>Pure Sensory</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Ankle Jerks Absent</td>
<td>All Reflexes Absent</td>
<td>All Absent</td>
</tr>
<tr>
<td>Nerve Conduction Studies</td>
<td>Decreased amplitudes.</td>
<td>Normal amplitudes.</td>
<td>Decreased sensory amplitudes not length dependent</td>
</tr>
<tr>
<td></td>
<td>Normal velocities</td>
<td>Reduced velocities</td>
<td></td>
</tr>
</tbody>
</table>

Myasthenia Gravis

66 year-old woman noticed double vision when looking to the right over the last 3 months. She has been choking on solids and liquids. Her husband notes that her speech sounds as if she has a “stuffed nose” (palate weak). She also reports that she has difficulty getting out of her car and carrying groceries.

“Droopy face” (not Bell’s palsy – much more gradual onset)
- Assess: smile, can you whistle, etc

Pathogenesis (if autoimmune): Ab against Ach receptor
- NMJ messed up: Ach receptors may be cross-linked and endocytosed or destroyed by C’

Symptoms
- Fatigue following exertion
  - symptoms are often worse in the afternoon or evening.
- Diplopia is key (EOM not involved in ALS)
- Dysarthria
- Dysphagia (both liquids & solids – pharyngeal weakness)
- Dyspnea
- Proximal Weakness
Signs – can follow to assess treatment
- **Ocular** (diplopia, asymmetric ptosis) signs precipitated with sustained upgaze
- **Facial weakness** (eye closure, inability to whistle)

**Diagnosis:**
- Anti-AChR Ab (85%) – diagnostic
- Tensilon test (*administer edrophonium, an ACh inhibitor* - ↑ ACh in synaptic cleft, transient improvement of Sx)
  - Can become **bradycardic** (heart effects of ACh too) – don’t use anymore
- Repetitive nerve stimulation: electrophysiological way of **fatiguing muscle** in EMG lab (↓ over time in MG)
- Single fiber EMG

**Treatment**
- Most effective way: **SUPPRESS THE IMMUNE SYSTEM**
  - Steroids, IV/IG, immunosuppressants, thymectomy, plasmapheresis
  - ACh inhibitors too

---

**Myopathies**

**Myopathy:** “disease of muscle” (many different causes)
**Myositis:** muscle inflammation (subset of myopathy)

**Clinical Features**
- Symmetric weakness
- Proximal involvement (with exceptions)
- Preservation of reflexes
- Absence of sensory signs and symptoms
- Normal autonomic function

**Classification:** muscle can be affected by a lot of different disorders
- **Muscular dystrophies**
- **Inflammatory** myopathies
- **Metabolic** myopathies (e.g. steroid induced)
- **Endocrine** myopathies
- **Toxic** myopathies (statins)
- **Channelopathies, mitochondrial** myopathies

---

**Polymyositis**

45 year-old woman complains of a 6 month history of difficulty going upstairs. She also complains of difficulty braiding her daughter’s hair. She denies double vision, difficulty buttoning buttons, hand or foot numbness. On exam she has proximal weakness in the arms and legs. Her serum creatine kinase (CK) level was >2000 (<200 nL)

No double vision = less likely MG; ↑ serum CK = muscle being broken down

**Pathogenesis**
- Cytotoxic cell-mediated
- CD8 > CD4 T-cells and Mϕ; B-cells rare

**Clinical features**
- Almost always > 20 yo
- Dysphagia, ↑ CK common
- Associated with small but definite ↑ incidence malignancy; interstitial lung disease

Inflammatory myopathy: Lots of inflammatory cells pouring out into muscle; chewing up muscle bundles
**Dermatomyositis**
- Different from polymyositis (not just polymyositis with a rash)
- Presentation is the same (weakness, ↑ serum CK, etc)
- Also associated with malignancy and ILD like polymyositis

**Histology**
- CD4>CD8 T cells and Mφ; B-cells common
- C' deposition on capillaries
- Muscle fibers on border of fascile become atrophic

**Classic features (boards)**
- Heliotrope rash: looks like they’re wearing purple mascara
- Gautren’s papules (LL) – “warts” of the knuckles
- Calcinosis: calcium deposition in fascia

**Inclusion body myositis**
- Male preponderance > 50 yo
- Weakness of WRIST FLEXORS & QUADS – VERY SPECIFIC
- Refractory to corticosteroids (unlike polymyositis, dermatomyositis)
- No skin findings (unlike dermatomyositis)

**Histology:** RED-RIMMED VACUOLES and INCLUSION BODIES

---

**MUSCLE PATHOLOGY**

<table>
<thead>
<tr>
<th>Pathological Process</th>
<th>Example</th>
<th>Pathology</th>
<th>Pathogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denervation</td>
<td>Motor neuron disease; neuropathy</td>
<td>Fiber atrophy (small angular fibers)</td>
<td>Denervation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fiber type grouping</td>
<td>Denervation and reinnervation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grouped atrophy</td>
<td>Denervation, reinnervation, and subsequent repeat denervation</td>
</tr>
<tr>
<td>Myopathy</td>
<td>Dystrophies, Inflammatory myopathies</td>
<td>Necrosis, phagocytosis, fiber atrophy, proliferation of endomysial connective tissue, central nuclei</td>
<td>Genetic abnormality or immunological attack on muscle fibers</td>
</tr>
</tbody>
</table>
Muscular Dystrophy

**Definition:**
- **Hereditary** disease of muscle producing **progressive** weakness & wasting
- **Different from acquired** disorders of muscle (myositis, toxic myopathy, endocrine, etc)
- **Different from hereditary nonprogressive** disorders of muscle (congenital myopathies)

**The Basal-Lamina – Cytoskeletal Link**

**MD: Breakage** of link between cytoskeleton & basal lamina on outside
- Can break in **several different ways** and get **different muscular dystrophies**
  - Duchenne MD: loss of dystrophin
  - Sarcoglycans, others too

**Possible functions** of link: **structural stability** & **signaling**

**Common features** of muscular dystrophies
- Most due to **absence / altered** function of **structural component** of muscle fiber
- Undergo **dystrophic changes**:
  - Rounds of necrosis, degeneration and regeneration
  - Result: **remodeling** of muscle tissue with **fibrosis** and fatty infiltration.

**Muscular Dystrophies in General**
- ~ 40 different disorders
- **Variable:**
  - Involvement of muscle groups
  - Onset
  - Progression
  - Severity
  - Involvement of **other organ systems**

Patterns of muscle weakness in MD
Duchenne Muscular Dystrophy (DMD)

Epidemiology
- X-linked disorder affecting 1:3,500 live male births (common!)
- Dx before age 5, lose ambulation < 14yo
  - Calf hypertrophy (false – fatty infiltration, etc)
  - Gower’s maneuver: muscle weakness; walk self up off ground with hands (hip weakness)
- Deaths in early adulthood (cardiac / resp dz)

Dystrophin: largest in human genome (470kD subsarcolemmal protein)
- Lose dystrophin, lose entire dystrophin glycoprotein complex (DGC)
  - Membrane associated protein complex stabilized by dystrophin
- Big so susceptible to random mutations (30% are new mutations)
  - 2/3 are big deletions / duplications
  - DMD phenotype: due to disruption of reading frame
  - No C-terminal domain to interact with cytoskeleton

Becker Muscular Dystrophy phenotype
- Later onset, milder course
- Mutation preserves reading frame & protein-protein interaction (still have C-terminal domain)

Limb girdle muscular dystrophies
- Many different forms molecularly
- Common feature: hip, shoulder girdle weakness
- Most autosomal recessive, 2° to mutations in structural proteins of muscle fiber

Many are sarcoglycanopathies
- Sarcoglycan: transmembrane proteins associated with DGC
  - LGMD2C, 2D, 2E, 2F
  - Heteromeric unit: loss of one usually leads to loss of group function
- Early childhood onset, rapidly progressive, severe / Duchenne-like Sx
  - Autosomal recessive
  - Associated with cardiomyopathy

H&E (left) and Gomori Trichrome (right): shrunken, rounded fibers
Dystrophin stain: just under sarcolemma in normal sample (left); absent in DMD (right). Note one “revertant fiber” in DMD
**Adult LGMD (e.g. LGMD2I)**

**Pathogenesis**
- Another break in basal lamina – cytoskeleton link
- FKRP (Fukutin related protein) mutated
  - glycosylates α-dystroglycan, w/o glycosylation link to laminin-2 destroyed

**Histology**: similar to DMD histologically, some variability
- See lack of glycosylated α-dystroglycan on IHC
- Onset from early to late adulthood; slowly progressive
- Difficulty with standing, climbing, activities above head
- Can lose ability to ambulate
  - Gower-like maneuvers in adults!

**Congenital muscular dystrophy (MCD1C)**
- Neonatal hypotonia
- Rapidly progressive
- Loss of ambulation before adulthood

**Phenotype/genotype correlation**
- Both correlation & heterogeneity
- LGMD2I & congenital muscular dystrophy have same mutations in FKRP – but different phenotypes!
- In patients with identical mutations (e.g. sibs), can see different IHC results, different expression, different phenotypes

---

**Facioscapulohumeral (FSH) Muscular Dystrophy**
- Aut dom, 1:20k, deletion in telemetric region of 4q (non-coding)

**Findings**: affects face, scapula, upper limbs
- Transverse smiling
- Winged scapulae (double hump sign – deltoid is other hump)
  - can fix scapulae to rib cage to treat
  - Muscle weakness, can’t hold scapula down → winging
- Cachexia, muscle atrophy

---

**Myotonic Muscular Dystrophy**
- Aut dom, 1:20k, “most common” adult MD
- Multi-system involvement: congenital, opth, cardiac, GI, endocrine
- Men: frontal balding, wasting of temporalis, long face
  - Facial muscle weakness: open mouth, drooping eyelids

**Genetics**: Trinucleotide repeat (ANTICIPATION)
- Kids affected worse than parents

---

**Treatment**

**Neurologist** coordinates care
- Preserve muscle strength
- Reduce contractures (have muscle imbalances)
  - gastroc > tib anterior so tight heel cord
  - Biceps > triceps, finger flexors > extensor

Lots of stretching, etc.
Maintaining Muscle Strength
- **Exercise**: limit *eccentric* contractions (e.g. bear a load & extend at same time)
  - *Hard to do*
- **Pharmacology**: prednisone for DMD

#### Cardiology

<table>
<thead>
<tr>
<th>Problem</th>
<th>Conditions</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td>Dystrophinopathies (DMD/BMD), sarcoglycanopathies</td>
<td>ACEi/ARB/β-blockers</td>
</tr>
<tr>
<td>Cardiac conduction defects</td>
<td>Myotonic MD, laminopathies, Emery-Dreifuss</td>
<td>Pacemakers</td>
</tr>
</tbody>
</table>

**Pulmonary**
- Better Tx = ↑ survival over time
- Both inspiration & expiration are affected
- Non-invasive positive pressure ventilation (help with inspiration)
- Cough-assist (help with expiration)
- Vaccinations

**Orthopedic management**
- Contracture reduction
- Scoliosis surgery (muscles weak → can tilt to one side or another)
- Scapular fixation (for FSH MD)

#### Future Treatments

**Combination therapy:**
- gene therapy, other genetic modifications, stem cell therapy, growth factor modulation

**Gene therapy**: AAV vector
- Portion of *dystrophin* gene put in AAV vector, can get some *dystrophin* expression

**Other genetic modifications:**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Idea</th>
<th>Downside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisense oligonucleotides</td>
<td>Splicing modification of pre-mRNA</td>
<td>Repeat administration; mutation-specific</td>
</tr>
<tr>
<td>Nonsense suppression</td>
<td>Ribosomal read-through of stop codons in mRNA</td>
<td>Potentially benefits only ≈ 10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Becker MD</th>
<th>in-frame deletion</th>
<th>some dystrophin function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne MD</td>
<td>out-of-frame deletion</td>
<td>no dystrophin</td>
</tr>
</tbody>
</table>

**Antisense oligonucleotides:**
- use to skip the bad exon (with out-of-frame mutation) in DMD
- Could get a **Becker phenotype** instead of a truncated protein / DMD phenotype

**Nonsense suppression:**
- Give gentamicin or better newer agents to suppress nonsense mutations
- Works at ribosomal level
Cell-based therapies: Satellite cells
- Cells that are normally dormant but proliferate with muscle injury

Normal roles of satellite cells:

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophy</td>
<td>Growth, response to training</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Routine myonuclear turnover</td>
</tr>
<tr>
<td>Myofiber repair</td>
<td>Severe exercise, localized damage</td>
</tr>
<tr>
<td>Regeneration</td>
<td>After widespread damage</td>
</tr>
</tbody>
</table>

- Maybe ↑ satellite cells → regenerate muscle?

