Tarascon Clinical Neurology Pocketbook

From the publishers of the *Tarascon Pocket Pharmacopoeia*®

Melanie C. Hayden Gephart, MD, MAS

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Dedicated to my family, colleagues, teachers and patients.

I am eternally grateful.

Melanie

NOTE: To address the critical lack of trained neurosurgeons in developing countries, 1% of all proceeds of this book will be donated to the Foundation for International Education in Neurological Surgery (FIENS).

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Table of Contents

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CHAPTER 1 ■ STROKE[1,2]

Melanie G. Hayden Gephart, MD, MAS
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Pathophysiology: Alteration in the blood supply to the brain → decreased oxygen delivery → neuronal cell death

- Causes of hypoxia include[3]: Low blood oxygen content (carbon monoxide poisoning, drowning, respiratory arrest), ischemia, or decreased tissue oxygen utilization (cyanide toxicity)
- Stroke classically defined by either vessel rupture (hemorrhagic) or vessel occlusion (ischemic)

Risk factors[4]: Age, transient ischemic attack (TIA), smoking (2-fold), atrial fibrillation (5-fold), hypertension (>120/80), race (increased in African American), hypercholesterolemia

Hemorrhagic Stroke: Cerebral arteries prone to hemorrhage because they have no elastic laminae (Charcot-Bouchard microaneurysm in hypertension)

- Basal ganglia, pons, thalamus are affected more frequently because perforators branch directly from high pressure arteries
- Additional causes include: cerebrovascular malformation, vasculitis, amyloidosis, drug use (e.g., cocaine or methamphetamine), collagen/vascular disorders, area of prior ischemic stroke, anticoagulation, neoplasia

Ischemic stroke:

- Cortex Layers Particularly Sensitive to Hypoxia: Hippocampus (CA1, CA4), cortex (watershed, parietal-occipital layers[2,3,5]), basal ganglia (caudate, putamen), cerebellum (Purkinje's cells), thalamus
- Cortex layers particularly resistant to hypoxia: hippocampus CA2, cortex (Ufibers, extreme and external capsules)
- Additional causes include: arterial dissection (vertebral, carotid, aortic), embolic (e.g., cardiac, septic, cholesterol), antiphospholipid antibody syndrome, thrombolytic thrombocytopenic purpura, vasculitis, venous sinus thrombosis

Incidence[4]: 700,000 strokes/year

- Third leading cause of death in the United States
- In adults >55 years old, risk is 1:6
- 87% of strokes are ischemic
- Prevalence of "silent" strokes 11–40% at >55 years of age

Symptoms/Signs: see Table 1-1

Assessment: ABCs, GCS

- Start O_2, IV, EKG, cardiac enzymes
- Evaluate 3-hour window for IV tPA

Table 1-1 Stroke Signs and Symptoms by Location

Ischemic Stroke		
Vascular territory	*Vessel*	*Possible localizing signs*
Anterior	ICA, MCA, ACA	Left: Aphasia, right-sided weakness Right: Left hemi-neglect, left-sided weakness, denial of deficit
Posterior	PCA	Left: Right hemianopsia, alexia without agraphia Right: Left hemianopsia
Vertebro-basilar	Vertebral, Basilar	Cranial nerve palsies, vertigo, quadriparesis, nystagmus, ataxia, coma
Lacunar motor	Perforators to pons or internal capsule	Pure hemiparesis
Lacunar sensory	Perforators to thalamus or posterior limb of internal capsule	Pure hemisensory deficits
Hemorrhagic Stroke		
Location	*Possible localizing signs*	
Putamen/Internal capsule	Contralateral hemiparesis and sensory loss, contralateral conjugate gaze paresis (look toward lesion)	
Thalamus	Contralateral sensory loss, upgaze paralysis, somnolence, aphasia or neglect, pupil constriction, ipsilateral conjugate gaze paresis (look away from lesion)	
Lobar	Confusion, aphasia, neglect, hemianopsia, contralateral conjugate gaze paresis	
Caudate	Contralateral hemiplegia, agitation, memory deficit, ipsilateral Horner's	
Cerebellum	Nystagmus, vertigo, ataxia, ipsilateral pupil constriction	
Pons	Quadriparesis, coma, pupil constriction, ocular bobbing, horizontal gaze palsy, cranial nerve deficits	

- Determine NIH stroke scale (see Appendix 1)
- Labs: CBC, chemistry, coags, type and screen, glucose, tox screen
- Imaging: CT head to rule out hemorrhage, consider CT-Angio (to include cervical spine if history of trauma to rule out carotid dissection), MRI stroke protocol; echocardiogram, carotid duplex U/S

Treatment: Permissive hypertension if ischemic to 220/120 (185/110 for tPA), mean arterial pressure <90 if hemorrhagic

- Avoid hypotonic fluids
- Avoid hyperglycemia
- Maintain normothermia
- Manage intracranial hypertension (hyperventilation, diuresis, hemicraniectomy)

- Consider aspirin and statin for future stroke prevention
- tPA (see Table 1-2), preventative (aspirin, statin, anti-hypertensives), carotid endarterectomy
- If clinical status deteriorates, stop tPA infusion and order STAT head CT and appropriate labs
- If hemorrhage present, correct thrombolysis with cryoprecipitate, FFP, and platelets
- Consult neurosurgery when appropriate for consideration of surgical decompression or clot evacuation

Outcome: Associated with significant morbidity, depending upon extent and location of stroke

- Mean lifetime cost of $140,000[4]
- Cost of stroke in 2007 was 62.7 billion dollars
- Complications of tPA Treatment: 6% overall rate of symptomatic intracerebral hemorrhage

Transient Ischemic Attacks (TIAs)[4]

Definition: Focal neurological deficits resolving within 24 hours (if diffusion abnormality present on MRI, then infarction has occurred)
Prevalence: 1–4% for individuals >65 years old

- Preceeds approx 15% of strokes

Treatment: Stroke prevention (aspirin, statin, anti-hypertensives, carotid ultrasound)

Table 1-2 Criteria for Stroke Treatment with tPA[1]

Inclusion	*Contraindications*
• clinical diagnosis of stroke with significant, nonresolving deficit • age > 18 years • < 3 hours from last known to be neurologically intact • ICU level of care available • noncontrast head CT without evidence of hemorrhage	History: • history of CNS hemorrhage, aneurysm, or AVM • seizure at stroke onset • ongoing acute myocardial infarction • recent arterial puncture at noncompressible site • no lumbar puncture within 7 days • major surgery or serious trauma within 14 days • GI/GU bleed within 21 days • lactation or pregnancy within last 30 days • head trauma/bleed/surgery or stroke within 3 months Vitals: • SBP > 185, DBP > 110 Laboratory analysis: • platelets < 100,000 • treated with heparin within 48 hours • INR>1.7 • blood glucose < 50 or > 400

PEDIATRIC STROKE[4]

Incidence: 2.7/100,000 children

- Peaks in perinatal period
- Increased risk with preeclampsia, prolonged rupture of membranes, chorioamnionitis, cerebrovascular disease, sickle cell disease, trauma

Outcome: moderate-severe deficit in 42%

VERTEBRAL ARTERY DISSECTION[6–9]

Presentation: Acute onset of neurological deficit

- occipital neck pain, severe headache, altered mental status, SAH, TIA/stroke (usually lateral medullary syndrome), cerebellar infarction, neck hematoma, embolic stroke

Spontaneous origin: Due to oral contraceptives, fibromuscular dysplasia, Marfan's syndrome, moyamoya, cystic medial necrosis, Ehlers-Danlos, Takayasu's disease, and migraines

- Common in young males
- Commonly occur on the dominant vertebral
- 36% with other dissections present, 21% have bilateral vertebral dissections

Traumatic origin: Secondary to minor neck/posterior head trauma (chiropractor, MVA, sudden head turning) or sporting activity

- C1–C2 subluxation
- May lead to pseudoaneurysm development

Treatment: Anticoagulation or antiplatelet therapy for 6 months

- If SAH, symptoms despite medical therapy, progressing dissections, or intradural dissection, surgery, or interventional treatment (angioplasty and/or stent) may be indicated

INTERNAL CAROTID ARTERY STENOSIS [10,11]

Pathophysiology: Atherosclerosis of the common carotid artery

Presentation: TIA or acute neurological deficit

- Amaurosis fugax, blindness, MCA symptoms (such as contralateral arm/face motor/sensory deficits with hyperreflexia), and language deficits

Radiology: Duplex ultrasound (but cannot scan above the mandible), CT angiogram, angiography (expensive, invasive, and risky), or MRA (can overestimate the degree of stenosis)

Treatment: Antiplatelet therapy, blood pressure, and lipid control

- Intraarterial stenting
- Carotid endarterectomy (CEA) is helpful for stenosis 60–80% depending upon surgical risk and symptoms

- Complications of CEA include stroke, hemorrhage, vocal cord paralysis, hypoglossal nerve injury, mandibular nerve injury, bleeding, infection, seizures, and recurrent stenosis

Subclavian Steal Phenomenon (aka Vertebrobasilar Insufficiency): Occlusive disease of the subclavian artery proximal to the origin of the vertebral artery leads to shunting of blood into the left subclavian artery and retrograde vertebral blood flow with increased left arm activity → partial brainstem ischemia and transient ischemic attacks.

BOW HUNTER'S SYNDROME (VERTEBROBASILAR INSUFFICIENCY)

Pathophysiology: Occlusion of the dominant vertebral artery between C1 and C2 with head rotation

Treatment: Transposition of the vertebral artery, C1–C2 arthrodesis

CEREBRAL VENOUS SINUS THROMBOSIS[12–15]

Etiologies: Dehydration (esp. in infants from nausea/vomiting), diabetes mellitus (especially with ketoacidosis), infection (usually local, e.g., mastoiditis), pregnancy and puerperium (highest risk in first 2 wks after birth), birth control pills, homocystinuria, Behcet's syndrome, cardiac disease, ulcerative colitis, sickle cell trait, closed head injury, iatrogenic (radical neck surgery, transvenous pacer, postcraniotomy), periarteritis nodosa, malignancy, hypercoagulable state, and rarely lumbar puncture

Symptoms/Signs: Headache, nausea, vomiting, seizures, hemiparesis, cranial nerve dysfunction, papilledema, blurred vision, altered mental status

Diagnosis: CT ("delta sign" looking at sagittal sinus), MRI with MRV, angiography (for therapeutic intervention)

Treatment: Aggressive heparin anticoagulation to recover ischemic tissues (monitoring for the heightened risk of hemorrhage), +/- thrombolytics, correct underlying disorder, avoid steroids, control blood pressure, monitor ICP (lower ICP increases coagulability), intravascular stenting

Venous Infarct aka Cerebral Venous Sinus Thrombosis[16]: Occlusion of a venous sinus or cortical vein (thrombus or external compression)

Etiology: Hypercoagulable state (pregnancy, hormonal replacement or birth control pills, Factor V Leiden mutation, Antiphospholipid antibody syndrome, activated protein C resistance, elevated factor VIII, malignancy, protein C deficiency and protein S, homocystinuria, trauma, sticky platelet syndrome) dehydration, tumor, infection

Imaging: MRI/MRV (venogram)

- Distribution unusual for arterial infarct (deep white matter)
- High risk for hemorrhagic conversion

Antiphospholipid Antibody Syndrome:

Consider in cerebral infarcts in young women with hypercoagulable states (e.g., history of DVTs, multiple miscarriages, heart murmur)

- Systemic (including cerebral) arterial and venous thrombosis
- Additional neurological syndromes include ocular ischemia, dementia, atypical migraine, transverse myelitis, sudden sensorineural hearing loss, and transient global amnesia
- Primary (autoimmune) or secondary (systemic lupus erythematosus)

AMYLOID ANGIOPATHY[17–19]

Pathology: Deposition of beta amyloid in the media and adventitia of small- and mid-sized arteries

Epidemiology: Presents as lobar intraparenchymal hemorrhage (15% of ICH) in normotension, dementia

- Elderly
- Morphologic hallmarks of Alzheimer's disease (AD)
- Primary amyloid (secondary in DM, beta microglobulin)

Location: Frontoparietal, corticomedullary junction

Incidence[10]*:* Seen in up to 36% of autopsy specimens

- Frequently presents in the elderly as dementia, lobar intraparencymal hemorrhage (15% of ICH) in normotension (rostral parietal area, corticomedullary junction)
- Most sporadic, occasional familial

Imaging: GRE may reveal a higher number of hemosiderin depositions or "microbleeds"

Treatment: Supportive

- Surgery may be considered in patients with intermediate-sized hematomas (20–60 mL) who progressively deteriorate in their level of consciousness.

Outcome: Hemorrhage recurrence rate of 38% with mortality rate of 44%

STROKE SYNDROMES[5,20]

ANTON SYNDROME

- Bilateral occipital lobe strokes
- Bilateral PCA or top of the basilar syndrome
- Visual deficit without recognition of blindness (visual agnosia)

BALINT SYNDROME

- Bilateral posterior cerebral artery (parietal-occipital)
- Loss of voluntary but not reflexive eye movements
- Optic ataxia
- Asimultagnosia

CLAUDE'S (DORSAL MIDBRAIN) SYNDROME

- Ipsilateral CN III palsy with contralateral ataxia

DEJERINE (MEDIAL MEDULLARY) SYNDROME

- Basilar artery, vertebral artery, anterior spinal artery
- Contralateral spastic weakness (pyramidal tract) that spares face
- Loss of vibration/position sense (medial lemniscus)
- Ipsilateral tongue weakness (CNXII nucleus)

DEJERINE-ROUSSY SYNDROME

- PCA thalamic perforators
- Hemisensory loss
- Hemibody pain

FOVILLE (INFERIOR MEDIAL PONTINE) SYNDROME

- Basilar artery perforators
- Contralateral weakness (corticospinal)
- Facial weakness (CN VII nucleus)
- Lateral gaze deficit (CN VI nucleus)
- Decreased sensation/vibration sense (medial lemniscus)

GERSTMANN SYNDROME

- Dominant parietal lobe (MCA)
- Agraphia
- Acalculia
- Left-right confusion
- Finger agnosia
- Ideomotor apraxia

LOCKED-IN SYNDROME

- Basilar artery
- Paralysis of all movement except vertical gaze and eyelid opening (supranuclear ocular motor pathway preserved)
- Sensation and consciousness preserved (reticular formation spared)

MARIE-FOIX (LATERAL INFERIOR PONTINE) SYNDROME

- AICA occlusion
- Ipsilateral ataxia (cerebellar tract)
- Nausea, vertigo, decreased hearing (vestibular nucleus)
- Contralateral hemiparesis (corticospinal tract)
- Ipsilateral facial weakness (facial nucleus)
- Ipsilateral loss of facial sensation (spinal trigeminal nucleus)
- Contralateral hemihypesthesis (spinothalamic tract)

MILLARD-GUBLER (VENTRAL PONTINE) SYNDROME

- Basilar artery perforators
- Base of pons syndrome
- Contralateral weakness (corticospinal tract)
- Diplopia, strabismus, loss of extroversion (CN VI)
- Ipsilateral facial weakness (VII)

RAYMOND (VENTRAL PONTINE) SYNDROME

- Perforators of basilar artery
- Lateral gaze deficits (CN VI)
- Weakness (pyramidal tract)

TOP OF THE BASILAR SYNDROME

- Sudden onset of altered mental status
- Ophthalmoplegia, papillary, and visual field (homonymous hemianopsia) abnormalities
- Generally embolic or postangio stent complication

WALLENBERG (LATERAL MEDULLARY) SYNDROME

- Most commonly from verterbral artery occlusion or dissection, classically a posterior inferior cerebellar artery occlusion
- Facial pain and sensory loss (trigeminal nucleus)
- Ataxia (restiform body and peduncle of cerebellum)
- Nystagmus, nausea, vomiting, vertigo (vestibular nucleus)
- Hoarseness, dysphagia, dysarthria, loss of gag (nucleus ambiguus, glossopharyngeal nucleus or exiting intra-axial fibers $\rightarrow$ ipsilateral lower motor neuron paralysis of the larynx and soft palate)
- Loss of taste (solitary nucleus)
- Ipsilateral Horner syndrome (sympathetics)

- Contralateral hemisensory loss of pain and temperature (spinothalamic tract), ipsilateral numbness (cuneate/gracile nuclei)
- Hiccups (reticulophrenic)

WEBER SYNDROME

- PCA midbrain perforators leading to ventral midbrain infarct
- Contralateral weakness (corticospinal tract)
- Lateral gaze deficits and ipsilateral pupillary dilation (CN3)
- Contralateral corticobulbar dysfunction

CHAPTER 2 ■ SEIZURES[1–12]

Gregory Kapinos, MD, MS
Keith van Haren, MD

INTRODUCTION[6,7,9]

Seizure: Abnormal synchronous electrical discharge from cortical neurons

Epilepsy: Chronic disorder of recurrent seizures with clinical symptoms and EEG findings

Epidemiology: 10% of population will have a seizure in his or her lifetime

Classification:

- Focal (partial) versus generalized (diffuse at onset)
- Level of consciousness as preserved (simple) or altered (complex)
- Symptoms or aura may be determined by localization of seizure (e.g., uncinate seizures → olfactory hallucinations; hypothalamic hamartoma → gelastic seizures)

Pathophysiology: Paroxysmal depolarizing shift (long-lasting, synchronized depolarizations) → NMDA, voltage gated Ca channels open → action potential → hyperpolarization (inhibitory GABA-ergic neurons; "surround inhibition") → overcome by synchronous neuronal discharge → focal seizure → increased extracellular potassium → synchronization of thalamo-cortical loops or widespread cortical circuitry → generalized seizures

Workup: BMP, EEG (normal in 50% of patients), urine tox, CT (for mass lesion, not necessary in simple febrile seizure of infancy), MRI, LP

- Check therapeutic drug levels (phenytoin) level correction in patients with normal renal function = phenytoin/([albumin × 0.2] + 0.1)

Complications of prolonged seizures: Anoxia, lactic acidosis, hyperthermia, cardiac arrhythmia, rhabdomyolysis (may result in renal failure), brain neuronal death

DIFFERENTIAL DIAGNOSIS OF SEIZURE ETIOLOGY

Drugs (lower seizure threshold): Acyclovir, amphetamines, antipsychotics, cephalosporins, cocaine, cylosporins, heroin, meperidine, INH, interferon, lithium, penicillin, quinolones, SSRIs, theophylline, tacrolimus, tramadol

Withdrawal: Alcohol, benzodiazepine, barbiturates

Infection: Meningitis, encephalitis, CMV, cysticercosis, brain abscess, toxoplasmosis, neurosyphilis, measles, HIV, rabies, Rocky Mountain Spotted Fever, Lyme disease, Creutzfeldt-Jakob disease, mycotic aneurysm

