Neurology Exam Notes

Neuroanatomy Review

- Organization of Nervous System
  I. CNS: brain and spinal cord
  II. PNS: spinal nerves and 11/12 cranial nerves (except for the optic nerve)
    1.) Sensory division: carries sensory signals from receptors → CNS = AFFERENT
      a.) viscerosensory: sensation from the organs
      b.) somatosensory: sensation from skin, muscles, bones, joints
    2.) Motor division: carries signals from CNS → glands, muscles, effectors = EFFERENT
      a.) autonomic (viscromotor): innervations in motor muscles, cardiac muscles, smooth muscles, glands, GI neurons
        -neurons originate in brain or lateral horn
        -two neuron pathway
          -CNS → ganglion → target cell
        -usually involuntary
        -uses Ach and norep as NTs
        -excitatory or inhibitory effects
        -primary function is to regulate blood flow to where you need it
      i.) sympathetic division: automatic control for crisis reactions, fight or flight responses
        -cell bodies in the thoracolumbar region of spinal cord, sympathetic neurons exit this area to form a line of ganglia called the sympathetic trunk next to spinal cord
        -length of sympathetic trunk extends entire length of spinal cord
        -first synapse is in sympathetic trunk
        -postsynaptic neuron is adrenergic = communicates with target cell using norep (or epinephrine in the special case of the adrenal medulla)
      ii.) parasympathetic division: predominates with maintenance functions
        -cell bodies are in the brainstem and sacral regions
        -parasymp neurons exit from these regions
        -first synapse is in ganglia that are closer to or within target tissue
        -postsynaptic neuron is cholinergic = only uses Ach to communicate with target cell
        → dual innervation of smooth muscle by symp and parasymp = fine level of control
      iii.) enteric division: acts independently in the gut but can but can be modulated by sympathetics/parasympathetics
      b.) somatomotor: innervations of motor muscle and skeletal muscle
        -one neuron from CNS to target with NO ganglia = long neurons
        -neurons originate in ventral horn
        -usually voluntary
        -uses only Ach as NT
        -always excitatory effect

- Brain Anatomy & Physiology Refresher
  - Supporting cells are glial cells
  - Meninges: surround entire CNS including the optic nerve and spinal cord
    - layers:
      - dura mater is the thick outer layer
      - arachnoid mater is thin middle layer
      - pia mater is the delicate, highly vascularized inner layer that adheres tightly to the brain
    - isolate/pad brain from hard bones of the skull
    - CSF travels through the pia and arachnoid maters
    - innervation by CN V (trigeminal)
Blood supply via the circle of Willis:
- using this information + neurologic deficits will help you to locate a stroke

CSF nourishes neuronal tissue and removes waste
- penetrates into the subarachnoid space surrounding the cranial nerves and spinal cord
- produced by the choroid plexus in ventricles

Cerebral cortex contains cell bodies and interneurons of the CNS $\rightarrow$ gray matter
- association fibers connect the same hemisphere
- commissural fibers connect contralateral hemispheres = corpus callosum
- regions of fine discrimination (smallest receptor fields) take up more area in the cerebral cortex and tend to be located more laterally
  - ex. fingers, lips
  - regions can also be trained to be more sensitive

Internal capsule makes up the main passageway for ascending and descending tracts
- most neural traffic will pass through it
- contains most of the fibers connecting the cerebral cortex to the thalamus, basal ganglia, and other deep structures

Cerebellum coordinates voluntary body movement and muscle tone $\rightarrow$ smooth movements
- influence is not directly on lower motor neurons, but indirectly via the cortex and brainstem
- does not initiate movement, so damage does not lead to paralysis but does cause slow, clumsy, tremulous movements
- damage $\rightarrow$ ipsilateral effect on movement
  - awkwardness with intentional movement = intention tremor
  - hypotonia, decreased DTRs, asthenia (muscle fatigue), dysmetria (inability to gauge distance, power, or speed of movement), dysdiadochokinesis (impaired ability to stop one action and start another - RAMs), speech disorders, ataxia

Basal ganglia fine-tunes movement as it is constantly informed about most aspects of cortical function
- damage $\rightarrow$ contralateral effect on movement
  - unexpected, meaningless, unintentional movement, tremors at rest
  - uncontrollable abnormal movements: chorea (sudden jerky, purposeless movements), athetosis (slow, writhing, snakelike movements of mostly the fingers and wrists), hemiballismus (sudden, wild flailing movement of one arm)

Thalamus is the train station and connection center for the cortex, basal ganglia, hypothalamus, and brainstem
- integrates information and relays directional changes
- the final point where information can be transferred, modified, or coordinated before reaching the postcentral gyrus
- all sensory tracts synapse here before being directed to the cortex
  - exception: those involved in smell

Hypothalamus controls autonomic functions, regulates homeostasis, coordinates neuroendocrine functions, and integrates information with the limbic system and frontal cortex to express physical changes associated with emotion
- anterior = parasympathetic response
- posterior = sympathetic response
- synthesizes ADH and oxytocin

Limbic system functions in drive-related emotional behavior and memory
- acts as the bridge between the autonomic/automatic and voluntary responses to changes in the environment

Brainstem controls neurological functions necessary for breathing, digestion, HR, BP, awake/alertness
- most cranial nerves originate here
- forms the pathway for all fiber tracts traveling from peripheral nerves and spinal cord to the cerebral cortex
- contains the reticular activating system: plays a central role in bodily and behavioral alertness
- controls circadian rhythm, respiration, cardiac rhythms, and other essential functions
- has ascending connections that affect the function of the cerebral cortex and descending connections that affect bodily posture and reflexes
- route of action for many psychotropic drugs and general anesthesia
- bilateral damage can lead to permanent coma
- not a lot of space but a lot going on = major consequences with damage

-Aphasia and language centers
- Broca’s is a motor and expression center
  - damage → inability to express words and great difficulty producing them
  - words come out in a telegraphic manner- most important words only!
  - can comprehend but can’t respond
- Wernicke’s is a sensory and reception center
  - damage → inability to comprehend and respond in a meaningful way
  - words come out as a salad and don’t pertain to the conversation
- can have both kinds of aphasia

-Spinal cord
- ends at L1-L2
- spinal nerves exit above vertebrae up to C7, then C8 exits below C7

-Spinal nerves: all are mixed sensory-motor
- dorsal root contains afferent sensory fibers going towards the CNS
- ventral root contains efferent motor fibers going away from the CNS
  - remember: the motor is in front of the car!
- several spinal nerves can reassert into plexi so that all fibers going to a specific body travel together in one plexus (T1-T12 are independent)
  - cervical plexus = C1-C4
  - brachial plexus = C5-T1
  - lumbar plexus = L1-L4
  - sacral plexus = L4-S1
  - coccygeal plexus = S5-Co
  - provides for efficiency, but also leads to increased risk of injury

-Major peripheral nerves:
  a.) upper extremity: axillary (deltoid), musculocutaneous (biceps), radial (triceps, wrist & hand extensors), median (most of the forearm flexors & pronators), ulnar (intrinsic hand flexors and extensors)
  b.) lower extremity: obturator (adductors), femoral (iliopsoas and quadriceps), common fibular nerve/peroneal (tibialis anterior, fibularis), tibial (gastrocnemius, posterior tibialis)

-Check functioning of PNS with the CNS via reflex testing
- Dermatome = area of skin supplied by a single spinal nerve
- considerable overlap between dermatomes
- landmarks that are regular on most people despite body habitus:
  - C4 = shoulder
  - T4 = nipple line
  - T10 = umbilicus
  - L1 = groin

- Myotome = portion of skeletal muscle innervated by a spinal cord level
- most are innervated by more than one level for protection of function
- shoulder = C5-C6
- elbow = C6-C7
- hand = C8-T1
- hip flexion = L1-L2
- knee extension = L3-L4
- knee flexion = L5-S2
- plantarflexion of the foot = S1-S2

-Spinal tracts
- rules for ascending pathways:
  - they always synapse in the thalamus on their way to the cortex
  - exception: those involved in smell
  - they always cross
  - they are subject to the controls of descending neurons via interneurons
a.) dorsal column-medial lemniscus tract: ascending tract that carries sensory information regarding fine touch, vibration, stereognosis, conscious proprioception
- PE: light touch, joint position sense, vibration, two-point discrimination
- pathway:
  - first order neuron picks up information from specialized receptor
    - for fine touch = Merkel or Meissner's
    - for vibration or pressure = Pacinian corpuscle
    - cell body of first order neuron is in DRG
  - first order neuron synapses at medulla on 2nd order neuron
    = damage at level of 1st order neuron will cause ipsilateral loss of sensation
  - 2nd order neuron crosses medulla and ascends to thalamus where it synapses on a 3rd order neuron
    = damage at level of 2nd order neuron or above will cause contralateral loss of sensation
  - 3rd order neuron ascends to the cerebral cortex

b.) spinothalamic tract: ascending tract of axons through which pain and temperature information travels; includes lateral and anterior tracts
- lateral spinothalamic tract senses pain and temperature
- anterior spinothalamic tract senses light touch and pressure
- no special receptors, only free neuron endings sit in periphery
- PE: pinprick, temperature testing
- pathway:
  - 1st order neuron picks up info and synapses right away in dorsal horn onto 2nd order neuron
    - where “referred pain” can happen
  - 2nd order neuron crosses spinal cord and ascends to thalamus = any damage here will cause a contralateral loss below the level of the lesion
  - synapse onto 3rd order neuron in thalamus
  - 3rd order neuron ascends to the cerebral cortex (or synapses throughout midbrain in the case of slow pain)
    - fast pain response utilizes aδ fibers that are myelinated → response in 0.15 sec
      - ex. pin prick
    - slow pain response uses C fibers → response in ~1 min
      - ex. appendicitis

c.) spinocerebellar tract: an ascending tract that senses unconscious proprioception
- connects cerebellum with the same side of the spinal cord = any damage will have ipsilateral effects

d.) corticospinal tract: a descending tract of mostly motor axons that travel between the cerebral cortex of the brain and the spinal cord
- PE: graphesthesia, two-point discrimination testing
- impulses originate in the precentral gyrus in large cell bodies (pyramidal cells)
- axons pass down through the internal capsule to the midbrain and then to the medulla
-at the medulla 80-90% of the axons cross over and descend in the lateral (dorsal) corticospinal tract, while 10-20% descend on the same side as the anterior (ventral) corticospinal tract

-Motor neurons:
  • upper motor neurons: motor neurons that originate in the motor region of the cerebral cortex or the brain stem and carry motor information down to the final common pathway = any motor neurons that are not directly responsible for stimulating the target muscle
    -disease here causes spasticity, hypertonic reflexes, and possibly a Babinski reflex, clonus
      -ex. tumors of the brain and spinal cord, strokes, multiple sclerosis, meningitis, cerebral palsy, ALS
  • lower motor neurons: the motor neurons that connect the ventral horn to muscle fibers, bringing the nerve impulses from the upper motor neurons out to the muscles
    -disease here causes flaccidity, atrophy, fibrillations or fasciculations, and hypotonic reflexes
      -ex. trauma, polio, birth injuries, muscular dystrophies, Guillain-Barre syndrome, carpal tunnel, myasthenia gravis, ALS

-Spinal reflexes
  -can test somatosensory and somatomotor nerves in an unconscious patient
  -anesthesia eliminates reflexes in a predictable sequence, helping to determine if a patient is sufficiently sedated
  -absence indicates damage to sensory function, internuclear connections, or motor function

-Cranial nerves
  -those originating in the:
    -forebrain → I & II
    -midbrain → III & IV
    -pons → V
    -junction of pons/medulla → VI, VII, VIII
    -medulla: IX, X, XII
    -superior spinal cord: XI
  -sensory: I, II, VIII
  -motor: III, IV, VI, XI, XII
  -mixed: V, VII, IX, X

**Approach to the Neurologic Patient and Diagnostic Methods**

-**Neuro H&P**
  -Good history
    -PMH: trauma, meningitis, congenital abnormalities, cardiovascular disorders, neurologic disorders, cancer, surgeries or anesthetic complications
    -FH: known hereditary disorders, congenital cognitive deficits, seizure disorders, headaches, Alzheimer’s or other dementia, learning disorders, weakness or gait disorders, metabolic disorders, alcoholism
    -SH: environmental or occupational hazards, hand/eye/foot dominance, ability to care for self and ADLs, sleeping and eating habits, sexual contacts, alcohol use, illicit drug use, caffeine intake
    -ROS, allergies, and meds may reveal clues or missed information
  -Good physical
    -complete PE: includes general appearance, mental status, gait/coordination tests, cranial nerve exam, motor system exam, sensory testing, reflex testing, cerebral vascular exam, GI exam (autonomic function)
      -note speech: aphasia affects understanding, thought, and word-finding while dysarthria affects voice production (UMN or CN dysfunction)
    -mental status: visual spatial skills (drawing or copying), judgment, mood, memory, language
    -gait: Parkinsonian, marche a petit pas, asymmetrical, ataxic, hemiplegic, decreased arm swing, spasticity, broad-based, festination, waddle, foot-drop, dystonia, start-hesitation
-extremities:
  - general weakness: disease of the nerve (polyradiculopathy), neuromuscular junction (myasthenia gravis), or muscle (myopathy)
  - weakness in all limbs: UMN (cervical or brainstem) or LMN (polyradiculopathy, peripheral neuropathy)
  - unilateral limb weakness: hemisection of cervical cord, brainstem lesion, cerebral lesion, UMN (lesion above highest involved level), LMN (mononeuropathy if a single nerve, radiculopathy if a single nerve root)
  - weakness in both legs: UMN (spinal cord lesion), LMN (cauda equina lesion)

-reflexes:
  - UMN lesion \(\rightarrow\) increased DTRs, clonus, + Babinski
  - LMN lesion \(\rightarrow\) decreased DTRs
  - isolated decreased reflex \(\rightarrow\) peripheral neuropathy or nerve root lesion

-screening PE: inspection, mini mental status, CN II-XII, muscle strength, RAMs, Romberg, pronator test, gait & heel-toe walking, superficial pain, touch, vibration, DTRs bilaterally
  - pronator: one arm pronates and drifts down \(\rightarrow\) ipsilateral weakness, both arms drift \(\rightarrow\) bilateral weakness, arm rise \(\rightarrow\) cerebellar disease, fingers continuously move up and down (pseudoathetosis, deficit of joint position sense)

-want to know if there is a motor deficit, sensory deficit, or both
-want to determine location: CNS or PNS?
  - CNS: unilateral weakness or sensory complaints, language dysfunction, spatial disorientation, hemivisual loss, flattening of affect or social disinhibition (frontal lobe), alteration of consciousness, memory deficits
    - motor deficits:
      - if UMN is damaged above the medulla \(\rightarrow\) contralateral deficit with increased muscle tone and DTRs
      - if damage is below the medulla \(\rightarrow\) ipsilateral deficit with weakness, paralysis, decreased muscle tone, and decreased DTRs
    - cerebellar damage: limb clumsiness, unsteady gait or posture, impaired intentional movement
    - basal ganglia damage: involuntary movements
    - brain stem damage: contralateral weakness, sensory complaints with ipsilateral weakness, sensory complaints in the face, double vision, vertigo, alterations of consciousness
    - spinal cord damage: weakness, spasticity, anesthesia below a specified level, unsteadiness of gait, deficits are usually bilateral, weakness and sensory complaints in multiple contiguous radicular distributions
  - PNS: weakness, spasticity, anesthesia below a specified level, unsteadiness of gait, bilateral or asymmetric weakness, sensory complaints in multiple contiguous radicular distributions, distal weakness, unilateral special sensory loss or facial weakness
    = difficult to differentiate from spinal cord deficits
    - cranial nerve deficits: vision and eye movements, movement disorders, vertigo, sensorineural hearing loss, anosmia