Growth factor modulation
- If you could make mm grow randomly (not fixing dystrophin / etc), you could alter slope of curve of atrophy
- Might get more years before disability
- **Myostatin**: negative regulator of muscle growth (knockout = jacked cow)
  - Block myostatin: ↑ regeneration and ↓ fibrosis
  - Conserved in humans
Clinical Spectrum of Movement Disorders

Identification of abnormal movements: based on phenomenology
- Tremors, dystonia, myoclonus, chorea, tics

<table>
<thead>
<tr>
<th>Types of Abnormal Movements</th>
<th>Too Much</th>
<th>Too Little</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkinesias (tremor, dystonia, tic, stereotypy, HFS)</td>
<td>Bradykinesia (slow movement)</td>
<td></td>
</tr>
<tr>
<td>Dyskinesias (TD, HD, chorea gravidarum, L-DOPA induced)</td>
<td>Hypokinesia (small amplitude)</td>
<td></td>
</tr>
<tr>
<td>Akinesia (less spontaneous movement)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Parkinsonism: Parkinson’s Disease, Parkinson-plus syndromes, and 2° Parkinsonism

Parkinsonism: marked by four cardinal features:
1. Bradykinesia (slowing of movements)
2. Rest tremor (rhythmic oscillation of body part when not in use)
3. Cogwheel rigidity (↑ mm tone with “ratchet feel”)
4. Postural instability (& gait impairment: slow start, festination, loss of postural reflexes)

Other common clinical features:
- Pill-rolling tremors, worse on distraction (e.g. count backwards)
- One side worse than other

Evaluation of pt with parkinsonism:
- Hx: drugs/meds that can cause parkinsonism? Risk factors for 2° parkinsonism?
- Exam: check for Parkinson-plus syndrome features
- MRI to rule out vascular dz / hydrocephalus / check for park+, but not to confirm PD

Parkinson disease (PD)
- About 80% of all pts with Parkinsonism
  - May be a syndrome (multiple processes → PD?)
- Most not familial (can rarely get familial forms)
  - Rare familial forms: alpha synuclein, Parkin, pink1, etc.
- Pathology: DEGENERATION OF MIDBRAIN DOPAMINE NEURONS with LEWY BODY INCLUSIONS

Pathogenesis: Progression marches up brainstem
- ↓ dopamine cells → ↓ dopamine release → ↑dopamine receptor (upregulation!)
  - ↑ dopamine receptor # → give L-DOPA → dyskinesia!
- Substantia Nigra: lose the pigmented neuron
- Lewy Body is pathological hallmark (pic)

Epidemiology of Parkinson Disease
Prevalence: ≈ 1.2M, 1% of those over 65
Incidence: ≈ 50k/yr
Mean onset: 62 yo
Onset before age 40 in 4 - 10% of cases
Non-motor features of PD

<table>
<thead>
<tr>
<th>Mentation, behavior &amp; mood</th>
<th>Autonomic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Depression (up to 50%)</td>
<td>• Orthostatic hypotension (from both PD + meds)</td>
</tr>
<tr>
<td>• Dementia (bradyphrenia first, up to 40%)</td>
<td>• GI: gastroparesis (dose failure!), constipation</td>
</tr>
<tr>
<td>• Anxiety, panic attacks</td>
<td>• Other: skin (seborrhoea), sexual dysfunction</td>
</tr>
</tbody>
</table>

Basal Ganglia Circuitry in Parkinson Disease

- Left: normal, Right: Parkinson’s Disease
  - In PD, the substantia nigra gets knocked out. Inhibitory signals predominate to the GP, so inhibition of STN is decreased, STN activates Gpi, which inhibits thalamus / brain stem. **Inhibition is net result**

Etiology: Genes & environment probably overlapping!

PD risk factors:
- Age
- Twins: concordance 75% for MZ, 22% for DZ
- Positive family history
- Environmental factors: rural, pesticides
- Protective factor: smoking, coffee drinking

Treatment of PD

- Current goal: slow progression of disease (see chart to right) to limit symptom development
- Future directions: can we intervene before onset of Sx?

Brain surgery for movement disorders: NOT EXPERIMENTAL (using now!)
- For: PD, ET, dystonia, other conditions
- Ablative (irreversible) or DBS (electrical stimulation) – ablative is much less common these days, use DBS
### Parkinson-plus syndromes
- Several distinct diseases: characterized by **Parkinsonism & other features**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive Supranuclear Palsy (PSP)</td>
<td>3 subtypes, characterized by <strong>early falls &amp; vertical gaze defects</strong></td>
</tr>
<tr>
<td>Multisystem atrophy (MSA)</td>
<td>two subtypes (&quot;cerebellar&quot; and &quot;Parkinson-like&quot;). Early falls, limited DOPA response, ataxia in cerebellar type</td>
</tr>
<tr>
<td>Corticobasal degeneration (CBD)</td>
<td>path term, associated with &quot;cortico-basilar syndrome&quot;</td>
</tr>
<tr>
<td>Lewy body disease (LBD)</td>
<td>a.k.a. “<strong>Dementia with Lewy bodies</strong>” (DLB)</td>
</tr>
</tbody>
</table>

### Secondary Parkinsonism
- Parkinsonism due to **identifiable cause**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocephalic parkinsonism</td>
<td>Accumulation of CSF, expansion of ventricles. Normal pressure hydrocephalus (NPH): common cause of parkinsonism; may be confused with PD</td>
</tr>
<tr>
<td>Features:</td>
<td>Akinetic-rigid syndrome, Gait instability, Dementia, Urinary incontinence, Hydrocephalus on MRI</td>
</tr>
<tr>
<td>Treatment:</td>
<td>Shunt</td>
</tr>
<tr>
<td>Vascular parkinsonism</td>
<td>Caused by two patterns of cerebral ischemia: bilateral basal ganglia stroke, extensive confluent subcortical microvascular disease</td>
</tr>
<tr>
<td>Features: “Lower body parkinsonism”</td>
<td>Akinetic-rigid syndrome, Gait instability, Dementia, Ischemic disease on MRI</td>
</tr>
<tr>
<td>Treatment:</td>
<td>Risk factor prevention</td>
</tr>
<tr>
<td>Post-traumatic parkinsonism</td>
<td>Traumatic brain injury (e.g. dementia pugilistica in boxers – think Muhammad Ali)</td>
</tr>
<tr>
<td>Post-infectious parkinsonism</td>
<td>Certain viruses &amp; bacteria (e.g. encephalitis lethargica – Oliver Sacks)</td>
</tr>
<tr>
<td>Drug-induced parkinsonism</td>
<td>Lots of toxins / medications can cause MPTP (heroin addicts), CO, Mn, CN, methanol, antipsychotics, antiemetics, antidepressants, dopamine depletors, anti-HTN, anti-epileptics, anti-arrhythmics, antibiotics</td>
</tr>
<tr>
<td>Examples:</td>
<td>haloperidol, risperodone, amphotericin B, metaclopramide, valproic acid, SSRIs, Ca-blockers</td>
</tr>
</tbody>
</table>
Tremor

Rhythmic oscillation of a body part caused by alternating or synchronous muscle contractions
- Rate must be constant (“rhythmic”)

<table>
<thead>
<tr>
<th>Type of tremor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological tremor</td>
<td>Everybody has one (not pathological)</td>
</tr>
<tr>
<td></td>
<td>Due to kinetic energy generated by heart &amp; blood circulation</td>
</tr>
<tr>
<td>Exaggerated / enhanced</td>
<td>Most common tremor, often not considered pathological</td>
</tr>
<tr>
<td>physiological tremor</td>
<td>Essential tremor ↑ with stress / anxiety / after strenuous exercise</td>
</tr>
<tr>
<td></td>
<td>also ↑ with hyperthroidism, certain drugs</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>Most common pathological tremor (5% pop?, ↑ &gt; 50 yo)</td>
</tr>
<tr>
<td></td>
<td>high frequency action tremor with both postural / kinetic tremor</td>
</tr>
<tr>
<td></td>
<td>Average age of onset 45, 60% have relatives with ET</td>
</tr>
<tr>
<td>Parkinson tremor</td>
<td>#2 pathological tremor</td>
</tr>
<tr>
<td></td>
<td>Slow rest tremor most of the time; can see action (“re-emergent”) or global too</td>
</tr>
</tbody>
</table>

Others: cerebellar tremor (slow intention tremor), Holmes tremor (global, large amplitude, midbrain lesions), primary writing tremor (writing only), orthostatic tremor (fine tremor, only when standing still), dystonic tremor, palatal tremor, neuropathic tremors, cortical tremor (actually myoclonus), psychogenic tremor, etc.

Evaluation of tremor

Dx is hard! No markers; diagnosis is clinical, various sets of diagnostic criteria
- Dx criteria should be chosen depending on one’s purpose to Dx (e.g., genetic vs. clinical studies)

The question: is it Parkinson Disease or essential tremor? (the big two)

<table>
<thead>
<tr>
<th>Historical Features</th>
<th>Essential Tremor</th>
<th>Parkinson Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration since onset</td>
<td>5-10 years or more</td>
<td>1-2 years or less</td>
</tr>
<tr>
<td>Response to ethanol</td>
<td>usually positive</td>
<td>no effect</td>
</tr>
<tr>
<td>Response to levodopa</td>
<td>no effect</td>
<td>usually positive</td>
</tr>
<tr>
<td>Family History</td>
<td>positive in 60%</td>
<td>usually negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Examination Findings</th>
<th>Essential Tremor</th>
<th>Parkinson Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>When is it worse?</td>
<td>when limb is in use</td>
<td>at rest</td>
</tr>
<tr>
<td>How fast is it?</td>
<td>fast (5-9 Hz)</td>
<td>slow (4-6 Hz)</td>
</tr>
<tr>
<td>Amplitude</td>
<td>fine</td>
<td>coarse</td>
</tr>
<tr>
<td>What does it look like?</td>
<td>flexion/extension of wrists</td>
<td>&quot;pill-rolling&quot;</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>minimal</td>
<td>can be unilateral at first</td>
</tr>
<tr>
<td>What parts are involved?</td>
<td>hands/arms, head/neck, voice</td>
<td>hands/arms, legs/feet, jaw</td>
</tr>
<tr>
<td>Are there associated findings?</td>
<td>usually none</td>
<td>masked face, bradykinesia, cogwheel rigidity, gait impairment</td>
</tr>
</tbody>
</table>

Tremor causes disability! Lots of problems with handwriting, ↓ quality of life, impaired ADLs, etc.