Metabolic: Hyponatremia, hypocalcemia, hypomagnesemia, uremia, hypoglycemia, pyridoxine (B_6) deficiency (required for synthesis of GABA), thyroid storm, PKU, Tay-Sachs disease

Other: Hypoxia, eclampsia, fever, malignant hypertension, mass lesion (e.g., brain tumor, hematoma), trauma, subarachnoid hemorrhage, medication noncompliance, lupus, PAN, sarcoidosis, acute intermittent porphyria

Nonepileptic: Syncope, psychogenic seizure

SEIZURE SUBTYPES[7–9]

BENIGN FEBRILE SEIZURES

Generalized tonic clonic seizures occurring in children in the setting of systemic febrile illness, often at onset of fever

- Qualify as "provoked" seizures, therefore, even when recurrent, do not meet criteria for epilepsy

Epidemiology: 3–5% of children

- Onset age 6 months–4 years

Workup: Infectious workup

- Consider LP in children < 3 years if indicated as part of sepsis rule-out
- EEG and MRI are rarely indicated

Treatment: None needed unless > 5 min duration → benzodiazepines

Prognosis: 2–3% lifetime risk of epilepsy

- Complex febrile seizures may pose slightly higher risk

INFANTILE SPASMS (WEST SYNDROME)

Subsets: Symptomatic or idiopathic (15%)

Seizure type: Generalized epilepsy

- Flexor/extensor spasms of head

Epidemiology:

- M > F
- 2% of childhood seizures
- Onset before 6 months

Etiology: Infection, hypoxic injury, cerebral dysgenesis, metabolic disorders, tuberous sclerosis (20%)

EEG: Hypsarrhythmia

- High amplitude, irregular, asynchronous sharp and slow waves with slowed back ground → "chaotic" appearance

Treatment: ACTH, vigabatrin

Prognosis: Up to 90% of patients have cognitive impairment, though prognosis somewhat better if treatment initiated early

LENNOX-GASTAUT SYNDROME

Uncontrollable seizures, mental retardation

Epidemiology:

- M > F
- Presents between 2–4 years of age

EEG: Bilateral, slow, generalized spike and wave complexes at 1–2 Hz, slowed background

Etiology: CNS developmental anomalies, infection, anoxic injury, metabolic disorder, neurodegenerative conditions

Seizure type: Myoclonic, absence, tonic

Treatment: Valproate, lamotrigine, topiramate

Prognosis: 80% have seizures as adults

- < 10% respond to therapy
- If medically refractory, may consider corpus callosotomy

ABSENCE SEIZURES (PETIT MAL)

Epidemiology:

- F > M
- Presents between ages 4–12
- Can be AD
- 2–10% childhood epilepsies
- Annual incidence of 2–8/100,000
- + family history (generalized tonic-clonic and febrile seizures)

EEG: Irregular bilateral spike and wave complexes at 3 Hz

Seizure type: Generalized, 5–10s, automatisms, decreased level of consciousness, without overt tonic/clonic activity, minimal postictal state, inducible with hyperventilation

Treatment: Ethosuximide, valproate

- Avoid vigabatrin, tiagabine

Prognosis: Most resolve in adolescence

- 30–50% have generalized tonic-clonic seizures as adults

Syndromes associated with absence seizures: Childhood absence epilepsy (aka pyknolepsy), juvenile absence epilepsy, juvenile myoclonic epilepsy, myoclonic absence epilepsy, perioral myoclonia (jerks coinciding with polyspikes on EEG)

BENIGN CHILDHOOD ROLANDIC EPILEPSY

Epidemiology: Presents between ages 4–13

May be AD

Seizure type: Nocturnal simple-partial seizures (hemifacial spasm, speech arrest, drooling, sometimes with secondary generalization)

EEG: Central-midtemporal (rolandic) spikes

Treatment: Not always indicated

Prognosis: Uniformly resolves by adolescence with or without treatment

JUVENILE MYOCLONIC EPILEPSY

Epidemiology: Presents between 8–20 years old

- Prominent family history

Etiology: Idiopathic

Seizure type: Generalized myoclonic, tonic-clonic

- Myoclonic jerks on awakening → generalized tonic-clonic seizures
- 30% associated with absence seizures

EEG: Bilateral 4–6 Hz spike waves, polyspike EEG discharges

Prognosis: Seizure control in 80%

- Normal intelligence

LAFORA DISEASE

Epidemiology: Onset in adolescence

Symptoms: Myoclonic seizures, dementia

Genetics: AR

Pathology: Lafora bodies of PAS+ basophilic intracytoplasmic polyglycosan inclusions in brain, skin, liver

Treatment: Depakote, methsuximide

Outcome: May survive to mid 20s

TEMPORAL LOBE EPILEPSY

Epidemiology: Most common epilepsy syndrome of adults (70% of patients with complex partial seizures)

- Present in childhood/adolescence
- Predisposition with febrile seizures of infancy

Etiology: May be hippocampal sclerosis (cause or consequence)

Seizure type: Simple partial or complex partial, from mesial temporal lobe (hippocampus, amygdala, parahippocampal gyrus → auras, visceral sensations, automatisms, postictal confusion, may have secondary generalization

Treatment: Tegretol may prevent generalization

- If refractory may require temporal lobectomy

NONEPILEPTIC SEIZURES (PSEUDOSEIZURES)

Etiology: Unconscious, somatic manifestation of underlying emotional stress or psychiatric comorbidities

Features:

- No postictal confusion
- Rare incontinence
- Strong association with history of sexual abuse

EEG: Normal during events

Diagnosis: Supported by capturing several typical events with video EEG monitoring

- Often requiring several days of hospital stay
- Many patients with non-epileptic seizures also have organic epileptic events

MEDICAL TREATMENT OF SEIZURES (TABLE 2.1)

AED SELECTION[1,4]

Generalized Onset

1st line: Carbamazepine, Lamotrigine, Oxcarbazepine, Phenobarbital, Phenytoin, Topiramate, Valproate

- *2nd line:* Levetiracetam, Primidone, Zonisamide

Partial Onset

1st line: Carbamazepine*, Phenytoin*, Valproate*, Gabapentin, Lamotrigine, Oxcarbazepine, Phenobarbital, Topiramate, Vigabatrin

- *2nd line:* Levetiracetam, Pregabalin, Primidone, Tiagabine, Zonisamide

*most commonly used 1st line drugs because of higher level of evidence

SURGICAL TREATMENT OF MEDICALLY REFRACTORY SEIZURES

Focal Lesionectomy

Resection of focal epileptic origin from noneloquent area of the brain

- Lesion location diagnosed by MRI, PET, continuous EEG monitoring with scalp or subdural electrodes

Temporal Lobectomy

Mesial temporal sclerosis

- Complications: Superior quadrantanopsia, third nerve palsy, aphasia (dominant), stroke, hemorrhage, paralysis

Table 2-1 Antiepileptic Drug Table

Drug	Start dose	Titration	Maintain	Serum Levels	Clearance/ Half-life	Mechanism	Unique SEs
Carbamazepine *Tegretol – TID* *Teg XR - BID* *Carbatrol- BID*	200 mg BID 200 mg BID	200 mg/ day qwk	200–400 mg TID 400–600 mg BID	• 4 to 12 mcg/mL • 70% protein bound	• Hepatic cytochrome P-450 (CYP) • 12–17 hrs	• voltage-dep Na channels	• CYP450 • hyponatremia • neurotoxicity • leukopenia, aplastic anemia • SJS/TEN • hepatitis **HLA-B 1502 testing in Asian pts predicts rash
Ethosuximide *Zarontin*	250 mg BID	250 mg q4d	500 mg BID	40–100 mcg/mL	• hepatic • 30–60 hrs	• T-type Ca current in thalamus	• insomnia • pancytopenia • hyperactivity
Felbamate Felbatol	400 mg TID	600 mg/day q 2 wk	1200 mg TID		• CYp450 • 24 hrs	• NMDA R antagonist • GABA	• aplastic anemia • hepatotoxicity • anorexia
Gabapentin *Neurontin*	300 mg qd	variable	300–1600 mg TID		• renal • 4–6 hrs	• voltage dep Ca • inc Ih current in CA1 hippocampus • GABA(B) → dec glutamate	• sedation • weight gain

Lamotrigine *Lamictal*	1st 2 wks— 50 mg QDay; 2nd 2 wks— 50 mg BID	25–50 mg qwk (100 mg/day Q1–2 wks)	150–250 mg BID (monotherapy)	• 1.5 to 10 mcg/mL	• Liver glucuronidation • renal excretion • 10–60 hrs	• unknown: ? Na channels vs. glutamate/ • aspartate	• rash/SJS/TEN • angioedema • multiorgan failure/ DIC • somnolence • drug interaction • myoclonus
Levetiracetam *Keppra*	500 mg BID	500 mg BID Q2 wks	1000 mg BID		• renal • 6–12 hrs	• binds synaptic vesicle protein SV2A	• URI • aggression • depression
Oxcarbazepine *Trileptal*	150–300 mg BID	300 mg/ day every 3 days	600 mg BID		• hepatic • 8–10 hrs	• voltage-dep Na channels	• hypothyroid • SJS/TEN/rash • induces CYP450 • angioedema • hyponatremia
Phenobarbital	100–300 mg/day divided Qday-TID	none	300 mg/day divided TID	15–40 mcg/mL	• hepatic • 24–100 hrs	• GABA(A) R → inc duration of Cl channel opening	• lethargy • impaired cognition • fetal malformation

(*Continued*)

Table 2-1 Antiepileptic Drug Table (Continued)

Drug	Start dose	Titration	Maintain	Serum Levels	Clearance/ Half-life	Mechanism	Unique SEs
Phenytoin *Dilantin* ***Fosphenytoin*** *Cerebyx*	400 mg initial IV load for status epilepticus: 15–20 mg/kg	300 mg in 2 hrs & 4 hrs	200–500 mg/d div qd (extended release) to tid (immediate release)	• 10 to 20 mcg/mL • Free level: 1 to 2 mcg/mL	• Hepatic arene oxidase • 7–40 hrs	• voltage-dep Na channels • synaptic trans • Ca-calmodulin phosphorylation	• gingival hypertrophy • osteomalacia • fetal malformation • hirsutism • rash/SJS/TEN • lymphadenopathy
Pregabalin *Lyrica*	75 mg BID	75 mg qwk	150–300 mg BID		• renal • 6 hrs	• voltage-gated Ca • glutamate, norepi, subst P	• euphoria • myoclonus • weight gain
Tiagabine *Gabatril*	2 mg BID	4–8 mg/day qwk	32–56 mg/d div bid to qid		• hepatic • 4–8 hrs	• Inhibits GABA reuptake	• dizziness • fatigue, weakness • rash • seizures
Topiramate *Topamax*	25 mg BID	Wk 2: 50 mg BID; Wk 3: 75 mg BID; Wk 4: 100 mg BID; Wk 5: 150 mg BID	100–200 mg BID		• renal • 20 hrs	• GABA (A) Rs • NMDA R antagonist • weak CA inhi	• cognitive difficulties • weight loss • mood • somnolence • metabolic acidosis • nephrolithiasis

Valproate *Depakote* *Depakene* *Depakote ER*	10–15 mg/kg/day divided BID-TID 10–15 mg/kg/daonce daily	5–10 mg/kg weekly	60 mg/kg/day 60 mg/kg/day	• 50–150 mcg/mL • tight protein bound	• hepatic oxidation, conjugation • 9–12 hrs	• voltage-dep Na channels • increases GABA • T-type Ca	• weight gain • insulin resist • thrombocytopenia • hepatotoxicity • fetal malformation • pancreatitis • hyperammonanemia
Vigabatrin *not available in the US*	40 mg/kg/d div BID	30–40 mg/kg qwk	40–100 mg/kg/d div BID		• renal • 6–8 hrs	• Irreversible GABA-transaminase inhibitor	• concentric visual field loss • depression • weight gain
Zonisamide *Zonegran*	100 mg qd	100 mg/day q2wks	200–400 mg qd		• hepatic/renal • 60 hrs	• Sulfonamide derivative • Voltage dep. Na and T-type Ca channels • CA inhibitor	• renal stones • anorexia • rash/SJS • agranulcytosis

BID = two times per day; TID = three times per day; QID = four times per day.

Corpus Callosotomy

Division of anterior two thirds of the corpus callosum

- To limit secondary generalization (atonic seizures, generalized tonic-clonic)
- Complication: left/right dissociation (if extended too for found splenium), hemorrage, retraction or vaccine injury

Vagal Nerve Stimulator

Intermittent electrical stimulation of vagus nerve indicated for treatment of medically refractory seizures → decreased seizure frequency/duration and enabling decrease of medication

- Side effects: Cough, hoarseness, paresthesia, dyspnea
- Performed only on the left side so cardiac innervation by the vagus is unaffected

STATUS EPILEPTICUS (SE)[1,2,5,8,10–12]

Definition: Unremitting seizure or repeated seizures without interictal return to baseline (conventionally defined as seizure > 30 min, actually >5 min)

Pathophysiology: Paroxysm of hypersynchronous neuronal activity with perpetuation of synchronous discharges and disruptive spreading to contiguous neurons

Epidemiology: In the United States, 150,000 cases/year of SE, with 42,000 deaths; may be underrecognized. In neurological critically ill patients, 19–34% have seizures on continuous EEG, and up to 92% of which manifest as nonconvulsive (i.e., no motor manifestations) seizures. Eight percent of comatose patients in the ICU are in SE. In moderate to severe traumatic brain injury, 29% are in SE and 28% of ICH patients have seizures on continuous EEG.

Subtypes: 1. Partial 2. Generalized 3. Nonconvulsive

Etiology:

- Acute structural injury: Head trauma, ischemic or hemorrhagic stroke, tumor or metastasis, demyelinating or inflammatory lesion (MS, lupus), hypoxia or anoxia, hypertensive cerebral injury (PRES, eclampsia)
- Remote structural injury: Sequelae of tumor, stroke, AVM, trauma, surgery, cerebral palsy, remote ischemic/hypoxic injury
- Infectious: Encephalitis, meningitis, intracranial abscess, sepsis
- Toxic: Antibiotics (penicillin, imipenem, quinolones, metronidazole, isoniazid), antidepressants (bupropion, maprotiline), antipsychotics (phenothiazines, clozapine), analgesics or anesthetics (meperidine, fentanyl, tramadol, bupivacaine), antiarrythmics (lidocaine, mexiletin, digoxin), lithium, baclofen, theophylline, immunomodulators (tacrolimus, cyclosporine, interferons), chemotherapy (chlorambucil, busulfan), antiGABAergic (flumazenil), adrenergic illicit drugs (cocaine), high-dose phenytoin and radiographic contrast agents
- Drug withdrawal: Ethanol, benzodiazepines, barbiturates, baclofen

- Systemic metabolic insult: hypoglycemia or hyperglycemia with hyperosmolarity, hyponatremia, hypocalcemia, hypomagnesemia, renal or hepatic failure, pyridoxine deficiency
- New onset or uncontrolled epilepsy: change in anticonvulsant drug levels (noncompliance, discontinuation, drug interaction, altered absorption), intercurrent infection or metabolic abnormality, combined alcohol excess or withdrawal, auto-immune limbic encephalitis, or inherent to the underlying epileptic syndrome (Landau-Kleffner or Rasmussen)

Diagnosis: Clinical, EEG

- Consider SPECT if exam and EEG equivocal

Complications and prognosis:

- Neuronal death begins after 30–60 min of continuous seizure activity, convulsive or not
- Refractory in 30–43% of cases
- Once clinical seizures cease, 12–52% continue to have nonconvulsive seizures
- Overall mortality is ~22%, but in postanoxic coma, mortality is 70–80%
- Among survivors, ~23% have significant disability
- SE may trigger trauma, rhabdomyolysis, lactic acidosis, loss of airway protection, neurogenic arrhythmias, cardiac failure and pulmonary edema, due to the sympathetic hyperactivity

Management:

- Benzodiazepines are given first because of rapid onset and ease of delivery (although not to be mixed with phenytoin (PHT) in the same IV), but limited because of sedation and respiration depression
- Fosphenytoin is the drug of choice for IV administration and PHT for PO route.
- In focal SE and non-convulsant SE (NCSE), valproic acid (VPA) IV may be the drug of choice for 2nd-line agent. Beware of hyperammonemic encephalopathy, pancreatitis, thrombocytopenia, parkinsonism.
- Midazolam (MDZ) and propofol (PRO) infusions should be accompanied by high therapeutic level of phenobarbital (PHB), PHT, or VPA to reduce the risk of seizure recurrence.
- PRO infusion at > 5 mg/kg/h, > 48 hour, is linked to higher toxicity and mortality (propofol infusion syndrome). Avoidance of catecholaminergics and steroids may reduce PRO toxicity.

Table 2-2 Status Epilepticus Management

Time	Intervention		
0–5 min	• Assess **ABC**, give O2, intubate if necessary, set cardiac monitoring • Obtain history and perform PE including neuro exam • Start two IV lines and draw labs for electrolytes, Glc, Ca, Mg, LFTs, ABG, CBC, UTox, and anticonvulsant drug levels. Correct metabolic abnormalities, keep patient cool • Check fingerstick glucose, give thiamine prior to dextrose • **Lorazepam** 0.1 mg/kg IV at 2 mg/min (e.g., 2 mg IV x four doses at 1 min intervals)		
5–25 min	*If generalized convulsive SZs continue:* • **Fosphenytoin** 20 mg*/kg IV over 10 min (150 mg*/min). Monitor EKG and VS, slow down the rate if BP drops	*If focal, subtle or myoclonic SZs continue:* • **Valproate** 30 mg/kg IV over 10 min. Check paresthesias, ammonia, LFTs, lipase, platelets for the following days	
25–30 min	*If SZs continue:* • **Fosphenytoin** additional 10 mg*/kg IV over 5 min, followed by Phenytoin 5mg/kg/d divided in q8h doses, as a maintenance prophylaxis for the next days.	*If SZs continue:* • **Valproate** additional 20 mg/kg IV over 5 min, followed by Valproate 15mg/kg/d divided in q8h doses, as a maintenance prophylaxis for the next days.	
	• Intubate, mechanical ventilation, continuous BP and cardiac monitoring in the ICU. • Call for continuous EEG monitoring for diagnostic and prognostic purposes.		
> 30 min	*If SZs continue, patient is entering refractory status epilepticus, induce coma:*		
	If HR&BP stable and not at risk for prolonged ventilation:	*If hemodynamically unstable:*	*If at risk for prolonged ventilation:*
30–60 min	• **Phenobarbital** 20 mg/kg IV load at 75mg/min. May give additional 10mg/kg IV at the same rate, until SZ-free.	• **Midazolam** 0.2 mg/kg IV bolus. May repeat boluses q5min, 10 times maximum, until SZ-free.	• **Propofol** 2 mg/kg IV bolus. May repeat boluses q5min, 5 times maximum, until SZ-free.
	Once SZs controlled, start infusion of the effective coma-inducing drug:		
	• **Pentobarbital** infusion Initial rate 1 mg/kg/h, range 0.5–10 mg/kg/h. Titrate up to SZ-free or BSP on EEG for 12–24 h then taper by 5%/h. Watch BP, respiratory status and abdominal ischemia.	• **Midazolam** infusion Initial rate 0.1 mg/kg/h, range 0.05–3 mg/kg/h. Titrate up to SZ-free or BSP on EEG for 12–24 h then taper by 5%/h. Vasopressors prn.	• **Propofol** infusion Initial rate 2 mg/kg/h, range 1–12 mg/kg/h. Titrate up to SZ-free or BSP for 12–24 h then taper by 5%/h. Do not use > 48 h, check TG, CK, pH, Cr, Tn.