- Confirmatory Diagnostic Studies:
  1.) Lumbar puncture for CSF:
    - CSF background:
      - CSF is produced by the choroid plexus in the ventricles, circulates to bathe the spinal cord, and is reabsorbed back into blood vessels by the arachnoidal villi in the brain’s sagittal sinus
      - functions to enhance brain nutrition, remove metabolic byproducts, and protect against mechanical injury
      - 500 mL produced per day, with a total vol of 140 mL at any given time
    - less rapid but more specific than serologies
    - indications for LP:
      - diagnosis: lab analysis, determine spinal fluid pressure, administer imaging dyes
      - encephalitis
- meningitis: do immediately with suspected meningitis unless contraindicated
  - delayed LP $\rightarrow$ start antibiotics immediately
- subarachnoid hemorrhage with headache
- pseudotumor cerebri with idiopathic intracranial hypertension: the only time an LP is
done despite presence of papilledema
- MS
- normal pressure hydrocephalus and prediction of response to surgical shunting
- therapeutic: administer drugs into CNS, remove excess CSF
- headaches: severe, rapid-onset, recurrent, worst headache of life, or intractable
  - only do LP after normal CT and normal platelet count
- contraindications:
  - due to risk of brain herniation:
    - suspected brain abscess
    - elevated intracranial pressure
  - suspected mass lesion, ventricular obstruction, local infection at puncture site, suspicion of
epidural abscess, thrombocytopenia or anticoagulation therapy, position-related cardiorespiratory
  compromise, acute spinal trauma or prior lumbar surgery
- risks: headache (25%), back pain, allergic reaction, brain herniation, infection, bleeding, paralysis
  - headache due to decreased CSF volume from slight leakage, can last several days
  - can give an epidural blood patch (injection of autologous blood into the epidural space)
    for severe cases
- procedure:
  - may use sedative
  - insert needle into L3-L4 to reach the lumbar cistern (cauda equina region)
  - need to go lower in kids
  - elderly may need a cisternal procedure
- interpretation: most constituents of CSF will be present in $\geq$ or lower levels than in plasma
  - opening pressure
    - high elevation in purulent meningitis or intracranial tumors
    - moderate elevation in mild inflammation, encephalitis, neurosyphilis
  - appearance and color:
    - normal is clear and colorless
    - cloudy with increased WBCs or protein
    - yellow (xanthochromia) with ↑ bilirubin or carotene or melanoma
    - red-tinged from traumatic tap or bleeding into subarachnoid space
  - consistency
  - tendency to clot
  - cells:
    - count and differential
      - normally 0-5 lymphocytes or monocytes per mL
      - granulocytes, macrophages, and RBCs are never normal
    - WBCs:
      - high but under 100 = inflammation but not necessarily infection
      - greater than 100 = likely infection
      - neutrophil predominance = bacterial
      - lymphocyte predominance = viral or something else
      - eosinophils seen in shunt, parasitic infections, and allergic reactions
  - protein:
    - elevated protein means something is wrong but is not specific for infection
      - could be tumor, trauma, inflammation
    - decreased in CSF leak, hyperthyroidism, water intoxication
  - glucose: compare to plasma values, should be 70%
    - low glucose = bacterial or fungal
  - lactate: increased in CVA, intracranial bleed, bacterial meningitis
    - normal in viral meningitis = how to differentiate from bacterial
2.) Nerve conduction studies
   • electromyogram (EMG): measurement of electrical activity arising from muscle fibers; a needle is inserted into the muscle and the electrical activity is recorded during muscle rest and contraction
     - used to distinguish disorders of the neuromuscular junction or muscle
   • nerve conduction study (NCS): measurement of electrical activity arising from peripheral nerves; electrodes are placed on the skin overlying a muscle or nerve, and the area is stimulated by an electric shock
     - electrical stimulation of the muscle provides a measurable response that is recorded and compared to normal values
     - used to distinguish peripheral nerve disorders (axonal vs demyelinating)
     - repetitive stimulation used to diagnose neuromuscular junction disorders
     - numbers subject to change with temperature and technician skill and insight = careful judgment needed regarding utility of these tests
     - there are times when the EMG/NCS absolutely proves the existence of a problem and there are times when they are useless or misleading
     - consider this study to be an extension of the neuro exam
   ➔ when to use these studies: suspicion of peripheral nerve or muscle injury, detection of carpal tunnel, investigation of polyneuropathy, investigation of radiculopathy or muscle diseases
3.) Evoked potential studies: electrical studies used to study the conduction of CNS pathways; electrodes are placed on the scalp and brain potentials are recorded in response to a stimulus
   - values are compared to normal values
   - three kinds of tests: visual (switching checkerboard), brainstem/auditory (clicks), somatosensory (shocks)
   - used more commonly in the past before development of imaging
   - still useful for diagnosing MS, spinal cord diseases, optic neuritis, hearing abnormalities, balance difficulties
4.) Electroencephalography (EEG): electrodes are placed on a pattern on the scalp to create a graph comparing electrical potentials at 2 different points on the scalp over time
   - specific patterns of electrical activity have been identified as normal or pathological patterns
   - normal background is ~18 oscillations
   - abnormal: sharp wave followed by slow wave = epileptiform
   - not all variation is abnormal, it is all about the patterns, and interpretation is an art
   - not all spikes are epileptic
   - only works during a seizure
   - when to order: looking for evidence of epilepsy, trying to tell if shaking episode is true epilepsy, to determine state of consciousness, to detect absence of brain activity
     - EEG won’t be flat in brain death until the cerebral cortex has died, which takes several days after brainstem death
     - can also be used to determine if there is an intracranial mass, as EEG tracings are muted or slow over the mass
     - currently not used frequently as imaging techniques are more precise
5.) Tissue biopsy
6.) CT scan
   - without contrast best for lesions
7.) MRI
8.) PET

☐ Synthesis of Findings:
   - what levels are affected, and how many lesions are there?
     - small lesions in areas of high traffic (internal capsule, spinal cord, brainstem) cause widespread neurologic dysfunction
     - small lesions elsewhere may be asymptomatic
   - can the findings be grouped together to form a known syndrome?
   - which is the etiology: genetic, congenital, infectious, inflammatory, neoplastic, degenerative, metabolic, endocrine, or vascular?
     - temporal clues: degenerative diseases progress gradually while vascular diseases progress rapidly
Neurogenetics

Background
-Most diseases probably result from a combination of one or more genes interacting with environmental factors vs monogenetic inheritance (where a single defective gene causes disease)

- Expressivity: variation in degree of expression of the phenotype
- Penetrance: percent of individuals with the mutation who will show any clinical manifestation
- Non-allelic genetic heterogeneity: a clinical syndrome caused by more than one gene
- Allelic heterogeneity: when one gene causes > 1 clinical syndrome
- Lyonization: a normal biological process in females (or Klinefelter’s) where one X chromosome is inactivated in every cell
- Trinucleotide repeat expansion/anticipation: a biological phenomenon in neurologic disorders where disease severity increases in subsequent generations with expansion of trinucleotide repeats

Autosomal Dominant Disorders
- Characteristics:
  - multiple affected generations
  - males and females equally affected
  - parents of affected child have a 50% risk that subsequent child will be affected
  - male to male transmission is seen
  - variable expressivity
  - in neurology, generally involves late onset degenerative diseases

A.) Neurocutaneous disorders
  i.) tuberous sclerosis:
  ii.) neurofibromatosis: a genetically-inherited disorder in which the nerve tissue grows tumors that may be benign or may cause serious damage by compressing nerves and other tissues
  - NF 1 is autosomal dominant with 100% penetrance but variable expressivity
    - half the mutation is inherited and the other half is caused by a de novo NF1 mutation in the neurofibromin gene \( \rightarrow \) inactivation of Ras
    - diagnostic criteria (must have 2/7): 6+ café au lait macules, freckling in the axillary or inguinal region, 2+ neurofibromas of any type or one plexiform neurofibroma, 2+ Lisch nodules in the iris, optic glioma, distinctive osseous lesion such as sphenoid dysplasia or pseudoarthritus, 1\(^{st}\) degree relative with NF1
    - other presentations: astrocytoma, vestibular schwannoma, ependymoma, meningioma, congenital hydrocephalus, seizures, learning disabilities, glaucoma, pheochromocytoma, renal artery stenosis, GH deficiency, short stature, scoliosis, precocious puberty, cutaneous neurofibromas
  - management:
    - kids: regular physical exams, track development, correct skeletal abnormalities, annual eye exams, MRIs for suspected lesions
    - adults: regular physical exams, regular BP screening to catch renal artery stenosis, MRIs for suspected lesions
  - prognosis: main cause of death is malignant nerve sheath tumor
  - NF2 is also autosomal dominant and is a result of mutation of the schwannomin gene
    - diagnostic criteria: bilateral vestibular schwannomas (may exhibit facial nerve issues as this also runs through the external auditory meatus); FH of NF2 + unilateral vestibular schwannoma; two of the following: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities (looks like a cataract)
    - management: many teams, VEGF inhibitors
    - prognosis: depends on age of symptom onset, degree of hearing deficit, and number and location of tumors
      - now usually greater than 15 years
  iii.) Von Hippel-Lindau:
B.) Myotonic dystrophy
C.) Huntington’s disease: see movement disorders lecture
D.) Hereditary spinocerebellar ataxias
E.) Hereditary neuropathies
F.) Dementias
   i.) Alzheimer’s disease: the most common form of dementia that causes problems with the temporal and parietal lobes
      -results in decreased parenchymal volume, hippocampal atrophy, neurofibrillary tangles with tau, neuritic plaques with amyloid deposition, granulovacular degeneration, Hirano bodies
      -all cases are autosomal dominant and involve abnormal cleavage of amyloid precursor protein
      -risk factors: age, FH, Down’s syndrome, apolipoprotein E4 genotype (E2 is protective)
         -but < 10% of cases are familial, with familial Alzheimer’s associated with an earlier onset of presentation
      -presentation: memory impairment, language deficits, acaica (difficulty performing simple mathematical tasks), depression, agitation, apraxia (inability to perform skilled movements)
      -investigation: diagnosis is by exclusion
         -genetic testing is to provide information only, less sensitive than clinical dx
         -MRI or CT will show hippocampal atrophy
         -PET to detect amyloid
         -lumbar puncture to detect increased hyperphosphorylated tau
      -treatment:
         -cholinesterase inhibitors: tacrine, donepezil, rivastigmine, galantamine
         -NMDA receptor antagonist: memantine
      -prognosis: death usually occurs within 5-10 years secondary to aspiration pneumonia or infection
   ii.) frontotemporal dementia: degenerative illness of the frontal and temporal lobes as a result of accumulation of tau in neurons
      -genetic subtypes: frontotemporal dementia with Parkinsonism
      -presentation:
         -usually begins around ages 55-65 and runs a shorter course than Alzheimer’s
         -gradual onset of confusion with personal neglect, apathy, aphasias, personality changes, abulia (lack of will or initiative), frontal release signs, echolalia

☐ Autosomal Recessive Disorders
-Characteristics:
   -greater than 1 family member affected within a single generation
   -males and females equally affected
   -history of consanguinity
   -parents of affected child have a 25% risk that future child will be affected
   -carriers are usually asymptomatic
   -in neurology, usually seen in childhood inborn errors of metabolism
A.) Inborn errors of metabolism
   i.) phenylketonuria:
   ii.) Tay-Sachs disease: lysosomal enzyme deficiency \( \rightarrow \) ganglioside accumulation in brain
      -more common in certain populations: Ashkenazi Jews, French Canadians of Quebec, southern Louisiana Cajuns
      -presentation:
         -begins around 6 months
         -deterioration of mental and physical abilities: deafness, blindness, dysphagia, paralysis
         -cherry-red spot from degeneration of the fovea
      -investigation: blood test for hexosaminidase A activity
      -prognosis: death by age 4
   iii.) Maple syrup urine disease:
B.) Friedrich’s ataxia: see peripheral neuropathies lecture
C.) Wilson’s disease: see movement disorders lecture
D.) Homocystinuria:
E.) Sickle cell disease
X-Linked Recessive Disorders
-Characteristics:
  - female-to-male transmission of disease
  - males tend to have more severe disease
  - females tend to be carriers or have a mild, late-onset phenotype
  - affected males will have carrier daughters
  - carrier females have a 50% chance that sons will have the disease and a 50% chance that daughters will be carriers
A.) Duchenne/Becker’s muscular dystrophy: see muscular dystrophy lecture
B.) Adrenoleukodystrophy:
C.) Kennedy’s disease: spinal bulbar muscular atrophy
D.) Menkes disease:
E.) Lesch-Nyhan disease:
F.) Fragile X syndrome: the most common inherited form of mental retardation

X-Linked Dominant Disorders
-Characteristics:
  - multiple generations affected
  - female-to-male disease transmission
  - usually lethal in males
A.) Rett’s syndrome: mutation in MeCP2 gene → progressive neurodevelopmental disease
  - only in females (or males with Klinefelter’s)
  - presentation:
    - normal until 6-18 months of age, then decreased head growth, autistic behavior, writhing hands, ataxia, loss of speech, seizures
    - later cardiac issues, scoliosis
  - investigation: clinical and genetic testing
  - prognosis: patients may live into their 40s
B.) Aicardi syndrome:
C.) Lissencephaly 2: smooth brain with no sulci or gyri → severe mental retardation, seizure syndromes

Mitochondrial Inheritance Disorders
-Characteristics:
  - affects multiple generations but transmission is by females only due to cytoplasmic inheritance (only ovum contributes cytoplasm in the zygote)
  - equal numbers of males and females affected
  - variable expressivity and severity
  - affected males won’t transmit it to future offspring, but all affected females at risk of transmission to future offspring
A.) Monoclonic epilepsy with ragged-red fibers syndrome:
B.) Mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS): point mutation in tRNA for leucine
  - presentation:
    - onset before age 40
    - recurrent headaches, stroke-like episodes, seizures, short stature, progressive dementia
  - diagnosis: elevations in serum pyruvate and lactate, stroke lesions that don’t conform to normal vascular distributions
  - treatment: no proven therapy, but can give mitochondrial cocktails with antioxidants and coenzyme Q10
C.) Leber’s hereditary optic neuropathy (LHON):
D.) Kearns-Sayre syndrome: bad ophthalmoplegia

Genetic Testing
- Should only be done on well-informed, consenting ADULTS
- May be done for diagnosis, prediction, risk assessment, or pharmacogenetic purposes
Movement Disorders

☐ Background and Abnormal Movements
-Movement disorders commonly occur as a result of lesions in the basal ganglia or cerebellum and their connections
-Acetylcholine and dopamine act in opposing directions
-adding dopamine is equivalent to blocking Ach
-Abnormal movements:
  1.) tremors:
    - contraction (action) tremor: occurs when trying to maintain a fixed position; the most common kind of tremor
    - physiologic tremor: seen with fatigue, anxiety, hypoglycemia, hyperthyroidism, drug withdrawal, caffeine use, and in normal people with movements requiring a high degree of precision or power
    - essential tremor: a slower frequency physiologic tremor with varying mechanisms that is common later in life
      - can involve the extremities, head, and voice
      - called familial tremor if there is a FH
      - treatment: first line is a β-blocker, primidone, benzos for anxiety, alcohol
    - intention (ataxic) tremor: absent at rest and at the start of a movement but increases when fine adjustments are required
      - impaired finger-to-nose coordination
      - caused by disease of the cerebellum or its connections, including MS
      - treatment: meds are usually ineffective but surgery is last resort
  2.) athetosis and chorea
    - athetosis can be seen in cerebral palsy or as a result of kernicterus (elevated bilirubin at birth) or hypoxia
    - chorea can be the result of untreated strep infection (Sydenham’s chorea), pregnancy (chorea gravidum), or Huntington’s
      - can be caused by a state of dopamine excess
  3.) tics: quick, coordinated, repetitive movements
    - can occur alone or with other syndromes
    - Tourette’s syndrome: the onset of tics from ages 2-13 as well as involuntary whistles, grunts, and coughs
      - may exhibit echolalia or coprolalia (uncontrolled use of offensive language)
      - treatment: haloperidol or pimozide, but limited by side effects
  4.) hemiballismus
    - if unilateral, usually the result of a contralateral subthalamic nucleus of Luys infarct
  5.) myoclonus: shock-like contraction of a group of muscles (or generalized) that is irregular in rhythm and amplitude
    - from anoxic damage, spinal cord injury, uremia, hepatic encephalopathy, or rare neurologic disorder
    - treatment: clonazepam, valproate (limited efficacy)
  6.) dystonia: maintenance of a persistent extreme posture in one or more joints
    - generalized dystonia (dystonia musculorum deformans): a rare hereditary dystonia most commonly affecting Jewish families
    - focalized dystonias: includes torticollis, writer’s cramp, and blepharospasm
    - treatment: meds are usually not helpful, Botox is becoming more common and is helpful, surgery is available for torticollis