Treatment of tremor
- Counseling (reassure about PD; recognize that no treatment is perfect)
- Oral medications: propranolol, primadone, combo, others?
- Botulinum toxin (off label)?
- Surgery if really severe: thalamotomy, DBS
**Dystonia**

Involuntary twisting movements or abnormal postures, caused by:
- simultaneous, often sustained contraction of two or more muscles that normally oppose each other

**Classification** schemes:
- by age of onset (childhood / adult)
- by distribution (anatomical site) (focal, segmental, multifocal, hemidystonia, generalized)
- by etiology (primary = idiopathic, secondary = symptomatic)

---

**Dystonia: by anatomical site**

<table>
<thead>
<tr>
<th>Dystonia subtype</th>
<th>Affected region</th>
<th>Clinical appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal</td>
<td>Single body region</td>
<td>Limited to affected body region</td>
</tr>
<tr>
<td>Cervical dystonia</td>
<td>Neck muscles</td>
<td>Tilting / twisting of neck</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>Perioral muscles</td>
<td>Excessive prolonged blinking</td>
</tr>
<tr>
<td>Spasmodic dysphonia</td>
<td>Vocal cords</td>
<td>Strangled / whispy voice</td>
</tr>
<tr>
<td>Limb dystonia</td>
<td>Limb muscles</td>
<td>Writer’s cramp, inversion of foot</td>
</tr>
<tr>
<td>Segmental</td>
<td>Contiguous regions</td>
<td></td>
</tr>
<tr>
<td>Meige syndrome</td>
<td>Perioral – perioral (neck)</td>
<td>Blinking, mouth (neck) posturing</td>
</tr>
<tr>
<td>Oromandibular</td>
<td>Mouth, tongue, jaw</td>
<td>Abnormal speech, chewing</td>
</tr>
<tr>
<td>Hemi-dystonia</td>
<td>Half of the body</td>
<td>Usually arm/leg on one side</td>
</tr>
<tr>
<td>Generalized</td>
<td>Majority of the body</td>
<td>Many but not all areas</td>
</tr>
</tbody>
</table>

---

**Cervical Dystonia (spasmodic torticollis)**
- Most common focal dystonia; W>M, age of onset 40-60
- Insidious onset with progression in first few years; may spread to neighboring regions
- Rare remissions (<15%); usually recurs within 5 years

**Named for direction of head movement**

<table>
<thead>
<tr>
<th>Description</th>
<th>Image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torticollis</td>
<td><img src="image" alt="Torticollis Image" /></td>
</tr>
<tr>
<td>Laterocollis</td>
<td><img src="image" alt="Laterocollis Image" /></td>
</tr>
<tr>
<td>Anterocollis</td>
<td><img src="image" alt="Anterocollis Image" /></td>
</tr>
<tr>
<td>Retrocollis</td>
<td><img src="image" alt="Retrocollis Image" /></td>
</tr>
</tbody>
</table>

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**Dystonia: by etiology**

**Primary Dystonias**
- Most are genetic
- Dystonia is the only neurologic finding (except for tremor and myoclonus)
- No identifiable cause or other inherited degenerative disease

**Secondary dystonias**
- Acquired: trauma, infection, focal lesions of nervous system (e.g. dystonic CP, antipsychotic drugs)
  - Acute dystonic reactions: shortly after starting drug or ↑ dose
    - Sudden onset of tonic spasms, segmental (neck/craniofacial mm, eyes)
  - Tardative dystonia: with chronic neuroleptic dose (months/years)
    - Gradual development of tonic spasms, segmental (trunk / neck / craniofacial mm)
- Dystonia-plus syndromes (dystonia + other features)
- Psychogenic dystonias: often paroxysmal

---

**Clinical features:**
- Stereotyped and patterned abnormal movements and postures
- Repeatedly involves same muscle groups
- Sustained (compared with chorea) but tremor or myoclonus may be present
- Has a directional component
- Often activated by voluntary movements
- Benefit of "sensory tricks" (↓ dystonic movements)
Management of dystonia

Evaluation:

- FHx, age of onset (inherited cause?), duration / rate of progression
  - most progress over months/years & then remain static for life
  - slow / continuous suggests hereditary/degenerative or dystonia-plus syndrome
  - Young onset (<30 yrs) suggests inherited cause (clinical testing for DYT1)
- Physical exam
- Brain imaging (use for hemidystonia or segmental dystonia – identifiable lesions most often present this way)

Treatment:

- Treat underlying cause (if identifiable)
- Botulinum toxin if limited # of muscles involved
- Oral meds: limited role in focal dystonias, can be effective in generalized cases
  - Levodopa, trihexyphenidyl, baclofen (PO or intrathecal), clonazepam
- DBS for really bad, refractory cases
- Pay attention to depression & anxiety: big problem in these pts!

Myoclonus

involuntary, sudden, brief, shock-like movements caused by muscular contraction or inhibition (“jerk”)

- Are really “about the muscle” (can’t suppress, no urge: vs. stereotypies / tics, which are “about the movement”)

Classification: by frequency / speed, distribution, character (positive vs negative), etiology

Cortical myoclonus: “fragment of epilepsy” (abnormal cortical discharge → myoclonus)

- May or may not lead to full blown seizure (myoclonic epilepsy)
- Lance-adams syndrome: cortical myoclonus is part of post-anoxic encephalopathy syndrome
- Cortical tremor: really just a rhythmic cortical myoclonus

Subcortical myoclonia: generated by abnormal brain activity other than the cortex

- E.g. reticular myoclonus (part of post-anoxic encephalopathy, generated by brainstem)

Spinal myoclonia: generated by spinal cord, associated with longer muscle contractions

- E.g. with spinal tumor
- Segmental spinal myoclonus: one or a few spinal levels; myoclonic jerks in one or a few adjacent myotomes
- Propriospinal myoclonus: more extensive spinal pathology; many myotomes involved, spreads in marching pattern

Psychogenic myoclonus: probably most common manifestation of psychogenic movement disorders, very often paroxysmal

Evaluation of Myoclonus

- Clinical characterization; look for underlying pathology (Hx, neuro exam, MRI of brain/spine, etc.)
- Jerk analysis / myoclonus electrophysiology is very useful
  - Polygram: multi-surface EMG: help follow myotome involvement, measure length (brief = cortical, long=spinal)

Treatment of Myoclonus

- Treat underlying cause (remove spinal tumor, treat inflammatory process)
- Suppress CNS hyperexcitability (Levetiracetam, pyracetam, benzodiazepines, e.g. clonazepam, valproic acid)
- Direct relaxation (botulinum toxin to affected muscles)
**Chorea, Athetosis, Ballismus**

**Chorea:** involuntary, irregular, unpatterned, and unsustained movements with variable timing and distribution

**Athetosis:** involuntary slow and irregular writhing movements most often affecting the distal limbs.

**Ballismus:** faster flinging movements, typically involving proximal muscle that move an entire limb.

*These three often overlap: e.g. choreoathetosis, etc.*

---

**Causes of chorea**

- **Inherited:** present in children (20+ syndromes) or adulthood
  - Huntington’s disease/chorea: unstable trinucleotide repeat in *huntingtin* gene, aut-dom
- **Metabolic processes** (hyperthyroid)
- **Neuroacanthocytosis**
- **Stroke** of subthalaric nucleus (sudden-onset hemiballismus-hemichorea: just one side affected)
- **Drugs:** L-DOPA, dopamine agonists (phenytoin, theophylline, amphetamines / cocaine / other sympathetimetics too)
- **Autoimmune disease**
  - Sydenham’s chorea (post-strep infection)
  - Chorea gravidarum (women during / shortly after pregnancy: immune system changes)
  - SLE
- **Senile chorea** (perioral mm in elderly), psychogenic chorea (less common)

---

**Evaluation**

- Look for reversible causes (Hx: strep infection, pregnancy, drug history / L-DPOA?)
- FHx for hereditary forms, Brain MRI to rule out stroke / caudal atrophy in HD, ANA, etc.

---

**Treatment:**

- Remove causing condition
- ↓ dopaminergic neurotransmission in brain
  - DA receptor antagonists or depletors of DA-containing vesicles in brain (riserpine, tetrabenazine)
Tics & Tourette’s Syndrome

Tics: repetitive and unwanted movements or sounds
- typically preceded by an urge to perform the tic.
- urge and tic can be suppressed at least for a while, but the suppression results in a buildup of inner tension that ultimately proves irresistible and the tic must eventually be released (performed).

Usually wax and wane in severity over time (↑ with stress); can change appearance

Three types of tics

<table>
<thead>
<tr>
<th>Simple motor tics</th>
<th>Single movements that occur suddenly / executed quickly (cracking neck, shrugging shoulder)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Sometimes mistaken for “odd habit”, myoclonic jerk, brief dystonic spasm</td>
</tr>
<tr>
<td>Complex motor tics</td>
<td>Repetitive movements that involve several steps in a row (blink one eye, tilt head, pull ear)</td>
</tr>
<tr>
<td></td>
<td>• Can appear to be dystonic, choreiformic, or ballistic</td>
</tr>
<tr>
<td>Vocal tics</td>
<td>Audible events (snort/sniff/clear throat/grunt)</td>
</tr>
<tr>
<td></td>
<td>• can be more complex (repeat profanities = coprolalia, repeat what is heard = echolalia)</td>
</tr>
</tbody>
</table>

Tic Disorders
Tics are common but don’t usually represent a tic disorder:
- only when they cause problems (interfere with work / embarrassing)

<table>
<thead>
<tr>
<th>Transient tic disorder</th>
<th>Lasts for &lt; 6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic tic disorder</td>
<td>One or a few tics for &gt; 12 mo</td>
</tr>
</tbody>
</table>

Tourette syndrome
- Most severe; required for Dx:
  - multiple motor tics that wax/wane in severity, change over time
  - At least one vocal tic
  - Onset in childhood
  - Duration > 12 mo

Treatment of Tic Disorders
- Neuroleptics (antipsychotics) are most effective (be careful – can develop tardative dyskinesia)
- Other meds too: Gabapentin, Tetrabenzaine, Clonidine, Baclofen
### Glossary (for reference: no need to memorize)