(*Continued*)

Table 2-2 Status Epilepticus Management (Continued)

Time	Intervention
> 60 min	*If SZs continue, goal is now drastic cortical suppression:* • **Pentobarbital** 10 mg/kg IV at 75 mg/min. Half loads to be repeated until seizure stops, followed by infusion 1–10 mg/kg/h IV titrated up to BSP for 24 h then taper by 5%/h. • Vasopressors usually required. • No bolus, only gentle infusion along with pressure support. • Maintain FOS or VPA q8h with therapeutic levels of both barbiturate and PHT/VPA. • Promote systemic metabolic homeostasis.

NOTE: Fosphenytoin doses are given in mg*, which should be phenytoin equivalent milligrams.

ABBREVIATIONS

ABX = antibiotics, AVM = arteriovenous malformation, BSP = burst-suppression pattern, BZD = benzodiazepine, CK = creatine kinase, Cr = creatinine, EEG = electroencephalogram, EPC = epilepsia partialis continua, FOS = fosphenytoin, GTC = generalized tonic-clonic, ICH = intracerebral hemorrhage, ICU = intensive care unit, IV = intravenous, LFTs = liver function tests, MDZ = midazolam, MS = multiple sclerosis, NC= nonconvulsive, PCN = penicillin, PHB = phenobarbital, PHT =phenytoin, PRES = posterior reversible encephalopathy syndrome, PRO = propofol, SE = status epilepticus, SLE = systemic lupus erythematosa, SZ = seizure, TBI = traumatic brain injury, TG = triglycerides, Tn = troponin, VNS = vagus nerve stimulation, VPA = valproate.

CHAPTER 3 ■ DEMENTIA[1,4]

Sharon J. Sha, MD, MS

Definition: Acquired neurodegenerative condition that impairs cognition significantly enough to interfere with activities of daily living

- Does not improve or resolve with time (vs. delirium)

Differential diagnosis: Medication side effects, drug or alcohol intoxication, Wernicke's encephalopathy, B_{12} deficiency, syphilis (RPR/VDRL), thyroid function (TSH, free T4), hepatic encephalopathy (LFT), uremic encephalopathy (BMP), encephalitis (LP), and chronic SDH/meningitis/NPH (CT), pseudodementia (seen with depression)

ALZHEIMER'S DISEASE (AD)

Epidemiology: The most common form of dementia

- Prevalence in the US of 5 million people

Symptoms/Signs: Characterized by memory impairment → visuospatial, language impairment (aphasia, paraphasia)

- Non-amnestic clinical presentations with AD pathology are also possible. These clinical phenotypes include posterior cortical atrophy (simultanagnosia, oculomotor apraxia, optic ataxia), logopenic aphasia (anomia and impaired repetition for long sentences with intact grammar), corticobasal syndrome (similar symptoms to CBD), and frontal variant AD (similar presentation to behavioral variant FTD)

Risk factors: Age, family history, Trisomy 21

Imaging: Hippocampal and diffuse cortical atrophy

- PET with amyloid ligand, Pittsburgh compound B, can help discriminate AD from other dementias

CSF: Beta amyloid levels are decreased and tau is increased

Pathophysiology: Excess of Aß amyloid plaques (silver stain), Hirano bodies (actin), hyperphosphorylated tau (microtubule associated protein; aka neurofibrillary tangles), and granulovacuolar degeneration most prominent in nucleus basalis of meynert, hippocampus, and temporal cortex

- Also associated with decreased levels of acetylcholine and norepinephrine

Genetics: Presenilin-1 (chrom 14) and presenilin-2 (chrom 1) associated with early onset, familial AD

- Having one apo e4 allele or being homozygous for the e4 allele (chrom 19) is a risk factor for sporadic AD or late onset familial AD

Treatment: Donepezil, rivastigmine, and galantamine (anti-cholinesterase). Memantine (NMDA receptor antagonist)

Prognosis: Incurable, progressive neurological deterioration

- Average survival is 8–10 years with increasing disability

DEMENTIA WITH LEWY BODIES (DLB)

Epidemiology: Up to 20% of dementias

- Overlaps with Alzheimer's

Symptoms/Signs: Waxing and waning level of consciousness, visuospatial impairment, visual hallucinations, delusions/psychosis, and parkinsonism

- Patients may also have REM sleep behavior disorder, sensitivity to neuroleptics, and autonomic dysfunction

Imaging: Functional imaging of the dopamine transporter shows low activity in the striatum and helps distinguish DLB from AD but can be abnormal in PSP, Parkinson's disease, and multiple system atrophy (MSA)

- Occipital hypoperfusion on SPECT or hypometabolism on PET without occipital atrophy on MRI can be supportive in the diagnosis

Pathology: Lewy bodies, intracytoplasmic neuronal inclusions that stain with alpha synuclein, and Lewy neurites are present throughout the cortex and subcortical areas

Treatment: Symptomatic. Levodopa can be tried for parkinsonism, or cholinesterase inhibitors (donepezil and rivastigmine) can be used for hallucinations, and SSRIs or SNRIs are preferred for depression

*Prognosis:*Incurable, progressive neurological deterioration

- Average survival is 8 years with increasing disability

VASCULAR "MULTI-INFARCT" DEMENTIA

Epidemiology: Prevalence 1–2%

- Approx 20% of all dementias

Symptoms/Signs: A stepwise decline in neurologic function and/or focal neurological deficits

Risk factors: HTN, diabetes, coronary artery disease (atherosclerosis), atrial fibrillation, and stroke

Imaging/Pathology: Multiple ischemic strokes including lacunar infarcts

Treatment: Prevention via treatment of underlying comorbidities

Prognosis: Step-wise deterioration with each additional stroke

FRONTOTEMPORAL LOBAR DEMENTIA (FTLD)

Epidemiology: 10–15% of dementias

- M > F
- Subtypes of FTLD include: Pick's Disease, behavioral variant, progressive nonfluent aphasia, and semantic variant. Primary progressive aphasia implies many types of aphasia including the semantic variant, logopenic aphasia, and progressive nonfluent aphasia
- Mean onset 55 years old

Clinical: Changes in behavior and language are most characteristic

- Decline in social conduct, emotional blunting, loss of insight, impulsivity, inflexibility, disinhibition, repetitive behaviors, apathy, echolalia, hyperorality, hypersexuality, agitation, change in food preferences, and poor hygiene
- Executive impairment with sparing of memory and visuospatial function
- Difficulty making or understanding speech

Genetics: Approximately 30–50% of FTLD patients have a positive family history of dementia

- Genetic mutations of progranulin and tau genes on chromosome 17 are associated with autosomal dominant FTLD
- FTD with amyotrophic lateral sclerosis (ALS) is asssociated with chromosome 9

Pathology: Atrophy of the frontal or anterior temporal lobes is universal. Cortical and basal ganglia neuron loss, gliosis, tau or TDP-43 inclusions are evident microscopically

- FTD-MND typically has TDP-43 inclusions on pathology
- Pick bodies (intracellular inclusions that stain with silver and tau)

Treatment: None. SSRIs are used to treat the compulsions, depression, or other behavioral problems

Prognosis: 2–10 years with progressive severe disability requiring home monitoring or institutionalization

Behavioral Variant (70%)

- Disinhibition, apathy, emotional blunting, overeating, and executive deficits
- ALS develops in 15% of cases
- Tau or TDP43 inclusions represent a majority of the pathology

- **Semantic Variant (15%)**
  - Lack of knowledge for words, faces, and emotion
  - Prosody and syntax intact with fluent, empty speech
  - Asymmetric left greater than right anterior temporal atrophy
  - TDP-43 seen microscopically for most cases
- **Progressive Nonfluent Aphasia (10%)**
  - Speech deficits, nonfluent aphasia, oral apraxia, agrammatism, and frontal executive deficits (behavior spared until later in the illness)
  - Asymmetric, left-greater-than-right, frontal, opercular, and insular degeneration
  - Tau inclusions may be present and PSP or CBD pathology can be seen

CORTICOBASAL DEGENERATION (CBD)

Epidemiology: 5:100,000

- Average onset 60 years old

Clinical: Nonfluent aphasia, frontal executive deficits, apraxia, apathy, depression, acalculia, constructional and visuospatial impairment, asymmetric parkinsonism, myoclonus, alien limb, rigidity, dysmetria, disequilibrium, aphasia, and dystonia

Imaging: Atrophy of the frontal and parietal lobes with sparing of temporal and occipital lobes on MRI

Pathology: Grossly, atrophy is mainly seen in the parietal lobes, basal ganglia, insula and frontal lobes. Microscopically, astrocytic plaques and achromatic or ballooned neurons are seen with tau-positive neuronal inclusions four microtubule repeat isoform of tau (4R tau) with gliosis and neuronal loss in cortex and basal ganglia.

Genetics: Mutations in the gene on chromosome 17 that codes for the tau protein

Treatment: Symptomatic: SSRIs for depression, botulinum toxin injections for dystonia, and physical, occupational and speech therapy

Prognosis: Progressive decline with eventual death at 6–8 years from pneumonia or sepsis

PROGRESSIVE SUPRANUCLEAR PALSY (PSP)[3]

Epidemiology: Mean age of onset 55–70 years

- 7:100,000 in age >55

Clinical: Cognitive and physical decline (executive deficits, nonfluent aphasia, axial rigidity, falls, postural instability, dysphagia, pseudobulbar palsy), occular deficits (impaired vertical gaze, square wave jerks, hypometric saccades), alterations of mood/behavior (impairment of judgment, apathy)

- The "applause sign" (patient asked and demonstrated to clap three times, but on execution, continues clapping) can help distinguish PSP PD and FTD

Imaging: Midline sagittal views of the brainstem on MRI may show a decreased midbrain to pons ratio that can be described as a "penguin silhouette sign" or "hummingbird sign"

Pathology: Microscopically, 4R tau is found in neurons and glia; neurofibrillary tangles or neuropil threads in the basal ganglia and brainstem

Treatment: Symptomatic, anti-parkinsonian, anti-depressant medication

Prognosis: Incurable, progressive

- Duration of illness 5–10 years, but expected life expectancy of 70 years

CREUTZFELDT-JAKOB DISEASE (CJD)

Epidemiology: 1:1 million

Clinical: Rapidly progressive dementia, cortical blindness, ataxia, rigidity, mutism, or myoclonus

- There are four forms: Variant (contaminated beef with bovine spongiform encephalopathy), sporadic, iatrogenic, and familial (AD)

EEG: Abnormal, high amplitude, and periodic sharp wave complexes may be seen (positive predictive value 95%) in sporadic CJD, but not seen in variant CJD

CSF: Elevated levels of 14–3-3 brain protein and enolase may be seen in CSF examinations but it is not highly specific to sporadic CJD and less specific for variant CJD

Imaging: MRI with cortical "ribboning" (DWI) or basal ganglia hyperintensity in sporadic CJD

- Variant CJD can show high signal in the posterior thalamus ("pulvinar" sign)

Pathology: Neuronal loss, astrocytic proliferation, spongiform change, and deposition of an abnormal form of prion protein.

Treatment: None

Outcome: Rapidly progressive to invariably fatal in less than 1 year

GERSTMANN-STRAUSSLER-SCHEINKER

Epidemiology: Extremely rare

- Found in only a few families
- Inherited spongiform encephalopathy
- Onset between 35 and 55 years old

Clinical: Neurodegenerative

- Ataxia → dementia, nystagmus, spasticity, visual disturbances, deafness

Treatment: None

Outcome: Deterioration and death after 2–10 years

FATAL FAMILIAL INSOMNIA[2]

Epidemiology: Rare, autosomal dominant

Pathophysiology: Prion encephalopathy

- Preferential thalamic degeneration, cingulate gyrus, orbitofrontal cortex
- Missense mutation at codon 178 of the prion protein gene (PRNP) coupled with the presence of the codon methionine at position 129

Symptoms: Psychosis, insomnia, weight loss

Treatment: None

NORMAL PRESSURE HYDROCEPHALUS[6]

Epidemiology: Incidence as high as 1.8:100,000

- Up to 5% of individuals with dementia

Clinical: Dementia, gait disturbance (feeling "stuck" or a shuffling gait), urinary incontinence

- Classified as probable, possible, and unlikely

Radiology: Increased ventricle size on head CT

Treatment: Large volume LP with opening and closing pressures, both to measure intracranial pressure and determine any improvement with removal of CSF

- May require ventriculoperitoneal shunt placement

WERNICKE'S ENCEPHALOPATHY AND KORSAKOFF AMNESTIC SYNDROME[5]

Etiology: Vitamin B_1 (thiamine) deficiency

- Seen in alcoholism, gastrointestinal disorders

Clinical: Mental confusion, ataxia, nystagmus and ophthalmoplegia

- For Korsakoff, includes memory loss and confabulation
- Usually seen in alcoholics, severe malnutrition

Imaging: Diffuse cerebral atrophy, involving bilateral mammillary bodies

Pathology: Bilateral damage to hippocampus, amygdala, thalamus, mammillary bodies

Treatment: B_{12}, thiamine, folate, multivitamin, "banana bag"

Outcome: Wernicke's symptoms will improve with administration of thiamine

- Korsakoff's is irreversible

PANTOTHENATE KINASE ASSOCIATED NEURODEGENERATION SYNDROME

Epidemiology: Rare

- Presents in early adolescence

Clinical: Dystonia, oromandibular abnormalities, dementia, pyramidal signs, retinal degeneration

Pathophysiology: Pantothenate kinase deficiency (cysteine dioxygenase deficency) $\rightarrow$ accumulation of cysteine, free-radicals, iron deposition in BG

Genetics: Gene 20p13

- Familial in 50%

Pathology: Vacuolization, iron deposition in GP, degradation of pars reticulate, substantia nigra

Radiology: "Eye of the tiger" on T2 in the pallidum and substantia nigra

Treatment: None

PELLAGRA[5]

Etiology: Nicotinic acid deficiency (vitamin B_3)

- Occurs in alcoholism, gastrointestinal disorders, Hartnup disease, antituberculosis medications

Clinical: Dermatitis, diarrhea, dementia

- May include memory loss, myelopathy, delirium, seizures, peripheral neuropathy

Pathology: Chromatolysis of Betz cells and neurons of the pons, cerebellum, anterior horns of spinal cord

CHAPTER 4 ■ COMMUNICATION DISORDERS[1,2]

Melanie G. Hayden Gephart, MD, MAS

ANATOMY OF LANGUAGE

95% of individuals' language center is in the left, dominant hemisphere

- A small percentage of left-handed individuals have bilateral innervation
- Important to distinguish sensory (visual, auditory) from the motor ability to formulate or perceive language

BROCA'S AREA (44, 45)

Location: Inferior frontal gyrus of dominant hemisphere, anterior to motor cortex for mouth/tongue, middle cerebral artery territory

Function: Controls expressive language (ability to coordinate muscle movements and produce the complex sounds and intonations associated with language)

WERNICKE'S AREA (22)

Location: Superior temporal gyrus, auditory association cortex

Function: Language comprehension (speech, written, signs, etc.)

ARCUATE FASCICULUS: White matter tract connecting Broca's and Wernicke's areas

ANGULAR GYRUS

Posterior temporal-parietal junction

- At the end of the superior temporal sulcus and continuous with the middle temporal gyrus
- Involved in visual function and in the dominant hemisphere (generally left sided), functions in language, specifically comprehension of writing

APHASIA

BROCA'S APHASIA (EXPRESSIVE OR NONFLUENT)

Lesion: Broca's area

Symptoms Signs: Difficulty with language production, however, comprehension is intact

- Agrammatism, anomia
- Repetition impaired

- Patient acutely aware of deficits
- Due to location near motor cortex, may also involve contralateral motor weakness (arm > leg)

WERNICKE'S APHASIA (RECEPTIVE OR FLUENT)

Lesion: Wernicke's area

Symptoms/Signs: Ease with production of speech, however, content is classically nonsensical

- Neologisms, literal and verbal paraphasias, circumlocutory
- Difficulty with language comprehension, repetition, and following verbal commands
- Patient may be unaware of deficit

CONDUCTIVE APHASIA

Lesion: Injury of the arcuate fasciculus

Symptoms/Signs: Results in difficulties with repetition as the connection between Broca's and Wernicke's areas has been disrupted

- Anomia

GLOBAL APHASIA

Lesion: Involvement of Broca's, Wernicke's and the arcuate fasciculus

- Usually secondary to large strokes of the middle cerebral artery of the dominant hemisphere

Symptoms/Signs: Leads to a dense expressive and receptive aphasia

ADDITIONAL LANGUAGE DISORDERS

ANOMIA

Lesion: Can occur secondary to focal cortical lesion in the dominant hemisphere or global encephalopathy

Symptoms/Signs: Inability to name an object when presented

- May occur as part of a fluent aphasia
- Repetition and comprehension generally intact

Pure word deafness: Cannot understand spoken words, but can hear sounds and understands written language

- Results from temporal lobe lesion

ALEXIA

Lesion: Classically associated with lesions of the angular gyrus (posterior temporal-parietal)

Symptoms/Signs: Inability to read

- Can be with or without agraphia
- May be associated with aphasia

AGNOSIA

Lesion: Nondominant (usually right) temporoparietal lobe

Symptoms/Signs: Inability to recognize and identify objects or persons

- Can be limited to one sensory modality (e.g., auditory, gustatory, olfactory, tactile, or visual)

Anosognosia: Denial of a physical deficit (e.g., hemiparalysis); when shown the paralyzed body part patients may deny that it is his or hers

- Usually associated with hemi-neglect

VERBAL APRAXIA

- Developmental or acquired
- Impairment involving planning, executing and sequencing of speech

ALEXIA

- Inability to comprehend written language

AGRAPHIA

- Inability to compose written language

DYSARTHRIA

Lesion: Disruption of speech mechanics, i.e., corticobulbar (cranial nerve nuclei or cranial nerves V, VII, IX, X, XII), cerebellar (coordination), or musculature of speech production

Symptoms/Signs: Decreased phonation, poor articulation, and changes in resonance/respiration

- Composition of speech is normal

CHAPTER 5 ■ NEURO-OPHTHALMOLOGY AND NEUROTOLOGY

Marie Gonella, MD
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NYSTAGMUS[1,2]