☐ Parkinson’s Disease: a degenerative disorder of the central nervous system as a result of the death of dopamine-generating cells in the substantia nigra in the midbrain and accumulation of Lewy bodies in neurons
-Degeneration of connection between substantia nigra and the striatum, as well degeneration of the raphe nuclei, locus ceruleus, and the motor nucleus of the vagus nerve
- results in decreased dopamine and increased Ach
-Most cases are idiopathic
  -monogenic forms only represent 5% of cases
    -may be autosomal dominant or autosomal recessive
      -dominant forms involve the PARK1, 4, and 8 genes
        -PARK1 and PARK4 involve the α-synuclein gene (α-synuclein is the main component of Lewy bodies)
        -rare but involve early onset disease with dementia and rapid progression
        -PARK8 is the most common genetic form of Parkinson’s, and is associated with late-onset disease with psychiatric features
    -recessive forms involve the PARK2, 6, 7, and 9 genes
      -associated with Arabic and Ashkenazi Jewish descent
  -risk factors: age, exposure to MPTP (byproduct of synthetic heroin), manganese exposure, flu epidemic
    -caffeine and nicotine may be protective

-Presentation:
  -usually begins after age 65
  -most cases have unilateral symptoms: resting tremor (pill-rolling), bradykinesia, stiffness, fatigue, stooped posture, cogwheel rigidity, shuffling steps, festinating gait (unwanted acceleration of gait once commenced), masked facies, memory loss, micrographia, postural instability, difficulty initiating movements, disturbance of postural reflexes (can’t adjust upon being pulled upright)
    -if bilateral, it is more likely that the disease is a result of pharmacologic exposure

-Investigation:
  -genetic testing is available but should be performed only after careful consideration due to inconclusive testing results and lack of specific treatment for the disease

-Treatment:
  -meds:
    -**levodopa**: dopamine precursor that can cross the blood-brain barrier to replace the dopamine deficit
      -problem: levodopa will be converted in the periphery to dopamine, so you must also give *carbidopa* to prevent this and allow for more availability of levodopa in the CNS
        -can’t cross the BBB
        -also helps to minimize nausea and vomiting
      -can be administered to help diagnose Parkinson’s
      -treatment should begin when patient experiences functional impairment
      -first-line therapy in older patients (> 65) as its efficacy decreases over time
      -80% of patients significant improve on it
      -won’t improve postural instability, dementia, autonomic dysfunction, or “freezing”, or prevent progression of the disease
      -side effects: nausea, vomiting, anorexia, postural hypotension, cardiac arrhythmias, mental disturbances, dyskinesias (increase with duration of treatment), overactivity, restlessness, agitation, hypomania
      -drug interactions: nonselective MAOIs, antipsychotics, iron salts, metoclopramide, phenytoin
      -contraindications: narrow angle glaucoma, melanoma, undiagnosed skin lesions
    -**dopamine agonists**: act directly on dopamine receptors in the corpus striatum
      -first-line therapy for younger patients with milder disease
      -may delay need for levodopa
      -can be used as additional therapy for patients already on max dose levodopa
      -two generations:
        -1st gen derived from ergot alkaloids
          -**bromocriptine**:
        -2nd gen
          -**pramipexole**:
          -**ropinirole**:
          -**apomorphine**: rescue therapy for “off” episodes
            -must monitor BP with test dose
• rotigotine: currently being reformulated for the US
- side effects: retroperitoneal, pleural, pericardial, cardiac valve fibrosis, dizziness, headache, insomnia, somnolence, confusion, hallucinations, GI, orthostatic hypotension, syncope, dyskinesias
  - because dopamine is involved in the reward center of the brain, people on these may start showing impulsive behaviors such as gambling and hypersexuality
- drug interactions: lots, including serotonin modulators, can increase risk of serotonin syndrome

• COMT inhibitors: prevent breakdown of levodopa by another pathway → increased levodopa avail to cross BBB
  - allows for decreased levodopa use (which will help decrease side effects)
  - types:
    • entacapone:
    • tolcapone: watch for liver failure
- side effects: dyskinesias, nausea, dizziness, hallucinations, urine discoloration, abdominal pain, diarrhea, orthostasis, somnolence, headache
- drug interactions: nonselective MAOIs, ethanol

• MAO-B inhibitors: inhibit metabolism of dopamine
  - can help delay need for levodopa
  - types:
    • selegiline: acts centrally to prevent destruction of dopamine
    • rasagiline: can cause headache, dizziness, nausea, dyskinesias
  - side effects: insomnia, nausea
  - drug interactions: lots including SSRIs- risk of serotonin syndrome

• amantadine: antiviral agent that increases dopamine release from the nerve terminals
  - can help reduce dyskinesias with levodopa use
  - side effects: tachyphylaxis develops within 3 months, may need to d/c and re-initiate later, insomnia, cognitive, convulsions, ankle edema, orthostasis, livedo reticularis
- anticholinergics: block Ach
  - no longer considered 1st line
  - may be more effective for treatment of resting tremor in younger patients
- other treatments:
  - vitamin E supplementation not shown to be beneficial
  - coenzyme Q10 not shown to be beneficial
  - creatine and minocycline still being studied
- surgery
- deep brain stimulation

Huntington’s Disease: abnormal CAG repeats on chromosome 4 → loss of caudate and squared-off lateral ventricles
- Presentation:
  - onset by ages 20-40, which is affected by anticipation
  - symptoms often begin with a psychiatric disorder
  - subcortical dementia, chorea, dystonia, motor impersistence, incoordination, gait instability, depression, anxiety, impulsivity, apathy, OCD, athetosis
- Investigation: diagnosis is clinical, but CT or MRI will show cerebral atrophy and loss of caudate
- Treatment: no cure, but symptomatic control and genetic counseling are important
  - chorea is like a dopamine-excess state → give dopamine-R blockers such as haloperidol or risperidone or dopamine reserve depleters such as reserpine
    - but may cause depression
  - SSRIs for depression and anxiety
  - tetrabenazine decreases monoamine uptake into synaptic vesicles and depletes monoamine stores
- Prognosis: death within 10-15 years of onset of symptoms
**Wilson’s disease**: impairment of ceruloplasmin synthesis due to hepatolenticular degeneration → copper accumulation in tissues and basal ganglia → neurological or psychiatric symptoms and liver disease

- **Presentation:**
  - usually in teenage years
  - first sign is hepatitis which leads to cirrhosis
  - neuro: tremor, slowness, dysarthria, dysphagia, hoarseness, chorea/dystonia, psychiatric disturbances, “wing-beating” tremor with arms held out
  - progressive disease: limb rigidity, fixed empty smile

- **Investigation:**
  - labs: low serum ceruloplasmin, low serum copper, high copper on liver biopsy, Kayser-Fleischer rings (brown ring around cornea)

- **Treatment:**
  - reduce copper intake: avoid chocolate, mushrooms, shellfish, nuts, and take sulfured potash with meals to prevent copper absorption
  - chelating agents: beware, may cause rebound freeing of copper reservoirs
  - may need liver transplant
  - early treatment prevents neurologic sequelae

**Tardive Dyskinesia**: abnormal buccal-lingual, head, and sometimes limb movements from long-term treatment with neuroleptics
- May be the result of dopamine-R supersensitivity
- **Treatment:** stop offending drug, use dopamine-depleting agents or vitamin E
- **Prognosis:** symptoms can fluctuate and may take months to years to resolve, can be permanent

---

**CNS Infections**

**Meningitis**: inflammation of the meninges that is typically acute, evolving over hours to days

- **General presentation:**
  - fever, headache, neck stiffness, lethargy
  - usually without any focal neuro signs

A.) **Purulent meningitis**: the typical meningitis, a medical emergency

  - **Typical organisms**: *Neisseria meningitidis, Strep pneumo, H. flu*
  - **Presentation:**
    - meningococcal: petechial rash is common, also associated with DIC
    - TB: gradual onset with listlessness and irritability, CN palsies, abnormal CXR
  - **Investigation**: lumbar puncture → increased WBCs with left shift, low glucose, high protein, markedly elevated opening pressure
  - **Treatment:**
    - get blood cultures then start on empiric antibiotic coverage: ceftriaxone
    - meningococcal → Pen G or ceftriaxone
    - nasal carriers: rifampin
    - contacts may need prophylaxis
    - pneumococcal → add vancomycin
    - consider *H. flu* if developed in the setting of otitis or sinusitis → ceftriaxone
    - TB → standard pulm TB treatments will work
  - **Special consideration**: patients with purulent meningitis who have received antibiotics for something else may have a milder clinical course and less severe CSF abnormalities (resembling aseptic meningitis) = always consider this possibility in a meningitis patient who has recently received antibiotics

B.) **Chronic meningitis**: usually not due to typical organisms, but fungi or TB

  - **Investigation**: lumbar puncture → mildly elevated WBCs that are mostly lymphocytes, low glucose, high protein, mild-moderately elevated opening pressure

C.) **Aseptic meningitis**: any acute meningitic syndrome not caused by acute bacterial infection, usually viral

  - **Presentation** may initially look just like purulent meningitis
  - **Investigation**: differentiate from purulent meningitis by lumbar puncture → more lymphocytes than PMNs, glucose not as low, total WBCs not as high, opening pressure not as high
-treatment: empiric antibiotics until cultures are negative

- **Encephalitis:** generalized or diffuse inflammation or infection of the brain tissue itself
  - Usually caused by a virus (herpes or arboviruses)
  - Arbovirus encephalitis is spread by insects, so it is more common in the spring and early summer
  - Herpes encephalitis is more common in the elderly
- General presentation:
  - Usually with fever, headache, lethargy, confusion, seizures, sometimes coma
  - Usually without any focal neuro signs
  - Herpes encephalitis often involves the medial temporal lobes and may be confused for stroke!
- Investigation: assays generally not done as they are not widely available and don’t change the course of treatment
- Treatment: IV antivirals are given empirically for nearly all patients with clinical syndrome suggesting viral encephalitis

- **Brain Abscess:** a localized infection in the brain which typically presents with focal signs due to abscess compressing brain tissue and mass effect
  - Common organisms: Strept, Staph, anaerobes
  - Initially begins as a focal area of inflammation = cerebritis
  - Progresses to form a pocket of pus with surrounding capsule
  - Presentation: may have fever, chills, or other signs of infection, focal deficits with increased ICP, may have concomitant sinusitis or history of surgical procedure to the area
- Investigation:
  - CT showing ring-enhancing lesions with surrounding edema
- Treatment:
  - Surgical drainage
  - Prolonged IV antibiotics with serial scan monitoring

- **Other Conditions**
  A.) Meningitis-like inflammatory conditions such as sarcoidosis, carcinoma, lupus, and chemicals or drugs can cause meningeal injury
  - Tend to be more subacute but can cause CSF abnormalities
  B.) Rabies: rhabdoviral infection transmitted in infected animal saliva via bite
  - Most common carriers are bats, skunks, foxes, and raccoons
  - Infected dogs are unlikely as they usually die within 5-7 days
  - Incubation period is usually 3-7 weeks as the virus travels up the nerves into the CNS
  - Presentation:
    - Prodrome of pain at the bite site, fever, malaise, nausea, and vomiting
    - Later delirium, painful swallowing, rage alternating with calm, or acute ascending paralysis
    - Progression to coma, autonomic dysfunction, and death
  - Treatment:
    - Keep biting animal in isolation for 7-10 days of observation
    - Post-exposure immunization with rabies Ig administered around the wound and IM
  C.) Prion diseases
  - Slow replication and long latency
    - **Creutzfeldt-Jakob disease:** prion disease transmitted through infected tissue or genetically inherited
      - Cases can be sporadic or in a familial autosomal dominant pattern
      - Presentation: rapidly progressive dementia, myoclonus, ataxia, and somnolence
      - Investigation: may have epileptiform EEG

- **Multiple Sclerosis**
  A.) Background
  - Pathophysiology: infectious agents, genetic predisposition, and environmental factors may all play a role in causing an abnormal immunologic response that leads to MS
  - Course: inflammation → demyelination → axonal loss
-there will be a period of time with no clinical features prior to first attack
-can’t diagnose MS from just one attack, need to have at least 2
-demyelination continues to occur during the clinically silent periods between relapses
-as disease progresses, MRI lesion burden and disability increase as cognitive function decreases

-Forms:
  1.) relapsing-remitting: partial recovery from disability between relapses
     -accounts for 55% of cases
     -all meds are for this form of MS!
     -may convert to a progressive form
  2.) secondary progressive: increasing disability with distinct relapses
     -accounts for 30% of cases
  3.) primary progressive: nearly continuous worsening of disability
     -accounts for 10% of cases

-Average age of onset is 20-40 years
-More prevalent in women and in individuals living further from the equator
    -prior to puberty, you will inherit the incidence of the place you move to
    -if moving after puberty, your risk will remain the same as where you grew up
-Common manifestations: optic neuritis (retro-orbital with patchy loss of vision), transverse myelitis (one level of the spinal cord vs all the way down), paresthesias, ataxia, weakness, incoordination, spasticity (LMN lesions), cognitive impairment

-Investigation:
  -diagnostic criteria: none are very good, really all they say is you must look for other explanations, and that there needs to be occurrence in > 1 area of the brain > 1 time
    = only used for defining cohorts for research purposes
  -history of episodes that come and go- must be separated in space and time!
  -MRI of brain and spinal cord showing multiple characteristic lesions or plaques (periventricular or subcortical U-fibers, corpus callosum lesions)
    -T1 weighted imaging makes use of gadolinium contrast that can penetrate the blood-brain barrier to enhance areas of inflammation (active lesions)
      -“black holes” seen on this kind of imaging represent areas of serious brain injury such as axonal loss
    -T2 weighted imaging does not use contrast and shows various lesions to represent the cumulative disease burden
    ***remember that may healthy individuals have incidental white spots, so these spots need to be in the characteristic places for MS, such as the cervical spinal cord and ventricles
  -CSF: evidence of oligoclonal bands or increased IgG index
  -evoked potentials may be helpful

-Treatment:
  -may be most effective early in disease to prevent brain atrophy
  -goals are to treat the whole disease, slow down disability, reduce relapse rate, reduce CNS inflammation, reduce brain atrophy, and improve patient’s quality of life
  -meds:
    -immunomodulators: IFN, glatiramer acetate injections
      -problem is they don’t make you feel better and sometimes make you feel worse (flu-like symptoms), although they will make you better long-term
    -immunosuppressants: azathioprine, methotrexate, cladribine, fingolimod, mitoxantrone, cyclophosphamide, IV IgG, mycophenolate mofetil, natalizumab (must test for JC virus before giving or risk causing a demyelinating process worse than original MS!)
    -large-dose corticosteroids for relapses or aggressive disease
  -vitamin D supplementation (association between low vit D and MS attacks)

-Prognosis:
  -if untreated, brain atrophy will occur and half of all MS patients will need an assistive device to walk within 5 years, relapsing MS will give way to progressive MS within 10 years, and most patients will experience cognitive impairment
  -early intervention at time of diagnosis associated with better outcomes
Primary Brain Tumors

