Pediatric Neurology
Multi-topic Review
and Questions

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Topics

- Headache
- Seizures / Epileptic Syndromes
- Peripheral Nervous System Disorders
- Brain Malformations
- Ataxia
- Neurocutaneous Syndromes
- Additional questions and answers
HEADACHE IN CHILDREN
Epidemiology of Headache

- uncommon < 4 years
- prevalence increases with age
- female predisposition with puberty
  - < 10-12 years $\rightarrow$ girls = boys (1 : 1)
  - > 10-12 years $\rightarrow$ girls > boys (1.5 : 1)
- most are MIGRAINE or TENSION
- remission occurs in 70% of cases ages 9-16 years
Headache Classification

- PRIMARY (Benign) - Migraine, Tension, Cluster
  - exam normal
  - no papilledema
  - no fever / meningismus
  - normal neuroimaging
  - normal CSF (including opening pressure)

- SECONDARY
  - Something’s wrong
Migraine

- **Anterior location** (frontotemporal, uni- or bilateral)
- **Pulsating quality** (throbbing, pounding)
- **Autonomic symptoms required**
  - nausea / vomiting, photo- or phono-phobia, pallor
- “**Classic migraine**” - begins with a transient aura
  - **Visual** aura most common (15-30 min)
  - Genetically predisposed
- “**Common migraine**” - no aura (70-85 % children)
- **Triggers** - sleep deprived, hunger, illness, travel, stress
  - only 50 % migraineurs can identify trigger
Migraine common with other conditions:

- Somatic pain complaints
  - non-localizing abdominal discomfort
- Epilepsy
- Psychiatric
  - depression
  - anxiety
Migraine-related syndromes (variants)

- **Benign paroxysmal vertigo**
  - recurrent vertigo (suddenly looks afraid, grabs onto someone)
  - nausea, vomiting, nystagmus

- **Cyclic vomiting**
  - recurrent severe nausea and vomiting (q weeks-to-months)
  - attacks last hours-to-days
  - symptom-free between attacks

- **Alternating hemiplegia**
  - repeated attacks of L or R hemiplegia
  - onset before 18 months
  - normal at birth, neurodevelopmental issues after onset

- **Paroxysmal torticollis**
  - benign intermittent self-limited episodes of head tilt
  - spells last hours to days
  - start in 1st year of life, resolve by age 5 years
“Chronic Daily Headaches” (months)

- Migraines that have changed character
  - Poor pain control
  - Psychosocial causes
  - Medication overuse (aka “rebound headaches”)
- 5+ per week
- 15+ per month
- No underlying pathology
Tension

- Pain posterior > anterior, or band-like
- Squeezing quality (tight, vice-like)
- Neck muscles sore
- Common trigger: STRESS!
- NO autonomic symptoms
  - NO nausea / vomiting / photo- or phonophobia
- NO aura
- Best treatments:
  - NSAIDs, relaxation / biofeedback
Dx and Work-Up of chronic recurrent headache

- Diagnosis based on H & P
- No neuroimaging if exam normal
- Inadequate evidence to support the value of routine labs or CSF analysis
- EEG may be normal or show non-specific abnormalities (focal slowing, occipital spikes after migraine)
  - Does not distinguish headache types
  - Does not distinguish headache cause
- NOT RECOMMENDED for routine evaluation
Treatment for primary recurrent headache

- Practice parameters adapted from adult studies
- Avoid / minimize triggers (MIGRAINES)
  - Optimize hydration
  - Good sleep hygiene / avoid sleep deprivation
  - Avoid hunger
  - Avoid food triggers (aged cheeses, chocolate, caffeine/ soda, processed deli meats, MSG, red wine)
- Mind-Body approach - minimize stress (TENSION)
  - Biofeedback / relaxation
  - Acupuncture
  - Self-hypnosis
ACUTE treatments for migraines

- Goals: reduce / ablate pain, restore function, minimize need for rescue medications
- Treat promptly at onset
- Include anti-emetics (if nausea / vomiting):
  - metoclopramide (Reglan)
  - prochlorperazine (Compazine)
  - promethazine (Phenergan)
- Avoid medication overuse (meds ≤ 2-3 x per week)
- 1st line meds: NSAIDs
- Triptans (serotonin 1B/1D receptor agonists)
  - sumatriptan (Imitrex) intranasal or oral tablets (≥ 12 yo)
CHRONIC (prophylactic) treatments for migraines

- Indicated if headaches 1-2 x/ week or prolonged/ debilitating
- propranolol (Inderal)
  - side effects – hypotension, bradycardia
  - avoid in asthmatics, depressed
- amitriptyline (Elavil)
  - side effects – drowsiness, orthostasis, dysrhythmia (EKG)
  - may require 6-12 weeks to determine effectiveness
- anti-epileptics (topiramate, valproic acid, carbamazepine, neurontin)
- calcium channel blockers (verapamil)
- serotonin agonists (cyproheptadine, methysergide)
- vitamins (B2 / riboflavin, magnesium)
Rethink the diagnosis of benign headache when headache:

- always in the same location
- fails to respond to multiple medical therapies
- focal neurologic signs appear
  - 6th nerve palsy, diplopia, new onset strabismus, papilledema, hemiparesis, ataxia
- worsening frequency / severity
- worse with valsalva (coughing, straining)
- awakens from sleep, worse in the morning, AM vomiting
- at-risk hx or condition: VPS, neurocutaneous disorder
Secondary “symptomatic” headache

- **Increased intracranial pressure** - brain tumor, brain abscess, hemorrhage, hydrocephalus, VPS malfunction, meningitis, pseudotumor**

- **Vascular** - stroke, intracerebral hemorrhage / ruptured aneurysm or AVM, vasculitis

- **Epilepsy** - postictal or ictal

- **Head and Neck pathology** - sinusitis, dental abscess, trigeminal neuralgia, TMJ pain, carotid dissection

- **Systemic Illness** - HTN, DM, cardiac disease-source of emboli/stroke

- **Drug Use** - analgesic overuse/rebound, drug abuse- cocaine, psychostimulants, OCPs, steroids