In central vertigo, horizontal, rotary, or vertical nystagmus may be present and may be bidirectional

- In peripheral vertigo, nystagmus should be horizontal and unidirectional or rotary
- Direction is described by the direction of the fast phase
- Should fatigue (lessen) with repeated testing

Abducting: Intranuclear ophthalmoplegia (INO), pontine medial longitudinal fasciculus

Brun's: Pontomedullary junction

Convergence: Adducting nystagmus

- Pineal lesion
- Seen with Parinaud's syndrome

Dissociated: See INO (usually multiple sclerosis)

Downbeat: Disruption between cerebellum and brainstem

- Posterior fossa lesion (cervicomedullary junction/foramen magnum; e.g., chiari, bilateral cerebellar lesions, cerebellar tumor) basilar invagination, metabolic, multiple sclerosis, spinocerebellar degeneration, bilateral MLF lesions, platybasia

Horizontal: Peripheral etiology

Ocular bobbing: From large destructive lesion of the pons

Opsoclonus: Myoclonic triangle

- "Dancing eyes"; chaotic, unrelenting saccadic movements in all directions
- associated with viral infection (encephalitis) or tumors (commonly pediatric)

Optokinetic: Physiologic

- Brought out by black lines on white background
- Impaired in parietal lesions (not occipital)

Periodic alternating, square wave jerks: Conjugate, horizontal

- Cerebellum

Retractorius: Cocontraction of all extraocular muscles

- Midbrain tegmentum lesion (e.g., pineal tumor, stroke)

Rotary: Jerk (fast and slow phase) and pendular (equal velocity oscillations)

- Disruption of semicircular canals, brain stem/cerebellum lesion
- May be associated with vision loss
- Lateral medullary syndrome (fast away from lesion side)
- Accentuated on lateral gaze
- Vestibular system dysfunction (see with horizontal/vertical nystagmus)

Seesaw: Intorting eye up, extorting eye down

- Diencephalic or parasellar lesion, chiasmal compression

Spasmus mutans: Nystagmus, head nodding, torticollis

- Infants with or without an intaracranial mass

Upbeat: Medulla

PAPILLEDEMA

Secondary to axoplasmic stasis from increased intracranial pressure

- Generally takes 24–48 hours to develop (not before 6 hours)
- Causes include pseudotumor cerebri, mass lesion, multiple sclerosis (acute optic neuritis and pale disks as a result of past optic neuritis); patient may be obtunded (increased intracranial pressure) and have nausea and vomiting

DDx of Unilateral Papilledema[2]

Tumor (orbital, meningioma, optic glioma), inflammatory, Foster-Kennedy syndrome, demyelination, eye prosthesis

FOSTER-KENNEDY SYNDROME[3]

Direct pressure on the optic nerve from a mass lesion (e.g., tumor) → ipsilateral anosmia, ipsilateral scotoma with optic atrophy (direct pressure on optic nerve → visual loss), contralateral papilledema (→ enlarged blind spot) secondary to increased intracranial pressure

- May have visual loss in the atrophic eye

PSEUDO-FOSTER KENNEDY SYNDROME[4]

More common

- Remote ischemia or demyelination in one eye leading to atrophy (chronic visual loss) and new ischemia or demyelination in the second eye (new visual loss)

CONJUGATE GAZE[5]

1. Super nuclear gaze center (SNGC) located in the frontal lobe receives (voluntary) input from bilateral hemispheres, cerebellum, vestibular nuclei, neck, and initiates saccadic eye movement to the contralateral side
   - SNGC lesion causes deviation to the affected side
2. SNGC corticobulbar fibers travel through the genu of the internal capsule and synapse with the ipsilateral pontine gaze center (PGC) located at the parapontine reticular formation (PPRF aka horizontal gaze center)
   - PGC directs eye movement to the ipsilateral side
   - Caudal PPRF stimulation leads to conjugate, ipsilateral horizontal eye deviation, whereas rostral PPRF stimulation leads to vertical eye movement
3. Fibers from PGC synapse with the ipsilateral CNVI (abducens) nucleus and crosses via medial longitudinal fasciculus (MLF) to synapse with the contralateral CNIII nucleus (medial rectus)
   - MLF contains fibers from Cajal's interstitial nucleus, medial vestibular nucleus, pontine reticular formation, superior colliculus
   - Inhibitory signals travel to the opposing medial rectus
   - Lesion of PGC causes eye deviation to the side opposite the lesion
   - Lesion at MLF causes loss of adduction of the ipsilateral eye and nystagmus of the contralateral eye on abduction

HORIZONTAL GAZE PALSY

Commonly from injury to the horizontal gaze center or CNVI nucleus → loss of horizontal gaze *ipsilateral* to the lesion

- Range in severity from complete (nonresponsive to voluntary or vestibular control) to nystagmus with stimulation
- Usually secondary to stroke

VERTICAL GAZE PALSY

MLF fibers and nucleus, cranial nerve nuclei, interstitial nucleus of Cajal, superior colliculus → rostral interstitial nucleus of the MLF

- Causes: Tumors (e.g., midbrain glioma, pineal tumor), stroke (midbrain pretectum), increased ICP (Parinaud's syndrome aka dorsal midbrain syndrome), progressive supranuclear palsy (impaired downward gaze with preservation of upward gaze)

Parinaud's Syndrome[6]

Vertical gaze palsy, lid retraction (Collier's sign), "setting-sun" sign (downward gaze preference), light near dissociation, convergence retraction nystagmus

SUPRANUCLEAR GAZE PALSY

- SNGC (frontal lobe) normally directs conjugate deviation of the eyes to the opposite side
- Presents with ipsilateral conjugate eye deviation despite preservation of brainstem reflexive conjugate eye movement

PONTINE GAZE PALSY

Limits ipsilateral gaze (abducens nucleus), causing eye deviation away from the lesion (toward the hemiparesis)

- Lesion of the pontine horizontal gaze center
- May be associated with hemiparesis

INTERNUCLEAR OPHTALMOPLEGIA (INO)

(Figure 5-3): Lesion of the MLF leads to lateral gaze palsy

- Ipsilateral eye cannot adduct when looking to contralateral side
- Nystagmus in the adducting eye contralateral to the medial longitudinal fasciculus lesion
- *Can still ADduct on convergence* (differentiates this from a cranial nerve palsy where the eye cannot ADduct even when attempting to converge)

ONE-AND-A-HALF SYNDROME[7]

(Figure 5-2): Conjugate horizontal gaze palsy in one direction (lesion of the lateral gaze center/PPRF or abducens nucleus) in addition to an internuclear ophthalmoplegia in the other (lesion of the ipsilateral MLF $\rightarrow$ failure of adduction of ipsilateral eye)

- Prevents the eye ipsilateral to the PPRF from moving horizontally in either direction while the contralateral eye is only able to ABduct
- Most commonly caused by multiple sclerosis

CN III (OCULOMOTOR NERVE) PALSY

Affected side has ptosis, dilated pupil, ADducted and inferior gaze (unopposed CNIV and VI)

CN IV (TROCHLEAR NERVE) PALSY

Controls the superior oblique muscle (intorts, depresses and ABducts the eye)

Symptoms: Vertical or torsinal diplopia

- Leads to head tilt away from the lesion to compensate (Bielschowsky's sign; in kids may be misdiagnosed as torticollis)
- Diplopia worsens when looking down (e.g., walking down stairs)

DDx: Trauma, congenital, iatrogenic, stroke, multiple sclerosis, tumor, thyroid, myasthenia, aneurysm

CN VI (ABDUCENS NERVE) PALSY[1]

(Figure 5-1): CN VI controls the lateral rectus muscle (ABducts the ipsilateral eye) has a longest intracranial course, therefore, is more susceptible to traumatic shearing, stretching with tension on dura or increased intracranial pressure (ICP)

Symptoms: Binocular horizontal diplopia, ipsilateral estropia in primary gaze

DDx: Multiple sclerosis (most common cause of isolated palsy), diabetes, temporal arteritis, increased ICP (hydrocephalus, pseudotumor, tumor), trauma,

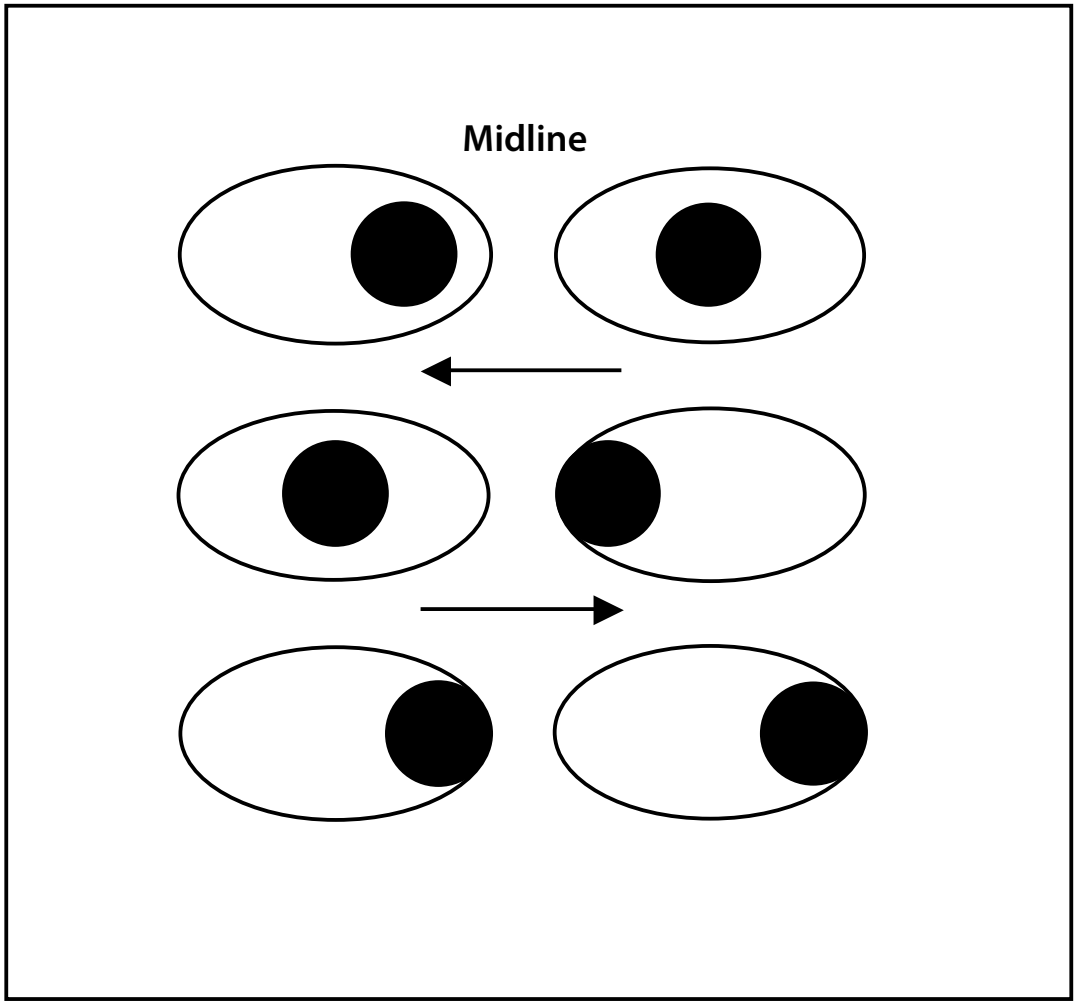


Figure 5-1 Abducens Nerve (CNVI) Palsy (Right)

aneurysm, carotid-cavernous fistula, tumor, inflammation, intracranial hypotension (CSF leak, e.g., after lumbar puncture), skull-based fracture (e.g., clivus), mastoiditis (Gradenigo syndrome)

Gradenigo Syndrome

Otalgia (ophthalmic branch of trigeminal nerve), ipsilateral paralysis of abducens nerve, otitis media/mastoiditis (involving apex of petrous temporal bone)

TOLOSA-HUNT SYNDROME[8]

Granuloma of superior orbital fissure; required for diagnosis

- Painful, unilateral ophthalmoplegia
- May extend into the cavernous sinus to involve any nerve there (generally lateral wall: CN III, V1, V2, VI)
- Pupil sparing
- Treat with high-dose steroids

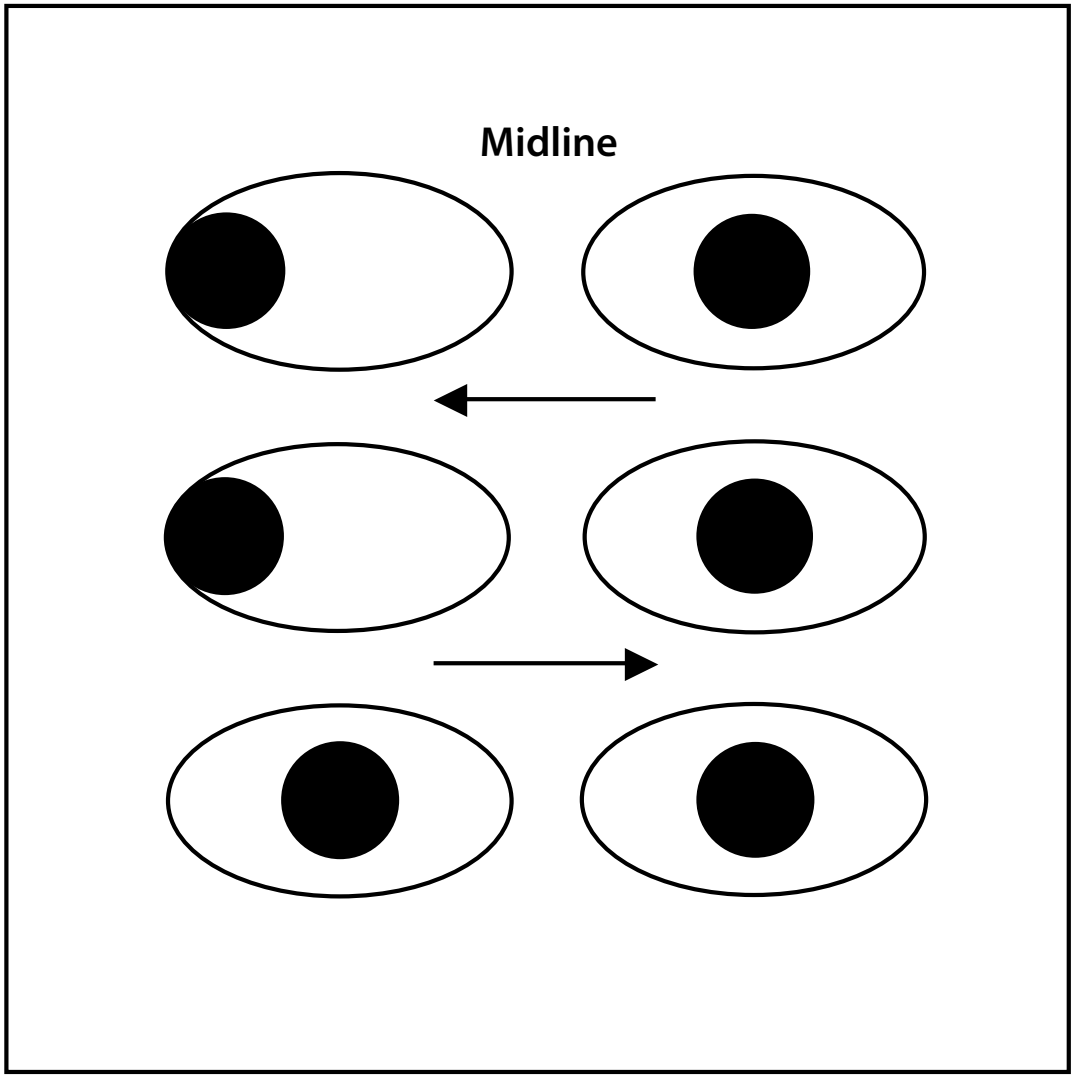


Figure 5-2 One-and-a-Half Syndrome

FOIX SYNDROME

Syndrome of the superior orbital fissure (through which passes CN III, IV, V1, VI)

Symptoms: Ophthalmoplegia, corneal anesthesia, proptosis, pupillary dilation

DDx: Tumor, aneurysm, trauma (facial fracture)

PUPILLARY REFLEX AND ABERRATIONS IN PUPIL SIZE AND REACTIVITY[2,9]

PUPILLARY LIGHT REFLEX

CN II afferent, CN III efferent

- Unilateral light → retinal photoreceptors → optic nerve (CN II) → hemi-decussation at the optic chiasm → optic tracts → exit optic tracts before the lateral geniculate body (LGN) → enter the brainstem

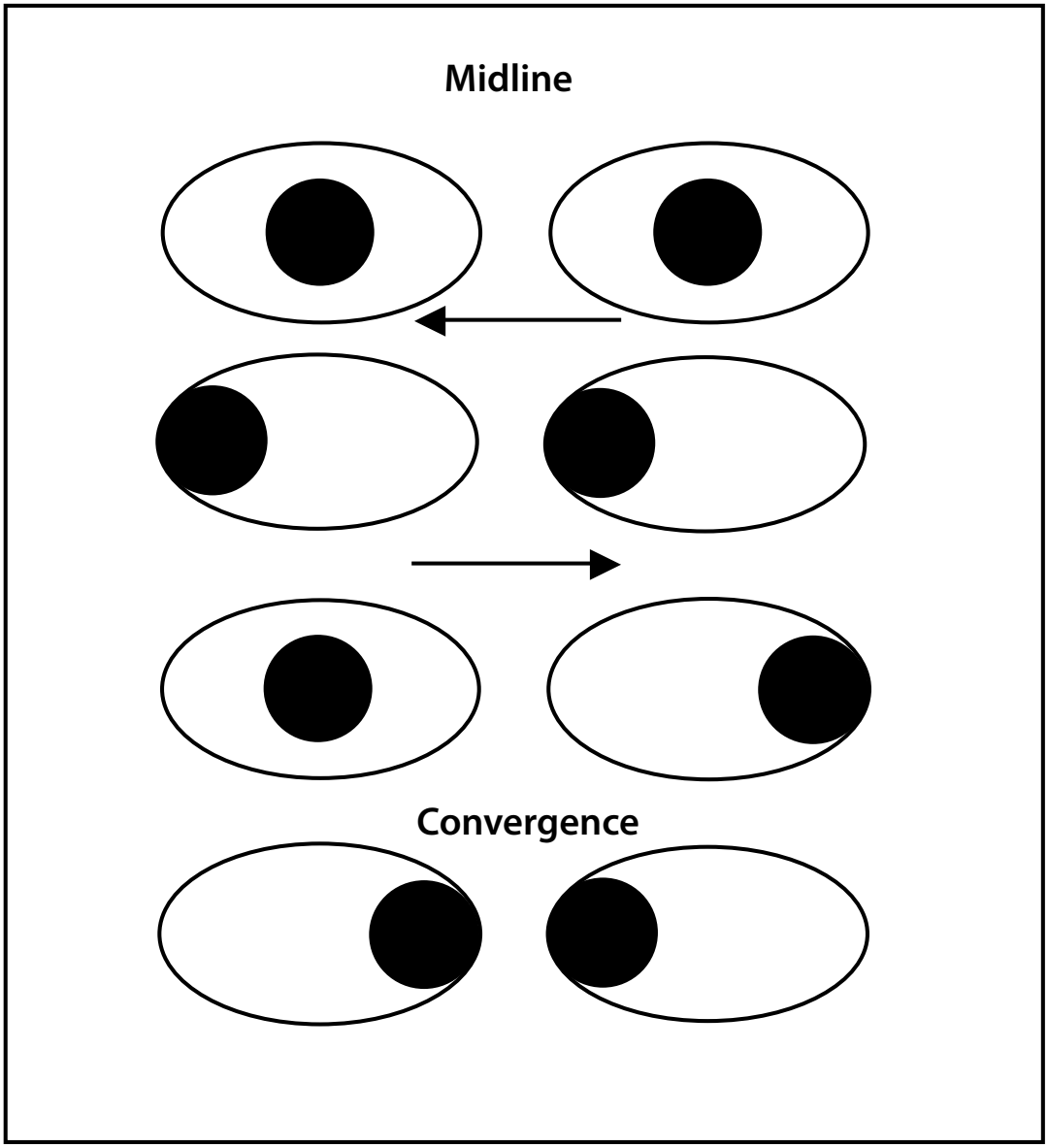


Figure 5-3 Internuclear Ophthalmoplegia (Right)

in the brachium of the superior colliculus → synapse in pretectal olivary and sublentiform nuclei → cross in posterior commissure and ventral to the cerebral aqueduct to bilateral Edinger-Westphal nuclei → pupillary fibers travel with CN III (oculomotor) to ciliary ganglia → short ciliary nerve to iris sphincter, ciliary body → bilateral pupillary constriction