- Originate in the CNS
- ex. non-Hodgkin lymphoma confined to the CNS
- 100+ types, arising from different cells of the CNS
- Focus today is on malignant neoplasms, but even histologically benign tumors can cause mass effect
- Incidence is rising (may be due to increased detection or environmental factors)
  - Associated with level of economic development of a population
  - Higher incidence in Caucasians, uncommon in Asians and Native Americans
  - Slightly more common in males
  - Risk increases with age and peaks at age 50
- Risk factors: healthcare and lab research worker, electrical worker, oil refinery worker, agricultural worker, exposure to ionization radiation (including atomic bomb survivors), history of head trauma, exposure to N-nitroso compounds (diet or tobacco), genetic predisposition
  - Potential risk factors: viral infections, Toxoplasma infection, alcohol, tobacco, radiofrequency and EMF radiation exposure (microwaves, radar)
  - Cell phone use for > 10 years doubles chance of getting a glioblastoma or acoustic neuroma
- Presentation: headaches, sensory loss, focal weakness, may cause obstructive hydrocephalus
  - Headaches are usually secondary to increased ICP, with progressive increase in frequency and severity
  - Classically occur as a headache upon waking or a headache that wakes pt up
  - Occur in 20% of brain tumor patients
  - High grade tumors tend to present more as headaches due to mass effect, while low grade tumors tend to present more as seizures because they irritate synapse sites
  - Seizures are often what precede the diagnosis
  - Occur in 35% of brain tumor patients
  - Cognitive dysfunction is probably the most common problem in patients with brain tumors
    - Frontal personality: impulsiveness, hypersexuality, irritability, etc.
    - Memory problems, especially short-term
    - Depression from altered brain chemistry
    - Language dysfunction in left hemispheric tumors
    - Problems with visual perception and scanning in right hemispheric tumors
    - Focal neuro deficits: hemiplegia, hemiparesis, ataxia, nystagmus, CN palsies
      = Can mimic a stroke!
  - Nausea and vomiting secondary to increased ICP
    - Higher incidence with posterior fossa tumors
    - Symptomatic endocrine dysfunction from effects on hypothalamus: hypothyroidism, decreased libido
    - Visual disturbances from pressing on optic nerve: contralateral flashing lights, visual field loss, diplopia
      - Transitory episodes of altered consciousness and visual disturbances known as plateau waves
- Investigation:
  - Full neuro PE: CN, DTRs, strength
  - CT +/- MRI
  - Work up for metastatic disease of suspected: chest or abdomen CT, breast mammogram
  - EEG if there are seizures
  - Serial LPs: the old school way of detecting tumors
  - PET: help distinguish active lesions from old/dead lesions
  - Biopsy: primary tumors are classified by their predominant cell type and are graded low or high by presence or absence of standard pathologic features
- Treatment:
  - Surgery +/- radiation +/- chemo
  - Quality of life issues
  - Anti-epileptics only needed for patients with seizures at time of diagnosis
    - Be aware of side effects and metabolism interactions with chemotherapeutics
    - Increased seizures aren’t always a sign of tumor progression
  - Steroids are a mainstay of treatment of symptoms
    - Consider prophylaxis after 2 months due to risk of PCP
-need to prophylax against thromboembolic events (increased risk in cancer and treatment): LMWH, heparin, warfarin, IVC filters
-cognitive dysfunction secondary to tumor and treatment
  -need neuropsych eval
  -drugs avail for memory deficits and attention deficits
-Poor prognosis with an average 5 year survival rate of 33%
-survival has not improved significantly over the last 50 years

☐ Secondary Brain Tumors
-Originate as solid tumors in other parts of the body that then metastasize to the brain
  -frequently carcinomas from the breast, lung, and colon, and melanoma
-More common than primary brain tumors

☐ Gliomas: arise from support cells of the CNS, including astrocytes and oligodendrocytes
-most primary brain tumors are this kind
-most are malignant
-Grade 1:
  • pilocytic astrocytomas: usually found in kids, tend to occur in cerebellum or 3rd ventricle, rarely invasive
    -treatment of choice is surgery
    -prognosis: 10-year survival rate is 80%
  • pleomorphic xanthoastrocytoma:
    -> treatment: surgery +/- radiation
-Grade 2: diffuse or well-differentiated astrocytomas or oligodendrogliomas
  • well-differentiated astrocytoma: occurs around age 35, usually located in cerebral hemispheres or cerebral cortex, slow-growing
    -prognosis: avg survival is 7 years because malignant transformation to aplastic astrocytoma or glioblastoma is common
  • well-differentiated oligodendroglioma: occurs in young to middle-aged adults
    -investigation: histology shows characteristic “fried egg” cells
    -prognosis: survival is ~10 years
    -> treatment: surgery, observation, chemo if progression or intractable seizures
-Grade 3: considered high-grade due to ability to invade normal brain via white matter tracts, with spread to contralateral brain via corpus callosum
  • anaplastic astrocytoma: occurs around age 45, most commonly located in cerebral white matter, fast-growing
    -prognosis: average survival is about 3 years with high incidence of progression to glioblastoma
    -> treatment: surgery, radiation with temozolomide, consider clinical trials
-Grade 4: glioblastoma or giosarcoma
-characterized by necrosis with vascular proliferation
  • glioblastoma: accounts for half of all astrocytomas and is the most common primary brain neoplasm, usually arises after age 60, usually located in cerebral white matter
    -spreads rapidly, will double in size in 14 days if left untreated
    -investigation: appears on CT as a ring of tissue around a necrotic core
    -prognosis: survival with appropriate treatment is 1 year
    -> treatment: surgery, radiation with temozolomide, 1 year chemo +/- bevacizumab, consider clinical trials
-Glioma treatment:
-if low grade:
  -if no symptoms other than well-controlled seizures, defer treatment until disease progression
  -with progressive symptoms: resection +/- chemo
    -radiation only in refractory cases
-if high grade: surgical resection, radiation therapy, chemo
 -goals of surgery: confirm pathological diagnosis, rapid improvement of symptoms, reduce # of cancer cells requiring treatment (especially the core that is relatively resistant to radiation and chemo)
- can surgically implant chemo wafer (Gliadel- 2 month survival benefit), use radiolabeled antibodies, or use intratumoral gene therapy
- radiation: focal or conventional high-dose (intensity-modulated or stereotactic)
  - side effects:
    - acute encephalopathy in first few days: give steroids
    - early delayed encephalopathy in weeks to months: steroids
    - focal cerebral necrosis in months to years
      - hard to distinguish from tumor recurrence
      - steroids, hyperbaric oxygen therapy
- chemo limited by blood-brain barrier
  - dexamethasone use may close tumor-brain barrier to chemo
  - consider interactions with anti-epileptics pt may be on
  - temozolomide shown to improve survival in studies
  - VEGF antibodies may be useful (bevacizumab) to inhibit tumor angiogenesis
- new therapies: vaccines, inhibitors of resistance, growth factor inhibitors, anti-angiogenesis therapies
- ideal future therapies: targeted to high percentage of gliomas, activated in tumor, something that is important to the tumorigenic process, ability to penetrate blood-brain barrier, P450 metab
- Overall prognosis: most important factors are extent of surgical resection, age, and performance status
- skill of neurosurgeon may be most important treatment decision
- better outcome with gross total resection

- Other Cranial Neoplasms
  A.) Ependymomas: arise from cells lining the ventricles or spinal canal, with most tumors being in the brain
    - slow growing
    - affects children and young adults
    - prognosis: significantly worse if under age 3
  B.) Meningiomas: slow-growing tumors arising from the meninges that are attached to the dura mater
    - benign?
    - account for 1/3 of primary brain tumors
    - prior radiation is a risk factor
    - presentation: often asymptomatic, visual complications if affected optic nerve tract
    - investigation: consider neurofibromatosis
    - treatment: surgery is mainstay of therapy
  C.) Nerve sheath tumors: arise from Schwann cells, which are the glial cells of the PNS
    - ex. vestibular schwannoma
  D.) CNS lymphomas: affect lymphoid tissue confined to the CNS and eyes, usually are multifocal and very deep in the brain parenchyma
    - majority are non-Hodgkin
    - risk factors: immunodeficiency, AIDS, organ transplant, older adults
    - treatment: steroids, methotrexate-based chemo regimens
    - prognosis: survival without treatment is less than 1 year, with treatment is about 4 years

Motor Neuron Diseases, Disorders of Neuromuscular Transmission, and Muscular Dystrophy

- Motor Neuron Diseases
  - Background
    - presentation of UMN disease: loss of dexterity, increased muscle tone, spasticity, hyper DTRs, + Babinski, spastic dysarthria, pseudobulbar affect (pathological over-response to emotional situations)
    - presentation of LMN disease: weakness, decreased muscle tone, muscle atrophy, fasciculations, reduced or absent DTRs

- Amyotrophic Lateral Sclerosis: aka Lou Gehrig's disease; caused by the degeneration of upper and lower neurons located in the ventral horn of the spinal cord and the cortical neurons that provide their efferent input
  - Highest incidence in ages 65-74, with average age of onset 56-63
  - rarely occurs before age 20
- Slightly more common in males
- 10% of cases are familial, with some of them due to the SOD1 mutation
  - autosomal dominant inheritance

- Presentation
  - focal, painless limb weakness that spreads to contiguous areas over several months
  - distal to proximal spread: foot drop, hand weakness, head drop
  - some start with corticobulbar weakness (this tract contains UMN of cranial nerves): slurred speech, difficulty swallowing or choking
  - cramps
  - fasciculations
  - cognitive changes such as frontotemporal dementia
  - no sensory symptoms or problems with coordination (cerebellum), this is purely a motor disease!

- PE:
  - UMN signs: hyperactive reflexes, abnormal reflexes such as Babinski, decreased RAMs, increased tone/spasticity, pseudobulbar affect
  - LMN signs: weakness, fasciculations, muscle atrophy

- Investigation:
  - differential: cervical myelopathy, motor neuron disease secondary to HIV, multifocal motor neuropathy, HTLV-1 infection, adult-onset hexosaminidase deficiency, Lyme disease, lead intoxication, vit B12 deficiency, paraneoplastic syndromes (lymphoma), hyperthyroidism, benign cramp-fasciculation syndrome

- Diagnosis:
  - upper and lower motor neuron signs in at least ¾ regions: bulbar, cervical, thoracic, or lumbosacral regions
  - UMN signs as detected in PE
  - LMN signs as detected by EMG: denervation (fibrillations, + sharp waves), small fasciculations not visible on PE, reinnervation → large, complex motor units

- Labs: serum CK may be normal or elevated

- Treatment:
  - goals: slow disease progression, maintain function, maintain safety, maintain comfort
  - what needs to be managed: sialorrhea (drool), secretions, pseudobulbar affect, depression, laryngospasm, head drop, communication, hypoventilation, contractures, cognitive impairment, foot drop, quads weakness, ADLs, dysphagia, constipation, urinary urgency, muscle cramps
    = may need multidisciplinary clinic referral
  - meds:
    - botox for refractory sialorrhea
    - dextromethorphan or quinidine for pseudobulbar affect
    - riluzole: slows progression by reducing presynaptic release of glutamate
      → costly with little increase in survival but improves quality of life
    - baclofen, benzos, tizanidine for spasticity
    - SSRIs for pseudobulbar affect, depression
    - early PEG placement to prevent aspiration, stabilize weight and lengthen survival
    - anticholinergics to reduce secretions
  - RT:
    - noninvasive ventilation to treat respiratory insufficiency
    - cough assist devices and chest physical therapy
    - tracheostomy and mechanical ventilation
    - communication devices for dysarthria

- Prognosis: 60% of patients die within 5 years of symptom onset (not diagnosis), but many live beyond 10 years

### Upper Motor Neuron Diseases

#### A. Primary lateral sclerosis
- a rare neuromuscular disease characterized by progressive voluntary motor muscle weakness
- onset is typically in middle age
- slight male predominance
- presentation:
  - common: leg stiffness or weakness that eventually spreads to the arms and bulbar muscles
-other: hyperreflexia, unilateral onset, dysphagia, dysarthria, late emotional lability, urinary urgency, subclinical frontal lobe abnormalities
-treatment: supportive only as there is no evidence for riluzole
-prognosis: disease itself lasts 8+ years, and many patients go on to develop LMN symptoms and transition to the diagnosis of ALS (could take as long as 27 years)
-can do serial EMGs to monitor LMN function

B.) Pseudobulbar palsy: an upper motor neuron lesion to the corticobulbar pathways in the pyramidal tract
C.) Hereditary spastic paraplegia: a group of inherited diseases whose main feature is progressive stiffness and contraction in the lower limbs as a result of damage to dysfunction of the nerves
D.) Adrenomyeloneuropathy: a rare inherited disorder that is a milder form of X-linked, where young children generally exhibit cerebral dysfunction, with rapid progression to dementia and quadriplegia

**Lower Motor Neuron Diseases**

A.) Progressive muscular atrophy: a slower-progressing relative of ALS that affects only the LMNs
-presentation: focal and asymmetric distal extremity weakness, atrophy, and fasciculations, hyporeflexia
-bulbar musculature often spared
-investigation:
- differential: ALS, multifocal motor neuropathy, adult onset spinal muscle atrophy
-diagnosis is done by exclusion, takes 3+ years from onset
-labs: CK elevated up to 10x the normal

B.) X-linked spinal-bulbar atrophy: a recessive, slow progressing, neurodegenerative disease associated with mutation of the androgen receptor
-onset from adolescence to mid-80s
-presentation: facial fasciculations, weakness of mouth and tongue, dysphagia, proximal limb weakness, gynecomastia, diabetes mellitus, oligospermia
C.) Hereditary spinal muscular atrophy:
D.) Poliomyelitis:

**Myasthenia Gravis:** an autoimmune neuromuscular disease leading to fluctuating muscle weakness and fatigability due to circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction, inhibiting the excitatory effects of the neurotransmitter acetylcholine on nicotinic receptors

- Presentation:
  - fluctuating weakness of specific muscles that worsens with repetition and improves with rest
  - repeated strength tests will progressively weaken
  - asymmetric proximal or distal extremity weakness
  - difficulty holding up head
  - shortness of breath
  - ocular: fatigable and fluctuating ptosis that is often asymmetric, double or blurry vision, fluctuating ophthalmoplegia (paralysis of 1+ extraocular muscles)
  - symptoms worse at end of the day
  - bulbar/facial: difficulty chewing or swallowing, tired facial appearance, difficulty smiling or whistling, difficulty keeping food in mouth
- Investigation:
  - administer Tensilon (Ach converting enzyme inhibitor) \( \Rightarrow \) temporarily overcome neuromuscular junction Ach deficit
  - labs: Ach-R antibody, MuSK (muscle specific kinase) antibody
  - repetitive nerve stimulation showing amplitude drop off over time
  - single fiber EMG: the most sensitive test for myasthenia gravis
  - CT chest to rule out thymoma
- Treatment:
  - meds:
    - cholinesterase inhibitors (pyridostigmine) for symptoms
    - immunosuppressants: steroids to induce remission (high dose with slow taper), then mycophenolate mofetil, azathioprine, and cyclosporine to maintain remission
    - thymectomy: best response in younger patients with hyperplasia
    - MG exacerbation or crisis: acute worsening of symptoms that can lead to respiratory failure
-occurs with infection, pregnancy, medication noncompliance, steroid use, illness, surgery, or certain medications
- meds to avoid: neuromuscular blocking agents, quinine, quinidine, procainamide, aminoglycosides, azithromycin, telithromycin, quinolones, botox, β-blockers, Ca channel blockers, Mg, iodinated dyes (including IV contrast)
- treat with plasmapheresis to remove pathologic antibodies or IV Ig, as well as supportive respiratory care

Lambert-Eaton Myasthenic Syndrome: a rare autoimmune disorder that is characterized by muscle weakness of the limbs as a result of antibody formation against presynaptic voltage-gated calcium channels in the neuromuscular junction, or as a result of a neoplasm
-Half of the cases are autoimmune, 2/3 are paraneoplastic
-Presentation: proximal weakness and autonomic symptoms such as dry mouth, hypo or absent reflexes
-Investigation:
  - labs: voltage-gated Ca channel antibodies
  - EMG with decrementing pattern similar to myasthenia gravis
-Treatment:
  - treat underlying malignancy if present
  - meds:
    - diaminopyridine: blocks K⁺ efflux → increased Ca influx in nerve terminal → greater Ach release at synapse
    - acetylcholinesterase inhibitors such as pyridostigmine
    - immunosuppressants

Botulism: blockade of Ach release due to botulinum toxin → flaccid paralysis
-Caused by ingestion of contaminated canned foods, or in kids, contaminated honey
-Can also be iatrogenic from bad Botox injections
-Wound botulism possible in trauma cases where soil is involved
-Potential for airborne bioterrorism agent
-Presentation:
  - symptoms begin within 24 hours of ingestion
  - diplopia, ptosis, dilated pupils
  - facial and respiratory weakness
  - descending paralysis
  - autonomic dysfunction
-Treatment: supportive, horse serum antitoxin from CDC
-Prognosis: recovery takes months

Muscular Dystrophies: inherited muscle disorders characterized by muscle weakness and wasting
-abnormalities in ultrastructural proteins
-progresssive vs. congenital myopathies which are stable
-classified by distribution, inheritance, and clinical features
-muscle biopsy reveals necrosis of muscle fibers
-presentation and evaluation:
  - look for stiffness, cramps, and myalgias
  - temporal evolution and age at onset
  - FH
  - precipitation factors: meds, toxins, exercise, fever, carbs, cold
-systemic manifestations: cardiac disease, respiratory failure, hepatomegaly, cataracts, hearing loss, dysmorphic features, contractures
-weaknesses: evaluate distribution
  - facial: inability to bury eyelashes, horizontal smile, can’t whistle
  - ocular: double vision, ptosis, dysconjugate eye movements
  - bulbar: nasal speech, weak cry, nasal regurgitation of liquids, poor suck, difficulty swallowing, recurrent aspiration pneumonia, cough during meals
-neck: poor head control
-trunk: scoliosis, lumbar lordosis, protuberant abdomen, difficulty sitting up
-shoulder girdle: difficulty lifting objects overhead, scapular winging
-forearm/hand: inability to make a tight fist, finger or wrist drop
-pelvic girdle: difficulty climbing stairs, waddling gait, Gower’s sign (hard to get up off floor)
-leg/foot: foot drop, inability to walk on heels or toes
-respiratory: use of accessory muscles