- **Psychological** - depression

** scan will be normal, but + papilledema
NEUROIMAGING for headache (before LP) if:

- abnormal neurologic exam
  - altered mental status
  - papilledema, VI nerve palsy, diplopia, new onset strabismus
  - focal findings (hemiparesis)
  - nuchal rigidity, fever
- change in headache frequency, intensity, type
- studies of choice:
  - CT – BONE (skull fracture), BLOOD (intracranial hemorrhage), EMERGENCY (altered MS); also ventricles (hydrocephalus), sinuses, mass lesions
  - MRI – acute STROKE, vascular malformation; also ventricles (hydrocephalus), sinuses, mass lesions
  - LP – NOT with focal mass lesion on CT or MRI, but OK for pseudotumor, meningitis, subarachnoid hemorrhage after CT
CT of the brain with contrast:

- enhancing tumor (the white mass) with surrounding edema (the darkened region surrounding the tumor)

- mild effacement of the left lateral ventricle

Headache due to Brain Tumor
Headache due to Intracranial hemorrhage

EPIDURAL – acute (white) lens-shaped blood collection, significant mass effect

SUBDURAL – sub-acute (gray) blood collection, less severe mass effect
Headache due to Intracranial Hemorrhage:
Ruptured AVM

Headache followed by acute deterioration in mental status
Headache due to Hydrocephalus

Choroid Plexus Papilloma
CSF secreting intra-ventricular tumor
which obstructs ventricular system
Obstructive / Non-communicating Hydrocephalus due to Aqueductal Stenosis

CT of the brain:
- large frontal and temporal horns of lateral ventricles
- large third ventricle
- 4th ventricle small
Obstructive / Non-communicating Hydrocephalus due to Chiari Malformation:

- low lying tonsils alone (Chiari I) – usually asymptomatic
- low lying tonsils + hydrocephalus (Chiari II) – diffuse headache

Chiari I

Chiari II (+ lumbosacral myelomeningocele)
Non-Obstructive / Communicating Hydrocephalus due to Meningitis

CT of the brain reveals enlarged frontal and temporal horns of the lateral ventricles and enlarged 3rd and 4th ventricles.

Headache, photophobia, fever, nuchal rigidity (meningeal irritation due to infection and inflammation).
Headache due to Stroke

MRI of the brain revealing posterior circulation strokes (occipital cortex, cerebellum and brainstem)

Child with sickle cell anemia presenting with headache, ataxia and cranial nerve palsies.
Traumatic dissection of right internal carotid artery (ex. running with pencil in mouth, ex. whiplash on amusement park ride):
- “string sign” on angio
- right MCA stroke on CT
“Sunsetting Eyes”: clinical sign of increased intracranial pressure
SEIZURES AND EPILEPSY IN CHILDREN
Seizures and Epilepsy

- Neonatal Seizures (not epilepsy)
- Febrile Seizures (not epilepsy)
- Infantile Spasms (epilepsy)
- Lennox-Gastaut Syndrome (epilepsy)
- Childhood Absence (Petit Mal) Epilepsy
- Juvenile Absence Epilepsy
- Juvenile Myoclonic Epilepsy
- Benign Rolandic Epilepsy
- Complex Partial Epilepsy
Epidemiology of Seizures and Epilepsy in Children

- 4-6% incidence of a single seizure
- 1% incidence of epilepsy (≥2 unprovoked seizures)
- 70-80% achieve remission ("outgrow" seizures)
- HISTORY is the most important tool in differentiating a seizure from a non-seizure look-alike
- EEG is an adjunctive test to clinical history
- after 1st unprovoked seizure:
  - If EEG normal, 40% recurrence risk
  - If EEG abnormal, 80% recurrence risk
- 50% of 2nd unprovoked seizures occur within 6 months of 1st seizure
Epidemiology of Seizures and Epilepsy

- Increased recurrence risk if:
  - symptomatic etiology (dev delay, MR / CP)
  - abnormal EEG
  - complex febrile seizures
  - Todd’s paresis
  - nocturnal seizures
  - + FHx childhood onset epileptic seizures

- Factors that do NOT influence recurrence risk:
  - age
  - seizure duration
Neonatal Seizures (not epilepsy)

- Benign Neonatal Familial Convulsions

- Onset 2\textsuperscript{nd} or 3\textsuperscript{rd} day of life
- No perinatal complications
- Autosomal dominant condition (+FHx)
  - chromosomes 20 and 8
  - affected gene product: alpha-subunit of Ach Receptor
- Mixed seizure types
  - apneic, clonic, tonic, autonomic, oculofacial
- Typically easy to control seizures which resolve in 1\textsuperscript{st} year of life
- Neuroimaging and EEG normal
Neonatal Seizures that may progress to epilepsy

Multiple Causes

- Hypoxia-Ischemia (HIE)
- Infection (meningitis, sepsis)
- Hemorrhage (IVH, subarachnoid, intraparenchymal)
- Infarction (thrombotic, hemorrhagic)
- Metabolic derangement (low sodium, low calcium, glucose)
- Inborn errors of metabolism
- CNS malformation

- Treatments: IV phenobarbital, IV phenytoin, IV benzodiazepine
- If seizures do not respond to conventional meds above, trial of IV pyridoxine 100 mg (pyridoxine deficiency)
Febrile Seizures (not epilepsy)

- 2-4 % of children age ~ 6 months – 6 years
- Provoked by a sudden spike in temp usually with URI, Acute OM, AGE (genetic predisposition)
- **“Simple”**
  - Generalized convulsion (whole body shaking)
  - Brief (< 15-20 minutes)
  - Only one in the course of an illness
  - Future risk of epilepsy 1% like other children
- **“Complex”**
  - focal seizure (one side of body shaking, staring)
  - prolonged (> 15-20 minutes)
  - multiple in 24 hours
- Complex febrile seizures hint at an increased risk of future epilepsy
Treatment of Febrile Seizures (not epilepsy)

- Considered benign not warranting daily anti-seizure medication
  - but phenobarbital or valproic acid provide some prevention

- Rectal Diastat (valium gel) may be used to:
  - abort prolonged complex febrile seizure
  - prevent complex febrile seizure clusters (if child known to cluster)
  - prevent febrile seizure recurrence during a febrile illness

- Anti-pyretics have NOT been proven to decrease the risk of recurrent febrile seizures
Infantile Spasms (West Syndrome) – a severe epilepsy

Clinical spasms (1-2 secs)
- a subtle momentary flexion or extension of the body
- occur in clusters when drowsy (waking or falling asleep)

Severely abnormal EEG pattern: disorganized, discontinuous, high amplitude, multifocal spikes called HYPSARRHYTHMIA

Treatment: ACTH
Infantile spasms

- may be mistaken for colic, reflux, hiccups, or a startle!