Pupillary sympathetic pathway: Hypothalamus to lateral horn cells of C8-T3 → superior cervical ganglion → iris

DIFFERENTIAL DIAGRAM OF PUPILLARY ABNORMALITIES

Amaurotic: Optic nerve lesion

- Equal sized pupils; normal direct, consensual, and near reflex

CN III compression: from interruption of more peripheral, circumferential parasympathetic fibers, leads to pupillary dilation

- Uncal herniation (accompanied by decreased level of consciousness), aneurysm (CNIII compression by posterior communicating artery aneurysm, classically involves the pupil)

Tonic (Adie's) pupil: postganglionic parasympathetic interruption (ciliary ganglion)

- Women, 30–40s
- Loss of direct or consensual light reflex, light-near dissociation
- 0.125% pilocarpine in both eyes → constriction of affected pupil (denervation hypersensitivity) but not in normal pupil
- Reinnervation allows pupil to constrict
- May occur with pineal region tumors

CN III neuropathy: Controls superior rectus, medial rectus, inferior rectus, inferior oblique

- Lesion leads to inferiorly abducted eye with ptosis and pupillary dilation from DM (thought to be from ischemic vasculopathy as it spares the more peripheral parasympathetic fibers → pupil sparing CNIII palsy), Drugs (scopalamine, tropicamide, pheneylephrine)

Traumatic iridoplegia

Marcus-Gunn pupil (afferent pupillary defect): consensual reflex stronger than direct—retina or optic nerve lesion, e.g., MS

Argyll Robertson pupil: accommodates but doesn't react (light-near dissociation), tertiary syphilis, midbrain lesion

Pupil sparing oculomotor palsy: DM, atherosclerosis, temporal arteritis, chronic progressive ophthalmoplegia, myasthenia gravis

Pupil involving oculomotor palsy: Tumor (chordomas, mengioma), vascular (posterior communicating), uncal herniation, cavernous sinus lesion (also involves V1, V2, IV, VI—cavernous sinus syndrome)

Horner's syndrome: Interruption of sympathetics at a central, pre- or postganglionic location → miosis, anhydrosis, ptosis

- Differentiate pre- from postganglionic sympathetic denervation via administration of Hydroxyamphetamine 1% (stimulates endogenous norepi release → pupillary dilation if preganglionic, no mydriasis if postganglionic)
- DDx includes cluster headache, cavernous sinus disease

Ross syndrome: Adie's tonic pupil (increased papillary diameter and sluggish constriction to light), excessive sweating, decreased deep tendon reflexes (especially Achilles), occasionally cardiovascular abnormalities

- Generally starts unilateral, then progresses to the other side
- Young women
- Caused by inflammation/damage to the cilliary and spinal ganglia

CORTICAL VISUAL ABNORMALITIES

BALINT'S SYNDROME

Visual inattention

- Cannot gaze to a specific point in visual field
- Extraocular movements intact
- Caused by bilateral parieto-occipital lesions

PROSOPAGNOSIA

Inability to identify familiar faces (e.g., of close friends or family); from a lesion of the right fusiform gyrus

ACHROMATOPSIA

Inability to recognize colors

- From occipitotemporal lesion

NEUROTOLOGY

VERTIGO

Important to distinguish from syncope/near syncope or disequilibrium and clarify "dizziness"

- Vertigo can be peripheral or central in origin

Peripheral causes: Include benign positional vertigo (BPV), vestibular labyrinthitis/neuronitis, Ménière's disease, ototoxic drugs (e.g., gentamicin), acoustic schwannoma, trauma, compression of vestibular nerve

Central causes: Include CVA/TIA of brainstem, vertebral dissection, tumor, multiple sclerosis affecting brainstem/cerebellum

- Central causes may involve additional brainstem structures causing symptoms such as diplopia or dysphagia

Benign Positional Vertigo (BPV)

- Otoliths moving in semicircular canals cause vertigo
- Can be preceded by viral illness
- No hearing loss

Treatment: Head movements recreate symptoms, lasting seconds to minutes

- Dix-Hallpike maneuver may be positive in BPV
- Meclizine may be tried but is often not effective
- Teach Epley maneuver in attempt to move otoliths and relieve symptoms

Ménière's Disease[10]

- Tinnitus, deafness, vertigo
- Typically, vertigo lasts hours and hearing worsens with vertigo

Pathophysiology: Rupture of the membranous labyrinth → endolymph mixes with perilymph

Table 5-1 Brainstem Auditoy Evoked Potentials (BAERs)

Wave	Lesion
I	cochlear nerve
II	cochlear nuclei (pons)
III	superior olivary complex (pons)
IV	lateral lemniscus (pons)
V	inferior colliculus (midbrain)
VI	medial geniculate (thalamus)
VII	auditory radiations

Table 5-2 Gardner Robertson Scale[11]

Grade	Description	Pure Tone Audiogram (dB)	Speech Discrimination (%)
I	good–excellent	0–30	70–100
II	serviceable	31–50	50–69
III	nonserviceable	51–90	5–49
IV	poor	91–max	1–4
V	none	not testable	0

NOTE: If pure tone audiogram and speech discrimination do not correlate, use the lower class.

Treatment: Diuretics, eliminate Etoh/caffeine, salt restriction

- Labyrinthectomy (sacrifices hearing), vestibular neurectomy (preserves hearing)
- Direct injection of gentamycin into the middle ear

CENTRAL HEARING ABNORMALITIES

Auditory Agnosia

Right temporal lobe lesion

- Inability to interpret sounds

Amusia

Right temporal lobe lesion

- Inability to interpret music

BRAINSTEM AUDITORY EVOKED RESPONSES (BAERS)

Average of a series of potentials generated from the major processing centers of the auditory system in response to a repetitive sound stimulus

- Sample lesion and effects include acoustic neuroma (retro-cochlear) → prolonged I–III and I–V interpeak latencies; cochlear lesions → progressive disappearance at high-intensity stimulation of the interaural difference in the latency of wave V

CHAPTER 6 ■ DISORDERS OF MYELIN

Keith Van Haren, MD

AUTOIMMUNE DISORDERS OF MYELIN

MULTIPLE SCLEROSIS[1]

Description: Multiple CNS demyelinating events separated by time and space

- Three major subtypes: relapsing remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS)
- In one year of disease, patients generally have 1–2 clinical exacerbations, with 5–10 new MRI findings

Epidemiology: In the US, prevalence 400,000, incidence 10,000 cases/year; worldwide prevalence 2.5 million

- Mainly northern European ancestry
- Onset at age 18–50

Symptoms: (Table 6-1) Episode of neurologic disturbance that is likely to be inflammatory and demyelinating in nature, with clinical symptoms of > 24-hrs duration, with objective clinical findings, and separated by > 30 days from other clinical events

- Symptoms onset usually takes place in a subacute fashion over 3–5 days
- Beware of mimics such as systemic infection (e.g., UTI) that can exacerbate underlying/prexisting MS symptoms.

DDx: Clinically isolated syndrome (CIS), acute disseminated encephalomyelitis (ADEM), lymphoma, CNS infection, stroke

Diagnostic evaluation: (See Table 6-1) MRI brain (and spine as clinically indicated) + gadolinium demonstrates a wide range of T2 signal abnormalities in almost any region of the white matter

- CSF for oligoclonal bands
- Visual-evoked potentials may identify prior or current episodes of optic neuritis

Radiology: Multiple circumscribed lesions on MRI with T2 hyperintensity

- Gadolinium enhancement may or may not be present

Treatment: Selection of disease modifying agents (i.e., slows progression) varies by subtype

- Symptomatic therapies (i.e., no alteration of underlying disease) can be broadly applied

Table 6-1 McDonald Criteria for Diagnosis of MS[2]—2005

Clinical Presentation	Additional Data Needed for MS Diagnosis
Two or more attacks; objective clinical evidence of two or more lesions	None
Two or more attacks; objective clinical evidence of one lesion,	**Dissemination in space**, demonstrated by: - MRI ***or*** - >/=2 MRI-detected lesions consistent with MS ***plus*** positive CSF ***or*** - Await further clinical attack implicating a different site
One attack; objective clinical evidence of two or more lesions	**Dissemination in time**, demonstrated by: - MRI ***or*** - Second clinical attack
One attack; objective clinical evidence of one lesion (monosymptomatic presentation; clinically isolated syndrome)	**Dissemination in space**, demonstrated by: - MRI ***or*** - >/=2 MRI-detected lesions consistent with MS ***plus*** positive CSF ***and*** **Dissemination in time**, demonstrated by: - MRI or Second clinical attack
Insidious neurological progression suggestive of MS	One year of disease progression (retrospectively or prospectively determined) ***and*** Two of the following: - Positive brain MRI (nine T2 lesions ***or*** four or more T2 lesions with positive VEP) - Positive spinal cord MRI (two focal T2 lesions) - Positive CSF oligoclonal bands

Acute Attack (Any Subtype)

Methylprednisolone 20–30 mg/kg/day × 3–5 days. *Note*: Glucocorticoid treatment speeds recovery but has no clear long-term benefit

Relapsing Remitting MS

There is no formal consensus regarding initial choice of disease-modifying therapy, however, IFNB-1a or Glatiramer are favored due to relative tolerability, safety, efficacy, and/or ease of administration

- IFNB-1a (Avonex): 30 mcg intramuscular (IM) injection weekly
- IFNB-1a (Rebif): 22 or 44 mcg subcutaneous (SC) three times a week
- Glatiramer acetate (Copaxone): 20 mg SC injection daily
- IFNB-1b (Betaseron): 0.25 mg (1 mL) SC every other day
- Natalizumab: usually reserved as 2nd-line monotherapy because of risk of progressive multifocal leukoencephalopathy (PML)—estimated risk of 1/1000, though probably higher when used in combination with other immunosuppressives

- Mitoxantrone: Also reserved as 2nd-line agent for patients with rapidly advancing disease who have failed other therapies because of cardiac toxicity and limited evidence of benefit

1. Primary progressive MS (PPMS): Represents about 10% of cases and is characterized by a steady decline in function from onset with no acute attacks.
   - Unfortunately, there are no trials to support any one therapy for PPMS. Choice of therapy is empiric, but includes those for SPMS as well as mitoxantrone
2. Secondary progressive MS (SPMS): This subtype causes the greatest amount of disability. Begins as relapsing-remitting, but later evolves to a steady deterioration in function, unrelated to acute attacks. About 80% of patients with relapsing remitting disease go on to develop this form.
   - Clinical trials have yielded only modest therapeutic benefits. Agents include: monthly glucocorticoid, methotrexate, cyclophosphamide, possibly interferon-beta
   - Outcome: Life expectancy 6 years lower than that of the general population, with increased likelihood of disability from neurological deficit

CLINICALLY ISOLATED SYNDROME (CIS)[3]

Description: A single, subacute event of clinically manifesting CNS demyelination (the formal diagnosis of MS usually requires > one event)

- Includes optic neuritis and transverse myelitis

DDx: Stroke, arterial dissection, ADEM, CNS lupus, CNS lymphomas, vasculitis, progressive multifocal leukoencephalopathy, HIV, CNS lyme, CADASIL

Diagnostic evaluation: MRI brain + contrast to stratify risk for MS (if MRI is normal, repeat in 3–6 months), lumbar puncture for oligoclonal bands

Treatment: glucocorticoids

- Interferon beta therapy can delay the timing of a second attack but does not alter risk of long-term disability

Outcome: Event frequently responds to steroids

- 80% of these cases will proceed to MS

TRANSVERSE MYELITIS

Description: Spinal cord dysfunction developing over hours or days due to an inflammatory lesion of the cord

- Usually idiopathic and thus classified as CIS (see previous) but may herald the onset of MS, NMO, or ADEM.

DDx: Spinal vascular malformation (including AVM or dural AV fistula), mycoplasma, HIV myelopathy, B_{12} deficiency, copper deficiency, adrenomyeloneuropathy, hereditary spastic paraparesis, spinal cord ischemia/stroke

Diagnostic evaluation: MRI of spine including diffusion weighted sequences + gadolinium

- CSF for infection and oligoclonal bands

Treatment: Corticosteroids (for demyelinating lesion when infection has been ruled out)

NEUROMYELITIS OPTICA (NMO; AKA DEVIC'S DISEASE)[4,5]

Description: An autoimmune disorder classically manifesting as bilateral optic neuritis in combination with transverse myelitis, although they do not usually occur simultaneously

- Disease course can be continuously progressive or relapsing-remitting
- May occur with other autoimmune diseases (such as Lupus or Sjogren's)

Etiology: Serum IgG autoantibody (NMO-IgG) that selectively binds to the aquaporin four-water channel

DDx: MS, ADEM, CIS

Diagnostic evaluation: Should meet 2/3 of the following (99% sensitivity and 90% specificity[1]): 1. MRI evidence of a contiguous spinal cord lesion three or more segments in length; 2. Initial brain MRI nondiagnostic for multiple sclerosis; 3. NMO-IgG seropositivity (NMO-IgG seropositivity 76% sensitive and 94% specific for NMO)

- Note, CNS involvement beyond the optic nerves and spinal cord is compatible with NMO.

Treatment: Immunosuppression (glucocorticoids or rituximab)

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)[6]

Description: CNS demyelination presenting as a monophasic disorder associated with multifocal neurologic symptoms and encephalopathy, ranging from drowsiness to coma.

Epidemiology: Typically young patients who present with encephalopathy and fever.

- Typically occurs following a viral or bacterial illness, most commonly an upper respiratory infection, or, less commonly, following vaccination

Etiology: Antigenic mimicry where myelin proteins (myelin basic protein, proteolipid protein, and myelin oligodendrocyte protein) share antigenic similarity with those of an infecting agent.

DDx: MS, NMO, CIS, infectious encephalitis, progressive multifocal leukoencephalopathy (PML) in immunosuppressed patients, meningitis, encephalitis

Diagnostic evaluation: MRI brain + gadolinium, CSF (shows inflammation, rule out active infection)

Radiology: Multiple and bilateral deep and subcortical white matter lesions

- Brainstem, spinal cord, and basal ganglia are also commonly involved

Treatment: Immunosuppression: IV glucocorticoids, IV immunoglobulin (IVIG), or plasmapheresis.

Outcome: Neurologic deficits usually reach their peak within 1 week

- Most children make a full recovery, however, residual motor and cognitive deficits are not uncommon

GENETIC DISORDERS OF MYELIN[7]

ADRENOLEUKODYSTROPHY, X-LINKED (XALD)

Description: Peroxisomal disorder of beta-oxidation that results in accumulation of very long chain fatty acids (VLCFA) in all tissues, but typically manifests symptoms in the central nervous system and the adrenal cortex

- XALD consists of a spectrum of phenotypes (including both adrenomyeloneuropathy (AMN) as well as a form of Addison's disease) that vary in the age of onset as well as the severity of clinical presentation. These conditions are known as the ALD/AMN complex and typically takes one of three forms:
  1. Classical childhood cerebral form: This form represents about a third of all phenotypes in the ALD/AMN complex. Patients with this form typically develop symptoms between 4–8 yrs of life and is rare after 15 and almost never occurs before 3 (neonatal adrenoleukodystrophy is a separate disorder from XALD). Symptoms include behavioral changes and cognitive decline.
  2. Adrenomyeloneuropathy: Represents the clinical course of about 40% of XALD males, with the usual presentation in early adulthood. The primary manifestation is spinal cord dysfunction with progressive spastic paraparesis, abnormal sphincter control, and sexual dysfunction. About half of AMN patients have some form of cerebral involvement on MRI. The majority have comorbid adrenal insufficiency. About half of female carriers (heterozygotes) develop an AMN-like syndrome by late adulthood.
  3. Addison-only disease: XALD is a common cause of idiopathic Addison's disease. It usually presents in males before age 10, but can present as late as adulthood. Most individuals go on to develop AMN, though it may be the only sign of ALD in approximately 10% of affected individuals.

Epidemiology: 1:21,000 males

- Symptom onset ranges from early childhood to late adulthood

Etiology: X-linked ALD is caused by mutations in the ATP-binding cassette, subfamily D, member 1 gene (ABCD1 gene), located at Xq28 → prevention of normal transport of VLCFAs into peroxisomes resulting in failure of beta-oxidation and breakdown of VLCFA.