A.) Duchenne/Becker muscular dystrophy: X-linked or sporadic disease characterized by absent dystrophin (Duchenne’s) or reduced dystrophin (Becker’s)
-dystrophin is a muscle membrane protein needed for stabilization
-mutation in dystrophin gene \(\rightarrow\) progressive muscular degeneration leading to loss of ambulation and death
-presentation:
-mostly males but females can rarely have it due to lyonization or Turner’s syndrome
-begins in childhood around age 6 (a little later for Becker’s) with weakness in lower extremities, Gower’s sign, pseudohypertrophy of calves, cardiomyopathy (dystrophin in heart)
-braces by age 10
-wheelchair by age 12 (later for Becker’s)
-diagnosis: muscle biopsy with immunostain for dystrophin, genetic testing, elevated CK, EMG
-treatment:
-supportive care
-meds:
-corticosteroids
-new: gene therapies, losartan, pentoxifylline, aminoglycosides
-eval by PT, ortho, cardiology, and pulm
-cardiac transplant for Becker’s (cardiomyopathy may be more disabling than the weakness)
-prognosis:
-Duchenne: lifespan of 20-40 years
-Becker: milder course of disease

B.) Myotonic dystrophy type 1: a chronic, slowly progressing, highly variable inherited multisystemic disease characterized by distal myopathy with myotonia
-inherited in an autosomal dominant pattern
-onset can occur at any age
-2\textsuperscript{nd} most common muscular dystrophy
-presentation: wasting of the muscles, endocrine changes, myotonia (cramping in hands with slowed relaxation), cardiac conduction defects, frontal balding, early cataracts, diabetes mellitus, infertility, cognitive impairment
-investigation: electrical myotonia with myopathy on EMG
-treatment:
-meds: phenytoin, mexililrine for myotonia
-DM management
-annual EKG

C.) Limb-girdle dystrophies: a host of diseases characterized by slowly progressive symmetric proximal muscle weakness
-dominant and recessive inheritance
-requires specialist referral

D.) Facioscapulohumeral muscular dystrophy: a usually autosomal dominant inherited form of muscular dystrophy that initially affects the skeletal muscles of the face, scapula, and upper arms
-3\textsuperscript{rd} most common muscular dystrophy
-onset in childhood to age 50
-presentation: asymmetric weakness, scapular winging, sleeping with eyes open, sensorineural hearing loss, vascular retinal disease, rarely epilepsy or cognitive impairment
-investigation: genetic testing and FH are most helpful
-muscle biopsy is rarely helpful
E.) Emery-Dreifuss muscular dystrophy: a condition that chiefly affects skeletal muscles and cardiac muscle, resulting in contractures of the ankles, neck, and elbows
   -an X-linked mutation in the emerin gene or an autosomal dominant mutation in lamin gene
   -onset in adolescence
   -presentation: humeroperoneal or scapuloperoneal weakness with early contractures, cardiac arrhythmias
   -treatment: early pacemaker placement

Epilepsy and Coma

- **Background**
  - **Seizure:** paroxysmal, excessive, synchronous discharge of a group of neurons
    - **risk factors:** head trauma, CNS infections, cerebrovascular disease, alcohol, drug overdose or withdrawal, metabolic disorders, genetics, malignancy
    - **focus:** the location of the original group of firing neurons
      - propagation of seizure activity from focus to other structures determines symptoms at the onset of seizures (aura) and the activity that occurs during the seizure’s evolution
      - common seizure mimics: hyperventilation, migraine, panic attack, pseudoseizure, syncope, transient global ischemia, TIA
  - **Pseudoseizure:** an episode that clinically looks like a seizure but occurs for emotional or psychological reasons and is not accompanied by EEG evidence of a seizure during the episode
    - can occur as a result of prior physical, sexual, or emotional abuse
    - investigation:
      - proper diagnosis requires EEG
      - no response to epilepsy meds
      - complication: can have both seizures and pseudoseizures
  - **Epilepsy:** documented history of 2+ seizures that are not temporally related to an obvious metabolic or febrile cause
    - febrile seizures, even several, do not mean that the patient has epilepsy!
    - incidence is highest in first year of life, drops off up to age 30-40, then begins to increase again
    - most epileptics who will go into remission do so within 3 years of their first seizure
      - factors against remission: FH of epilepsy, psychiatric comorbidity, h/o febrile seizures, > 20 seizure history, adult age (except for the elderly), failed monotherapy due to lack of efficacy
      - 1/3 of epileptics who being taking a single anticonvulstant will never have another seizure
    - seizures may increase or decrease during pregnancy
  - H&P for seizures: investigate feeling before the seizure, aura, onset of seizures, incontinence, tongue-biting, length of post-ictal confusion, provoking factors, predisposing conditions (DM, uremia, lupus, arrhythmia, hypoponatemria, hypocalcemia), history of substance abuse, trauma, use of seizure-inducing prescription drugs
      - common provoking factors: sleep deprivation, excessive use of stimulants, withdrawal from sedatives or alcohol, substance abuse (cocaine & amphetamines), high fever, hypoxia, hypoglycemia, electrolyte disturbance
    - investigation:
      - differential: seizure mimics like syncope, pseudoseizures, breath holding spells, REM behaviors like sleep walking, panic attacks (can involve numbness and tingling around the mouth and fingers and dropped CO2)
      - EEG is what determines seizure type
      - labs: electrolytes, glucose, anticonvulsant levels, alcohol and tox screen, ABG if suspecting hypoxia
      - LP to rule out meningitis
      - CXR, CT, or MRI
  - **Treatments**
    - drugs are selected based on type of seizure, adverse effects, toxicity potential, cost, and patient-specific considerations like gender and family planning
    - patients with newly diagnosed epilepsy can be placed into categories of treatment responsive or treatment resistant
      - 2/3 of patients will become seizure-free after the first or second drug is tried and will be on it for several years = want to select the drug that is most tolerable with least side effects
      - monotherapy is preferred due to risks of toxicity and drug interactions
-consider second agent if inadequate trial of 2 different single agents
-monitor drug levels, but treat the patient, not the level
-when to treat after a single seizure:
  -TREAT: patients with a structural lesion (tumor, AVM, herpes encephalitis, stroke) or recognized abnormal EEG pattern, person with focal seizure
  -DON’T TREAT: patients without structural or EEG abnormality, alcohol withdrawal, drug abuse, provoked seizure, single seizure after head injury without structural abnormality.
    -because 5-year risk of recurrent after a single unprovoked seizure is only 30%
 → in both cases, most patients can’t drive for 6-12 months, and some states have mandatory reporting
-important drugs:
  -carbamazepine: inhibits voltage-gated Na channels
    -for seizure as well as bipolar disorder, trigeminal neuralgia, and glossopharyngeal neuralgia
    -side effects: diplopia, dizziness, drowsiness, nausea, unsteadiness, lethargy, Stevens-Johnson syndrome (= don’t use in patients of Asian descent), hypocalcemia, hyponatremia, SIADH, hematologic, hepatitis
    -drug interactions: acts as an enzyme inducer → will lower levels of warfarin, decreased efficacy of oral contraceptives
    -contraindications: pregnancy (D), hypersensitivity to TCAs, bone marrow depression
    -monitoring: CBC, LFTs, mental status, bone mineral density, levels
  -oxcarbazepine: blocks voltage-gated Na channels, modulates Ca channels, increases K conductance
    -for partial seizures
    -side effects: sedation, dizziness, ataxia, nausea, Stevens-Johnson, hyponatremia
    -drug interactions: decreases bioavailability of estrogens, increases phenytoin
    -contraindications: pregnancy (C)
    -monitoring Na
  -clonazepam: a benzo that modulates GABA-related transmission in the brain
    -not a first-line choice
    -a schedule IV controlled substance
    -frequently added as a second agent with levetiracetam
    -abrupt d/c may ppt withdrawal and seizures
  -ethosuximide: increase seizure threshold and suppress paroxysmal spike and wave pattern, depresses nerve transmission in the motor cortex
    -indicated for absence seizure
    -side effects: ataxia, drowsiness, GI, unsteadiness, hiccups, Stevens-Johnson, hematologic, SLE
    -drug interactions: lowered levels with concomitant carbamazepine use, increased levels with concomitant valproic acid use
    -contraindications: pregnancy (C)
  -felbamate: glycine receptor agonist
    -indicated for partial and generalized seizures
    -side effects: anorexia, nausea, vomiting, insomnia, headache, Stevens-Johnson, aplastic anemia, hepatic failure—it WILL destroy your liver!
      = reserve for patients that don’t respond to any other therapy!
    -drug interactions: inhibits clearance of carbamazepine, phenytoin, valproic acid, and phenobarbital
    -contraindications: pregnancy (C)
      -requires signing an informed consent
    -monitoring: weekly LFTS, bilirubin, CBC
  -gabapentin: modulates Ca channels
    -indicated for combination therapy for seizure and also for neuropathic pain
    -renal dosing needed
    -side effects: dizziness, fatigue, somnolence, ataxia, nystagmus, tremor, headache, peripheral edema, Stevens-Johnson (rare)
- contraindications: pregnancy (C)

• pregabalin: similar to gabapentin
  - indicated for partial seizures and neuropathic pain
  - titrate initial dose slowly to avoid sedation
  - a schedule V controlled substance

• lamotrigine: blocks voltage-gated Na channels, inhibits glutamate release
  - indicated for seizure, bipolar disorder
  - side effects: nausea, diplopia, dizziness, unsteadiness, headache, hypersensitivity rash
  (titrate slowly to avoid), Stevens-Johnson, hematologic, liver failure
  - drug interactions: valproic acid inhibits clearance big time
  - contraindications: pregnancy (C), caution in renal, hepatic, and cardiac impairment

• levetiracetam: inhibits Ca channels, facilitates GABA, reduces K currents, modulates NT release
  - indicated for partial seizure, tonic-clonic, and myoclonic seizure
  - side effects: sedation, behavioral, suicidal ideation, pancytopenia, liver failure
  - contraindications: pregnancy (C)

• phenobarbital: decreases post-synaptic excitation
  - indicated for seizure and sedation
  - side effects: ataxia, hyperactivity, headache, unsteadiness, sedation, nausea, cognitive
  impairment, blood dyscrasias, Stevens-Johnson, hepatic injury, osteopenia
  - many drug interactions
  - contraindications: pregnancy (D), hepatic impairment, dyspnea, airway obstruction,
  caution in renal and hepatic impairment
  - monitoring: CBC, LFTs, mental status, levels

• primidone: similar to phenobarbital
  - may be used more frequently in familial tremor but also indicated for tonic clonic,
  psychomotor, and focal seizures

• phenytoin: stabilizes neuronal membranes by altering Na efflux
  - may be given as fosphenytoin for faster effects
  - indicated for generalized tonic-clonic and complex partial seizures
  - side effects: ataxia, nystagmus, behavior changes, dizziness, headache, sedation,
  lethargy, incoordination, cognitive impairment, fatigue, blurred vision, blood dyscrasias,
  rash, immune rxn, gingival hyperplasia, skin thickening, hirsutism, coarsening of facial
  features, folate deficiency, peripheral neuropathy
  - many drug interactions
  - contraindications: pregnancy (D)
  - monitoring: levels, hypotension/bradycardia after administration

• tiagabine: inhibits GABA reuptake
  - indicated as adjunct therapy for partial seizures
  - contraindications: pregnancy (C)
  - side effects: dizziness, fatigue, difficulty concentrating, nervousness, tremor, blurred
  vision, depression, weakness

• topiramate: modulation of Na channels, enhances GABA, antagonizes glutamate-R
  - indicated for partial or generalized tonic-clonic seizure or for migraine prophylaxis
  - side effects: difficulty concentrating, psychomotor slowing (“dopamax”), speech or
  language problems, somnolence, fatigue, dizziness, headache, metabolic acidosis, kidney
  stones
  - drug interactions: decreases efficacy of oral contraceptives
  - contraindications: pregnancy (C)
  - monitoring: electrolytes

• valproic acid: increases GABA
  - indicated for absence, complex partial, or mixed-type seizures, as well as bipolar
  disorder and migraine prophylaxis
  - side effects: GI upset, sedation, unsteadiness, tremor, thrombocytopenia, palpitations,
  immune hypersensitivity, ototoxicity
  - many drug interactions
  - contraindications: pregnancy (D), hepatic dysfunction
-monitoring: mental status, CBC, LFTs

• **vigabatrin**: irreversibly inhibits GABA transaminase → increased GABA in brain
  -indicated for infantile spasms, refractory complex partial seizures, refractory generalized seizures
  -side effects: permanent visual loss, psychiatric disturbances including acute psychosis, acute abnormal MRI findings in infants
  = in a restricted distribution program

• **zonisamide**: mechanism unknown
  -indicated for adjunct therapy for partial seizure
  -side effects: sedation, dizziness, cognitive impairment, nausea, kidneys tones, Stevens-Johnson, schizophreniform disorder
  -contraindications: pregnancy (C)

→ special considerations for women on antiepileptics:
  -many AEDs can decrease efficacy of oral contraceptives
  -estrogen in oral contraceptives can decrease lamotrigine levels
  -estrogen is seizure-triggering while progesterone is seizure-protective = women can be more vulnerable to seizures around ovulation and menstruation
  -pregnancy:
    -if AED must be used, use monotherapy at lowest possible dose and supplement with folic acid
    -adverse fetal effects greatest with valproic acid, phenytoin, and carbamazepine
    -lamotrigine may be the safest
    -vitamin K is given from week 36 to delivery to prevent hemorrhagic disease

→ special considerations for the elderly on antiepileptics:
  -start low, go slow
  -the lower the albumin, the greater the amount of free drug
  -elderly are more susceptible to adverse neuro and cognitive effects

→ kids:
  -neonates need lower doses
  -kids ages 2-3 have a more active liver, so they need higher doses

**Partial Seizures**: when electrical discharge begins in a small region of the brain

A.) **Simple partial seizure**: no alteration of consciousness
  -alternating contraction and relaxation of muscle groups
  -eye movements and turning of head to the same side
  -speech arrest, vocalization
  -may see flashes of light or colors, hallucinations
  -may hear humming, buzzing, or hissing
  -may experience unpleasant odors and tastes
  -dizziness
  -autonomic symptoms: flushing, incontinence, nausea, vomiting, goose bumps, pupillary dilation, sweating, tachycardia
  -psychiatric symptoms: detachment, memory distortion, time distortion, unprovoked emotion
  -can manifest in a continuous form known as **epilepsia partialis continua**
  -can turn into a complex partial seizure

B.) **Complex partial seizure**: involves an alteration of consciousness
  -will have **automatisms**: coordinated, involuntary motor activity such as lip smacking, picking, patting, chewing, swallowing
  -inability to carry out simple commands or execute willful movement
  -lack of awareness of surroundings and events
  -can secondarily generalize to tonic clonic seizures = patient jerking all 4 extremities does not rule out partial seizure onset
  -most common kind of seizure
  -usually begins between ages 10-30
    -may be seen in 30-60 year olds with brain tumors (?)
    -may be a stroke in > age 60 (?)
-common after head trauma
- many of these patients will have abnormal tissue in their temporal lobe: sclerosis, hamartomas, tumors, infections, vascular lesions
  -in patients with seizures of the temporal lobe, surgery has a better outcome than meds
- investigation:
  - EEG may reveal a small, focal unilateral abnormality or may look normal
  - abnormal imaging due to metabolic abnormality may be present in half of these patients

→ Treatment for partial seizures:
- first line: carbamazepin, phenytoin, lamotrigine, valproic acid, oxcarbazepine
- alternatives: gabapentin, topiramate, levetiracetam, zonisamide, tiagabine, phenobarbital, felbamate

☐ Generalized Seizures: when electrical discharge occurs simultaneously in multiple areas of both sides of the brain
A.) Absence (petit mal) seizure: 5-10 second recurrent episodes of staring, sometimes associated with minor motor automatisms
  - patients have no memory of the spells but are normal immediately at completion
  - may be brought on by hyperventilation
  - not associated with any other seizure type
  - begins around age 4-8
  - patients are of normal intelligence
  - investigation: EEG shows 3/sec spike and wave with no other abnormalities
    - considered to be diagnostic, and will be present even when individual is not having an absence seizure
  - treatment:
    - first-line: valproic acid, ethosuximide
    - alternatives: lamotrigine, levetiracetam
  - prognosis: most cases will resolve spontaneously