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
<td>inner sensation of restlessness often expressed by pacing or body rocking.</td>
</tr>
<tr>
<td>Apraxia</td>
<td>loss of skilled movement</td>
</tr>
<tr>
<td>Asterixsis</td>
<td>brief lapses of posture due to loss of muscle tone; most readily seen as flapping movements when the hands are held out in front and dorsiﬂexed at the wrists.</td>
</tr>
<tr>
<td>Ataxia</td>
<td>a syndrome characterized by lack of coordination that includes dysmetria (inability to judge distances, power, or speed), dysdiadochokinesis (inability to stop one act and follow with another), and dysrhytmia (inability to maintain rhythm).</td>
</tr>
<tr>
<td>Athetosis</td>
<td>involuntary, slow and continuous, small-amplitude, writhing movements that tend to affect distal body parts.</td>
</tr>
<tr>
<td>Ballismus</td>
<td>involuntary, rapid, large amplitude, flinging movements that tend to affect proximal body parts (resembles throwing a baseball).</td>
</tr>
<tr>
<td>Chorea</td>
<td>involuntary, fluent, irregular movements of variable speed that tend to travel from one part of the body to another (resembles dancing).</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td>a generic term for any abnormal involuntary movement, more specifically used to describe choreiformic movements.</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>impairment in the ability to produce voice sounds using the vocal organs. Spasmodic dysphonia is a form of focal dystonia.</td>
</tr>
<tr>
<td>Dystonia</td>
<td>involuntary, excessive contraction of muscles leading to twisting movements or abnormal postures that are often repetitive.</td>
</tr>
<tr>
<td>Freezing</td>
<td>inability to initiate the next step while walking resulting in sudden halt.</td>
</tr>
<tr>
<td>Hyperekplexia</td>
<td>abnormally increased reactivity to external stimuli e.g. unexpected noises</td>
</tr>
<tr>
<td>Hyperkinetic</td>
<td>a movement disorder featuring too much movement, such as chorea.</td>
</tr>
<tr>
<td>Hypokinetin</td>
<td>a movement disorder featuring too little movement, such as parkinsonism.</td>
</tr>
<tr>
<td>Hypomimia</td>
<td>reduced facial expression.</td>
</tr>
<tr>
<td>Hypophonia</td>
<td>reduced voice volume.</td>
</tr>
<tr>
<td>Movement disorders</td>
<td>are a group of diseases and syndromes affecting the ability to produce and control movement</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>involuntary, sudden, brief, shock-like movements caused by muscular contraction or inhibition.</td>
</tr>
<tr>
<td>Myokymia</td>
<td>fasciculation-like quivering, most frequently in muscles around the eyes.</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>syndrome of akinesia (reduced spontaneous movement), bradykinesia (slow movements), rigidity, and resting tremor or any combination of these.</td>
</tr>
<tr>
<td>Rigidity</td>
<td>a particular form of muscle hypertonia characterized by ratchet-like or cog-wheeling resistance to passive movements.</td>
</tr>
<tr>
<td>Stereotytyp</td>
<td>a repetitive and purposeless movement, usually a fragment of a normal movement.</td>
</tr>
<tr>
<td>Synkinesisis</td>
<td>Simultaneous occurrence of movements that do not normally go together.</td>
</tr>
<tr>
<td>Tardive Dyskinesia</td>
<td>involuntary choreiformic movements due to chronic antipsychotic exposure, most often involving the orolingual muscles.</td>
</tr>
<tr>
<td>Tic</td>
<td>a sudden movement (or sound) that is unwanted, often preceded by a premonition, and voluntarily suppressible only transiently.</td>
</tr>
</tbody>
</table>

**Tremor:** involuntary, rhythmic oscillations of a body part.

**Action tremor** refers to tremor that appears during active use and comprises
- kinetic tremor (tremor while a body part is being actively moved, such as in finger-to-nose testing)
- postural tremor (when a body part is maintained in a steady posture by active muscle contraction).
- Intention tremor (amplitude of tremor increases near the target (typical of cerebellar tremor).

**Rest tremor** is the opposite of action tremor and refers to shaking that develops while at complete rest.

**Global tremor** is a tremor that is seen “across the board”, i.e. during both rest and action.
Memory Loss and Alzheimer Disease

Memory is only one of the cognitive functions of the brain

- Also: learning / memory, language, orientation, calculation, recognizing faces/objects, executive functions, abstract thinking

Memory

- Frontal lobe: initial attention, repetition
- Hippocampus: memory consolidation
  - (short-term memory)
- Cortex: memory storage
  - (long-term memory)

Memory Disorders

- Age-associated memory impairment
  - Memory ↓ with age (expected)

- Mild Cognitive Impairment (MCI)
  - Significant memory loss above “normal” age-associated memory impairment, but still functional

- Dementia: umbrella term to cover various conditions
  - Memory loss + loss of at least one other cognitive ability
  - Loss of function in daily life
  - Can be caused by a variety of pathologies (Alz dz, vascular lesions, Lewy Body dz, AIDS, EtOH, iatrogenic)
  - “Senile dementia” is no longer used as a term (replaced by AD)

Alzheimer Disease

- Atrophy → hippocampus affected first → initially: memory symptoms

Plaques & Tangles

- Plaque: gum-like collection of β-amyloid
- Tangles: abnormal p-lation & aggregation of tau

Both cause cell death, inflammation, brain atrophy

- Plaques stain positive for inflammatory components with IHC
- Microglia activated, try to kill plaques but can’t
- Nearby cells damaged (collateral damage)

Vascular Lesions

- AD causes atrophy in hippocampal / cortical areas
  - (Tangles don’t affect basal ganglia/cerebellum for the most part)

- Small or large strokes cause atrophy in cortical, subcortical areas (“ministrokes”, etc) → vascular dementia

- Worse outcome with AD + strokes

**Pathogenesis**

<table>
<thead>
<tr>
<th>Early onset AD (more rare)</th>
<th>Late onset AD (most AD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaques / tangles are the big problem</td>
<td>Plaques / tangles + big contribution from ministrokes</td>
</tr>
</tbody>
</table>
The nun study:
- Some nuns were not demented but had severe AD pathology
- Some had dementia despite mild AD pathology (but had multiple strokes)
- A few plaques and tangles can lead to dementia, if patients have heavy vascular pathology

Vascular Risk Factors for AD
- ↑ AD risk with ↑ HTN and ↑ high cholesterol (3x risk)
- ↑↑ with multiple vascular risk factors
  - Diabetes, heart disease, ↑ BP, smoking history
- Stroke: up to 25% of patients have dementia 3mo after stroke
  - vascular dementia (58%), AD with stroke (38.7%), other forms too
- Silent brain infarcts: evidence of stroke on MRI but no associated symptoms
  - ↑↑ risk of dementia (2.26x)
- White matter lesions: see in lots of older patients
  - Often think of them as “normal” in older pts
  - Not good: ↑ cognitive decline with ↑ white matter lesions

Obstructive Sleep Apnea and Dementia
- ↑ silent brain infarcts in patients with OSA
  - ↑ platelet activation, ↑ systemic inflammation, ↑ epinephrine, ↑ severe HTN, ↑ MI, ↑ stroke, ↑ CHF, ↑ pulmonary HTN
  - Hypercoagulable, chronic hypoxia, inflammation, etc.

Atrophy (↓ gray matter brain volume) in OSA pts
- Temporal lobes, frontal lobes, posterior areas, parahippocampal gyrus all affected

Factors that contribute to development of AD

Evaluating Dementia

ABCs of Dementia Symptoms
- Activities of Daily Living
- Behavior
- Cognition

MMSE
- Below 25 – probably going to be referred to neurologist, symptomatic, etc.
- Below 10 – disruptive behavior starts, etc.

Clock drawing
- Great test – very high yield (requires a lot of functions to be intact)
  - Some patients can carry on a good conversation but fail this
  - Can follow over time to assess progression of cognitive decline

Dx: workup
- MMSE & Hx (primary physician) – talk to family separately
- CBS (anemia), B12, TSH, RPR (syphilis), CRP (inflammation), ESR (vasculitis), EKG (vascular risk), Head CT (↑ # tests with younger patients!)
• Clock-drawing test
• Refer to memory clinic if borderline
• PET scan in younger pts (can help, not necessary)
  o Selective parietal/temporal hypometabolism (+ frontal lobes in advanced dz)

**Treatment**
• AChE inhibitor: donepezil (Aricept), galantamine (Reminyl), rivastigmine (Exelon)
• NMDA (glutamate) receptor blocker: memantine (Namenda): along with AChEi
• Psych meds (for agitation, anxiety, insomnia, aggression): antidepressants can help
  o Antipsychotics may help too, but ↑ mortality risk
• Mild benefits only: helps ↓ behavior disturbances, etc.

**MMSE < 10**
• Get really hard to live with at home
• Nursing home – tell pts’ family that they need special treatment
  o If they had cancer, you’d get them to appropriate care!

---

**Prevention of AD**

**Risk factors:**
• High BP, diabetes, obesity, OSA, alcoholism, depression, high homocysteine, head trauma

**Goal:** find things that would change the trajectory of decline
• Vitamin E, Vitamin C, NSAIDs: may have synergistic benefit
• NSAIDs: ↓ inflammation (but can’t give as PGx: GI side effects, etc)

**“Brain reserve”**
• Memorizing lots of information: good for brain (↑ synapses in hippocampus)
• Lose synapses in AD: if you had more synapses to begin with, you’re better off!

**Protective factors**
• Diet ↑ in antioxidants
• Fish 2-3x/wk
• 1-2 glasses of wine with dinner
• EXERCISE
• Leisure activities
• Education, cognitive stimulation

**Hippocampus is vulnerable (smaller hippocampus = more vulnerable to these insults)**
• Hypoxia post cardiac arrest
• Diabetes
• High BP
• Head trauma
• Depression / PTSD
• Aging

---

**Memory & the Hippocampus**
• Studied medical students before, just after taking, 3 mo after boards: Increase in brain volume (cortex & hippocampus!)
  o ↑ cortex while you study, levels off over summer (not studying)
  o ↑ hippocampus: and ↑ even over the summer (not studying)
    • Hippocampus keeps working & consolidating!

**Hippocampus is very plastic** (good for memory!)

**What determines hippocampal size?**
• Genetics
• Use (going to school = ↑ levels)
Some Cases

70 yo man, lives wife, bad memory for names, reads technical journals, socializes, scared he has AD (mom had it)
  o Talk to his wife! Has there been a progression?
  o Any other medical conditions or drugs? (vascular problems, iatrogenic, etc.)
  o How old was his mother when she was diagnosed? Who made the diagnosis?
  o Depressed? Lots of people who present like this have depression!
  o Behavior changes? Fronto-temporal dementia → mostly behavior problems!
  • Dx: “Worried well” probably not dementia, memory decline but limited. Check CBC, TSH, B12, probably no CT / PET
  • Tx: still help them! exercise, teach tricks for memory, evaluate for depression

75 yo dentist, lost driving in own neighborhood, wrote wrong checks, gets into arguments, accuses others of stealing, thinks memory is fine for his age, MMSE 18
  o Meds, medical problems, talk to family
  o CBC, TSH, B12, MRI, PET, etc.
  • Dx: Probably AD

76 yo grandmother, can’t take care of finances, figure out tip, asks people to repeat things, still likes reading, volunteering, etc., has been taking notes more often
  o Probably not AD, probably not normal → check hearing loss
  • Dx: Mild cognitive impairment (primarily memory problems only!)

56 yo woman, once taught 2 languages, lost job (multiple complaints by parents → confused!), can’t take care of errands around house, developed limited vocabulary even in English (give me “that thing”), ½ family got AD in 50s
  • Dx: Early onset AD
Clinical Features of Cognitive Disorders

<table>
<thead>
<tr>
<th>Distributed (bilateral) processes</th>
<th>“Localized” (unilateral) processes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Visuospatial</td>
</tr>
<tr>
<td>Executive (planning, etc)</td>
<td>Praxis (programming of learned movements)</td>
</tr>
<tr>
<td>Memory</td>
<td>Language</td>
</tr>
</tbody>
</table>

Note that “localized” processes aren’t really local – they still require networks

Attention

Attention: “physiological mechanisms which allow us to selectively focus on a subset of available sensory inputs or thoughts”

Why is attention important?