DDx: Metachromatic leukodystrophy, multiple sclerosis, vitamin B_{12} deficiency, progressive spastic paraparesis

Diagnostic evaluation: Elevated plasma concentration of VLCFA, + mutation analysis of the ABCD1 gene

- All individuals with suspected or confirmed ALD or AMN should be evaluated for adrenal insufficiency and followed closely

Treatment:

1. Definitive cerebral ALD: Patients with mild CNS disease should be promptly referred for hematopoietic stem-cell transplant evaluation. The treatment effect appears strong in patients who are treated early in the disease. In patients who have more advanced CNS disease, treatment options are less certain
2. AMN: Lorenzo's oil may reduce the risk of developing cerebral disease; symptomatic management of spasticity
3. Adrenal insufficiency: All individuals with adrenal insufficiency, with or without other manifestations of ALD or AMN, should be treated with corticosteroid replacement therapy
4. Patients with known gene defect without evidence of CNS disease: Lorenzo's oil may reduce the risk of developing cerebral disease

VANISHING WHITE MATTER DISEASE (VWM)[8]

Description: CNS myelin disease from dysfunction of protein transcription

Epidemiology: Can present at almost any age, usually with an inverse relationship between age and severity

Symptoms/Signs: Progressive, often stepwise neurologic deterioration with prominent ataxia and spasticity, but relative sparing of intellectual function

- Optic atrophy, seizures, and ovarian dysfunction are not uncommon.

Etiology: Autosomal recessive

- Mutations in any of the five genes that encode the subunits of the eukaryotic translation initiation factor eIF2B

DDx: ADEM, infectious encephalitis, Alexander disease, Megalencephalic leukoencephalopathy with subcortical cysts

Diagnostic evaluation: + Genetic testing for eIF2B abnormalities

- Suggestive MRI findings include diffuse signal abnormalities of the cerebral white matter, the disappearance of the cerebral white matter occurs in a diffuse "melting away" pattern with relative sparing of the temporal lobes and the cerebellum, and the absence of contrast enhancement

Treatment: Prevention, including no contact sports, liberal use of antibiotics and antipyretics, vaccinations kept up-to-date

Outcome: Incurable. Prevention slows disease progression

- Febrile illness, minor head trauma, or severe fright classically lead to sudden neurologic deterioration with incomplete recovery. Life expectancy is highly variable and depends largely on the age of symptom onset

METACHROMATIC LEUKODYSTROPHY (MLD)

Description: Lysosomal storage disease affecting both the central and peripheral myelin

Epidemiology: 1 of 40,000 live births

- Age of onset ranges from infancy to adulthood

Symptoms/Signs: Regression of motor skills, ataxia, hypotonia, seizures, optic atrophy, spasticity, and diminished reflexes

Etiology: Autosomal recessive

- Mutations in the arylsulfatase A gene (ARSA gene; rarely from a deficiency of an ARSA-related protein, saposin B) → diminished activity of arylsulfatase A (ARSA) → decreased desulfation of cerebroside sulfate (a major glycolipid of myelin) → accumulation of cerebroside sulfate in the central nervous system (CNS), peripheral nerves, kidneys, and other visceral organs → destruction of oligodendroglial and Schwann cells, causing central and peripheral demyelination

DDx: Metachromatic leukodystrophy, multiple sclerosis, vitamin B_{12} deficiency, progressive spastic paraparesis

Diagnostic evaluation: MRI, EMG (diminished nerve conduction velocity), LP (elevated CSF protein)

- Demonstrate deficient ARSA activity (undetectable to less than 10% of normal values) in leukocytes or cultured skin fibroblasts
- Distinguish from ARSA pseudodeficiency alleles (present in approximately 1% of the general population) when low but not absent levels are detected in prenatal testing or screening of asymptomatic relatives

Imaging: MRI reveals symmetric white matter lesions in the early form of the disease and cortical atrophy in the later forms

Treatment: Symptomatic. Bone marrow transplantation remains controversial.

PELIZAEUS MERZBACHER DISEASE (PMD)[9]

Description: PMD results in dysmyelination leading to the most severe manifestation of the disease spectrum

- PMD also encompasses hereditary spastic paraplegia 2, resulting from mutations of the proteolipid protein 1 gene (PLP1)

Symptoms/Signs: Patients typically present with nystagmus, spasticity, tremor, and ataxia although onset and severity are variable, which can delay diagnosis

Etiology: X-linked

- PMD duplication of the PLP1 gene → overexpression of proteolipid protein → protein misfolding, impaired structural integrity of the myelin sheath, and oligodendrocyte apoptosis

Diagnostic evaluation: Characteristic clinical and imaging findings, as well as a family history consistent with X-linked disease inheritance

- Genetic testing for a mutation in the PLP1 gene is confirmatory

Radiology: MRI reveals patchy or diffuse T2 hyperintensity involving the cerebral hemispheres, cerebellum, and brainstem

Treatment: Symptomatic

ALEXANDER DISEASE[10]

Description: Alexander disease (OMIM #203450) is a rare genetic disorder that predominantly affects infants and children and is associated with cerebral white matter disease

Symptoms/Signs: megalencephaly, psychomotor retardation, pseudobulbar signs, spasticity, and ataxia, with progressive deterioration

Etiology: Mutation in the gene that encodes glial fibrillary acidic protein (GFAP)

DDx: ALD, MLD, canavan disease, megalencephalic leukodystrophy, ADEM

Diagnostic evaluation: Serial MRI scans can establish the diagnosis, demonstrating increasing frontoparietal white matter atrophy with cystic degeneration with characteristic contrast enhancement of selected gray and white matter structures

- Genetic testing is confirmatory

Pathology: Intracytoplasmic astrocytic inclusions (Rosenthal fiber)

Treatment: Symptomatic

CANAVAN DISEASE

Description: Neurodegenerative disease with typical onset in early infancy, characterized by diffuse white matter changes and spongy degeneration of the brain

Symptoms/Signs: Present with macrocephaly and hypotonia, followed by optic atrophy, hypertonia, seizures, and progressive neurologic deterioration

Etiology: Genetic defect in the gene coding for aspartoacylase → build of N-acetylaspartic acid (NAA) levels in the brain

Diagnostic evaluation: Neuroimaging demonstrates diffuse white matter abnormalities with a lack of contrast enhancement. MR spectroscopy shows elevated N-acetylaspartic acid

Treatment: Symptomatic

OTHER DISORDERS OF MYELIN

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)[11,12]

Description: PML is a severe demyelinating disease of the central nervous system that is caused by reactivation of the polyomavirus JC (JCV)

Symptoms/Signs: Subacute neurologic deficits including altered mental status, hemiparesis, ataxia, visual symptoms (hemianopsia and diplopia), and seizures

Etiology: Primary infection with JC virus is asymptomatic and cumulative risk of exposure increases with age. Symptomatic reactivation occurs in the setting of severe immune compromise, such as advanced HIV (CD4 count < 200) and less commonly in the setting of iatrogenic immunosuppression for solid-organ transplant. It is a possible complication of some immunosuppressive regimens, including natalizumab, where the risk is ~1/1000 (possibly higher), although this risk is dependent on duration of treatment and previous JC virus exposure

DDx: Immune reconstitution inflammatory syndrome (IRIS), primary CNS lymphoma, HIV encephalopathy

Diagnostic evaluation: Clinical history and MRI often suggest the diagnosis

- Testing for JC virus by polymerase chain reaction of cerebrospinal fluid is specific but may lack sufficient sensitivity to rule out the diagnosis entirely
- Brain biopsy is confirmatory though risky in the affected population

Radiology: MRI usually demonstrates multiple large confluent areas of T2 hyperintensity affecting only the white matter and without associated contrast enhancement or mass effect

Treatment: There is no specific treatment for the JC virus that causes PML

- Treatment is dependent on the underlying cause of immune suppression and is directed at maximizing underlying immune competence

Outcome: Progressive course and fatal if untreated

- Those who do recover are typically left with severe deficits as affected areas do not appear to remyelinate effectively

CHAPTER 7 ■ HEADACHE[1]

Melanie G. Hayden Gephart, MD, MAS

Note: Headache may be secondary to systemic or intracranial pathology, including subarachnoid hemorrhage (SAH), increased intracranial pressure, infection (meningitis), local pathology (giant cell arteritis, dental disease, etc.), postcraniotomy, or head trauma

- Symptoms such as new onset headache, "worst headache of life" (SAH), and associated new seizure, all warrant neuroimaging because these symptoms may be indicative of a more life-threatening etiology of headache

MIGRAINE

Subtypes: Migraine with aura, common migraine (without aura), complicated migraine (with infarction), migraine equivalent (without headache), retinal migraine

Epidemiology: Affects approximately 10% of the population (second in frequency to tension headaches), F > M, possible increased risk of stroke

Pathophysiology: Involves serotonin receptors

- Common triggers include alcohol, chocolate, light, diet changes, medications, stress
- May occur after administration of angiogram contrast

Symptoms: Prodrome (tinnitus, photophobia, scotomas, dizziness, thirst)

- Visual symptoms (tunnel vision, visual scintillations)
- Nausea, vomiting
- Rare transient neurological deficit (usually visual, rarely with somatosensory or motor deficits)
- Headache unilateral or bilateral, typically throbbing or pounding
- Symptoms should resolve within 24 hours

Abortive treatment: Cool, dark quiet room

- Acetaminophen, aspirin, NSAIDs, keterolac, Triptan class of 5-HT1 agonists, dihydroergotamine, antiemetics

Preventive (Prophylactic) treatment: Beta-blockers (propranolol, nadalol), anticonvulsants (topiramate, valproate), calcium blockers (verapamil), tricyclics (amitriptyline, nortriptyline)

TENSION-TYPE

Classification: Episodic or chronic (daily)

Epidemiology: 15%, F > M

Pathophysiology: Unknown, some may overlap with migraine headache

Symptoms: Recurrent, moderate pain, "tightness" or "band-like"

- May be associated with muscular tension of neck and scalp, stress

Treatment: Acetaminophen, aspirin, NSAIDs, keterolac

CLUSTER

Classification: Episodic or chronic

Epidemiology: < 1%, M > F, may have family history

Pathophysiology: Unknown

Symptoms: Unilateral, severe periorbital pain, ipsilateral autonomic symptoms (rhinorrhea, lacrimation, flushing, injected conjunctiva), occasionally partial Horner's, no prodrome, last 1–4 hours, recurrent (generally on the same side)

INTRACRANIAL HYPOTENSION

Etiology: May occur after lumbar puncture, epidural anesthesia, lumbar drain, CT myelogram, may also occur spontaneously (e.g., rupture of Tarlov cyst)

Pathophysiology: Intracranial hypotension creates tension on dura → pain

Symptoms: Positional headache that is worse when upright and improve when supine

Analysis: CT head, CT myelogram of spine to evaluate for CSF leak, MRI spine

Complications: May lead to subdural hematomas

Treatment: Strict bedrest for 24 hours with head of bed flat, hydration, caffeine, analgesics, epidural blood patch

TEMPORAL ARTERITIS (GIANT CELL ARTERITIS)

Epidemiology: 1–5/10,000, F > M, age > 50

Pathophysiology: Inflammation of medium- and small-sized vessels, mainly branches of aortic arch, multifactorial etiology, associated with polymyalgia rheumatica

Symptoms: Headache, usually nonspecific characteristics

- Constitutional symptoms
- Jaw claudication

- Tenderness to palpation over superficial temporal artery
- Visual loss/blindness

Analysis: ESR, CRP, superficial temporal artery biopsy

Treatment: Steroids (Prednisone)

- Do not delay treatment for definitive biopsy to avoid irreversible vision loss

CHAPTER 8 ■ VASCULITIS[1–4]

Melanie G. Hayden Gephart, MD, MAS

Diagnosis: MRI, diagnostic cerebral angiogram, brain biopsy, labs (ESR, CRP, CPK, ANCA)

WEGENER'S GRANULOMATOSIS

Necrotizing, granulomatous systemic vasculitis

Symptoms/Signs: Classically involves the respiratory tract (cough, nasal drainage) and renal

- Neuro symptoms in 30%: cranial nerve dysfunction, peripheral neuropathy, diabetes insipidus

Treatment: Cyclophosphamide, prednisone, methotrexate, septra

■ Lymphomatoid Granulomatosis

Similar to previous, angiodestructive lymphoproliferative B-cell lymphoma

- Associated with EBV
- Lungs > skin, nervous system
- Lymphocytic infiltration of nervous system in 25%

GIANT CELL ARTERITIS

■ Temporal Arteritis

Epidemiology: Caucasian; M:F = 2:1

- 50% have polymyalgia rheumatica

Symptoms/Signs: Headache, temporal artery tenderness, vision loss

Etiology: Inflammation of branches of the external carotid artery

Diagnostic workup: Superficial temporal artery biopsy, ESR

Treatment: Treat with steroids (prednisone 40–60 mg/day PO divided bid-qid to start, when symptoms resolve, gradually taper) if suspected without waiting for results of biopsy, follow with symptoms and ESR

Outcome: If untreated can lead to blindness

■ Takayasu's Arteritis

Similar to previous but is chronic inflammation of the aorta and branches in young women

Symptoms/Signs: May present with myocarditis and heart failure

- Neuro symptoms include ischemic stroke, TIA, visual disturbances

Treatment: Cyclophosphamide, prednisone, methotrexate

POLYARTERITIS NODOSA

A group of necrotizing vasculitides of small- to medium-sized arteries including classic periarteritis nodosa, Churg-Strauss syndrome, systemic necrotizing vasculitis

- Rare
- Mortality up to 30%

Classic Periarteritis Nodosa

Multisystem disease leading to arterial necrosis, occlusions, and hemorrhage

- Palpable arterial nodules

Symptoms/Signs: Neurological manifestation of mononeuritis multiplex, cranial nerve palsy, polyneuropathy (from compromise of vasa vasorum) in addition to systemic symptoms

- Central CNS symptoms in 30%: HA, subarachnoid and retinal hemorrhages, ischemic stroke, encephalopathy, seizures
- Severity based upon the five-factor score: proteinuria, renal insufficiency, cardiomyopathy, GI manifestations, CNS involvement

Treatment: Steroids, cyclophosphamide, plasma exchange (if refractory)

SYSTEMIC LUPUS ERYTHEMATOSUS

Neurological symptoms: Embolic or local stroke, diffuse cerebritis, aseptic meningitis, posterior reversible encephalopathy syndrome (PRES), seizures, peripheral neuropathy, transverse myelitis, encephalopathy, movement disorders, pseudotumor, venous sinus thrombosis, cranial neuropathy

BEHCET'S DISEASE

Uveitis, oral/genital ulcers, arthritis ("can't see, can't pee, can't climb a tree")

- Likely autoimmune
- Neuro symptoms 5%: Cerebellar findings, seizures, dural sinus thrombosis, spastic paralysis

MEDICATIONS/DRUGS

Methamphetamines, cocaine

CALL-FLEMING

Acute, severe headaches, focal neurological deficits and reversible segmental cerebral vasoconstriction

- Frequently with history of migraines or depression and use of triptans or serotonin associated medications (vasoactive drugs)

CHAPTER 9 ■ NEUROLOGIC PARANEOPLASTIC DISEASE[1–5]

Roopa Bhat, MD, PhD

DEFINITION

Neurologic paraneoplastic diseases (PND) are rare, diverse, and disabling conditions in which signs and symptoms occur remote from the diagnosis of cancer

- Diagnosis of a PND can therefore aid in the early diagnosis of cancer
- Can affect any part of the central nervous system (CNS) or peripheral NS (PNS) and often affect multiple areas simultaneously.

CLASSIC PND

Thought to be secondary to autoimmune inflammation

Brain and cranial nerves: paraneoplastic encephalomyelitis (PEM), limbic encephalitis (LE), cerebellar degeneration (PCD), and opsoclonus-myoclonus syndrome (OMS), paraneoplastic chorea and parkinsonism

Spinal cord: Subacute motor neuronopathy (ALS-like syndrome), inflammatory myelitis (similar to Devic's), necrotizing myelopathy, and stiff-person syndrome (SPS)

Visual syndromes: Cancer-associated retinopathy, melanoma-associated retinopathy, and paraneoplastic optic neuritis

Peripheral nerve, NMJ, and muscle: Subacute/chronic sensorimotor neuropathies (similar to Guillain-Barré), myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), dermatomyositis, autonomic neuropathy, vasculitic neuropathy, neuromyotonia, sensory neuronopathy, necrotizing myositis, and polymyositis

INDIRECT PND

Secondary to cancer growth or damage to non-neurologic tissue. Include encephalopathy (caused by hypercalcemia from hyperparathyroidism or paraneoplastic), Cushing syndrome, Trousseau's syndrome (as a result of hypercoagulation), and neurologic consequences of chemotherapy

ETIOLOGY AND PREVALENCE

PND are thought to be autoimmune syndromes precipitated by the immune response against cancer that cross reacts with normal tissues/processes as evidenced by the detection of antineuronal antibodies in CSF or serum

- Tumors create an antigen load with a resultant humoral and immune response that targets neural tissues which present the antigen normally
- PND are most commonly associated with neuroendocrine (e.g., small-cell lung cancer SCLC, neuroblastoma), neuroectodermal (teratoma),

immunoregulatory or immunoglobulin-producing cancers (thymoma, blood dyscrasia, lymphoma)

- In the small proportion of PND cases where the cancer is never detected, the immune response may have cleared the cancer before it became evident or perhaps these are true idiopathic autoimmune diseases

Cytotoxic CD8 T cell-mediated: Shows antibodies and lymphocytic infiltrates in the target neural tissues

Humoral immunity: Includes LE from anti-NMDA antibodies, SPS from antiglutamic acid decarboxylase anti-GAD antibodies, and anti-VGKC antibodies in PEM

T-Cell immune response: Anti-hu and anti-yo antibody-associated syndromes

EPIDEMIOLOGY

< 1/1000 of cancer patients although prevalence in SCLC is 3–5%, thymoma is 15–20%, plasma and B-cell dyscrasias 3–10%, and much less in breast, testicular, and other cancers

- 80–85% of antibody-confirmed PND cases harbor a cancer
- The median age of onset 60, although with a secondary peak in OMS in children with neuroblastoma

DIFFERENTIAL DIAGNOSIS

Neurologic dysfunction due to metabolic or toxic causes (thiamine or vitamin E deficiency, alcohol related), medications, postinfectious or infectious (HIV, prion disease, PML, syphilis, Guillain-Barré), metastasis (intracranial, spinal, or neuronal), noncancer systemic disease (sarcoid), and idiopathic autoimmune causes (e.g., autoimmune MG or autoimmune SPS, celiac disease)

- Idiopathic autoimmune SPS is associated more often with anti-GAD antibodies and late-onset type 1 diabetes
- Paraneoplastic SPS is associated with amphiphysin antibodies and gynecologic malignancy

DIAGNOSTIC CRITERIA (TABLE 9-1 AND 9-2)

COMMON ANTIGENS (TABLE 9-3)

Include channels and receptors (VGKC, NMDA, GluR, AchR), intracellular (amphiphysin, GAD, hu and ma proteins, proteasome proteins, CRMP5), glial (Gliadin)

Intracellular antigens: Hu, Ma2, CRMP5 (or CV2), amphiphysin

- Frequently found in CSF along with pleocytosis
- Rarely responsive to immunomodulatory treatment

Cell membrane protein antigens: VGKC (thymoma or SCLC), MDA receptors (ovarian teratomas)