B.) Tonic-clonic seizure: tonic phase begins with loss of consciousness, tensing of skeletal muscles, and often a loud moan or yell from forceful exhalation of air, clonic phase commences with convulsions of muscles, eyes rolling back, and strong jaw contractions
  - patient may have an aura
  - lasts 5-20 minutes
  - there may be incontinence
  - patient may remain unconscious for a period of time after the seizure and awaken confused and sleepy
  - most common cause with onset before age 30 is idiopathic epilepsy
  - treatment:
    - first-line: phenytoin, carbamazepine, valproic acid
    - alternatives: lamotrigine, levetiracetam, topiramate, phenobarbital, primidone, oxcarbazepine

C.) Myoclonic seizure: brief major motor seizure with quick, lightning-like jerking movements of the trunk or extremities associated with a paroxysmal EEG abnormality
  - may occur throughout body or limited to certain muscle groups
  - onset may be so sudden that patient falls to the ground
  - so brief that consciousness may not be lost
  - causes: metabolic abnormalities (hepatic or renal failure)
  - treatment:
    - first-line: clonazepam, valproic acid
    - alternatives: lamotrigine, levetiracetam, topiramate, felbamate, zonisamide

D.) Clonic seizure: impaired consciousness followed by asymmetric bilateral jerking, with muscles relaxing completely then returning to produce rhythmic jerks
E.) Tonic seizure: relatively rare alone; involves stiffening of the body, upward deviation of the eyes, dilation of the pupils, and altered respiratory patterns
F.) Atonic seizure: sudden loss of muscle tone that may cause a fall, lasting 1-4 seconds but without a detectable loss of consciousness
  - ranges from mild and affecting only one body area to a severe loss of all body tone
  - treatment:
    - first-line is valproic acid

29
-alternatives: lamotrigine, topiramate, zonisamide

G.) Infantile spasms: characterized by a particular jack-knife posturing of the child’s body
- spasms occur throughout the day or may be continuous
- most children are found to have neurologic problems eventually

Other Kinds of Seizures
A.) Unclassified seizure: incomplete data to say whether seizure is partial or generalized
B.) Status epilepticus: prolonged or recurrent seizures without regaining consciousness
- does not apply to simple continuous seizures
- EEG can be helpful in determining a seizure etiology if there are no convulsions
C.) Febrile seizures: also known as a fever fit or febrile convolution, is a convolution associated with a significant rise in body temperature
- often patients have a FH of febrile seizures
- slightly increases risk for later epilepsy
- especially if there are multiple seizures during one illness, focal seizures, an abnormal neurological exam, or delayed development
- treatment: supportive, anticonvulsants are not routinely given
- prophylax at first sign if illness with antipyretics to prevent seizures
D.) Alcohol withdrawal seizures: usually a generalized seizure but can be focal
- if focal, patients can be left with a temporary focal deficit (Todd’s postictal phenomenon)
- treatment: anticonvulsants can be used to temporarily break seizures, but long-term resolution depends on cessation of alcohol use

Coma

Coma Background
- Defined as an inability to sense or respond to external stimuli or inner needs
- Not a disease itself but an expression of underlying pathology
- Consciousness:
  • awareness: a high level function residing in the cerebral cortex that permits understanding of self and environment
  • arousal: a more primitive function residing in the brainstem that involves a set of primitive responses
  → loss of consciousness means that either both cerebral hemispheres must be damaged or there must be a brainstem lesion
- Causes of coma: cerebral infarction, cerebral hemorrhage, metabolic causes, drug ingestion, hypoglycemia, psychiatric
  - sudden onset → think cardiac arrest, subarachnoid hemorrhage secondary to aneurysm, brainstem infarct or hemorrhage, bicerebral hemispheric infarction
  - onset in minutes to hours → think drug overdose, hypoxia, hypoglycemia, subarachnoid hemorrhage, acute hydrocephalus, vascular malformation, meningitis, encephalitis, metabolic (uremia or hepatic failure), hypertensive encephalopathy
- History for the comatose patient:
  - ask everyone who was around what happened
  - check previous medical and psychiatric history
  - trauma?
  - medication use, alcohol, and other drugs
  - timeframe for onset
- PE:
  - skin: look for trauma, signs of liver disease, needle marks (insulin), rash (infection), signs of embolism
  - head: trauma (Battle’s sign at mastoid), raccoon eyes (orbital fracture), CSF rhinorrhea or otorrhea (basilar skull fracture),
  - eyes:
    - funduscopic exam: look for signs of bleeding or increased ICP
      • Roth spots: retinal hemorrhages with white or pale centers composed of coagulated fibrin, usually caused by immune complex mediated vasculitis often resulting from
bacterial endocarditis but may also be observed in leukemia, diabetes, subacute bacterial endocarditis, pernicious anemia, and ischemic events.

- Hollenhorst plaques: a cholesterol embolus seen in the retinal vessels, often from plaque broken off from neck vessels
- papilledema from increased ICP

-reactive pupils
  - usually indicates that the midbrain is intact and that the cause of coma is a metabolic abnormality (hypoglycemia or drug ingestion (barbiturates)
  - small + reactive = pontine damage or drugs (opiates, pilocarpine)

-unreactive pupils: make sure light source is adequate!
  - if truly unreactive = midbrain damage
  - if bilaterally unreactive + midposition = hypothermia

-dilated or “blown” pupil:
  - if unilateral + nonreactive = CN III compression, DM, or some drugs

-eye movements:
  - eye deviates TOWARDS a unilateral hemispheric lesion
  - eye deviates AWAY from a unilateral brainstem lesion

-tests:
  - **Doll’s head (oculocephalic) reflex:** rapidly turning the head from side to side
    - normal: eyes move in direction opposite to the movement of the rotating head
    - abnormal: absent or asymmetric eye movement suggests disease of the midbrain or pontine level (or barbiturate toxicity)
  - **oculovestibular reflex (ice water calorics):** irrigation of cold water into the auditory canal to see if eyes deviate
    - normal, conscious response: tonic (sustained) deviation of the eyes toward the stimulated side, with quick nystagmus towards the opposite side
    - comatose with intact brainstem response: tonic deviation towards stimulus without nystagmus
    - comatose with brainstem dysfunction: loss of tonic deviation
    - ***does not distinguish between metabolic and structural causes of coma!***
  - corneal sensation: checks CN V (trigeminal); abnormal response suggests pontine lesion
  - neck: stiffness (meningitis or subarachnoid hemorrhage)
  - breath: ketoacidosis, fetor hepaticus (liver disease), alcohol, uremia
  - cardiac: murmurs or arrhythmias
  - neuro:
    - sensation: noxious stimuli like a sternal rub is applied to the face, trunk, and extremities bilaterally
      - potential responses: purposeful withdrawal bilaterally, absent response unilaterally, facial grimace, posturing
      - **decorticate posturing:** painful stimuli ⇒ flexion of arms, clenching of hands into fists, and extension of legs with feet turned inward
        - correlates to a hemispheric or diencephalic dysfunction due to destructive lesions or metabolic abnormality
        - better outcome than decerebrate
      - **decerebrate posturing:** painful stimuli ⇒ involuntary extension of the upper extremities, head arches back, arm and leg extension with internal rotation, elbow extension; patient is rigid, with the teeth clenched
        - correlates to midbrain or upper pons dysfunction due to a metabolic or structural abnormality
  - lungs:
    - **Cheyne-Stokes:** small breaths going up incrementally to a crescendo then back down
-seen with bilateral hemispheric lesions, as well as non-neurologic disorders such as CHF
  • central neurogenic hyperventilation: commonly has a metabolic cause such as sepsis or DKA
  • apneustic: deep breaths held for prolonged periods of time
    -associated with pontine infarction
  • ataxic breathing (Biot’s respirations): irregular breathing seen with damage to the medullary respiratory centers

Glasgow Coma Scale
-Made up of three tests, with values considered separately as well as conglomeratively:
  1.) eye response
    4 = spontaneous opening
    3 = opening to speech (if they were just sleeping they are a 4!)
    2 = opening in response to pain
    1 = no eye opening
  2.) verbal response
    5 = fully oriented
    4 = confused
    3 = inappropriate words, no conversational exchange
    2 = incomprehensible sounds
    1 = no sounds
  3.) motor response
    6 = obeys commands
    5 = localizes to painful stimuli
    4 = withdrawal from painful stimuli
    3 = decorticate response to painful stimuli
    2 = decerebrate response to painful stimuli
    1 = no motor response
-Lowest possible GSC is 3 = deep coma or death
-Highest is 15 = fully awake and responsive

Coma Investigation
-Labs: glucose, Na, K, Cl, CO2, renal functions, Ca, P, ABG, CBC, tox screen
-EEG: can help determine presence and degree of coma but won’t tell you about the etiology
-EKG
-CXR
-Neuroimaging

Coma Prognosis
-Lower the Glasgow score, the lower the chance for making a recovery of any kind
  -almost all comatose patients will eventually wake up to some degree in 2-4 weeks
  -most will develop a sleep wake cycle
  -they may open their eyes in response to verbal stimuli or appear to follow a light, but there is no response to visual threat
  -they do not discreetly localize motor responses, follow commands, or speak comprehensibly
-“Brain death” means that the patient does not make any purposeful movements, has no pupillary responses, no extraocular movements (spontaneously or with stimulation), no corneal reflexes, no spontaneous respirations or movements
  -a clinical diagnosis
  -DTRs may be present
  -there are no documented recoveries from brain death in an adult patient
  -EEG may be completely flat but there are some patients who meet the clinical criteria for brain death that still have some EEG activity
**Stroke**

- **Background**
  - Defined as an acute neurological deficit of vascular etiology with symptoms lasting longer than 24 hours.
  - Causes: infection, autoimmunity, metabolic disorder, neoplasm, trauma, epilepsy, demyelinating disease, psychiatric disease.
  - 4th leading cause of death in the US.
  - More common in women.
  - More prevalent in the “stroke belt” in SE US.
  - Diagnosis is based on history, PE, and selected labs.
    - Correlate patient’s symptoms and signs with brain anatomy.
    - CBC, PT/PTT, electrolytes, glucose, and renal function.
    - EKG for signs of cardiac ischemia.
    - Brain CT or MRI.

- **Types of Stroke**
  1. Hemorrhagic: accounts for 15-20% of strokes.
     a.) Parenchymal intracranial hemorrhage: bleeding within brain itself.
        - Primary ICH originates from the spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy.
        - ICH from chronic hypertension:
          - Tend to occur in weaker deep vessels of the thalamus, basal ganglia, pons, and cerebellum.
          - Presentation: history of HTN, currently severely hypertensive, severe headache, nausea, vomiting, focal neuro deficits.
          - Investigation: CT showing white mass.
          - Remember that 3 things are white on a CT: blood, rocks, or contrast.
        - ICH from amyloid angiopathy: brain arterioles weaken from deposition of amyloid.
          - Presentation: dementia, episodic worsening, no history of HTN.
        - Secondary ICH occurs in association with trauma, vascular abnormalities, tumors, impaired coagulation, or vasculitis.
          - Presentation:
            - If in the thalamus or basal ganglia: contralateral motor and sensory deficit, aphasia, language or spatial neglect, depressed level of consciousness due to mass effect, intraventricular extension → hydrocephalus.
            - If in the cerebellum: ipsilateral ataxia, depressed level of consciousness.
            - If in the pons: vertigo, diplopia, crossed signs, depressed level of consciousness.
     b.) Subarachnoid hemorrhage: bleeding outside the brain.
        - Most common cause is a ruptured aneurysm.
        - Most common location is the anterior communicating artery.
        - Can also occur at the bifurcation of the carotid artery, PCCM, MCA, basilar tip artery, PICA.
        - Risk factors: hypertension, smoking, heavy alcohol, genetics (Ehlers-Danlos, inherited polycystic kidney).
        - Presentation: abrupt, severe headache, meningismus (inflammation consciousness, non-focal neuro exam (because it’s outside the brain).
        - Less common causes: vasculitis, infection, neoplasms, blood coagulopathies.
        - Treatment: general emergency management, blood pressure control, aneurysm occlusion, surgical evaluation.
  2. Ischemic: accounts for 80-85% of strokes.
     a.) Atheroembolic: occlusion of artery supplying brain or within the brain due to CAD stenosis or cholesterol embolus; the most common kind of stroke.
- **lacunar stroke**: a type of stroke that results from occlusion of one of the penetrating arteries that provides blood to the brain's deep structures
  - presentation: there will be warning signs with a stepwise progression to full-blown stroke!
    - history of HTN or CAD
    - transient language disturbances and weaknesses
    - vertebrobasilar stroke: affects CN III (oculomotor) → dilated pupils
    - the more subcortical the stroke location, the more areas of the body will be affected because the tracts begin to run together as they go deeper into the brain
    - lacunar strokes can appear as a pure motor stroke, pure sensory stroke, ataxic hemiparesis, or dysarthria + clumsy hand
  - investigation:
    - head CT: caution, may look normal
    - doppler US to look for carotid stenosis
    - catheter angiography: an invasive test that is not first-line

b. **cardioembolic**: embolus thrown from the heart goes to the brain
  - sources: afib, cardiomyopathy, acute MI, valvular heart disease
  - most common lodges in the middle cerebral artery
  - presentation: history of afib, aphasia, focal neuro deficits with max deficits occurring at onset
    - can break up into many clots and travel to multiple vascular territories
  - investigation:
    - carotid US will be normal
    - brain CT will be normal during first few hours of stroke
    - 24-48 hour EKG to check for intermittent afib
    - echo: transthoracic or transesophageal
  → embolic strokes can cause a hemorrhagic infarction as the ischemic blood vessels die and split open, but you must differentiate if cause of a detected hemorrhage is primary/secondary ICH vs embolism
    - cause is primary/secondary ICH → can’t give blood thinners or lytics ever again because you will kill them if they bleed again
    - cause is truly embolic → must be put on a blood thinner regimen to prevent future embolic strokes

→ a **transient ischemic attack** (TIA) is an acute focal neurologic deficit as a result of ischemia that resolves within 24 hours
  - incurs a greater risk of having a stroke in the near future
→ treatment for ischemic stroke (or TIA with symptom recurrence):
  - start TPA if within 4.5 hours of onset of symptoms (cutoff point for prevention of disability)
    - must make sure head CT has no evidence of hemorrhage or other complication
    - within 3 hours of onset relative contraindications: recent head trauma or stroke, prior ICH, recent arterial puncture, active bleeding or acute trauma, on oral anticoagulants with high INR, normal aPPT if recent heparin, low platelets, hypoglycemia, HTN >185/>110, CT with hypodensity in > 1/3 of cerebral hemisphere, rapidly improving symptoms, seizure with postictal impairment, recent MI, recent GI or urinary tract hemorrhage, recent major surgery
    - further contraindications after 3 hours of onset: over age 80, oral anticoagulant therapy regardless of INR, history of prior stroke + diabetes
    - TPA increases risk of hemorrhage by 10x but the benefit generally outweighs this risk as long as the protocol is followed
  - if TPA is not an option, consider endovascular repair or mechanical removal of clot
  - give fluids but avoid D5W as glucose crosses the blood-brain barrier and is quickly metabolized to water, creating greater free water in a brain already at risk for swelling
  - blood pressure management
    - want to keep MAP up as brain blood vessels are maximally dilated during a stroke = reduce resistance in blood vessels
-consider lowering BP in severely hypertensive patients (>220/>120) or with other concomitant organ system injury by 15-2% within the first day
-temperature: induction of hypothermia in febrile stroke patients may lessen ischemia (still being researched)
-antithrombotic agents
-later PT, OT, speech therapy
-pharmacologic therapy for recovery is being researched

→ prognosis:
-everyone improves to some degree after a stroke
-where you end up depends a lot on starting severity
-quickest period of recovery after a stroke is in the first 30-60 days

☐ Stroke Primary Prevention
-Healthy lifestyle
-Assess and treat modifiable risk factors for ischemic stroke:
  -HTN:
  -afib:
    -for clinical benefit, dabigatran (direct thrombin inhibitor) > warfarin = rivaroxaban > aspirin
    -but dabigatran and rivaroxaban are not reversible
-carotid stenosis:
  -screen for with carotid bruits, US, MR or CT angiography
  -surgery if asymptomatic is generally not indicated as the risk now outweighs benefit
-diabetes:
  -even diabetics with well-controlled blood glucose are at same risk of macrovascular complications as poorly controlled DM
  -puts greater emphasis on need for tight HTN control and statin use in this population
-hyperlipidemia:
  -diet, niacin, cholestyramine, etc not shown to reduce stroke risk
  -statins reduce risk of stroke by 20% in patients with CAD or risk factors
  -aspirin or other antiplatelet
-Assess and treat modifiable risk factors for hemorrhagic stroke:
  -biggest risk factor is HTN!
  -smoking
  -alcohol
  -can consider prophylactic clipping or endovascular coiling in patients with FH stroke in > 2 1st degree relatives

☐ Stroke Secondary Prevention
-Based on mechanism for initial stroke
-Platelet anti-aggregants: warfarin > aspirin
-Anticoagulants
-Blood pressure control
-Lipid lowering: statin proven to reduce risk of recurrent stroke
-Endarterectomy for patients with carotid disease
  -may be useful in carotid artery stenosis
-Prevent complications of hospital admission and treatment: UTI, DVT, pneumonia, etc.