- common etiologies:
  - perinatal insults (ex. hypoxia-ischemia, meningitis)
  - brain malformation
  - neurocutaneous disorder (Tuberous Sclerosis)
  - metabolic disorder
  - ARX Aristaleless X-linked homeobox gene mutation

- prognosis best (10% good outcome) if idiopathic
  - normal development at onset of infantile spasms
  - extensive etiology testing negative

- prognosis poor for:
  - seizure control (infantile spasms and future seizures)
  - future neurocognitive and developmental abilities
Lennox-Gastaut Syndrome – a severe epilepsy

- Often evolves from infantile spasms
- Developmentally impaired
- Syndrome defined by a TRIAD of:
  1. mixed seizure types
     - atonic, atypical absence, myoclonic, tonic-clonic, partial
  2. developmental delay
  3. abnormal EEG pattern
     - slow (< 2.5 Hz) spike wave discharges
- Prognosis poor
Childhood Absence (Petit Mal) Epilepsy
a genetically predetermined generalized epilepsy = a ‘primary generalized’ epilepsy

- Sudden onset of staring, interrupting speech or activity
- Occurs multiple times per day
- Short duration (seconds)
- Occurs in school aged children ~ 4-12 years, otherwise normal
Childhood Absence (Petit Mal) Epilepsy (continued)

**EEG findings characteristic:**
- bilateral generalized 3 Hz spike-and-wave discharges
- provoked by hyperventilation and photic stimulation

**Treatment:** ethosuximide (Zarontin)

Commonly resolves by adolescence

**Presumed genetic cause:** chromosome 8 (8q24) and 5 (5q31)
Juvenile Absence Epilepsy
(another ‘primary generalized’ epilepsy)

- **onset** a bit **older** than childhood absence epilepsy
  - in adolescence (closer to middle school than elementary school)
- similar staring **seizures** but:
  - longer duration
  - fewer (less frequent)
- higher risk for other generalized seizures:
  - GTC
  - Myoclonic
- less likely to outgrow
- **EEG** generalized spike wave discharges:
  - Faster than 3 Hz (4-6 Hz)
**Juvenile Myoclonic Epilepsy (JME)**  
(another ‘primary generalized’ epilepsy)

**Seizure types:**
- myoclonic in AM
- “grand mal”
- absence

**EEG:** bilateral generalized 4-6 Hz spike-wave or polyspike-wave activity
Juvenile Myoclonic Epilepsy (JME) (continued)

- Seizures provoked by:
  - sleep deprivation or arousals from sleep
  - photic stimulation
  - alcohol
- Mean age at onset 14 years
- EEG: 4-6 Hz spike wave provoked by photic stimulation
- 90% relapse if medications discontinued
  - require lifelong treatment
- Genetic predisposition
  - possibly chromosome 6
Benign Rolandic Epilepsy
(a genetically predetermined focal epilepsy)

- Onset 3-13 years old, boys > girls
- 15% of epileptic children
- Normal IQ, normal exam, normal MRI
- May have + FHx sz
- Seizure description:
  - When awake:
    - twitching and/or tingling on one side of body
    - speech difficulty, may drool / gag
    - no loss of consciousness, usually < 2 minutes
  - When asleep (nocturnal):
    - “grand mal” with focal features
Benign Rolandic Epilepsy

Aka Benign Focal Epilepsy of Childhood with Centrotemporal Spikes

EEG has characteristic pattern:

bilateral independent centrotemporal spikes
Benign Rolandic Epilepsy

- **Treatment** recommended only if:
  - Seizures frequent (which is unusual)
  - Socially stigmatizing if occur in wakefulness
  - Anxiety provoking for parents if occur in sleep

- **Effective treatments:**
  - **Avoidance of sleep deprivation**
  - **Medications:** carbamazepine, oxcarbazepine
  - **Time** (outgrown by adolescence)
Other Epilepsy Syndromes

1) Landau-Kleffner Syndrome

- an acquired EPILEPTIC APHASIA in a PREVIOUSLY NORMAL child, usually 3-7 years old
- Gradual or sudden inability to understand or use spoken language ("word deafness")
- Must have EEG abnormalities in deep sleep (sleep activated)
- Additional behavioral and psychomotor disorders (hyperactivity, aggressiveness, depression, autistic features)
- May have additional overt clinical seizures (80%) in sleep
Other Epilepsy Syndromes

2) Rett Syndrome

- Occurs only in girls (X-linked lethal mutation) – MECP2 gene mutation
- Initial normal development → dev regression / autistic (loss of motor / language / social skills)
- Acquired microcephaly (deceleration of head growth)
- Hand wringing / alternating hand movements
- Irregular breathing patterns
  - Apnea
  - Hyperpnea
  - Breathholding
- Seizures
Complex Partial Epilepsy

- Impairment of consciousness (staring)
- Temporal lobe onset (80%) most common

Mesiotemporal sclerosis
Differentiating “Staring” Seizures

- Complex Partial Seizures
  - + aura
  - + incontinence
  - + postictal lethargy
  - EEG with focal spikes
  - lasts minutes
    (but can be shorter)

- Absence Seizures
  - NO aura
  - NO incontinence
  - NO postictal period
    (immediate recovery)
  - EEG with generalized 3 Hz
    spike wave activity
  - lasts seconds
    (but can be longer)
Spells that mimic seizures

- Apnea / ALTE
- GER
- Sleep disorders (nocturnal myoclonus, night terrors, narcolepsy/cataplexy)
- Migraine variants (esp. aura)
- Benign breathholding spells
  - No neuro consult / lab / EEG / CT, Fe for cyanotic type
- Syncope
- Movement Disorders (tics, tremor, dystonia)
- ADD
- Behavioral Stereotypies (PDD)
- Pseudoseizures (psychogenic seizures)
  - Strange posturing, back arching, writhing
  - Alternating L and R limb shaking during same seizure
  - Psychosocial stressor
Medical triggers of seizures (acute symptomatic seizures)