- **Pre-requisite** for normal cognitive function
- **Impaired** attention can mimic disorders of memory, language, etc.
- **Attention lapses** often account for everyday “forgetfulness”
  - Preoccupation, “absent-minded professor syndrome” (older, lots of things on mind)

Clinical conditions that impair attention: closed head injury, delirium, R. hemispheric stroke, dementia

Delirium (encephalopathy)

**Etiology**

- **Systemic / metabolic dz**
  - infection, hypoglycemia, kidney failure – uremia, liver failure, hyperthyroidism, etc.
- **Medication side-effects**
  - benzos, anti-Ch – benadryl!, many more esp. polypharmacy
- **Drug/alcohol withdrawal**
  - alcoholic delirium - DTs
- May occur in 30% of hospitalized elderly pts

**Clinical features of Delirium**

- Fluctuating level of consciousness / alertness
- Subacute onset of Sx
- Confusion, disorientation
  (place and time, not person)
- Hallucinations, perseveration
  (multiple repetitions of previous response)

To have delirium”

- Healthy people must be really sick
- Dementia pts can be just slightly sick

Diagnosis

- No single “diagnostic test”
- **History**: subacute onset, waxing/waning consciousness
- **Impaired attention / concentration**
  - Digit span (how many can pt remember?), test working memory

Unilateral Spatial Neglect (Hemispatial neglect)

- Typically **RIGHT HEMISPHERE lesion**, e.g. right hemispheric stroke

- Pt “ignores” left half of space or left half of individual stimuli on both sides
  - May fail to acknowledge hemiparetic arm (hemiparesis if stroke)
  - Eat food on right half of plate, reads right half of words
    - Airways → “byways”; Chair → “air”

Line cancellation test: cross out all the lines; pt doesn’t attend to left side
Clock drawing test: all numbers on one side of the clock
**Viewer-centered USN**

**Neglect**
- Left half of space/view

**Lesions**
- **R. Parietal** lesion (supramarginal gyrus, angular gyrus, frontal cortex, TPO junction)

**Visual stream affected**
- “Right dorsal stream” (planning movements in space, etc.: viewer-centered)

---

**Stimulus-centered USN**

**Neglect**
- Left half of things (will attend to right side of things in left half of view)

**Lesions**
- **R. Temporal** lesion (superior temporal gyrus, inferior/middle temporal)

**Visual stream affected**
- “Ventral stream” of visual information (recognition of objects, reading: representation irrespective of where they are to the viewer)

---

**Behavior**

- Fidgety, restless, repeatedly distracted, inappropriate behaviors (impaired executive fn → ↓ inhibition)

---

**HIV Dementia**

- A “subcortical disease” – diffuse process (note subcortical lesions)

**Clinical presentation:**

- Motor slowing
- Memory impairment
- Visuo-constructual impairment
- Fluctuating attention
- Preserved language and other cortical functions

---

**Key Points: Attention**

- Impaired attention may produce deficits in multiple cognitive domains
- Delirium is characterized by severe, fluctuating attentional deficits
- Right-hemisphere parietal lobe injury often associated with “focal” deficits of attention, (e.g. hemispatial neglect)
- Diffuse brain injury often results in significant attentional deficits

---

**Aphasia**

- Most right-handers are left-hemisphere dominant for language
  - (and = 50% left-handers)
  - Remember: Speech ≠ Language!

**Aphasia:** acquired deficit of language secondary to brain dysfunction

- Usually multi-modal (involves written + spoken)
- Can have isolated deficits too (more rare):
  - **Alexia:** impairment of reading
  - **Agraphia:** impairment of writing
  - **Pure word deafness**

---

**The Basic Language Model** (generally the left hemisphere!)

<table>
<thead>
<tr>
<th>Area</th>
<th>Location</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broca’s</td>
<td>Posterior inferior frontal ctx</td>
<td>Production: articulate language, motor speech, grammatical constructions</td>
</tr>
<tr>
<td>Wernicke’s</td>
<td>Posterior superior temporal ctx</td>
<td>Comprehension, meanings of words</td>
</tr>
<tr>
<td>Arcuate Fasiculus</td>
<td>Connects Wernicke’s and Broca’s areas</td>
<td></td>
</tr>
</tbody>
</table>
Speech disorders

- **Dysarthria** (articulation – e.g. muscle weakness, ALS, MG, etc)
- **Apraxia of speech** (motor planning / programming of speech articulation)
- **Dysphonia** (voice disorder)
- **Stuttering** (often developmental)

- Writing, reading, other aspects of language **intact** in pure motor speech disorders
- **Mutism** (behavioral or anarthria = very severe dysarthria)

Language laterality

- **Right-handers**: mostly left hemisphere language
  - About 5% right hemisphere dominant: “crossed aphasia”
- **Left-handers**: majority with left hemisphere language
  - About 30% with right hemisphere language (correlates w/ FHx, degree of left-handedness)

Global Aphasia

Clinical presentation

- All modalities of language are severely impaired; no usable speech / comprehension
- **Stereotypical or recurrent utterances** (Broca’s pt: “tan-tan” – often profanities)
- Reading, writing, repetition also impaired
- Most severe type of aphasia
- Caused by **large lesions**: both Broca’s & Wernike’s areas
  - Clot in entire L MCA

“Partial” aphasias

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Fluent” aphasias</td>
<td>lots of words, jargon major defect in comprehension / meanings</td>
<td>• Wernike’s aphasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Conduction aphasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anomic aphasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• transcortical sensory aphasia</td>
</tr>
<tr>
<td>“Non-fluent” aphasias</td>
<td>production impaired “telegraphic” or “texting” speech leave out small grammatical words</td>
<td>• Broca’s aphasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• transcortical motor aphasia</td>
</tr>
</tbody>
</table>

Broca’s aphasia

- Non-fluent, effortful speech; poor articulation, sparse output, sometimes agrammatic
  - Telegraphic (omits function words)
- Writing impaired to similar degree as speech
- Comprehension less severely impaired (except syntactically complex sentences)

Lesions:

- Superior division, left MCA
- Posterior, inferior frontal lobe

Conduction Aphasia

- Disproportionate difficulty with repetition
- Fluent, paraphasic speech
  - Semantic paraphasia: “coat” → “jacket”
  - Phonemic paraphasia: “coat” → “goat”
- Relatively preserved comprehension
Lesion: left inferior parietal lobule (working memory)
- Problem of working memory: can’t remember exact words
  - (“It’s a sunny day in Baltimore” → “it’s nice outside”)
- Role of arcuate fasciculus?
  - Often see lesion here too, but if only arcuate fasciculus, no repetition problem

Wernicke’s Aphasia
- Fluent, paraphasic speech; sound or word substitutions, lots of jargon
  - Neologistic jargon: not real words ("jabberisy fardle buffik")
  - Semantic: word substitutions ("coat" → "jacket")
  - Phonological: sound substitutions ("coat" → "goat")
- Normal articulation, prosody (rhythm, stress, intonation)
- Auditory comprehension & repetition markedly impaired
- Not aware that they’re not making sense (pts will talk to each other just fine!)
  - Often: certain phrases preserved
  - Think that they’re making sense & understanding!
  - Often recover & say they didn’t think anything was wrong

Lesion:
- Inferior L. MCA territory
- Posterior, superior temporal lobe (Wernicke’s area)

Transcortical Aphasias
- Spared repetition

<table>
<thead>
<tr>
<th>Transcortical motor</th>
<th>like Brocas with spared repetition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcortical sensory</td>
<td>like Wernicke’s with spared repetition</td>
</tr>
<tr>
<td>Mixed transcortical</td>
<td>like Global but spared repetition (echolalic, usually due to dementia, not stroke)</td>
</tr>
</tbody>
</table>

Aphasia: Etiology
A symptom of brain injury, not a disease

Acute onset aphasia: usually stroke
Gradual onset of aphasia: degenerative disorders
- Primary progressive aphasia: front-temporal lobar degeneration is most common
- Creutzfeldt-Jacob dz (rare)

Key Points: Aphasia
- Aphasia is a disorder of language
- All language modalities usually involved
- Anterior lesions associated with non-fluent speech
- Posterior lesions associated with fluent speech, but receptive and expressive
  - Receptive vs expressive not too helpful of a dichotomy (if you’re not receiving, you’re not expressing, etc.)
Apraxia

An acquired deficit of purposeful movement
- Can’t explain by ↓ strength, muscles, sensory loss, language comprehension, ↓ cooperation, confusion, delirium
- Pts rarely recognize inability to perform skilled movements

Clinical syndromes: Stroke, cortical dementia (e.g. fronto-temporal dementia), cortico-basal degeneration

Limb apraxia:
- Lesion: parietal lobe or SMA (supplementary motor area, in frontal lobe) lesion;
  - Contralateral to dominant hand, but you get bilateral apraxia
- Slow to organize movement, ± improvement with demonstration, sometimes delayed
- May exchange one movement for another “throw a ball” → clap hands

Apraxia of speech: Anterior lesions (Broca’s aphasia)

Agnosia

- Impairment in recognition
- Not caused by deficit in sensory processing or dysnomia (naming what they see)
- Generally modality specific (visual agnosia most commonly studied)
- Rare but dramatic

Visual object agnosia (associative):
- can describe physical features (color, size, shape)
  - but can’t recognize object!
- copy line drawings, but can’t identify even after making copy!

Clinical syndromes with visual agnosia: DIFFUSE OR BILATERAL lesions
- Stroke: bilateral temporo-occipital (BASILAR artery)
- Degenerative conditions: advanced Alz dz or posterior cortical atrophy (variant of Alz dz)
- Trauma, cardiac arrest

Auditory agnosia: may not recognize words or sounds
- Can recognize picture of dog, but not bark

Amnesia

Global amnestic syndrome

- Most severe form of memory impairment
  - Severe anterograde amnesia (can’t learn new information)
  - Variable retrograde amnesia (can’t recall old information)

- Other aspects of cognition preserved
  - Consciousness, language/intellect, attention ok
  - Implicit/procedural memory ok (can get better at doing a maze, but don’t remember practicing)
  - Semantic memory ok (memory for the meanings of things)

Etiologies (e.g. hippocampal problems)
- Herpes simplex encephalitis
- Korsakoff’s syndrome
- Iatrogenic (surgical lesions – e.g. HM)
- Alz Dz (advanced)
- hypoxia / ischemia (hippocampus sensitive to hypoxia → bilateral damage)
Herpes simplex encephalitis
- Uncommon, caused by common virus HSV
- Subacute onset (1-3 days) w/ severe H/A, fever, confusion, memory loss / aphasia
  - AMNESIA / APHASIA + FEVER → ACYCLOVIR!

Wernicke – Korsakoff syndrome: (two-part syndrome)
- Acute: Wernicke's encephalopathy
  - eye movement abnormalities, ataxia, confusional state
- Chronic: Korsakoff's amnesia
  - Typically follows acute Wernicke’s encephalopathy
  - Severe anterograde amnesia, disorientation, confabulation (make up stories)
- Thiamine (vit B₁ deficiency)
  - Co-enzyme in carbohydrate metabolism
  - Classic: alcoholics (↓ dietary intake, ↓ GI absorption, ↓ hepatic storage, ↓ utilization of B1)
  - Also: Dieting/exercise (ballerinas, jockies), Crohn's disease, Gastric restrictive surgery
- Treatment: give thiamine (memory improves)
  - Incidence ↓ with food fortification (even in countries with high alcohol use)

Transient Global Amnesia (TGA)
- Acute onset of memory loss, benign but scary, pretty common
- Mostly Anterograde (can’t form new memories)
  - Mild retrograde component: can’t remember day before, but can remember week before
- Preserved consciousness & self-awareness
- Self-limiting (usually recover within 12 hours)
- Etiology unknown (sometimes misdiagnosed as stroke
  - Maybe very small TIAs/hippocampal strokes?
  - Usually unilateral, subtle

Memory loss due to general medical conditions
- Vitamin deficiencies (B12, folate, thiamine)
- Hormonal (thyroid abnormalities)
- Sleep disorders (sleep apnea)
- Chronic pain
- Liver disease

Evaluating memory loss

<table>
<thead>
<tr>
<th>Memory process</th>
<th>What it looks like</th>
<th>Impaired with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>New learning (encoding)</td>
<td>Learn information, give other tasks, then patient forgets what they’d learned!</td>
<td>Attentional disorders (depression, medications)</td>
</tr>
<tr>
<td>Delayed recall (consolidation; recall and retrieval affected)</td>
<td>Who’s the president of the US? Pt. doesn’t know. Is it Obama, McCain, or Palin? It’s Obama!</td>
<td>Hippocampal lesions (Encephalitis, Alzheimer’s)</td>
</tr>
<tr>
<td>Retrieval (spared recognition)</td>
<td>Can’t retain sequences of numbers or words</td>
<td>Executive dysfunction (Fronto-temporal dementia, Subcortical dementia)</td>
</tr>
<tr>
<td>Working memory (multi-tasking)</td>
<td></td>
<td>Fronto-subcortical disease</td>
</tr>
</tbody>
</table>

“Hollywood amnesia” (retrograde w/o anterograde) is atypical (person probably wants to be in ED for another reason!)
**Anosognosia**

- **Unawareness of illness**
- Often: severe forms of diffuse brain injury (e.g. dementia)
  - Also: focal R. parietal lobe injury
- Patients aren’t just in denial: genuinely unaware of deficits

**Executive Functions**

*Phineas Gage*: struck with tamping iron through frontal lobe $\rightarrow$ executive function changes

**Executive / frontal lobe functions**

- Abstract reasoning
- Problem solving
- Multi-tasking
- Motivation
- Response inhibition
- Planning
- Hard to quantify with standardized neuropsych tests
  - Wisconsin Card-sorting test, trail-making test, verbal fluency test
- Bedside evaluation challenging too
  - Luria “hand sequencing test” – strike table with fist, open hand, side

How much of our brain do we use? Pretty much all of it.
Seizures and Epilepsy

Seizure: a sudden, excessive, temporary discharge of a large group of neurons.