Headache

☐ Background
-Headache differential: systemic infection, HTN, vision decline, cervical radiculopathy, occipital neuralgia, temporal arteritis, TMJ, trigeminal neuralgia, tumor, mass lesions, chronic subdural hematoma, ischemia, arteriovenous malformation, aneurysm, pseudotumor cerebri (young, obese females with papilledema & compressed ventricles)
  -Primary headache: not a symptom or caused by another disease or condition
-includes tension-type headaches, cluster headaches, chronic daily headaches

- Secondary headache: a symptom or result of another underlying disease or condition such as brain tumor or infection

- when to be concerned: systemic symptoms, risk factors like HIV or cancer, odd neurologic symptoms, sudden onset, new headache in an older patient, progressively worsening headache in a middle-aged patient, major change in attack frequency or severity, different headache than before, headache precipitated by exercise, coughing, sneezing, bending over, or sexual arousal

- imaging not necessary with:
  - no abnormal neuro findings
  - patient has history of recurrent headache
  - no history of seizures

- get an MRI with:
  - abnormal neuro findings
  - progressively worsening headache
  - new persistent headache
  - new, rapid onset headache
  - headache not responding to standard therapy

☐ Tension-Type Headache
- Most common type of headache
- More common in women than in men
- 2 major forms:
  a.) episodic tension headache: attacks occur on average 3 days a month
  b.) chronic tension headache: 15+ attacks per month

- Presentation:
  - no aura, nausea, or vomiting
  - with or without photophobia or phonophobia
  - may have head muscle tender points

- Investigation:
  - diagnostic criteria = at least 2 of the following along:
    - bilateral head pain from 30 minutes to 7 days (like a “tight hat”)
    - steady, non-pulsating pain (dull, tightness, or pressure)
    - mild to moderate pain intensity
    - normal physical activity does not aggravate the headache

- Treatment:
  - if episodic:
    - DOC are OTC analgesics: ibuprofen, naproxen, aspirin, acetaminophen, Excedrin tension headache
    - non-responders may require prescription NSAIDs like diclofenac
    - last-line treatments for non-responders: butalbital + aspirin or acetaminophen + caffeine, isomethetene + dichloralphenazone + acetaminophen, acetaminophen + opioid
      - can result in chronic daily headache if overused, especially with butalbital and codeine
  - consider prophylaxis if meds are needed > 2 days/week:
    - tricyclics:
      • amitriptyline: very sedating = take at bedtime
        - start low and titrate up
      • nortriptyline: moderately sedating
        - also start low and titrate up
      → side effects: weight gain, dry mouth, constipation
      → contraindicated in severe heart disease
    • duloxetine: for patients with major depressive disorder + chronic daily headache
      - usually an 8 week course for improvements in both depression and headache
    - skeletal muscle relaxants: cyclobenzaprine, methocarbamol, tizanidine
      - to be taken at first sign of head or neck tension as prophylaxis
      - can cause liver disease if used for long periods of time
      - can help with weaning from other analgesics like narcotics
-tizanidine has a lot of drug interactions and can cause hypotension and sedation, needs LFT monitoring
-botox injection into CN muscles at tender points

**Migraine Headaches**

- More common in women
  - but increased incidence in men as they get older
- Usually beings in teens or perimenopausal
- Highest prevalence in 25-45 year olds
  - decreased incidence during childbearing years
- Genetic component that can incur vascular abnormalities as well as hypercoagulability
  - migraine can increase risk for future stroke
- High incidence with concomitant depression
- Common precipitators: stress, hormones, hunger, sleep deprivation, odors, smoke, alcohol, meds, high tyramine foods
  - may be a load factor requiring presence of multiple triggers to provoke a headache
  - very common triggers to avoid in all migraine sufferers: sleep disturbance, skipping meals, caffeine, alcohol
- May begin with sensitization of peripheral nociceptors that pass this on to central nociceptors
  - patients may have sensitivity to things like touch and combing hair
- Often begin in the morning with gradual onset of pain
  - 5 phases: prodrome → aura → headache → termination → postdrome
- May be confused for a “sinus headache”

- Types:
  a.) *migraine without aura*: accounts for most migraine cases; headaches last 4-72 hours
    - the most common kind of migraine
      - presentation: nausea, vomiting, photophobia, phonophobia, unilateral, pulsating frontotemporal pain
      - investigation:
        - usually need 5+ attacks for a diagnosis along with 2+ of the following:
          - unilateral location
          - pulsating quality
          - moderate or severe pain intensity
          - aggravated by physical activity
  b.) *migraine with aura*: headaches will begin during the aura or within 1 hour of it
    - most common kind of aura is a scintillating scotoma
    - up to 50% of patients with this also have a patent foramen ovale
    - presentation: visual, sensorimotor, speech, or brainstem disturbances
    - investigation:
      - diagnostic criteria involve having an aura for a minimum of 5 minutes and 1+ of the following:
        - fully reversible visual symptoms
        - fully reversible sensory symptoms
        - fully reversible dysphasic speech disturbance
      - never use a triptan during an aura because there is diminished cerebral blood flow and you could cause a stroke = wait til the pain starts before taking
  c.) *complicated migraine*: headache accompanied by major neurologic dysfunction
    - presentation: looks like a stroke
    - neurologic changes can outlast headache by 1-2 days
  d.) *confusional migraine*:
  e.) *ophthalmoplegic migraine*: occurs with changes in vision
  f.) *basilar migraine*: severe episode headache that accompanies or precedes cerebellar dysfunction
    - typically occurs in teenage girls
    - presentation: diplopia, tinnitus, bilateral vision abnormalities, ataxia, dysarthria, bilateral sensory or motor disturbance, CN deficits, coma
  g.) *menstrual migraines*: occur prior to, during, or after menstruation, or during ovulation
-treatment:
  - abortive: triptans
  - prophylaxis:
    - begin NSAIDs 2-7 days prior to menses, continue through last day of flow
    - also consider oral contraceptives in women who do NOT have an aura

h.) chronic migraine: chronic daily headache with migraine qualification at least 8 days a month that is not caused by drug overuse or secondary cause
- may develop from episodic migraine due to snoring, sleep apnea, obesity, caffeine, medication overuse, and psychiatric comorbidities

-Migraines in kids:
  - kids have symptoms like abdominal pain, motion sickness, sleep disturbances, and cyclic vomiting

-Treatment
  - exercise shown to be just as good as meds
  - patients with chronic migraine need to be given a prophylactic therapy, an abortive therapy, and a rescue med if the abortive underperforms or fails

- abortive therapy
  - goals are to treat attacks early and consistently, restore ability to function, minimize use of rescue meds, emphasize self-care, use cost-effective therapy, and avoid side effects
  - non-opioids that can be used: NSAIDS or acetaminophen, rectal indomethacin, IM ketorolac, Excedrin migraine
    - MOA: inhibition of prostaglandin synthesis
    - side effects: GI tox with prolonged use, possible rebound headache, sodium and water retention, renal dysfunction, exacerbation of CHF, antiplatelet effects
    - contraindications: GI bleed or history, renal insufficiency, hepatic failure
    - caution in PUD

- triptans: constrict intracranial blood vessels, inhibit vasoactive neuropeptide release, interrupt pain signal transmission centrally
  - cost per trade name for oral dose is $20-$28 ➔ health plans and hospitals will usually have contracts for a preferred agent
  - types:
    - sumatriptan: good place to start as insurance covers it as a generic
      - avail subq for fast onset
      - may cause HTN in the elderly
    - zolmitriptan: wafer form avail
      - caution in hepatic impairment
    - naratriptan:
      - can’t use MAOIs, caution in renal and hepatic impairment
    - rizatriptan: wafer avail
    - almotriptan:
      - can’t use MAOIs
    - frovatriptan:
      - can’t use MAOIs
    - eletriptan:
      - can’t use MAOIs
        - side effects: paresthesias, fatigue, dizziness, flushing, warm sensations, somnolence, chest tightness, possible rebound headache with overuse
        - drug interactions: MAOIs, ergot, caution with SSRIs (serotonin syndrome)
        - also monitor for serotonin syndrome with SNTRIs, TCAs, and linezolid
        - contraindications: ischemic heart disease, uncontrolled HTN, stroke, basilar or hemiplegic migraines
      - patients at risk for unrecognized heart disease should be assessed prior to triptan use

-ergots: direct smooth muscle vasoconstriction, non-selective 5-HT1-R agonist
  - ergotamine
  - dihydroergotamine: most common form, avail injection, nasal, oral, rectal, sublingual
- side effects: vasoconstriction, HTN, peripheral ischemia, nausea, vomiting, diarrhea, pruritus, vertigo, cramps, paresthesias, cold skin, decreased pulses in extremities, rebound headache, fibrosis if long-term
  = this is a last-resort medication!
- drug interactions: triptans in last 24h, CYP 3A4 inhibitors
- contraindications: CAD, PVD, HTN, renal or hepatic failure, protease inhibitors, pregnancy (X)
- combination sympathomimetics: isometheptene + dichloralphenazone + acetaminophen
- opioids: transnasal butorphanol, Percocet, Vicodin
  - overuse can lead to chronic daily headache or rebound headache
- combination products with barbiturates: butalbital + aspirin or acetaminophen
  - decreased cognition and high abuses potential
- antiemetics: prochlorperazine, metoclopramide
  - give 15-30 minutes before abortive therapy
  - when used alone can stop the migraine
- intranasal lidocaine
- corticosteroids
- droperidol
- nitrous oxide
- propofol
- consider prophylactic therapy for patients with incomplete response to acute therapies, with contraindications to acute therapies, with migraine significantly affecting quality of life, of those with frequent attacks requiring medication > 2x per week
- patients with rebound headaches with acute treatments may also benefit
- β-blockers: propranolol, timolol, metoprolol, nadolol, atenolol
  - MOA: central/serotonic, β-1 mediated
  - helpful in patients with anxiety, HTN, or angina
  - side effects: sedation, fatigue, dizziness, depression, orthostatic hypotension, impotence
  - contraindications: 2nd or 3rd degree heart block, asthma, decompensated CHF, bradycardia, PVD, IDDM (mask hypoglycemia)
- Ca channel blockers: verapamil
  - MOA: prevent vascular spasm
  - β-blockers work better
  - these take up to 8 weeks to work
  - side effects: edema, bradycardia, tachycardia, hypotension, constipation, dizziness, fatigue, CHF exacerbation
  - caution in 2nd or 3rd degree heart block, systolic heart failure
- NSAIDS: aspirin, ibuprofen, naproxen
  - for use with migraines that have a predictable pattern (menstrual)
  - start 1-2 days before expected onset and continue for expected duration
- TCAs: amitriptyline, imipramine, doxepin, nortriptyline, protriptyline
  - best evidence is with amitriptyline
  - side effects: anticholinergic, sedation, postural hypotension, arrhythmias, tremor, weight gain
  - contraindications: MAOIs, recent MI
  - caution in elderly, BPH, glaucoma
- SSRIs: fluoxetine, fluvoxamine, sertraline
  - not as much data
- atypical antidepressants: bupropion, venlafaxine
  - also not a lot of data
- MAOIs: phenelezine
  - can’t eat tyramine-containing foods
  - side effects: anticholinergic, hypotension, impotence, skin rash, hypertensive crisis
  = we should not use this
- drug interactions: severe and potentially fatal with SSRIs, meperidine, triptans
-anticonvulsants: carbamazepine, gabapentin, tiagabine, topiramate, valproic acid or divalproex, oxcarbazepine, lamotrigine, vigabatrin, zonisamide
  -valproic acid and divalproex are FDA approved
  -requires monitoring of LFTs, blood
  -carbamazepine requires monitoring
  -newer anticonvulsants still being researched

-Botox: approved for chronic migraine prophylaxis (15+ days/month of migraine)
  -5U injected IM into 31 different sites = costs $2000
  -needs to be done every 12 weeks
  → must give 6-8 week trial for each therapy
  → prolonged headache-free intervals can signal time for dose reduction or discontinuation with slow taper

  -behavioral strategies: relaxation training, thermal biofeedback, EMG biofeedback, cognitive behavioral therapy
  -insufficient evidence for acupuncture, TENS, chiropractic, hyperbaric oxygen, hypnosis, avoidance of triggers, and lifestyle/stress management

-When to refer: symptoms are refractory to treatment efforts, worsening disability, status of symptomatology changes and no longer fits diagnostic criteria, comorbid conditions requiring polypharmacy, habituated patient/rebound headaches
  -most migraine patients can be effectively managed in primary care

Trouble Daily Headache:
-Headache of any kind occurring 15+ days out of the month
  -includes chronic migraines, chronic tension headaches
    • hemicrania continua: a daily strictly unilateral primary headache associated with miosis, ptosis, eyelid edema, lacrimation, nasal congestion, and rhinorrhea
      -similar to paroxysmal hemicrania, which goes through bouts of 2-30 minute attacks
      -only responds to indomethacin!
  -May be primary or secondary, usually primary
  -episodic migraine and tension headaches can transform into this
  -promoted by medication overuse
  -Causes: disrupted sleep regulation, sleep apnea, insomnia
  -Treatment:
    -give bridge therapy when d/c analgesic that has been overused

Cluster Headaches
-Characterized by unilateral excruciating, steady pain in the eye, periorbital region, or temple
  -increased sweating on ipsilateral side of face
  -lasts 15-180 minutes untreated and typically occurs every other day, or up to 8 attacks per day
  -usually occurs in bouts lasting for weeks or months followed by remission for months or years
  -More common in spring and fall
  -Can be precipitated by sleep, occurring 90 minutes after falling asleep
  -More common in men
  -Presentation: patients often complain of “worst headache of life”
  -Diagnostic criteria: 5+ attacks along with at least 1 of the following:
    -ipsilateral conjunctival injection and/or lacrimation
    -ipsilateral nasal congestion or rhinorrhea
    -ipsilateral eyelid edema
    -ipsilateral forehead and facial sweating
    -ipsilateral miosis or ptosis
    -a sense of restlessness or agitation
  -Treatment:
    -abortive therapy:
      -100% O2 on a non-rebreather @ 6-12L/min for 15 min
      -subq sumatriptan
      -nasal sumatriptan or zolmitriptan
-octreotide: for patients with HTN or heart disease
-**dihydroergotamine**: IV, sublingual, or rectal
-nasal lidocaine

**Prophylaxis:**
-**DOC** is verapamil: remember it takes 8 weeks to work
-lithium
-**ergotamine**: can be used for brief periods sublingually or injected to prevent nighttime attacks
-corticosteroids: prednisone taper over 2-3 weeks
-takes 1-2 days to work
-headaches may recur after d/c of therapy
-nerve block

**Thunderclap Headache**
-Presentation: severe headache of abrupt onset, “worst headache of life”, mimics pain of ruptured cerebral aneurysm
-pain from 1 hour to 10 days
-Treatment: send to ER no matter what to rule out subarachnoid hemorrhage

**Mass Lesions and Headache**
-1/3 of patients with an intracranial mass will have headache as a symptom
-**Presentation:**
  -pain stays in same location and progressively gets worse
  -subtle changes in mental status
  -increased ICP when laying down or bearing down

**Peripheral Neuropathies**

**Background**
-Physiology
  -neuronal APs are mediated by Na
  -NTs at the synapse:
    -motor/sensory: nicotinic Ach, L-glutamate, GABA
    -homeostatic: muscarinic Ach, serotonin, histamine, adenosine

  **Classification of peripheral neuropathies:**
  -by location: mononeuropathy vs polyneuropathies
  -by course of disease:
    -acute: vasculitic, toxic, porphyria, AIDP/GBS
    -chronic: diabetic, uremic, HIV, CMTD
  -by pathophysiology:
    -axonal: normal or slightly slowed conduction velocity
    -demyelinating: slow or absent conduction velocity
    -vasculitic: normal or slightly slowed conduction velocity
    -mixed pattern
  -by cause: hereditary, physical, endocrine, infectious, inflammatory, toxic, paraneoplastic, critical illness
     -there are 1,000,000 ways to get a peripheral neuropathy!