- ↓ or ↑ glucose
- ↓ calcium
- ↓ or ↑ sodium
- CNS infection (meningitis, encephalitis)
- acute trauma
- toxic exposure
- acute ↑ bp
Treatment of epileptic seizures

- After the second unprovoked seizure
- Choice of AED - maximum effectiveness for that particular seizure type, minimal side effects
- 70% become seizure free on monotherapy
- an additional 15% become seizure free on polypharmacy
- 15% remain intractable
- Discontinue AED after 2 years seizure free EXCEPT for JME
- Alternate treatments:
  - Ketogenic diet (high fat diet)
  - Vagal nerve stimulator – FDA approved for partial seizures in 12 years+
  - Epilepsy surgery
Classic side effects of AEDs

- valproic acid (Depakote): liver toxic, weight gain, acute pancreatitis
- lamotrigine (Lamictal): Stevens-Johnson syndrome
- phenytoin (Dilantin): gingival hypertrophy, acute ataxia, osteoporosis
- phenobarbital: adverse behavior / hyperactivity
- carbamazepine (Tegretol): agranulocytosis, aplastic anemia
- oxcarbazepine (Trileptal): low sodium
- ethosuximide (Zarontin): lupus-like reaction (+ANA)
- topiramate (Topamax): weight loss, acidosis, renal stones, anhidrosis
- felbamate (Felbatol): aplastic anemia
Status Epilepticus

- **Def:**
  - seizure lasting > 30 minutes or
  - repeated seizures > 30 minutes without recovery in mental status between seizures
  - seizures > 1 hour associated with neuronal injury due to glutamate excitotoxicity

- **Evaluation and treatment if seizure lasts > 5 minutes:**
  - ABC’s (RR, HR, BP)
  - check temp, glucose, electrolytes, CBC, renal and hepatic function, AED levels
  - Benzodiazepine → phenytoin → phenobarbital
PERIPHERAL NERVOUS SYSTEM DISORDERS

Presents as weakness with NO UMN signs
  no hyperreflexia
  no clonus
  no upgoing toes
1. **ANTERIOR HORN CELL**
   A. Spinal Muscular Atrophy (SMA) (genetic),
   B. Poliomyelitis (acquired)

2. **Peripheral nerve**

3. **Neuromuscular junction**

4. **Muscle**
A. Spinal muscular atrophy (SMA)

Type 1 SMA - Werdnig-Hoffman

- Prenatal – decreased fetal movements
- Neonatal / early infancy
  - severe hypotonia
  - breathing / swallowing difficulties
  - absent reflexes
  - tongue fasciculations
  - no face / eye weakness
- Motor milestones: never sit
- Autosomal recessive - SMN (survival motor neuron) gene mutation, chromosome 5
- **Type 2** – less severe, less slowly progressive
  - Motor milestones: *typically sit, don’t walk*

- **Type 3** (Kugelberg-Welander) – least severe
  - Motor milestones: may walk, but ultimately wheelchair bound too

- **Diagnosis of SMA:**
  - **Genetic analysis** – highly sensitive and specific
  - If gene study positive, no additional testing required
  - If gene study negative,
    - **EMG** → fibrillations (muscle denervation)
    - Muscle biopsy
Treatment of SMA:

- aggressive and early respiratory toilet
- **assisted ventilation** for most type 1 SMA + many type 2 SMA
- **physical therapy** to avoid / minimize contractures
- encouragement of full educational pursuits—intellect unaffected
B. Poliomyelitis (infantile paralysis)

- viral infection -> destruction of anterior horn cells
- flaccid **asymmetric** paralysis, usually legs
- may involve face (bulbar muscles)
- decreased or absent reflexes
1. Anterior horn cell
2. PERIPHERAL NERVE
   A. Guillain-Barre Syndrome (acquired),
   B. Charcot-Marie-Tooth disease (genetic)
3. Neuromuscular junction
4. Muscle
A. Guillain-Barre Syndrome (GBS)

- Most common ACUTE neuropathy in children
- Most common cause of rapidly progressive weakness
  - 1st “pins and needles” in hands and feet
  - ascending bilateral paralysis (hours-to-days)
  - absent reflexes
  - back and hip pain common
- ICU observation if:
  - autonomic nerves affected → cardiac dysrhythmia
  - respiration affected
  - symptoms may worsen in 1st 4 weeks
- Miller-Fisher variant = Areflexia + Ataxia + CN palsies
  (abnormal eye movements, facial paralysis = “flat affect” = “decreased facial movements”)
Guillain-Barre Syndrome (GBS)

- aka **Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP)**

- 2/3 report **antecedent infection** 1-3 weeks prior
  - Campylobacter jejuni (esp. China)
  - CMV
  - EBV
  - Hepatitis
  - Flu or vaccine
  - mycoplasma
  - HSV
Diagnosis of GBS:
- CSF (≥ 1 week) – elevated protein, normal cells
- NCV (Nerve Conduction Velocity) – slowing
- MRI – enhancement of spinal roots
- Send titers for suspected pathogens

Management:
- IVIG or plasmapharesis if ventilation affected, or rapidly worsening and has not nadired
- OT/PT

Prognosis:
- Usually good (~75%), recovery may take weeks to months
- Poor prognostic signs:
  - rapidly progressive weakness < 7 days
  - assisted ventilation
  - Axonal involvement (not just demyelination) – seen on NCVs as decreased amplitudes
B. Charcot-Marie-Tooth (CMT) Disease

- the most common CHRONIC neuropathy in children, slowly progressive over decades

- a hereditary sensory motor neuropathy (HSMN)

- Initial symptoms noted > 10 years:
  - “pes cavus” – high pedal arches
  - “champagne glass deformity” - muscle atrophy below the knees
  - bilateral foot drops - slaps feet when walks, difficult to heel walk, tend to toe walk
  - poor or absent reflexes
CMT Disease

“Champagne-Glass Deformity”: Distal Muscular Atrophy of Lower Extremities

High Arched Foot Deformity “Pes Cavus”
Diagnosis of CMT:
- NCVs abnormal - conduction slowing

Genetic testing (autosomal dominant)
- peripheral myelin protein 22 (PMP22) mutation