New-onset seizures:
- Often present in childhood / adolescence
- Biggest # of new-onset cases: OLD PEOPLE (>70yo)
  - Due to underlying causes!

Epilepsy vs seizures
- Epilepsy: recurrent seizures or the propensity to have recurrent seizures
  - a single seizure is not epilepsy (10% pop has seizure lifetime); about ½ epilepsy will remit (more common in children)
- Provoked seizures are seizures caused by:
  - metabolic causes (e.g. low glucose), medications (e.g. tramadol), substance (e.g. alcohol), etc.

Seizure type: determined by patient behavior and EEG pattern during the ictal event

Epileptic syndrome defined by:
- Seizure type(s)
- Natural history
- EEG (ictal + interictal)
- Etiology
- Response to AED

Syndromes:
- Begin in childhood or early adolescence
  - Juvenile myoclonic epilepsy: common, important myoclonic epileptic syndrome; seizures not associated with other neuro abnormalities
  - Have important prognostic value for course

Classification of seizures

Partial seizures
- begin from focal area of brain
- Symptoms depend on which part of area is affected
  - E.g. hand twitches if in motor strip, etc.
  - 57% of all seizures, most are complex partial

Auras: mostly with temporal lobe partial seizures
- Commonly: nausea, unusual smells, déjà vu, fear
- Don’t alter consciousness, last only seconds
  - But can be followed by a complex partial seizure, for instance
- Auras = simple partial seizures, often involving deep brain structures (e.g. hippocampus), may not provoke EEG changes

Types of Partial Seizures
- Simple partial (focal, local): DON’T involve impaired consciousness
- Complex partial: impaired consciousness at outset (can be simple partial evolving to impaired consciousness)
  - Most common type of seizure
  - 70-80% complex partial seizures are preceded by aura
  - Can have automatisms, lip-smacking, hand picking, etc. during seizure
- Partial can evolve to generalized seizures

EEG: focal, rhythmic discharge (starts in one area)
Post-ictal state: several minutes of confusion following seizure
Generalized seizures

- begin from both sides of brain simultaneously (or at least appear to – probably deep brain structures)
- Not due to identifiable brain abnormality (may be complex genetics)
- Not progressive or associated with other neurological deficits
- 80% controllable by medicine

Types:

- **Absence (petit-mal):** brief staring episode for several seconds
  - **Total unawareness** but prompt return to full awareness
  - Thalamus, thalamocortical projections involved?

- **Tonic-clonic (grand-mal)**
  - Loss of consciousness
  - Bilateral tonic & clonic arm/leg movement
  - ± tongue biting or urinary incontinence

- **Myoclonic** (brief muscle jerks ± LOC / other neuro defects)
- **Atonic** (drop attacks: pt loses consciousness & body tone → falls → can be injured)
- **Clonic / tonic** on their own too

**EEG:** everything starts discharging at once

---

**Terminology**

<table>
<thead>
<tr>
<th></th>
<th>Complex Partial</th>
<th>Absence (Petit Mal)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Adult / childhood</td>
<td>Childhood</td>
</tr>
<tr>
<td><strong>Aura</strong></td>
<td>Common</td>
<td>None</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Minutes</td>
<td>Seconds</td>
</tr>
<tr>
<td><strong>Post-ictal confusion</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>EEG</strong></td>
<td>Focal abnormalities</td>
<td>Generalized discharges</td>
</tr>
</tbody>
</table>

**Etiologic Categorization of Epilepsies**

<table>
<thead>
<tr>
<th>Idiopathic</th>
<th>Symptomatic</th>
<th>Cryptogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age-related onset</td>
<td>CNS disorder / lesion is the cause – treat it!</td>
<td>Presumed symptomatic</td>
</tr>
<tr>
<td>Clinical, EEG characteristics</td>
<td></td>
<td>Etiology unknown</td>
</tr>
<tr>
<td>Presumed genetic etiology</td>
<td></td>
<td>Think something’s causing it but can’t find it</td>
</tr>
</tbody>
</table>

**Predisposing factors** for epilepsy

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>cerebral palsy</td>
<td>military head injury</td>
</tr>
<tr>
<td>mental retardation</td>
<td>civilian head injury</td>
</tr>
<tr>
<td>febrile convulsions</td>
<td>stroke</td>
</tr>
<tr>
<td>CNS infection</td>
<td>CNS infection</td>
</tr>
<tr>
<td>head trauma (esp. adolescents)</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Tumor / AVM (later adults)</td>
</tr>
</tbody>
</table>

**Gunshot wounds** or “missile injuries” are major cause in military!

**Things that get confused with seizures**

- Breath-holding, hyperventilation, vasovagal events, nocturnal myoclonus, parasomnias
- Panic attacks – some pts can have seizures with fear as aural (but only lasts a minute or so)
Basic mechanisms of epilepsy

- **Hyperexcitability** for a brief period of time $\rightarrow$ repetitive firing of action potentials
- **Paroxysmal depolarizing shift (PDS)**
  - Prolonged depolarization
  - Activation of NMDA receptors
  - Inward sodium & calcium fluxes

**Long-standing seizure disorders:** alterations in temporal lobe synaptic organization

- Progressive neuronal cell loss $\rightarrow$ mossy fiber synaptic reorganization, sprouting
- End result: ↑ NMDA-mediated events
  - Basically: injure $\rightarrow$ sprout new fibers $\rightarrow$ predilection for seizures!

**Characteristics of epileptic seizures**

- Abnormal synchronous firing of neuronal networks
  - Note: normally have synchronous firing in brain – not just in seizures!
- ↑ excitation
- Self-limited, short duration (< 2m)
- May occur in clusters
- Multiple neurotransmitter systems involved

**Treatment implications**

- We have anti-epileptic drugs but not yet anti-epileptogenic drugs: can we hit that window of epileptogenesis?

---

**Evaluating a Patient with Epilepsy**

- Hx, physical, lab studies
- EEG: sleep, hyperventilation, intermittent photic stimulation, sleep deprivation, ambulatory day / prolonged video
- MRI: thin cut, coronals, T1 / T2 / FLAIR
- Also: CT/PET/SPECT/MRS/etc
- Identify comorbidities / underlying causes, monitor when in doubt

**EEG**

- Scalp or intercranial
- **SUMMED ACTIVITY** of LARGE GROUPS OF NEURONS (not single neurons)
  - Summed potentials produced by dipoles
- Use for: Dx, classification, treatment decisions

**EEG & Epilepsy**

*In individuals with known epilepsy:*

- 50% positive after one awake EEG (80% to 85% if sleep is included)
  - 0.4-2% of adults without epilepsy have epileptiform activity on EEG
- Sleep deprivation may increase EEG yield
- A normal EEG does not rule out epilepsy (35% have normal EEG inter-ictally)

**Other Imaging**

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>good for emergencies, hemorrhages, skull fractures, generally not appropriate for elective evaluation</td>
</tr>
<tr>
<td>MRI</td>
<td>imaging of choice for epilepsy</td>
</tr>
<tr>
<td>MRS</td>
<td>can reveal cell loss (NAA/Cr)</td>
</tr>
<tr>
<td>PET</td>
<td>Metabolism: interictal demonstrates areas of hypometabolism; specific ligands</td>
</tr>
<tr>
<td>SPECT</td>
<td>Blood flow (interictal unreliable; ictal can show focal increases)</td>
</tr>
</tbody>
</table>
Treatment of Epilepsy

- Antiepileptic drugs (mostly don’t affect natural history)
- Seizure surgery
- Ketogenic diet (esp. children)
- Neurostimulation

Pharmacotherapy

Goals of Pharmacotherapy

- Control seizures, ↓ severity of acute / chronic side effects
- Maintain / restore psychosocial, behavior, cognitive, vocational functioning

Antiepileptics: a ton of different drugs, but haven’t rendered a lot of people seizure-free

- Pt who’s failed 3 drugs at good doses & still having seizures, < 5% chance of having a different drug work!
- All of the drugs active against partial seizures, only a few for primary generalized seizures
- Certain syndromes are more refractory to drugs (e.g. complex partial: very common & refractory)

Surgery

- Temporal lobectomy
- Focal resections
- Hemispherectomy
- Corpus callosotomy

- If focal seizures: go focal and remove areas of brain that are dispensable (yes, they do exist)
- Digitized EEG, imaging really helpful in surgical treatment (ID areas of cortical dysplasia)

Contraindications

- Bilateral or multiple seizure foci
- Nonlocalizable seizures
- Nonlocalizable seizures
- Seizures located in eloquent cortex (motor / speech, etc)

Decision for surgical evaluation

- AED failure (antiepileptic drugs) – 2 or 3 tried, tolerated, failed
- Seizures are disabling (severity, frequency interfere with quality of life)
- Surgery can cause: developmental regression (in children), cognitive decline (all ages)
- About 70% seizure free at 12 mo (vs. ~8% for medical treatment)

Hemispherectomy: mostly in kids who had insult when young

- Motor / language has moved to other side; can take out hemisphere & be OK

Anterior temporal lobectomy: see pic

- Really no deficits except minor visual loss if you cut Meyer’s loop

Other treatments

Vagus nerve stimulator: pacemaker-like pulse generator

- Idea: alter background activity
- ↓ seizures (30-50% cut # seizures in half)
- No drug related side-effects but usually doesn’t make pts seizure-free (not replacement for surgery)

Other investigational tools too

- Implantable RNS: record seizures, look at EEGs, stimulate after detecting seizures: But still doesn’t make pts seizure-free
TNDs, TIAs, & Neuro-electrical Auras: Pathogenesis of Episodic Neurologic Symptoms

Categories

<table>
<thead>
<tr>
<th>Mechanical</th>
<th>Ischemic</th>
<th>Neuro-electrical</th>
</tr>
</thead>
<tbody>
<tr>
<td>(usually have history of triggers)</td>
<td>(usually spontaneous)</td>
<td>(+/- trigger history)</td>
</tr>
<tr>
<td>• Fluid dynamic (BPPV, colloid cyst...)</td>
<td>• Global (MI / arrhythmia)</td>
<td>• Ephaptic (trigeminal neuralgia, MS)</td>
</tr>
<tr>
<td>• Compressive (temporary entrapment...)</td>
<td>• Focal (TIA)</td>
<td>• Channelopathic (seizure, migraine)</td>
</tr>
</tbody>
</table>

Transient neurological symptoms: characteristics
- Seconds to hours (up to a few days)
- Any quality of symptom (brain-region specific)
- Some triggered (e.g. BPPV)
- Most spontaneous TNDs indicate...