  **Common neuropathic presentations:**
  -motor: weakness, incoordination or ataxia, muscle wasting
  -sensory: numbness, tingling, loss of sensation, pain, ataxia
  -autonomic: dizziness, lightheaded, loss of consciousness, exercise intolerance, difficulty digesting foods,
    constipation, urinary symptoms, sexual dysfunction, visual symptoms

  **Important components of the complete history:**
  -allergies
  -meds: HIV, chemo
  -PMH: diabetes, hypothyroidism, sarcoid, amyloid, uremia, anemia, liver failure, cancer, previous
    radiation, recent infection, nutritional deficiencies
- recent surgeries
  - FH: neuropathy, gait problems, foot deformities, similar symptoms
  - SH: alcohol use, exposure to toxins, occupational activities
- comprehensive ROS needed

- PE: vitals, HEENT, CV, pulm, abdominal, complete neuro, derm
- Investigation:
  - formation of differential diagnosis:
    - try to localize the lesion
      - unilateral extremity affected ➔ brain or entire plexus
      - symmetric disease ➔ bicortical, brainstem, cord lesion, peripheral neuropathy
      - portion of limb or trunk affected ➔ brain, spinal cord, plexus, peripheral nerve
      - dermatome or myotome affected ➔ specific spinal cord segment
    - determine pathophysiology
      - axonal: sensory symptoms > motor symptoms, greater distal weakness, decreased DTRs
      - demyelinating: motor symptoms > sensory symptoms, greater proximal weakness, decreased or absent DTRs
      - vasculitic: varied clinical features
      - mixed: varied clinical features
    - determine pattern of nerve involvement
      - if focal:
        - acute ➔ neuro consult
        - subacute or chronic ➔ EMG/NCS needed
          - common compression site ➔ referral if indicated
          - uncommon compression site ➔ neuro consult
      - if multifocal ➔ EMG/NCS needed
        - if axonal or demyelinating ➔ neuro consult
        - if symmetric ➔ EMG/NCS needed
          - if axonal ➔ unusualness of features determines referral
          - if demyelinating ➔ neuro consult needed
  - diagnostics:
    - common tests: EMG/NCS, B12 levels, CBC, glucose tolerance, rapid plasma reagin, CMP, serum protein electrophoresis, thyroid function tests
    - tests for select cases: anti-Hu, ESR, ANA, RF, SS-A, SS-B, genetic studies for HMSN, HIV, Lyme, phytanic acid, 24 hour urine for heavy metals, CSF, nerve biopsy
  - even after all of this, up to 1/3 of patients with neuropathy remain undiagnosed

☐ Single Peripheral Mononeuropathies

A.) Carpal tunnel syndrome: compression of median nerve
  - risk factors: repetitive wrist motion, pregnancy, diabetes, rheumatoid arthritis, wrist injury, inflammatory tenosynovitis, myxedema, localized amyloidosis, sarcoidosis, acromegaly, hyperparathyroidism
  - presentation: median nerve distribution, early pain/burning/tingling, later weakness/thanar atrophy, worse at night
    - atypical: proximal radiation
  - investigation:
    - Phalen’s, Tinel’s
    - EMG/NCS rarely indicated
  - treatment: want to relieve pressure on the median nerve
    - conservative: modify hand activities, extensor wrist splint for a month, carpal bone mobilization, yoga
    - invasive: steroid injection, surgical decompression

B.) Ulnar neuropathy: stretching or compression of ulnar nerve
  - may be caused by cubital tunnel syndrome or Guyon’s canal syndrome
  - risk factors: pressure, trauma, bone spurs, congenital tumors or cysts
  - presentation: early pain/burning/tingling, later weakness of hand and forearm
    - worsened by elbow flexion (cubital tunnel) or wrist extension (Guyon’s) at nighttime
-atypical: proximal radiation
-investigation: EMG/NCS can help differentiate site of lesion
-treatment: want to relieve pressure on ulnar nerve
-conservative: modify elbow or wrist activities, extensor splint at nighttime, NSAIDs
-invasive: surgical nerve transposition or ligament release
-cant do steroid injections due to high risk of nerve injury!

C.) Radial neuropathy: stretching or compression of radial nerve
-risk factors: injury to the axilla (crutches), Saturday night palsy (falling asleep on outstretched arm), wrist restraints, humeral fx
-presentation: motor deficits > sensory, weakness on finger/wrist/forearm extension, weakness on external rotation of the arm, forearm atrophy
-investigation: EMG/NCS, x-ray of shoulder + humerus
-treatment:
- patient education & behavioral changes, braces, splits, PT/OT
-surgery

D.) Meralgia paresthetica (Bernhard-Roth syndrome): compression or stretching of the lateral femoral cutaneous nerve
-a sensory nerve
-risk factors: obesity, diabetic peripheral neuropathy, pregnancy, hyperextension of the hip, lumbar lordosis, tight clothing
-presentation: pain, paresthesia, numbness on outer aspect of thigh
-usually unilateral, sometimes relieved by sitting
-no motor symptoms
-further investigation by EMG/NCS rarely indicated
-treatment: not always needed as symptoms can resolve spontaneously
-anticonvulsants, hydrocortisone injection, nerve decompression by transposition

E.) Femoral neuropathy: compression or stretching of the femoral nerve
-risk factors: lithotomy position (pressure on inguinal ligament), diabetic peripheral neuropathy, retroperitoneal neoplasm or hematoma, pelvic fx, nerve trauma from femoral artery catheterization
-presentation: weakness and atrophy of quads, buckling of the knee, sensory deficits over thigh and leg to the medial malleolus, depressed or absent patellar DTRs
-investigation: EMG/NCS, CT, MRI
-treatment: aimed at etiology
-splints and braces
-PT

F.) Sciatic nerve palsy (sciatica): stretching or compression of the sciatic nerve
-causes: misplaced deep IM injections, trauma to butt/hip/thigh, piriformis syndrome, hip replacement surgery, pelvic injury, degenerative disk disease, spinal stenosis, CNS or PNS tumor, lumbar disc herniation
-presentation:
-weakness with leg flexion/foot dorsiflexion/foot eversion, depressed or absent ankle DTRs
-sensory deficits on the posterior thigh, leg, and foot
-tingling, burning, or lanceting
-aggravated by prolonged sitting or standing, nighttime, when sneezing, coughing, or laughing
-patients can usually draw a line down affected dermatome to help the provider localize which nerve root is being impinged
-investigation:
-EMG/NCS to distinguish from peroneal neuropathy
-x-ray of spine, pelvis, hip, femur
-treatment: based on cause
-patient education and behavioral changes
-anti-inflammatory meds
-PT
G.) **Peroneal (common fibular) nerve palsy:** stretching or compression of the peroneal nerve
- may be caused by crossing legs for a long period of time, trauma or injury to the knee, fracture of the ibula, use of tight casts on the lower leg, wearing high boots, knee positions during deep sleep or coma, knee surgery
- presentation:
  - motor deficits: weakness on dorsiflexion and foot eversion
  - sensory: paresthesias or sensory loss on anterolateral calf and top of foot
- investigation:
  - diagnosis is usually clinical
  - must distinguish from sciatic nerve palsy (EMG/NCS)
- treatment: based on cause
  - patient education and behavioral changes
  - anti-inflammatories
  - PT
  - splints and braces

H.) **Tibial neuropathy:**
I.) **CN VII (facial nerve) palsy (Bell’s palsy):** impairment due to compression, ischemia, or inflammation
- causes: mostly idiopathic, can also be HIV, sarcoid, Lyme, tumors, reactivation of HSV
- risk factors: diabetes, pregnancy
- presentation: abrupt onset that may progress over several days
  - motor deficits: facial paralysis, ptosis
  - sensory disturbances: ear pain, taste disturbance, hyperacusis
- investigation:
  - must distinguish peripheral cause from central
    - peripheral cause will result in complete paralysis of frontalis muscle
    - central cause will result in partial sparing of frontalis because there is bicortical input from the brain, so half the input is still functioning
- EMG/NCS will indicate severity but won’t guide treatment
- treatment: controversial
  - prednisone taper
  - artificial tears
  - NOT HELPFUL: surgical procedures or nerve decompression
- prognosis: 60% recover completely without treatment, 10% have permanent dysfunction
  - best indicator of severity of palsy is progress in first 2-3 days
  - poor prognosis with complete palsy at onset, advanced age, hyperacusis, severe initial pain

**Multiple Peripheral Mononeuropathies**
A.) **Discogenic neuropathies:** caused by impingement of a spinal nerve by lateral disc protrusion or arthropathy
- presentation: motor, sensory, and autonomic dysfunction
- investigation:
  - neuroimaging: MRI, CT myelogram
  - EMG/NCS
- treatment:
  - rest, immobilization
  - PT
  - surgical intervention
B.) **Plexopathies:** compression or invasion of a neuronal plexus (cervical, brachial, lumbar, sacral)
- causes: trauma, diabetic peripheral neuropathy, congenital anomalies, neoplastic involvement, radiation injury
- presentation: motor, sensory, and autonomic dysfunction that corresponds with nerves involved and degree of invasiveness
- investigation: labs, EMG/NCS
treatment depends on cause
-prognosis is variable

C. Mononeuritis multiplex:

-Peripheral Polyneuropathies

A. Hereditary peripheral polyneuropathies

- Charcot-Marie-Tooth disease type (HMSN): inherited disorder of nerves characterized by loss of muscle tissue and touch sensation
  -results in myelin damage (type I) or axonal damage (type II)
  -usually inherited autosomal dominant but can be sporadic X-linked recessive
  -onset in childhood or early adulthood
  -presentation: slow progression
    -motor deficits > sensory
      -muscle wasting and secondary weakness: pes cavus, hammer toes, foot drop, slapping gait
      -postural tremor
      -lower extremities more affected than upper
    -deficits less prominent in type II
  -numbness and vibratory sensory losses
  -depressed or absent DTRs
  -kyphosis
  -peripheral nerve hypertrophy (not present in type II)

-investigation:
  -nerve or muscle biopsy is confirmatory
  -genetic testing
  -EMG/NCS to differentiate type I from type II
    -type I → reduced conduction velocity
    -type II → normal or slightly reduced conduction velocity, reduced or absent sensory action potential

-treatment:
  -no cure, goal is to maintain independent functioning
  -splits, braces
  -orthopedic surgery
  -PT & OT

- Dejerine-Sottas disease (aka Charcot-Marie-Tooth disease type III or HMSN III): abnormal phytanic acid metabolism leads to progressive demyelinating neuropathy
  -onset in infancy or childhood
  -presentation:
    -motor weakness and ataxia
    -loss of sensation
    -global hypoactive DTRs

-investigation:
  -labs: elevated CSF protein
  -EMG/NCS: reduced motor velocity and sensory conduction

-treatment is supportive
  -plasmapheresis to remove excess phytanic acid
  -dietary restriction: cow products, fish

- Refsum disease (aka Charcot-Marie-Tooth disease type IV or HMSN IV): progressive demyelinating neuropathy
  -onset in early childhood
  -presentation: same as type III plus retinitis pigmentosa

-investigation:
  -labs: normal CSF protein
  -nerve biopsy
  -EMG/NCS same as type III

-treatment is supportive
• Friedrich’s ataxia:
• Porphyria:

B.) Endocrine peripheral polyneuropathies
• Diabetic peripheral neuropathy: axonal involvement that can affect DM1 or DM2
  - Presentation can take many forms:
    - Distal symmetric polyneuropathy such as stocking-glove paresthesias
      - Sensory proceeds motor disease
      - Lower extremity disease precedes upper extremity disease
    - Isolated peripheral neuropathy
      - Focal, sudden onset, complete recovery in 6-12 weeks
    - Painful diabetic neuropathy
    - Autonomic neuropathy
  - Investigation:
    - Semmes Weinstein filament test on bottom of feet
    - Lab confirmation of DM
    - EMG/NCS showing normal to mildly slow conduction
  - Treatment: symptomatic, glycemic control won’t improve symptoms but will delay progression
  - Complications:
    • Charcot arthropathy: Arthritic foot change from peripheral neuropathy, autonomic dysfunction, and trauma
      - Acute presentation: pain and swelling
      - Chronic presentation: “rocker bottom” deformity, ulceration
      - Diagnosis is clinical
      - Treatment: daily foot care, custom molded shoes, management of ulcers
    • Uremic peripheral neuropathy: probably from a combination of metabolic and toxic factors
      - Presentation: symmetric sensory-motor deficits
        - Lower extremities > upper
        - Distal > proximal
        - Severity correlates with degree of renal insufficiency
      - Investigation:
        - Labs: CMP
        - EMG/NCS
      - Treatment: supportive/symptomatic, long-term dialysis, kidney transplant
    • Alcohol and nutrition deficiency peripheral neuropathy: neuronal dysfunction secondary to inadequate nutrition
      - Axonal > myelin involvement
      - Presentation: slow progression of distal symmetric polyneuropathy
        - Sensory precedes motor involvement
        - Lower extremity precedes upper involvement
        - Sensory disease: cramps, painful paresthesias, tenderness
        - CNS symptoms often precede PNS symptoms
      - Investigation:
        - Labs: B12, CBC, LFTs
        - EMG/NCS
      - Treatment: stop alcohol, nutritional supplementation, management of malabsorption, PT
    • Paraproteinemias

C.) Infectious peripheral polyneuropathies
• Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome): an immune-mediated progressive demyelinating neuropathy
  • Subtypes: Acute motor axonal neuropathy and acute motor-sensory axonal neuropathy
  • Risk factors: recent infective illness or immunization, recent surgery
  • Presentation:
    - Motor deficits: symmetric weakness
    - Proximal precedes distal
    - Lower extremities precede upper
-advanced: respiratory muscle compromise, CN involvement
  -sensory deficits: paresthesias, loss of sensation
  -distal precedes proximal
-global hyporeflexive DTRs
-autonomic dysfunction: tachycardia, cardiac irregularities, BP changes, pulm
dysfunction, loss of rectal tone
-investigation:
  -elevated CSF protein 2-3 weeks after onset
  -EMG/NCS showing demyelination with delayed conduction 3-4 weeks after onset
-treatment indicated for gait or respiratory impairment or progressive weakness
  -plasmapheresis
  -IV Ig
  -mechanical ventilation
-prognosis: mortality rate of 10%, lasting disability in 10-20% of cases, can become chronic
  • HIV-related peripheral neuropathy: may be caused by infection of nerve root ganglion or involvement
    with CMV
    -presentation may be acute, subacute, or chronic
    -motor deficits > sensory, may also have autonomic dysfunction
    -treatment is supportive
-leprosy
-Lyme
-sarcoidosis
  • polyarteritis:
  -rheumatoid arthritis

D.) Inflammatory peripheral polyneuropathies
E.) Toxic peripheral polyneuropathies
  -from exposure to neurotoxins such as industrial agents, pesticides, heavy metals, medications
  -presentation: motor, sensory, autonomic, and mixed features depending on agent
  -treatment: prevent further exposure, PT, OT, time
F.) Metastatic peripheral polyneuropathies
  -result of invasion of plexus or peripheral nerves by malignant cells
  -investigation:
    -EMG/NCS
    -MRI for soft tissue
  -treatment: radiation, less commonly surgery
G.) Paraneoplastic peripheral neuropathies
  -immune-mediated response to neoplasm
  -investigation: paraneoplastic antibody panel
  -treatment: management of primary tumor
G.) Peripheral polyneuropathies as a result of critical illness
  -a result of axonal dysfunction, mechanism uncertain
  -presentation:
    -associated with ICU admission, sepsis, multi-organ dysfunction, and difficulty weaning from
      ventilator
    -motor deficits > sensory
    -weakness and muscle wasting
  -investigation: EMG/NCS
  -treatment is supportive