Management:
- OT/PT
- Bracing for the foot drop improves gait
- Relatively rare to need a wheelchair later in life
1. Anterior horn cell
2. Peripheral nerve
3. NEUROMUSCULAR JUNCTION
   A. Myasthenia Gravis (autoimmune or genetic)
   B. Infant botulism (acquired)
4. Muscle
A. Myasthenia Gravis (MG) – 3 forms

- **Neonatal**
  - transplacental passage of maternal Ach R antibodies
  - severe hypotonia at birth, but self-limited (days-to-weeks)
  - may require temporary feeding and respiratory support

- **Congenital – not autoimmune**
  - neonatal, infantile or very early childhood onset
  - anatomic or physiologic abnormality of NMJ (muscle bx)
    - abnormal presynaptic acetylcholine packaging
    - presynaptic acetylcholinesterase deficiency
    - abnormal post-synaptic Ach receptors

- **Autoimmune - most common**
Autoimmune MG

- 2 subtypes recognized:
  - Ocular (ptosis, ophthalmoplegia)
  - Generalized weakness

- Onset acute or subacute:
  - eye weakness
  - difficulty swallowing, poor gag
  - generalized weakness
  - diurnal fatigue (worse at night)
  - may require ventilatory support at presentation
  - symptoms **exacerbated by infection, hot weather, medications**
Medications that may worsen Myasthenia Gravis

- D-penicillamine
- Aminoglycosides
- beta-blockers
- Ca channel blockers
- laxatives / antacids (Mg salts)
- iodinated contrast dyes (gad)
Autoimmune MG

- **Dx:** Tensilon (edrophonium) test
- **Management:**
  - Cholinesterase inhibitors
    - Pyridostigmine (Mestinon)
      - monitor for hyper-cholinergic symptoms
        - increased lacrimation / salivation
        - bradycardia
        - stomach cramps
  - Prednisone
  - Plasma exchange
    - for acute and severe weakness
    - for respiratory depression
  - Thymectomy
    - for medication refractory generalized MG
B. Infant Botulism (6 weeks – 6 months)

- Toxin of the bacteria *Clostridium botulinum* (which grows in the intestine) irreversibly binds to the acetylcholine receptor at the NMJ

- Symptoms:
  - poor feeding, poor suck, absent gag, weak cry
  - descending paralysis, hypotonia, head lag
  - reflexes reduced
  - constipation
  - respiratory compromise, apnea
Infant Botulism

- Source of C. botulinum spores
  - Soil
  - Foods
    - honey
    - corn syrups

- Diagnosis
  - Isolation of organism or toxin in stool

- Treatment
  - Botulism immune globulin (BIG)
1. Anterior horn cell
2. Peripheral nerve
3. Neuromuscular junction
4. MUSCLE

Duchenne and Becker Muscular Dystrophy
Muscular Dystrophy

- Duchenne MD- X-linked (only boys) – Xp21
- Preschool age of onset
- Proximal muscle weakness – difficulty running, hopping, stair climbing, standing from sitting (“Gower”)
- Face and eye weakness NOT present
- Pseudohypertrophy of calf (gastroc) muscles
- Toe walking, lordotic waddling gait
- Wheelchair bound by early-to-mid teens
- Progressive dilated cardiomyopathy occurs
- Death by late teens-to-early 20s
  - resp failure due to weakness, scoliosis
Pseudohypertrophy of calf muscles

Gower Sign
Becker MD
- slowly progressive
- onset after preschool (elementary or later)
- prognosis more variable
  - may live past middle age
  - may self-ambulate without a wheelchair for may decades
- progressive dilated cardiomyopathy occurs
  - may result in end-stage cardiac failure
Diagnosis:
- Elevated CPK (>10,000 in DMD)
- Genetic testing (dystrophin mutation)
- Muscle biopsy - dystrophin staining
  - absent in Duchenne MD
  - reduced in Becker MD
  - normal in all other muscle disorders

Optimal management:
- orthotics to preserve ambulation
- OT/PT to minimize contractures
- when non-ambulatory, prevent scoliosis with:
  - proper fitting wheelchair
  - spinal fusion if necessary
Question 1:

An 8 year old boy presents with blurry vision, difficulty seeing the blackboard in school and trouble watching television for about 1 week. He also has headache in the back of his head. On exam, he has a right esotropia (right eye deviates medially). There is no papilledema. The rest of the exam is normal.
The test MOST likely to establish the diagnosis is:

1. **CT of the head**
2. Electroretinography
3. Lumbar puncture
4. Radiographs of the cervical spine and skull base
5. Visual evoked response (VER)
A. **CT of the head** – pt has sixth nerve palsy with recent onset of headache (ominous signs)

B. Electroretinography – for retinal problems; boy’s visual complaints are due to diplopia / VI nerve palsy

C. Lumbar puncture – not safe to do unless mass lesion ruled out by CT (but if CT were normal, could be pseudotumor although patient has no stated risk factors for pseudotumor)

D. Radiographs of the cervical spine and skull base – only for headaches associated with base of skull problems (ex. platybasia, Klippel-Feil deformity) but these conditions can be associated with hydrocephalus so CT of the head still preferable

E. Visual evoked responses – for optic nerve problems which could present with blurry vision, but patient has VI nerve palsy
Question 2:

A 17 year old boy reports constant headaches since suffering a minor laceration to his right frontal scalp 5 months ago. There was no LOC. Now he has daily frontotemporal headaches for which he frequently takes acetaminophen, ibuprofen or naproxen, but obtains little relief. His exam is otherwise normal. A urine tox screen is negative.
Of the following, the MOST appropriate next step in the management of this child is:

1. initiate sumatriptan and propranolol
2. obtain computed tomography (CT) of the head
3. perform a lumbar puncture
4. refer the patient to a psychiatrist
5. stop all analgesics and start amitriptyline
A. initiate sumatriptan and propranolol – no; sumatriptan will contribute more to medication overuse (propranolol prophylaxis OK)

B. obtain computed tomography (CT) of the head – no; exam is normal; not likely to have an injury due to trauma becoming symptomatic after 5 months

C. perform a lumbar puncture – no; no papilledema and exam is normal (but if papilledema without fever, think pseudotumor)