Affects: Symptoms

<table>
<thead>
<tr>
<th>TIA</th>
<th>sensory = motor</th>
<th>negative &gt;&gt; positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>motor &gt; sensory</td>
<td>positive &gt;&gt; negative</td>
</tr>
<tr>
<td>Migraine</td>
<td>sensory &gt;&gt; motor</td>
<td>positive ≈ negative</td>
</tr>
</tbody>
</table>

SYMPTOMS: “POSITIVE” or “NEGATIVE”?

<table>
<thead>
<tr>
<th>Positive (“Too Much”)</th>
<th>Negative (“Too Little”)</th>
<th>Can’t Tell</th>
<th>Misleading</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Limb-shaking</td>
<td>• Paralysis/weakness</td>
<td>• Dizziness/nystagmus</td>
<td>• Release hallucinations</td>
</tr>
<tr>
<td>• Tingling</td>
<td>• Numbness</td>
<td>• Confusion</td>
<td>• Hemiballismus</td>
</tr>
<tr>
<td>• Flashing lights</td>
<td>• Dim/dark vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Auditory hallucinations</td>
<td>• Hearing loss</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Benign positional paroxysmal vertigo

Intermittent clinical syndrome: brief, episodic vertigo & mild nausea triggered by specific head movements
- Caused by single, excited semicircular canal (usu. posterior canal) on one side
- Mechanical, due to ‘rocks’ (otolith crystals) in the canal
- Characteristic nystagmus diagnostic

Pathogenesis: Canalolithiasis

1. There are little rocks (crystals) in ear
2. They sometimes get knocked loose and fall into the posterior semicircular canal (usually), because of its dependent loop
3. When this happens, head movements cause them to slide around, stimulating that canal, producing intermittent vertigo

Dix-Hallpike Test:
- Turn head 45° to right, bringing R PC into register with mid-sagittal plane
- Lie patient back expeditiously onto bed, making rocks slide in R PC by applying max gravity
- See: mixed vertical-torsional nystagmus
  - Upbeat, geotropic (towards the ground)
  - Examined only looking straight ahead
  - Fatigues quickly (seconds), reverses on sitting up (rocks slide back the other way)
Epley Canalith Repositioning to fix (see pic)
- Start in Dix-Hallpike position
- Make 270° rotation of head, then body
- Gets rocks out of canal! Immediate fix!

Ischemic TNDs: TIA
- Come on quickly (seconds)
- Technically last <24h, most <1hr
- Different mechanisms → different clinical patterns

<table>
<thead>
<tr>
<th>Mechanism of TIA</th>
<th>Symptom Pattern</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac embolism</td>
<td>vary between spells</td>
<td>depends on where embolus goes each time</td>
</tr>
<tr>
<td>Thrombo/athero-embolism</td>
<td>similar between spells</td>
<td>throwing emboli, but not exactly the same place each time</td>
</tr>
<tr>
<td>Low flow across stenosis</td>
<td>usually stereotyped</td>
<td>every time you drop pressure, same areas affected</td>
</tr>
</tbody>
</table>

- Risk for stroke is highest in first few days / weeks (5% 1st 2 days, 10% in first 90 days)

Big blood vessel diseases are bad for the brain
- High risk diseases (larger vessel diseases):
  - Carotid / vertebral / basilar stenosis or dissection
  - Vasculitis (esp. giant-cell arteritis)
  - The question isn’t “has the patient has a TIA” – it’s “are they going to have a stroke?”
  - Depends a lot on their vascular state!

Neuro-electrical TNDs: Migraine Aura

Migraine with aura
- “Recurrent disorder manifesting in attacks of:
  - reversible focal neurologic symptoms
  - that usually develop gradually over 5-20 minutes and last for less than 60 minutes.
  - Headache with the features of migraine without aura usually follows the aura symptoms.
  - Less commonly, headache lacks migrainous features or is completely absent.”
- May have variation in patient from attack to attack

Timeline of Migraine Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulnerability (baseline genetic predisposition)</td>
<td></td>
</tr>
<tr>
<td>Trigger (dietary, hormonal, sensory, emotional)</td>
<td></td>
</tr>
<tr>
<td>Prodrome (irritability, dysphoria)</td>
<td>(hrs-days)</td>
</tr>
<tr>
<td>Classic visual aura (fortification spectra)</td>
<td>(min-hr)</td>
</tr>
<tr>
<td>Hemicranial headache (contra-aura)</td>
<td>(hrs-days)</td>
</tr>
<tr>
<td>Anorexia, nausea-vomiting</td>
<td>(hrs-days)</td>
</tr>
<tr>
<td>Photophobia, phonophobia</td>
<td>(hrs-days)</td>
</tr>
</tbody>
</table>

Characteristics of visual aura
1. Positive leading edge
   a. Geometric (zig-zag, dashes, triangles, stars, fireworks)
   b. Often arranged in arc convex peripherally
   c. Scintillating/flickering
   d. White/gray or light yellow/pink
   e. Hemifield start
2. **Negative wake**
   a. Relative scotoma/blur
   b. Located within borders of positive arc

3. **Slow tempo**
   a. Expands or recedes slowly over minutes
   b. Lasts 2-60 minutes, usually 5-30 minutes
   c. Also a normal duration for TIA's! (seizures usually shorter: 3-5 min)

**Occipital Seizures** can have aura too: in comparison to migraine,
- More circular (less "geometric")
- More vividly colored (less achromatic)
- Shorter (5-30 min)

**Non-visual migraine auras**
- Sensory auras (common): visual, somatosensory, vestibular, auditory, gustatory/olfactory
- Cognitive auras (uncommon): aphasia, confusion, memory loss
- Motor auras (rare): hemiplegia, quadriplegia

**Evolution of auras**
Abnormal electrical wave spreading across cortical surface of brain

**Visual cortex → travel anteriorly**
- Vision → Somatosensory → motor strip → language in frontal lobe
- Most patients: stop at central sulcus (stop with sensory)
  - FHM (see next) – don’t stop!

Often have modality-specific triggers for a given patient

**Motor Auras** (rare)
- Hemiplegic migraine: familial or sporadic; paraplegic or quadriplegic: “basilar migraine”
- Headache: like other migraines, but auras are prolonged with motor manifestations
- Most have classic visual aura & other auras (hemisensory loss, hemiplegia, aphasia)
  - Progression: visual → sensory → motor → cognitive (back to front!)

**Familial Hemiplegic Migraine**
- Aura wave doesn’t stop at central sulcus! Goes on to motor & cognitive areas
- Channelopathy (Na/K ATPase & v-gated Ca channels)

**Channelopathies**
Various syndromes: FHM, also deafness, arrhythmia, ataxia, myasthenia, neuropathies
- Unifying theme: episodic neurologic dysfunction on a short time scale
- Some dysfunction is persistent/progressive and interictal, instead of just episodic / ictal with recovery

**More common diseases (migraine, seizure) with transient neuro disturbances: may have similar molecular mechanisms?**

**Pathophysiology of Visual Aura**
- Old theory: vasoospastic ischemia
- Lashley measured expansion of own aura, mapped to 3 mm / min spread over visual cortex
- Leao noted same rate: excitation/depolarization (on) followed by depression/hyperpolarization (off)
  - Contiguous spread (ECF), NO SYNAPTIC TRANSMISSION (NOT SEIZURE)
  - Seizure: gap-junctions & synaptic transmission; aura: excitation spreads via ECF
Neural / Spreading Depression model

1. Cortex excitable and/or irritated (genetic predisposition?)
2. Spreading depression (SD) triggered
3. Depolarizing wave (positive aura: lights)
4. Hyperpolarizing wave (negative aura: scotoma)
5. ↓ metabolic demand, ↓ caliber of vessels (“spasm”)
6. Headache cause (semi-)independent

Region-specific auras
- For instance: is Meniere’s disease region-specific aura in middle ear?
- Variety means migraine vs TIA DDx is tough

Spreading depression model explains:
- Spatial characteristics of aura (crossing vascular boundaries)
- Slow aura evolution, mix of positive and negative Sx; absence of tissue ischemia
- Regional ↓ in cerebral blood flow happen after aura has begun, persist long after it’s gone
- Modality specific triggers
  - abnormal ca channels in occipital cortex, stimulate with repetitive flashing lights → set off abnormal wave cycle?
  - Interictal hypersensitivity to certain stimuli (strobe, checkerboard)
- Dovetails well with channelopathy theory in FHM

Migraneurs have ↑ excitation
- Think of it as a balance: when “normal” people have ↑ excitation, still fall in “normal range” & no aura
- If migraneur has ↑ excitation (trigger), balance pushed out of normal range → aura

Spreading Depression model & pain (headache)
- Cortical spreading depression →
- lots of inflammatory mediators released →
- set off pain triggers

Details not understood
DDx: Migraine vs. Seizure

<table>
<thead>
<tr>
<th></th>
<th>Migraine</th>
<th>Seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time course</td>
<td>spreads over space in 5-60m (longer is better)</td>
<td>Evolves quickly (seconds to a few minutes)</td>
</tr>
<tr>
<td>Involves</td>
<td>Sensory only, not motor</td>
<td>Motor involvement</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Episodic head/neck pain &lt; 72hrs</td>
<td>Loss of consciousness</td>
</tr>
<tr>
<td>Aura characteristics</td>
<td>Geometric / bland</td>
<td>Round / bright colors</td>
</tr>
</tbody>
</table>

Migraine and sensory partial seizures can look very similar; seizures are usually shorter.

DDx: Migraine vs. TIA

<table>
<thead>
<tr>
<th></th>
<th>Migraine</th>
<th>TIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time course</td>
<td>spreads over space in 5-60m (longer is better)</td>
<td>Starts “all at once” usually</td>
</tr>
<tr>
<td>Involves</td>
<td>Sensory only, not motor</td>
<td>Motor involvement</td>
</tr>
<tr>
<td>Aura characteristics</td>
<td>Mixed positive &amp; negative</td>
<td>Negative only</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Episodic head/neck pain &lt; 72hrs</td>
<td>Persistent head/neck pain &gt; 72 hrs</td>
</tr>
</tbody>
</table>

Migraine can mimic TIA in ALL RESPECTS!