- Shows frequent response to steroids, plamapheresis or IVIG

Table 9-1 Definite PNS

	Syndrome	Onconeural Antibodies	Cancer	Comments
1	classical	-	develops within 5 years of the diagnosis	
2	nonclassical	-	yes	syndrome improves after cancer treatment without concomitant immunotherapy
3	nonclassical	yes	develops within 5 years of the diagnosis	
4	neurological	anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin	no	

Source: Adapted from Graus et al.[4]

Table 9-2 Possible PNS

	Syndrome	Onconeural Antibodies	Cancer	Comments
1	classical	no	no	high risk for an underlying tumor
2	neurological	partially characterized	no	
3	nonclassical	no	presents within 2 years of diagnosis	

Source: Adapted from Graus et al.[4]

TREATMENT AND PROGNOSIS

Classical or possible PND → carefully screen for an underlying cancer, with repeat evaluations at regular intervals if nothing identified

Treatment: Discovery, removal, or treatment of the underlying cancer

- Immunosuppression including corticosteroids, IVIG, plasmapheresis, cyclophosphamide, 3,4 diaminopyridine

Prognosis: Patients with PND fare better either because of earlier detection or because PND implies an active immune response against the cancer

For cancers that cannot be cured such as small-cell lung cancer, prognosis is poor. Long-standing or severe neurologic damage unlikely to reverse, therefore, treatment goal is to prevent further deterioration

Table 9-3 Onconeural Antibodies

Antibody	Paraneoplastic Neurological Syndrome	Tumors
Anti-Hu (ANNA1)	encephalomyelitis, sensory neuropathy, paraneoplastic cerebellar degeneration (PCD), limbic encephalitis (LE)	small-cell lung cancer (SCLC)
Anti-Yo (PCA1)	PCD	ovary, breast
Anti-CV2 (CRMP5)	encephalomyelitis, chorea, sensory neuropathy, sensorimotor neuropathy, PCD, LE, paraneoplastic optic neuropathy (PON)	SCLC, thymoma
Anti-Ri (ANNA2)	brainstem encephalitis	breast, SCLC, ovary
Anti-Ma2 (Ta)	limbic/diencephalic and brainstem encephalitis (PCD)	testicular, lung
Antiamphiphysin	stiff person syndrome (SPS), various other syndromes	breast, SCLC
Anti-Tr, Anti-mGluR1	PCD	Hodgkin's disease
Anti-GAD 65	paraneoplastic optic neuropathy, SPS	thymoma, no cancer
Anti-VGKC	LE	SCLC, thymoma, no cancer
Anti-BGCC	Lambert-Eaton myasthenic syndrome (LEMS), PCD	SCLC, thymoma, no cancer
Anti NR1/2 heterodimer (NMDA receptor)	LE	ovarian teratoma
Antirecoverin	cancer-associated retinopathy (CAR)	SCLC, gyn, various
Antienolase	CAR, PON	SCLC, renal cell, thyroid
Anti-Zic	PCD (zic 1,4), Opsoconus myoclonus (zic2)	Melanoma, SCLC

Source: Adapted from Dalmau et al.[1], Darnell et al.[2], Graus et al.[3]

PARANEOPLASTIC ENCEPHALOMYELITIS (PEM)

- Subsets include paraneoplastic cerebellar degeneration (PCD), stiff person syndrome (SPS), and limbic encephalitis (LE)
- Antedates the cancer by a year, most commonly small-cell lung cancer (SCLC); is associated with anti-Hu, CRMP5, zic 1 and 4

PARANEOPLASTIC CEREBELLAR DEGENERATION (PCD)

- The cancer is usually detected within a year of the onset of PCD

- Most commonly associated with SCLC, gyn (ovarian) cancer, breast, thymoma, and lymphoma (Hodgkin's)
- Symptoms caused by severe loss of purkinje cells

Presentation: Abrupt onset of dizziness, nausea, vomiting, diplopia, ataxia, nystagmus with oscillopsia

- Symptoms stabilize in several months with patients frequently unable to walk without support

SCLC

Symptoms can be more widespread than just the cerebellum and can coexist with Lambert-Eaton myasthenic syndrome (LEMS) both secondary to P/Q VGCC antibodies

- Other common antibodies causing PCD in SCLC are anti-Hu but usually more widespread as part of PEM

LIMBIC ENCEPHALITIS (LE)

Presentation: Mood and sleep disturbances, psychosis, hallucinations, autonomic instability, seizures, hypothalamic dysfunction (temperature dysregulation, sleep disturbance, endocrinopathies), memory problems (that can progress to dementia)

- MRI shows FLAIR hyperintensity in the mesial temporal lobes

OPSOCLONUS-MYOCLONUS SYNDROME (OMS)

40% of OMS in kids is paraneoplastic, however, only 2–5% of neuroblastomas show OMS; in adults, 20% of OMS is paraneoplastic

Symptoms: Involuntary, irregular, large conjugate saccades in all directions of gaze, associated in many cases with truncal ataxia, titubations or myoclonus

Antibodies: In kids with neuroblastoma → anti-HU antibodies

- Antibody specific to cerebellar granule cells have been found
- In adults is associated most frequently with anti-Ri (breast and ovarian cancer) or SCLC

Treatment: In children, OMS responds to IVIG, plasmapheresis, rituximab, cyclophosphamide, and ACTH

- In adults is less responsive to immunomodulatory therapy

STIFF-PERSON SYNDROME (SPS)

More than 60% of SPS is idiopathic autoimmune

Symptoms: Progressive muscle rigidity, chronic contractions and spasms predominantly involving the trunk and proximal limbs

Antibody: Anti-GAD (rarely found in thymoma), antiamphiphysin antibodies (usually paraneoplastic)

Treatment: Benzodiazepines or baclofen may relieve symptoms, IVIG

PERIPHERAL NEUROPATHY AND NMJ DISEASE

Peripheral neuropathy is common in cancer patients, although more often caused by chemotherapy side effects, tumor invasion, and metabolic causes such as diabetes than from a paraneoplastic mechanism

- Paraneoplastic demyelinating polyneuropathies associated with monoclonal gammopathies of unknown significance (MGUS), multiple myeloma, Waldenström macroglobulinemia, cryoglobulinemia

EMG-NCV: Pure sensory neuropathy denotes dorsal root ganglion (DRG) pathology that occurs with other PND such as PEM with anti-Hu antibodies

- Anti-Hu antibodies also associated with autonomic neuropathies
- Pure motor neuropathy (GBS-like or multifocal with conduction block) associated with Hodgkin's and plasma cell dyscrasias

LAMBERT-EATON MYASTHENIC SYNDROME (LEMS)

Primarily humeral-mediated immune attack on postsynaptic voltage-gated calcium channel receptors of the neuromuscular junction (NMJ)

- Most commonly associated with SCLC (identified eventually in 50% of LEMS patients) or thymoma

Antibody: Anti-P/Q VGCC antibodies

Symptoms: Fatigability, weakness of the proximal muscles leading to difficulty climbing, heavy lifting, opening windows

- Cranial nerve involvement is much less severe than in myasthenia gravis but ptosis, dysarthria, dysphagia may also be present

EMG: Severely decreased CMAP amplitude and presynaptic pattern on repetitive nerve stimulation known as facilitation

Treatment: Tumor removal

- For SCLC, this takes precedence over LEMS treatment
- LEMS also responsive to di-aminopyridine (for symptom relief through facilitated release of acetylcholine at the NMJ), plasmapheresis, IVIG

NEUROMYOTONIA (ISAAC'S SYNDROME)

Associated with thymoma, Hodgkin's, SCLC, plasmacytoma

Symptoms: Cramps, muscle weakness, hypertrophic muscles, sweating

Antibody: Anti-VGKC (high acholine)

Treatments: Phenytoin, carbamazepine, and plasmapheresis

DERMATOMYOSITIS (DM)

T-cell mediated disease responsive to immunosuppression

- Associated with non-Hodgkin's lymphoma, ovarian, and lung (usually diagnosed shortly after the PND)

Symptoms: Subacute symmetric proximal muscle weakness with possible mild muscle tenderness, heliotrope rash on the face (rare), or on the sun-exposed areas of the chest and shoulders (more common)

- Muscle atrophy or loss of reflexes a rare and late finding

Laboratory Analysis: CPK levels usually elevated to more than 10 times normal

CHAPTER 10 ■ NEUROMUSCULAR DISEASES[1,2]

Doris Leung, MD

NEUROPATHY[3,4]

PERIPHERAL NEUROPATHY

All diseases or injuries that affect the peripheral nerves

- Divided by pathologic process (axonal versus demyelinating), location (multifocal, mononeuropathy, polyneuropathy), rapidity of onset (acute, subacute, chronic) or disease classification

MONONEUROPATHY

Often caused by compression, trauma, diabetes and other vasculitic processes

■ Radial Neuropathy

Radial nerve innervates most of the extensor muscles of the arm leading to wrist drop

- Injury at the axilla causes weakness of the triceps and all distal extensor muscles
- Injury at the upper arm (Saturday night palsy) spares the triceps

■ Median Neuropathy

Median nerve controls flexion and sensation of the first three digits and abduction of the thumb

- Most common is carpal tunnel compression as the nerve passes through the wrist

■ Ulnar Neuropathy

Ulnar nerve innervates the intrinsic muscles of the hand and wrist, flexion of the fourth and fifth digits, and finger abduction

- Most common site of injury is at elbow; causes sensory loss in the 4th and 5th digits of the hand plus weakness of finger abduction

■ Femoral Neuropathy

Femoral nerve controls hip flexion and knee extension

- Injury to the nerve can occur from compression by the inguinal ligament (during lithotomy positioning) or by mass/trauma in the iliacus (such as a retroperitoneal hematoma or pelvic fracture)

Sciatic Neuropathy

Sciatic nerve comprised of both the peroneal (knee flexion, ankle dorsiflexion and eversion, toe extension) and tibial nerves (knee flexion, ankle inversion, ankle plantarflexion, and toe flexion)

- Compression most commonly occurs with hip trauma, but isolated peroneal neuropathy most commonly occurs at knee

MONONEUROPATHY MULTIPLEX

Involves multiple noncontiguous nerves, associated with systemic vasculitides or disseminated tumors

POLYNEUROPATHY[5]

Etiology: No etiology identified in up to 25% of cases

- Endocrine: Diabetes (most commonly identified risk factor for peripheral neuropathy), hypothyroidism, hyperthyroidism, parathyroid dysfunction
- Toxic: Alcoholism, heavy metals, industrial toxins
- Nutritional: Vitamin B_{12} deficiency, or B_6 deficiency or toxicity
- Infectious: HIV-associated, leprosy, Lyme disease, syphilis, diphtheria
- Inflammatory/autoimmune: Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, systemic vasculitis, collagen-vascular disease, sarcoidosis
- Medication-induced: Drugs often associated with peripheral neuropathy include vincristine, cisplatin, antiretroviral agents, isoniazid, metronidazole, amiodarone, thalidomide, colchicine, and phenytoin
- Metabolic: Chronic renal failure
- Neoplastic/paraneoplastic/paraproteinemic: MGUS, Waldenström macroglobulinemia, lymphoma, myeloma
- Inherited: Motor/sensory (Charcot-Marie-Tooth disease), sensory/autonomic, pure motor, hereditary polyneuropathy with predisposition to pressure palsy (HNPP), familial amyloid polyneuropathy, and polyneuropathy due to inborn errors of metabolism

DDx: Myelopathy, bilateral radiculopathy/plexopathy

Diagnostic evaluation: Initial workup should focus on common and/or treatable causes of neuropathy

- Initial labs may include renal function tests, diabetes evaluation, thyroid function tests, vitamin B_{12} levels, syphilis serologies, serum protein electrophoresis with immunofixation, ESR, and ANA
- EMG/NCS to characterize the type of neuropathy
- Skin biopsy may be useful in the diagnosis of small fiber neuropathies. Nerve biopsy is usually low-yield unless vasculitis or amyloidosis is suspected

Treatment: If a causative agent or disease is identified, removal of the causative agent or treatment of the disease can produce improvement in symptoms or at least stop progression of disease

- Painful neuropathies can be treated with antiepileptics (gabapentin, pregabalin), or antidepressants (amitriptyline, nortriptyline, duloxetine)
- Gait training may be of benefit for those with balance problems related to sensory loss

Guillain-Barré Syndrome (GBS)[6]

Most common form is acute inflammatory demyelinating polyneuropathy (AIDP)

Symptoms: Symmetric ascending paralysis and areflexia that occurs over the course of days to weeks

- Often *preceded* 1–3 weeks by infection (campylobacter, cytomegalovirus, EBV, flu vaccine)
- Respiratory failure
- Sphincter tone intact

Variants: Acute motor axonal neuropathy (AMAN), acute motor sensory axonal neuropathy (AMSAN), and Miller-Fisher variant (ophthalmoplegia, ataxia, areflexia, often with antibody to GQ1b), bulbar (dysphagia, dysarthria), dysautonomia

Etiology: Autoimmune disease against the peripheral nerve roots

DDx: Acute myelopathy, neuromuscular junction disease (botulism, myasthenia gravis, Lambert-Eaton syndrome), chronic inflammatory demyelinating polyneuropathy (CIDP), multiple sclerosis, toxic neuropathy, B_{12} deficiency

Diagnostic evaluation: Imaging of the spine may be required if myelopathy cannot be excluded on a clinical basis

- Lumbar puncture typically shows elevated protein but can also have mild pleocytosis
- EMG/NCS is useful for diagnosis: Early stage may just show neuropathic recruitment from decreased motor units; changes of demyelination usually only after the second or third week of illness

Treatment: IVIG (2 g/kg total, divided into 3 to 5 days) or plasmapheresis (every other day for 5 exchanges total) can decrease the duration of the disease; acute management also supportive

- 25% of patients will develop respiratory compromise requiring ventilatory assistance
- Monitor with frequent spirometry measurements and consider intubation if mean inspiratory force (MIF) falls below -30 cm H_2O or vital capacity (VC) falls below 15–20 mL/kg
- Other complications include venous thromboembolism, aspiration, and autonomic disturbances (fluctuations in blood pressure, cardiac arrhythmia, ileus, bladder paralysis)

MYOPATHY[7]

Any disorder that disrupts the structure or function of muscle

- Can be inherited (as are many muscular dystrophies) or acquired
- Frequently occur secondarily in endocrine, infectious, and metabolic diseases; can be a side effect of commonly used drugs

MYOPATHIES

Etiology: Can be divided by disease classification

- Genetic: Muscular dystrophies (Duchenne, Becker, myotonic, fascioscapulohumeral, Emery-Dreifuss, limb-girdle, oculopharyngeal, distal myopathies, and congenital), congenital myopathies (central core disease, multicore disease, nemaline myopathy, myotubular myopathy, congenital fiber type disproportion), channelopathies (produce myotonias and periodic paralysis), metabolic myopathies (glycogen storage disorders, lipid metabolism disorders, hypokalemic, hypophosphatemic), and mitochondrial myopathies
- Inflammatory: polymyositis, dermatomyositis, inclusion body myositis
- Endocrine: Hypothyroidism, hyperthyroidism, hyperparathyroidism
- Infectious: HIV, viral myositis
- Drug-induced: Corticosteroids, statins, fibrates, chronic alcohol use, colchicine, nucleoside reverse transcriptase inhibitors, chloroquine, penicillamine

DDx: Myasthenia gravis, polymyalgia/arthralgia, deconditioning, neuropathic weakness, motor neuron diseases

- Systemic illness of all kinds can also present with chief complaint of weakness

Diagnostic evaluation: Initial evaluation should include levels of muscle enzymes (creatine kinase, aldolase)

- Based on clinical suspicion, can also send disease-specific tests, such as thyroid function tests, electrolyte counts, genetic studies, and autoantibody titres
- EMG/NCS helpful in characterizing and localizing pathology
- Muscle biopsy may be necessary to confirm myopathic disease; can also be sent for enzyme levels and special stains to evaluate for specific myopathies

Treatment: Dependent on etiology of myopathy

- Toxic myopathies usually benefit from removal of offending agent
- Inflammatory myopathies are usually treated with immunosuppressive agents

POLYMYOSITIS (PM)/DERMATOMYOSITIS (DM)

Etiology: Idiopathic, inflammatory

- PM is mediated by CD8+ T cells while DM is humorally mediated and attacks endomysial blood vessels

Epidemiology: Female-to-male predominance of 2:1

- Frequently associated with malignancies (DM > PM)

Symptoms/Signs: Subacute, proximal muscle weakness

- Often other signs of mixed connective tissue disease, including autoimmune antibodies
- Esophageal and pulmonary muscle commonly involved
- Dermatologic manifestations of DM include shawl sign, heliotrope rash, Gottron's sign (scaly rash over fingers and knuckles), and nail-bed abnormalities

Inclusion Body Myositis

Presents as diffuse weakness sometimes with predilection for the forearm flexors and quadriceps

- Rarely occurs in patients younger than 50
- Chronic progression
- Refractory to immunosuppressive therapy

NEUROMUSCULAR JUNCTION DISEASE[8]

MYASTHENIA GRAVIS

Description: Fluctuating weakness that worsens with exercise

- Common symptoms include ptosis, diplopia, bulbar symptoms, limb weakness, fatigability
- 15% of patients have ocular disease only

Etiology: Acquired autoimmune antibodies against the acetylcholine receptors in the postsynaptic membranes at the neuromuscular junction lead to transmission failure

- Some patients have antibodies against a muscle-specific kinase (MuSK)

DDx: Lambert-Eaton myasthenic syndrome, botulism, myopathy, motor neuron diseases

Diagnostic evaluation: Laboratory studies include acetylcholine receptor (AChR) antibodies (MuSK antibodies if AChR antibodies negative)

- Office evaluation can include cold-pack testing, where an ice pack placed over the ptotic eye for several minutes can cause transient improvement in ptosis
- Administration of cholinesterase inhibitor edrophonium may produce a transient improvement in symptoms (must be done in a monitored setting, because edrophonium can produce life-threatening bradyarrhythmias)
- EMG/NCS may be confirmatory and should include repetitive nerve stimulation
- CT chest to look for thymoma
- Thyroid function tests (associated with thyroid disorders)

Treatment: All with myasthenia gravis should be evaluated for thymoma; thymectomy may be considered

- Symptomatic treatment includes cholinesterase inhibitors (pyridostigmine)
- Immune suppression with corticosteroids, azathioprine, mycophenolate mofetil, or cyclosporine in more severe disease
- Multiple drugs, such as beta-blockers, calcium channel blockers, and antibiotics can make weakness worse and should be avoided if possible
- Myasthenic crisis is an acute exacerbation of weakness of the respiratory muscles necessitating mechanical ventilation
- IVIG and plasmapheresis can improve symptoms during acute exacerbation, but effect only lasts for several weeks
- Steroids alone are typically *not* used in myasthenic crisis because their effect is delayed and they may temporarily worsen weakness upon initiation