D. refer the patient to a psychiatrist – may be needed in the future, but first must address medication overuse

E. stop all analgesics and start amitriptyline – need to stop acute abortive medications to recover from “chronic daily headaches” caused by medication overuse; initiating prophylactic medication (amitriptyline) will begin to decrease headache
Question 3:

A 6 year old girl is brought to your office for clumsy gait of 3 days duration. On exam, she is afebrile and ataxic. She has a full right facial palsy. Deep tendon reflexes are absent at the knees and ankles.
Of the following, the MOST appropriate next step in the evaluation of this child is:

1. computed tomography (CT) of the head
2. electroencephalography (EEG)
3. lumbar puncture
4. magnetic resonance imaging of the spine
5. urine toxicology screen
C. **Lumbar puncture** – the ataxia plus areflexia plus facial palsy is pathognomonic for Guillain-Barre syndrome (Miller-Fisher variant). LP will reveal increased protein (due to breakdown of myelin proteins / demyelination of the nerve roots) with normal WBC count (“cytoalbuminemic dissociation”).
Question 4:

A 3 year old boy presents to the ER following a 2 minute seizure. The parents report that the seizure began with left upper extremity shaking, then shaking of the entire body with loss of consciousness. On exam, temp is 103 F (39.5 C). He remains lethargic for several hours. CT of the head with contrast is normal. LP reveals CSF with 62 WBC, 0 RBC, protein 72, glucose 46. Gram stain is negative.
The MOST appropriate next step in the management of this child is to:

1. administer rectal diazepam
2. initiate dexamethasone intravenously
3. observe him
4. provide a bolus of fosphenytoin intramuscularly
5. start acyclovir intravenously
E. Start acyclovir intravenously – The child in the vignette continues to appear lethargic after a focal seizure in the setting of fever. This is unusual for a febrile seizure so herpes encephalitis must be considered and promptly treated while tests (LP) are being obtained. IV dexamethasone is indicated for bacterial H. flu meningitis (not supported by the LP) or brain tumor (not supported by the CT). Because the child is not presently seizing, there is no need for rectal diazepam or fosphenytoin. To do nothing (observe him) is not prudent in view of the mental status change. The hallmark clinical features of HSV encephalitis include fever, altered mental status, and focal neurologic signs (on exam or during a seizure). Abnormal findings on CT of the brain (localized cerebral edema and hemorrhage in the temporal lobes) comes late in the clinical course and therefore, normal CT does not exclude the diagnosis.
Brain Malformations

- Chiari Malformation
- Dandy-Walker Malformation
- Porencephaly
- Holoprosencephaly
- Anencephaly
- Encephalocele
- Agenesis of Corpus Callosum
- Lissencephaly
- Schizencephaly
- Encephalomalacia
Chiari Malformation:
low lying cerebellar tonsils
Dandy-Walker Malformation: aplasia / hypoplasia of cerebellar vermis (midline cerebellum missing or underdeveloped)
Porencephaly
Holoprosencephaly
Anencephaly

Occipital Encephalocele
Agenesis of Corpus Callosum in Aicardi syndrome

- seizures (inf spasms), MR / dev delay, microcephaly
- retinal lesions
- symptom onset 3-5 months, only females
Lissencephaly = “smooth brain”
- achieve 3-5 month developmental milestones
- microcephaly, MR, seizures
- “Miller-Diecker syndrome” - when caused by the LIS-1 gene mutation
Schizencephaly: “clefted brain”
ATAXIA
Ataxia - diagnosed by the timeline of symptoms

- Acute Ataxia
- Episodic / Recurrent Ataxia
- Chronic or Progressive Ataxia

In vignettes, think ataxia if:
- problems walking
- clumsy, difficulty with balance
- problems reaching for objects
ACUTE ATAXIA

- Drug Ingestion
  - alcohol, benzodiazepines, phenytoin, antihistamines
  - thallium / pesticides
- Brainstem encephalitis
  - fever, ataxia + cranial nerve palsies, abnormal CSF
- Metabolic causes
  - low glucose, low sodium, elevated ammonia
- Neuroblastoma
  - ataxia + opsoclonus (roving eye movements) + myoclonus
- Brain tumors
- Trauma
  - ataxia not uncommon with concussion
ACUTE ATAXIA

- Vascular lesions
  - hemorrhage of a cerebellar AVM
- Kawasaki disease
  - ataxia due to multiple brain infarcts
- Polyradiculopathy
  - Guillain-Barre syndrome (Miller-Fisher variant)
  - tick paralysis
- Biotinidase deficiency
  - ataxia + seizures + hypotonia (dry skin, alopecia)
- Conversion reaction
- Postinfectious cerebellitis – DX OF EXCLUSION
  - 1-3 years old, post-varicella, ataxia maximal at onset
  - CSF normal or mildly increased protein
  - ataxia resolves after weeks-to-months
EPISODIC / RECURRENT ATAXIA

- Basilar migraine
  - Ataxia with occipital headache
  - AVOID TRIPTANS
- Multiple sclerosis
  - Ataxia a common presentation of MS in children
- Epileptic pseudoataxia
  - Ataxia a rare seizure manifestation
- Metabolic disorders
  - Hartnup Disease—impaired tryptophan absorption
  - Maple Syrup Urine Disease (intermittent)
  - Pyruvate Dehydrogenase Deficiency-E1
## EPISODIC / RECURRENT ATAXIA

<table>
<thead>
<tr>
<th>Episodic Ataxia type 1 (EA1)</th>
<th>Episodic Ataxia type 2 (EA2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- K+ channel gene mutation</td>
<td>- Ca+ channel gene mutation</td>
</tr>
<tr>
<td>- autosomal dominant (chr 12)</td>
<td>- autosomal dominant (chr 19)</td>
</tr>
<tr>
<td>- duration seconds (to hours)</td>
<td>- duration minutes to days</td>
</tr>
<tr>
<td>- triggers: STARTLE, exercise</td>
<td>- triggers: stress, exercise</td>
</tr>
<tr>
<td>- tx: Diamox, phenytoin</td>
<td>- tx: Diamox</td>
</tr>
</tbody>
</table>
CHRONIC OR PROGRESSIVE ATAXIA