Take-Home Points (know these)

TNDs

1. If TNDs are triggered, trigger usually indicates pathophysiology (e.g., BPPV)
2. Most “spontaneous” TNDs indicate...

<table>
<thead>
<tr>
<th>TIA</th>
<th>sensory = motor</th>
<th>negative &gt;&gt; positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure</td>
<td>motor &gt; sensory</td>
<td>positive &gt;&gt; negative</td>
</tr>
<tr>
<td>Migraine</td>
<td>sensory &gt;&gt; motor</td>
<td>positive ≈ negative</td>
</tr>
</tbody>
</table>

Migraine

1. Migraine is a syndrome with episodic...
   1. pain (usually in the head, face, or neck),
   2. autonomic changes (gastrointestinal > cranial),
   3. polysensory hypersensitivity, and, sometimes
   4. neurologic dysfunction (mixed pos. & neg.)
2. Migraine with aura is a polygenetic, (presumed) channelopathic disorder of neuronal excitability
3. Predisposition (irritability) is always present, but varies with triggers (endogenous/environmental)

TIA

1. TIA generally come on quickly (seconds)
2. TIA technically last < 24hrs; most < 1hr
3. Different mechanisms = different clinical patterns

<table>
<thead>
<tr>
<th>Mechanism of TIA</th>
<th>Symptom Pattern</th>
<th>Why?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac embolism</td>
<td>vary between spells</td>
<td>depends on where embolus goes each time</td>
</tr>
<tr>
<td>Thrombo/athero-embolism</td>
<td>similar between spells</td>
<td>throwing emboli, but not exactly the same place each time</td>
</tr>
<tr>
<td>Low flow across stenosis</td>
<td>usually stereotyped</td>
<td>every time you drop pressure, same areas affected</td>
</tr>
</tbody>
</table>

4. Risk for stroke is highest within days-wks
5. Big blood vessel diseases are bad for the brain

Aura

Neural hypothesis – hyperexcitable cerebral cortex & electrical spreading depression (excite/inhibit balance)

Migraine aura vs. TIA:

- Mixed positive & negative usually = migraine
- SPREAD OVER MINUTES (5-30) = migraine
  - true TIAs rarely cause spreading symptoms
Developmental Disorders in Childhood

Developmental disorders can be:
- **Structural** (alterations in development \(\rightarrow\) alterations in function
- **Functional** (alterations \(\rightarrow\) MR, CP, autism, other developmental delays)

**Stages of Nervous System Development**
1. *Induction*
2. *Neurulation*
3. *Cell Proliferation and Migration*
4. *Axonal Projection*
5. *Synaptogenesis*
6. *Myelination*

**Induction**: bilaminar embryo \(\rightarrow\) trilaminar embryo
**Neurulation**: Neural fold \(\rightarrow\) groove \(\rightarrow\) tube
- At about 25 days, you have a long tube with an anterior (rostral) neuropore & caudal neuropore
- Close off around day 25-27

---

**Neurulation: Neural Tube Defects**
- Neural tube fails to close (e.g. dorsally)
  - Closure at regionally distinct sites
- Overlying skeleton defective
  - Failure to close leads to chemical and mechanical trauma
- Range of defects, 1/1000 pregnancies affected

---

**Anencephaly**: failure of neural tube to close anteriorly
- Brain, ectoderm, skeletal defects
- Still see facial structure
- Incompatible with life

**Spina bifida**
- Posterior neural tube doesn’t close
- Range of defects
  - Myelomeningocele: have neural elements inside
  - Meningocele: just have meninges inside
  - Spina bifida occulta: defect in skeletal elements (mesoderm) but not neural axis itself

---

**Etiology of Neural Tube Defects**
- Genetic (animal models, syndromic/chromosomal)
- Environmental (teratogens: *folate* is important, ↑ in insulin-dependent diabetic mothers, exposure to valproate)
- Most cases: no clear cause or FHx

**Folate**: involved in synthesis of nucleotides (DNA/RNA/etc, cycles through methionine, homocystiene, etc)
- ↓ incidence of NTD (anencephaly & spina bifida) with ↑ folate supplementation
- USPHS: 400 mcg folic acid daily for all women capable of becoming pregnant
  - Rx, fortification of foods \(\rightarrow\) ↓ spina bifida rates

---

**Prenatal detection of NTD**
- Alpha fetoprotein (AFP) – made by fetal liver, leeches out into amniotic fluid / maternal serum if fetus disrupted
can detect as maternal serum alpha fetoprotein (AFP) or amniocentesis AFP

- Ultrasound useful too for detection of defects

Neurologic impairments with NTD
Like a spinal cord lesion at level of impairment
- Motor weak, no sensation below level
- Bowel / bladder impaired (sacral involvement)

Hydrocephalus common in SB pts
- 2° to Chiari 2 malformations; need ventricular shunting
- Pic: note cerebellum / brainstem tugged down (due to cord tethering) → obstructive hydrocephalus

Other impairments in Spina Bifida
- Cognitive impairments (in some: from hydrocephalus)
- Orthopedic: scoliosis, clubfeet (not moving in utero)
- Urologic: infections, stones, renal failure (bladder involvement)
- Pressure ulcers, osteomyelitis (↓ sensation & mobility)

Other NTD:
- Lipoma: Fatty tumor pulls tube down
- Tethering of cord
- Hairy patch (ectodermal malformation)

Normally: as you grow, nerve fibers grow downwards
In NTD pts: scarring tethers the cord
- as the patient grows, it gets stretched (later onset problems)

Encephalocele
- Most are occipital, maybe a disorder of anterior neural tube closure
  - Can be more subtle; can look like nasal polyps
- Associated with: microcephaly, MR, visual problems, hydrocephalus

Segmentation / Diverticulation of the Neural Tube
- Straw, top closed off, start doing some differential growing
  - Outpatching is secondary to growing, folding, bending
- Prosencephalon (forebrain) → telencephalon (cerebral hemispheres)
- Mesencephalon → midbrain
- Rhombencphalon → metencephalon & myelencephalon
**Holoprosencephaly:**
- Incomplete **midline cleavage** of developing forebrain (prosencephalon)
  - Various degrees: **Facial & endocrine abnormalities**
    - Single eye (cyclopsia), single central incisor, etc.
    - Various genetic abnormalities (*SHH*, etc)
  - End up with one central ventricle

---

**Microcephaly vera**
Disorder of proliferation: failure of neurons to proliferate
- Microcephaly at birth
  - Regular normal development
  - Variable mental retardation
- Sloping forehead, prominence of ears

---

**Neuronal migration**

**Lissencephaly**
“smooth brain” or agyria-pachygyria

Absence of gyration
- Due to failure of abnormal neuronal migration

Various types: e.g. Miller-Dieker syndrome (pics)
- Random trivia: Olive doesn’t migrate in MD-syndrome

**Doublecortin**
- Males have agyria
- Females have band of heterotopia
  - X-inactivation: some neurons get where they’re going, some don’t

---

**Pediatric Neurodevelopmental Disorders: Cerebral Palsy**

Not discussed here: mental retardation (3% prevalence), autism, epilepsy syndromes

---

**Cerebral palsy**

Abnormal control of movement & posture (MOTOR DISORDER) – “CP” doesn’t imply causation
- Voluntary movements that are normally complex, coordinated, varied → limited, stereotypic, uncoordinated
- Non-progressive abnormality of the developing brain

**Etiology / Epidemiology:**
- 1.5-2.5/1000 live births (↑ in premature, low birth weight, twins)
- Prenatal / postnatal events often involved
- Can co-exist with other brain injury manifestations (MR, seizures, autism, vision, hearing)

**Spectrum of motor dysfunction**
• Classified by **type, distribution** of motor abnormality (rarely pure presentation)
  o **Spastic**: 50% (*hemiplegic, diplegic, quadriplegic*)
  o **Dyskinetic**: 20% (*extrapyramidal, choreathetoid*)
  o **Atactic** (10%) or **mixed** (20%)

**Pathogenesis of CP**: many possibilities (two given here)

**Periventricular leukomalacia** (top pic)
• Damage to tracts that will become myelinated (e.g. internal capsule)
• Result: **spastic diplegia**
• Various mechanisms can be responsible

**Injury to Basal Ganglia** (bottom pic)
• Hypoxic/ischemic encephalopathy
• Infection
• **Kernicterus** (hyperbilirubinemia in the newborn)
• Results in extra movements!

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**Degenerative diseases**

• Heterogeneous group of disorders characterized by **loss of previously acquired skills**
• **Contrast** to the static encephalopathies (MR, CP, autism)

**A lot of different kinds**: **lysosomal storage diseases**, mitochondrial disease, peroxisomal disorders, copper metabolism, **amino/organic acids, vascular disease / stroke syndrome, others**. Focusing on **lysosomal storage diseases** here

**Difficult to diagnose**
• Is this **progressive** or **static** (esp. early)?
• “**Endless**” list of disorders
• **Classified by biochemical abnormality**
• Findings don’t appear all at once: **evolve**

**Classification of degenerative diseases**

<table>
<thead>
<tr>
<th>Gray matter (neurons)</th>
<th>White matter (myelin &amp; fibers)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(compare to AD in adults)</td>
<td>(compare to MS in adults)</td>
</tr>
<tr>
<td>↓ psychomotor development</td>
<td>• Lack of coordination (\rightarrow) <strong>spasticity</strong> (Babinski, hyperreflexive)</td>
</tr>
<tr>
<td>Intellectual deterioration (<em>dementia</em> in pediatrics)</td>
<td>• <strong>Peripheral neuropathy</strong></td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>• <strong>Optic atrophy</strong> (± cortical blindness)</td>
</tr>
<tr>
<td><strong>Retinal involvement</strong></td>
<td>• <strong>Ataxia</strong></td>
</tr>
<tr>
<td><strong>Ataxia</strong></td>
<td></td>
</tr>
</tbody>
</table>

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**Tay-Sachs**: a prototypical **gray matter** disorder

**Normal at birth**

**Early course**:
• Exaggerated **startle to sounds** (≈ 6mo) \(\rightarrow\) deterioration in motor abilities
• Axial hypotonia (shoulder girdle weak) & spasticity
• **Seizures**,
  • Blind with pendular nystagmus; **cherry red spot** over macula

**Late**: megalencephaly

**Populations**: ↑ in Ashkenazi Jews, French Canadians

**Cherry red spot**:
• Cells packed full of storage protein, die; remaining macula \(\rightarrow\) red spot
Molecular abnormalities:

- Accumulation of GM$_2$ gangliosides in neurons
  - “trash not getting taken out”
- Hydrolysis of gangliosides: need
  - Hexosaminidases (A & B)
  - GM$_2$ activator protein needed

Clinical management:

- Carrier detection & prenatal diagnosis in at-risk populations
- Symptomatic treatment (pharm Rx in development; nothing good available now)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Protein abnormality</th>
<th>Activity levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tay-Sachs</td>
<td>α subunit</td>
<td>↓ Hex A</td>
</tr>
<tr>
<td>Sandhoff</td>
<td>β subunit</td>
<td>↓ Hex B</td>
</tr>
<tr>
<td>AB variant</td>
<td>Activator def</td>
<td>N1Hex A &amp; B</td>
</tr>
</tbody>
</table>

Metachromic Leukodystrophy (MLD): a white matter disorder

- Progressive demyelinating disease
- Defect in arylsulfatase A
- Variable presentations (late infantile, childhood, adult)
  - Spasticity, ataxia, vision loss, areflexia
- Tons of other leukodystrophies too (krabbe, ALD, Canavan, Alexander)
- No screening (no specific populations at risk)

Legs held in extension, arms flexed (stronger muscles winning)

MRI: hyperintensity in myelinated areas (injured)

Treatment:

- Bone marrow transplant
- Other stem cells? Gene therapy?
- Symptomatic therapy

Exam Questions: KNOW THESE

Match the developmental malformation and its stage of development.

Myelomeningocele (A) → A. Neural tube closure
Holoprosencephaly (B) → B. Segmentation/Diverticulation
Anencephaly (A) → C. Synaptogenesis
Lissencephaly (D) → D. Neuronal migration

A patient with an open posterior lumbosacral meningomyelocele would be expected to have all but one of the following:

A. Chiari malformation which resulted in hydrocephalus
B. Bowel and bladder dysfunction
C. Normal amniotic fluid alpha fetoprotein
D. Paralysis of leg muscles

Lysosomal degenerative diseases of the nervous system may be divided into those affecting gray matter and those affecting white matter primarily. Choose the best answer for each of the early clinical manifestations listed below:

- A – Gray matter, B – White matter, C – Both

  - Seizures (A – gray)
  - Retinal involvement with “cherry red spot” (A – gray)
  - Affects myelinated fibers (B – white)
  - Spasticity (B – white)