- Friedrich Ataxia
  - most common hereditary progressive ataxia
  - multiple GAA repeats in frataxin gene, aut recessive
  - progressive degeneration of:
    - dorsal root ganglia → areflexia
    - posterior columns → decreased vibration / position sense
    - corticospinal tracts → upgoing toes (+Babinski’s)
    - spinocerebellar tracts + cerebellum → gait and limb ataxia
  - scoliosis and pes cavus can occur
  - often includes hypertrophic cardiomyopathy (need regular EKGs), Diabetes Mellitus, +/- hearing loss or optic atrophy
CHRONIC OR PROGRESSIVE ATAXIA

- Brain tumors
  - ataxia + signs of increased ICP / vomiting
  - infratentorial > supratentorial tumors for ages 1-8 years
  - common infratentorial types:
    - cerebellar astrocytoma
    - ependymoma
    - medulloblastoma
    - brainstem / pontine glioma (ICP elevation later in course)
- Congenital cerebellar hypoplasia
  - ataxia + nystagmus / dev delay / hypotonia
  - Dandy-Walker malformation, Chiari malformation
**CHRONIC OR PROGRESSIVE ATAXIA**

- Ataxia Telangiectasia
  - ATM (ataxia telangectasia mutated) recessive gene - encodes a mutated protein kinase involved in DNA repair
- Treatment:
  - prevent exposure to radiation
  - treat infections, malignancy
- Neurologic symptoms:
  - ataxic gait - dystonia, chorea, tics
  - unusual eye movements
  - peripheral neuropathy - dysphagia, choking
- Non-neurologic symptoms:
  - telangectasias (> 2 years old), 1st in conjunctiva
  - premature gray hair and senile keratosis (premature aging)
  - atrophy of thymus / lymphoid tissues, low WBC, low IgA / IgE / IgG → infections
  - lymphoma, leukemia, elevated alpha fetoprotein (AFP)
CHRONIC OR PROGRESSIVE ATAXIA

- Spinocerebellar Ataxia
  - over 16 distinct genetic loci, mostly autosomal dominant
  - many due to CAG expansion repeats
  - the larger the expansion, the earlier the age at onset

- Vitamin E Deficiencies
  - Acquired – fat malabsorption
    - ataxia, peripheral neuropathy, retinitis pigmentosa
  - Abetalipoproteinemia (Bassen-Kornzweig disease)
    - mutations in microsomal triglyceride transfer protein gene (MTP gene), autosomal recessive
    - In infants, steatorrhea and malabsorption
    - Dx: absence of apolipoprotein B in plasma
    - Tx: fat restriction and large doses of vitamin E
Neurocutaneous Syndromes

Neurofibromatosis

Tuberous Sclerosis

Sturge Weber
Neurofibromatosis

- Autosomal dominant
- NF 1
  - 1:3500 incidence
  - Mutation in *Neurofibromin* on chromosome 17
- NF 2
  - 1:40,000 incidence
  - Deafness (bilateral)
  - CNS tumors
  - Mutation in *Merlin* on chromosome 22
Neurofibromatosis

- NF 1 criteria (need 2 of the following 9):
  - + FHx (but ~ ½ cases sporadic mutation)
  - Skin criteria:
    - CAL (need 6+, > 0.5 cm prepubertal, > 1.5 cm post-pubertal)
    - Neurofibromas
    - Inguinal / axillary freckling
  - Bone criteria:
    - Pseudarthrosis (angulation deformity of long bone)
    - Scoliosis
    - Hypoplasia of sphenoid bone in base of skull
  - Eye criteria:
    - Lisch nodules (hamartomas in the iris)
    - Optic pallor (optic glioma)
Neurofibroma

Axillary Freckling
Pseudarthrosis

Scoliosis

Sphenoid Bone Hypoplasia
Lisch Nodules

Optic Glioma
Tuberous Sclerosis

- Autosomal dominant
- Chromosomes 9 (hamartin) and 16 (tuberin)
- Skin hypopigmentations ("Ash leaf" spots)
- Benign hamartomas:
  - skin
    - adenoma sebaceum on face
    - shagreen patch (brown leathery) on forehead or lower back
  - brain, retina, heart, kidney
- Seizures in 80-90 %
“Ash Leaf” Spot

Shagreen Patch

Adenoma Sebaceum
Tuberous sclerosis

Adenoma sebaceum

Shagreen patch

Ungual fibromas
Cortical Tubers
Sturge Weber

- Unilateral port wine stain over upper face
- Buphthalmos (infantile glaucoma) → enlargement of globe, corneal clouding
- Intracranial leptomeningeal vascular anomaly and calcifications in 90 %
- Seizures (partial / focal onset)
Port Wine Stain

Buphthalmos with enlarged globe, corneal clouding

Leptomeningeal Vascular Anomaly
ADDITIONAL QUESTIONS
Question 5:

A 15 year old boy who has cystic acne has experienced a frontal headache for 1 week. He reports that the only drug he takes is isoretinoin. Seen in the emergency room over night, a CT of the brain was normal. He was given meperididine and discharged home. He presents to your office today for follow-up. The boy has papilledema, but his neurologic exam is otherwise normal.
Of the following, the MOST appropriate next step in the evaluation of this patient is:

1. **lumbar puncture**
2. MRI of the brain with gadolinium contrast
3. neurosurgery consultation
4. ophthalmology consultation
5. urine toxicology screen
A. Lumbar puncture – headache and papilledema suggest increased intracranial pressure, but the CT of the head ruled out mass lesion. No MRI is needed as a lesion big enough to cause papilledema would be evident on CT. With normal CT of the brain, increased intracranial pressure headache suggests pseudotumor. Lumbar puncture would be both diagnostic and therapeutic. Follow-up with an ophthalmologist is reasonable, but is not needed before the LP because papilledema was already detected and the LP is necessary to make the diagnosis. Uncomplicated pseudotumor does not require neurosurgical consultation unless medical therapies are ineffective and the ongoing increased intracranial pressure jeopardizes (chokes) the optic nerves. Other causes of pseudotumor include: hyper- or hypo vitamin A, Addison disease, hypoparathyroidism, iron deficiency, polycythemia, otitis, mastoiditis, SLE, pregnancy, obesity, steroids, retinoids, OCPs, tetracycline, minocycline.
Question 6:

A 12 year old girl presents with paraparesis progressing over 2 days along with urinary incontinence and constipation. She complains of constant dull lower back pain. On physical exam, the child can not move her lower extremities and has brisk knee and ankle deep tendon reflexes. She has loss of pain sensation below dermatome T10.
Of the following, the test MOST likely to lead to this child’s diagnosis is:

1. edrophonium test (Tensilon test)
2. lumbar puncture
3. MRI of the spine
4. nerve conduction velocities
5. somatosensory evoked potentials
C. MRI of the spine – the differential diagnosis of low back pain with neurologic symptoms referable to the spinal cord (lower extremity weakness, bowel / bladder dysfunction, hyperreflexia and a sensory level) in children includes: spinal tumors, epidural abscess, diskitis, trauma, transverse myelitis, AVM, or Guillain-Barre syndrome. MRI of the spine helps to differentiate these entities. If the MRI was normal, LP would be obtained next to rule out transverse myelitis (associated with increased lymphocytic WBC and mildly elevated protein in CSF, due to post-infectious lymphocytic infiltration + demyelination of the spinal cord, usually at the thoracic level, triggered by EBV, HSV, flu, mumps, rubella, or varicella) or to suggest Guillain-Barre syndrome (increased protein and normal WBC in CSF). If the LP then suggested GBS, nerve conduction velocities would be obtained to confirm nerve conduction slowing of spinal nerves.
Question 7:

You are counseling the parents of a 3 month old girl who just underwent placement of a ventriculoperitoneal shunt for obstructive hydrocephalus secondary to aqueductal stenosis.
While talking with this family, you are most likely to state that:

1. antibiotic prophylaxis will be required before all dental procedures
2. lethargy and decreased spontaneity are sensitive indicators of shunt malfunction
3. most shunt infections with coagulase negative staphylococci occur between 3-12 months after shunt placement
4. the child will need to wear a helmet while she is learning to walk
5. the parents should depress the shunt bulb (or reservoir) daily to observe its refill and ensure the device works properly
B. Lethargy and decreased spontaneity are the most sensitive indicators of shunt malfunction. Most shunt infections arise from coagulase-negative staph epidermidis in the first 3 months after surgical placement. Whenever a child with a shunt presents with fever, a shunt infection must be considered. Signs of shunt infection or malfunction include fever, malaise, headache, irritability, anorexia and vomiting. Shunt malfunction is evaluated by CT of the head and radiographs along the path of the catheter tubing to confirm its continuity. Needle access to the bulb (reservoir) or manipulation of the bulb is best done by a neurosurgeon. Children with shunts do NOT require a helmet nor antibiotic prophylaxis.
Question 8:

After a year long history of twitching upon waking, a 16 year old girl experiences a generalized tonic-clonic seizure. Subsequent EEG demonstrates 4-5 cycle per second (Hz) generalized polyspike and wave; myoclonic seizures occur with photic stimulation. She will see a neurologist later this week, but she and her parents present now to your office for initial counseling.
The most likely statement you will make to the family is:

1. oxcarbazepine should be started, but can be stopped after a 2 year period free of seizures
2. oral contraceptives are contraindicated while she is receiving gabapentin
3. the girl may not drive a motor vehicle for 18 months
4. the girl must quit her school swim team
5. valproic acid will be required lifelong
E. Valproic acid will be required lifelong.
The patient in the vignette has juvenile myoclonic epilepsy, possibly the only epilepsy that requires lifelong treatment despite achieving a 2 year seizure free interval. Risk factors for seizure recurrence after a prolonged seizure free interval include mental or motor handicap, onset of seizures after age 12 years, and multiple medications needed to control the seizures. The girl should be encouraged to lead a normal life, including swimming (under direct adult supervision) or driving unaccompanied (which in most states requires only 3-12 months seizure free interval on medication). Girls who are sexually active should be counselled about the risk of fetal malformations associated with most anti-convulsant medications, particularly neural tube defects associated with valproic acid or carbamazepine. Oxcarbazepine and gabapentin are not indicated for generalized seizures (best for focal onset epilepsy).
Question 9:

A father brings his 6 year old daughter to you because her teacher has observed multiple daily episodes in which the child stares and is unresponsive to verbal cues. The teacher also noted facial twitching with some of these several second events. Her physical exam is normal.
Among the following, the MOST appropriate medication for this child is:

1. atomoxetine (Strattera)
2. carbamazepine
3. Clonidine
4. ethosuximide
5. methylphenidate
**D. Ethosuximide (brand name Zarontin).** The girl in the vignette has absence epilepsy (aka petit mal epilepsy). Alternative treatments include valproic acid or lamotrigine. Carbamazepine makes the absence seizures worse (though one might mistakenly prescribe carbamazepine on the basis of her seizure description; complex partial seizures mimic the staring of absence seizures though are prolonged in duration and commonly preceded by an aura; complex partial seizures are treated with carbamazepine). The differentiation between absence seizures and complex partial seizures requires EEG testing (absence seizures will be associated with generalized 3 cycle per second spike and wave activity; complex partial seizures will be associated with focal spikes, usually temporal lobe). Atomoxetine, clonidine and methylphenidate are treatments for ADD.
An 11 month old boy is brought to the ER because of a seizure. At home, he was “unresponsive and jerking all over” for 30 minutes. The father reports that he himself had febrile seizures as a child. On exam, the boy’s temperature is 103.5 F (39.7 C), HR 140, RR and BP normal. He is sleepy but arousable. The neuro exam is non-focal.
Of the following, the MOST likely factor to increase his chance of developing epilepsy is:

1. **his first complex febrile seizure**
2. family history of febrile seizure
3. male sex
4. onset of febrile seizures before 1 year of age
5. temperature greater than 103 F (39.5 C)
A. His first complex febrile seizure. Complex febrile seizures are 1) longer than 15 minutes in duration, or 2) more than one (multiple) within 24 hours or 3) focal in nature. Complex febrile seizures increase the risk of developing future epilepsy, particularly if other epilepsy risk factor is identified. Other risk factors for future epilepsy include: family history of epilepsy (NOT febrile seizures), and the presence of developmental or neurologic abnormalities at the time of the febrile seizure. Male sex is not a risk factor for future epilepsy.

Risk factors for the recurrence of FEBRILE seizures (not epilepsy) include: family history of febrile seizures, onset of febrile seizures before 1 year of age, and a low grade fever with the febrile seizure.