LAMBERT-EATON MYASTHENIC SYNDROME

Symptoms: Fluctuating weakness

- Often in lower extremities
- Frequently worsens with exercise
- Absent reflexes
- Autonomic symptoms (dry mouth, impotence)
- Strength decreases with rest, increases with repetitive use (recruitment)

Etiology: Autoimmune antibodies against PRE-synaptic voltage-gated calcium channels at the neuromuscular junction cause decreased influx of calcium into the nerve terminal, thereby limiting release of acetylcholine into the synapse

DDx: Myasthenia gravis, myopathy, motor neuron diseases

Diagnostic evaluation: Autoantibodies against voltage-gated calcium channels are sometimes discovered

- Some cases of LEMS associated with small-cell carcinoma of the lung, although other types of malignancy can also be found
- EMG/NCS shows small compound motor action potentials that increase in size markedly after exercise or rapid stimulation

Treatment: If cancer is found, treatment against an underlying malignancy may improve symptoms

- Potassium channel blocker 3,4-diaminopyradine or guanidine (which inhibits mitochondrial calcium uptake) may be used for symptoms
- Immunosuppressive therapy can also be considered

CRITICAL ILLNESS POLYNEUROPATHY (CIP)/MYOPATHY (CIM)[9]

Description: CIP and CIM are acquired conditions characterized by flaccid quadriparesis, areflexia, and respiratory insufficiency

- Risk factors include corticosteroid use, sepsis, multiorgan failure, use of neuromuscular blocking agents, prolonged intubation
- CIP, CIM, or a combination of the two should be suspected if a patient fails to wean off mechanical ventilation

Etiology: Not well understood, but believed to be a manifestation of the systemic inflammatory response in the nervous system

DDx: Deconditioning, Guillain-Barré syndrome, myasthenia gravis, motor neuron disease, rhabdomyolysis, spinal cord injury

Diagnostic evaluation:

- In CIM, CK levels may be elevated, NCS demonstrates low motor amplitudes with relatively preserved sensory potentials, EMG shows short-duration, low-amplitude motor unit potentials, sometimes with fibrillation potentials and positive sharp waves
- In CIP, both motor and sensory potentials tend to be low in amplitude on NCS, EMG may show fibrillation potentials and positive sharp waves consistent with acute denervation

Treatment: Includes aggressive treatment of medical problems, supportive care, and rehabilitation

- Recovery usually limited by the severity of the underlying illness, but patients who survive their primary illness can often regain their prior level of function over months to a year

BOTULINUM TOXIN

Binds to motor nerve end plate → presynaptic neuromuscular blockade

- Seen clinically in three forms: Food-borne botulism (ingested toxin from contaminated food), wound botulism (anaerobic infection by clostridium botulinum), and infantile botulism (toxin produced by clostridium in gut)
- Can be used to therapeutically produce weakness in isolated muscles for conditions such as torticollis, spasticity, and hyperhidrosis

MOTOR NEURON DISEASE

ALS (AMYOTROPHIC LATERAL SCLEROSIS, LOU GEHRIG'S DISEASE)

Pathophysiology: Degeneration of anterior horn alpha-motor neurons, corticospinal tracts in spinal cord and medulla → mixed upper and lower motor neuron manifestations

- Affects motor nuclei of CN V, VII, IX, XII, motor cortex, and spinal cord
- Eye movements spared

Epidemiology: Prevalence 1–5 per 100,000

- 10–20% familial

Symptoms: Weakness, spasticity, fasciculations, atrophy, dysarthria, dysphagia

- Usually asymmetric at onset

- Combined upper and lower motor neuron signs in most but not all patients: increased stretch reflexes even in weak muscles, atrophy and weakness of limb muscles
- Some patients have cognitive impairment
- Not affected: autonomic function
- Variants: progressive muscular atrophy (pure lower motor neuron), primary lateral sclerosis (upper motor neuron disease)

DDx: Inclusion body myositis, cervical cord lesion, multilevel radiculopathy, spinal muscular atrophy, multifocal motor neuropathy or other motor neuropathies such as heavy metal toxicity

Diagnostic studies: MRI C spine and possibly brain, EMG/NCS, lumbar puncture, TSH, Lyme, B_{12}, FTA-ABS, ANA, anti-GM1, CK, HIV, heavy metal screening, parathyroid hormone levels, serum protein electrophoresis with immunofixation

Treatment: Symptomatic (non-invasive ventilation, tracheostomy, gastrostomy, baclofen for spasm)

- Riluzole 50 mg twice daily (slight increase in survival)
- Eventual ventilator support

Prognosis: 3–5 years survival from symptom onset

CHAPTER 11 ■ MOVEMENT DISORDERS[1–5]

Paul Kalanithi, MD

INTRODUCTION

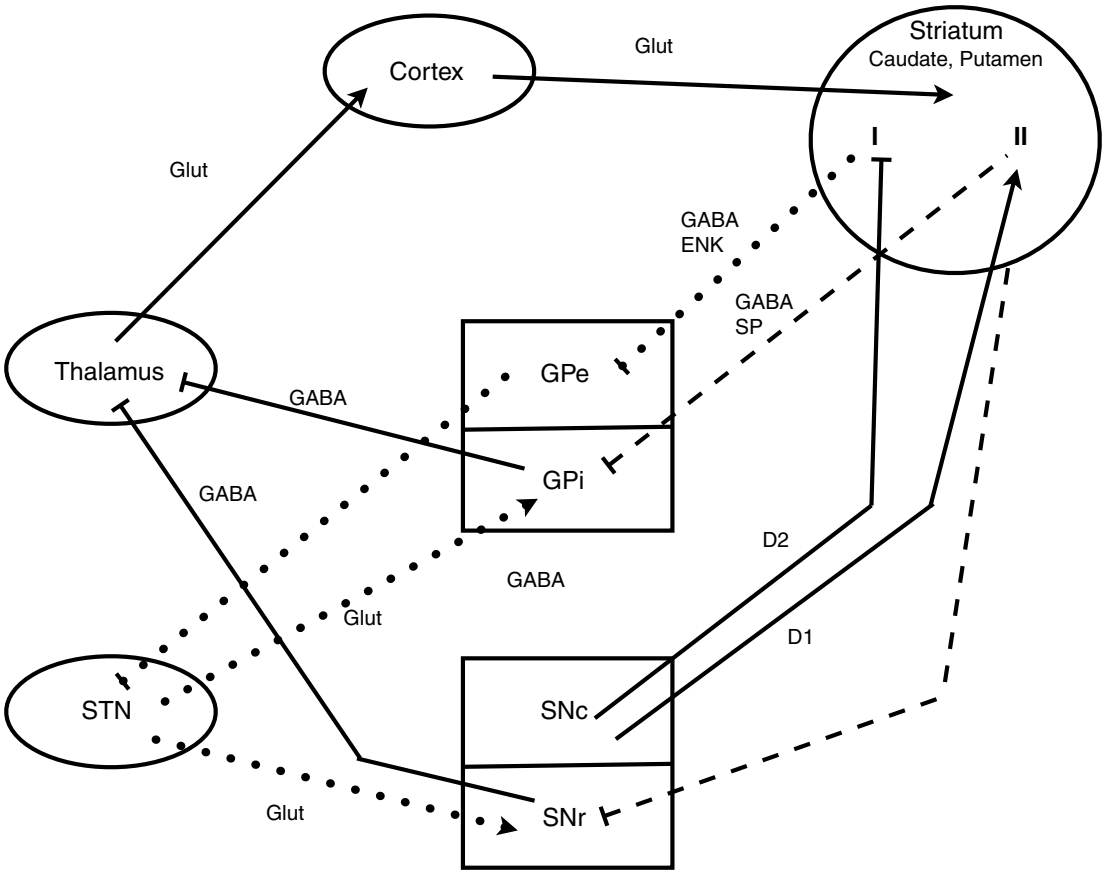
Movement disorders are clinically characterized by involuntary movements, slowed movements, or inability to initiate movements. Major disease types are tremors, stereotypies, choreas, athetosis, and dystonias. The pathology of these diseases primarily involves the cortico-striato-thalamo-cortical circuits with principal focus on the basal ganglia (BG). The cortex is the major input, and the globus pallidus interna outputs to the thalamus (Figure 11-1).

TREMOR[6]

Types

- Parkinsonian: Pill rolling, resting, 3–6 Hz, extrapyramidal due to disease of basal ganglia and substantia nigra, remits during sleep
- Cerebellar: Intention tremor
- Peduncular: Midbrain
- Benign essential tremor: Familial, may involve the head ("yes-yes, no-no" movement)
- Due to medical condition: Pheochromocytoma, hyperthyroidism, hypoglycemia, anxiety, Wilson's disease
- Adverse drug effect: Lithium, caffeine, methylphenidate
- Postural tremor: Alcohol withdrawal
- Dystonic
- Psychogenic
- Toxic (e.g., mercury poisoning)
- Infectious (e.g., syphilis)

Treatment: Beta-blockers (propranolol), thalamotomy, thalamic stimulation, botulism toxin, Parkinson's medications, benzodiazepines (clonazepam), antiseizure medications (primidone, gabapentin, topiramate), calcium channel blockers (nimodipine)



Stimulatory

Inhibitory

Direct Pathway => increased thalamic output => increased movement

Indirect Pathway => decreased thalamic output => decreased movement

Both

Parkinson's: decreased SNC => increased indirect pathway (D2), decreased direct pathway (D1) => DECREASED movement

Huntington's: decreased caudate output => increased GPE => decreased STN => increased thalamic output => INCREASED movement (inhibition of indirect pathway)

Hemiballismus: STN lesion => decreased GPi => increased thalamic output => INCREASED movement

STN - substantia nigra
GP - globus pallidus
SN - substantia nigra
Glut - glutamate
D - dopamine
ENK- enkaphalin
SP - substance P

Figure 11-1 Diagramatic representation of the connections between the cortex, striatum, and thalamus.

ESSENTIAL TREMOR

Clinical features: Tremor, usually of hands and forearms, worsened by movement, stress, anxiety

- Usual onset before age 30
- Improved with alcohol, propranolol

Pathophysiology: Unknown, may involve increased activity of inferior olives

Etiology: Usually familial

Medical treatment: Propranolol, primidone are first line

- Benzodiazepines

Surgical treatment: Thalamotomy or DBS of thalamus (Vim or dentatorubrothalamic tract) for severe cases; improves 90% of patients.[7]

Table 11-1 Tremor

Tremor	Frequency	Amplitude	Details
Parkinsonian	4–8 Hz	Variable	Worse at rest
Essential	4–8 Hz	Variable	Worse with action, stress
Physiologic	10–12 Hz	Low	Awake and asleep
Intention	2–3 Hz	Variable	Irregular

CHOREA

Rapid, involuntary, purposeless, nonrhythmic movements mostly of extremities or face

- Initially, patient may try to merge the chorea into a purposeful movement to hide the involuntary jerk
- May be accompanied by athetosis (slow, writhing movement)

Differential diagnosis: Huntington's disease, Sydenham's chorea (rheumatic fever from group A beta hemolytic strep infection), strokes or tumors of the basal ganglia or thalamus, contraceptive pills, pregnancy, lupus, thyrotoxicosis, polycythemia, senile chorea, hypercalcemia, cerebral palsy, and phenytoin toxicity

HUNTINGTON'S DISEASE

Clinical Features: Progessive choreiform movements (including oculomotor) associated with dementia, disinhibition and personality changes, abnormal eye movements

Genetics: Autosomal dominant

- Complete penetrance
- Chromosome 4 with CAG repeats (patients with >37 develop the phenotype)

- Anticipation (earlier presentation) with increased number of repeats
- Genetic test available

Pathophysiology: Loss of medium spiny neurons in striatum, particularly the caudate → choreiform movement and dementia secondary to thalamic facilitation of motor cortical areas

- Degeneration of cholinergic and GABA/enkephalin pathways from striatum to caudate nucleus and putamen; increased dopamine, norepinephrine, somatostatin; decreased GABA, acetylcholine

Radiology: Significant caudate atrophy → enlarged, "boxcar" ventricles

- Frontal temporal atrophy

Treatment: Tetrabenazine for symptomatic relief, no surgical treatment available

Prognosis: Fatal over 10–20 years

Westphal variant: Aggressive progression of symptoms, including parkinsonism and seizures

- < 20 years old at presentation

TARDIVE DYSKINESIA

Chronic neuroleptic use (less frequent with atypical antipsychotics)

- Involves the face/tongue, eye blinking
- Treat with stopping offending medication

DYSTONIA

Localized slow contractions of specific muscle groups (local, segmental, or multifocal)

- Common localized dystonias include blepharospasm, torticollis, writer's cramp, and oral-facial dyskinesia
- Primary or secondary
- Differential diagnosis includes drug reactions, encephalitis, Lesch-Nyhan (X-linked), DYT1 (AD), dentatorubropallidoluysial atrophy (AD), Wilson's disease (AR), Hallervorden-Spatz disease (AR), mitochondrial disease, stroke, toxic
- Treatment may include botulinum injections, anticholinergics, benzodiazepines, anticonvulsants, lithium, reserpine, baclofen, levodopa

TORTICOLLIS AKA CERVICAL DYSTONIA[8]

Clinical features: Sustained, involuntary muscular contractions of cervical musculature, often causing abnormal postures of the head

- Progresses from spasmodic to continual
- May be painful
- Generally affects adults (most prevalent in the fifth decade)

Etiology: May be genetic (loci on chromosomes 8 and 18), post-traumatic, or drug-induced (dopamine antagonists)

Pathophysiology: Unknown, may involve abnormal dopamine signaling, copper or manganese levels, neural plasticity

- Structures affected may be putamen, GPi (decreased thalamic inhibition by internal segment of globus pallidus leads to incomplete muscle relaxation), thalamus, midbrain, motor cortex, etc.
- Lesion of subthalamic nucleus may lead to dystonia or hemiballismus

Treatment: Periodic botulinum toxin injections, physical therapy, upper cervical ventral rhizotomies, spinal accessory neurectomy, stereotactic thalamotomy, microvascular decompression of spinal accessory nerve, myotomy

DYT1 DYSTONIA

Dystonia musculorum deformans

Subsets: Early-onset primary dystonia, idiopathic torsion dystonia (ITD), primary torsion dystonia, primary generalized dystonia

Clinical features: Mean age of onset 12

- Starts with dystonia of one extremity that then spreads

Genetics: Chromosome 9q34

- Autosomal dominant, reduced penetrance

HEMIBALLISMUS

Symptoms: Violent, involuntary, flinging movement of extremity

Pathophysiology: Vascular infarct or destruction (e.g., hemorrhage) of the subthalamic nucleus (STN) or connections to globus pallidus

Treatment: Dopamine antagonists, antipsychotics, ventrolateral thalamotomy if refractory or persistent

Prognosis: Usually self-limited and will resolve after 2 months

TICS/STEREOTYPIES[9]

Brief repetitive contractions of muscle groups, suppressible by patient concentration and preceded by a sense of tension. Etiology includes encephalitis, stroke, carbon monoxide poisoning, neuroacanthocytosis, idiopathic.

TOURETTE SYNDROME

Clinical features: Repetitive vocal or motor tics of varying complexity

- Usually preceded by somatosensory "urge"
- Very rarely involves coprolalia

- Worsened by stress
- Occurs in early childhood, peaks in adolescence, and often subsides
- Often comorbid with obsessive-compulsive disorder, attention deficit hyperactivity disorder
- Normal IQ

Pathophysiology: Likely involves defects in interneurons in striatum, impairing sensorimotor gating[10]

- May involve dopamine re-uptake defect to the anterior cingulate pathway

Etiology: Unknown

- Autosomal dominant

Treatment: Stress management

- Clonidine, pimozide, haloperidol, risperidone
- DBS of thalamic nuclei or GPi are reserved for severe, medically refractory cases

MYOCLONUS

Subtypes: Action (triggered by voluntary movement; anoxic etiology), cortical reflex, essential, palatal, progressive myoclonus epilepsy, reticular reflex (generalized seizure with bilateral myoclonic jerks), stimulus-sensitive (e.g., noise, movement, light), sleep

Treatment: Clonazepam, barbiturates, phenytoin, and primidone

PALATAL MYOCLONUS[11,12]

Involuntary contractions of the palate, up to 150/min; persists during sleep; heard as a "clicking" in the ear

Lesion: Central tegmental tract or Mollaret's triangle (inferior olivary nucleus, central tegmental tract (connects red nucleus to the olive), and superior olivary peduncle to the contralateral dentate nucleus); when the inferior olive is denervated (ipsilateral brainstem disease or contralateral cerebellar disease) → enlargement → rhythmic discharges

Pathophysiology: Stroke (40%), tumor (7%), trauma (8%), MS (8%), encephalitis (2%), and degenerative disease (2%)

PROGRESSIVE MYOCLONUS EPILEPSY (PME)

Symptoms: Myoclonus, seizures, walking/speaking difficulties; progressive and may be fatal

Subtypes: Lafora body disease (AR, symptoms include dementia), cerebral storage diseases (symptoms include visual, dementia, dystonia), system degenerations (symptoms include balance difficulty)

RESTLESS LEG SYNDROME

Uncomfortable feeling in the legs that leads to the uncontrollable desire to move the legs

- Associated with periodic limb movement disorder (involuntary extremity jerking during sleep)
- Etiology mainly idiopathic, but seen with uremia, DM
- Treatment: klonopin, neurontin, L-dopa; avoid neuroleptics, caffeine, calcium channel blockers

HYPOKINETIC DISORDERS

PARKINSON'S DISEASE[13–15]

Clinical features: Asymmetric symptoms at onset, bradykinesia, akinesia, "pill rolling" resting tremor (3–5 Hz) which remits during sleep, "cog-wheel" or "lead-pipe" rigidity, masked facies, postural instability, festinating gait, dementia (30%), depression

Epidemiology: 1% of population, peak incidence in 6th decade, M > F

Pathophysiology: Loss of dopaminergic neurons (80% to become symptomatic) in the substantia nigra (pars compacta) → overactivity of indirect basal ganglia circuit and underactivity of direct circuit of basal ganglia → causing decreased motor circuit activity (voluntary movement)

- Bradykinesia may be correlated with increased beta-band (10–30 Hz) activity in the Cd, Pt, and STN
- Resting tremor appears related to cerebellar inputs to thalamic nuclei

Etiology: Primarily idiopathic

- May involve mitochondrial dysfunction (decreased complex I activity), with increased alpha-synuclein and ubiquitin activity
- Toxic exposure may play a role

Medical treatment: Primarily dopamine agonism

- Levodopa (L-dopa) crosses into CNS where it is converted into dopamine; carbidopa (Sinemet) inhibits dopa decarboxylase to prevent systemic conversion into dopamine
- COMT (Catechol-O-Methyl Transferase) inhibitors (entacapone, tolapone) prevent metabolism of L-dopa
- Dopamine agonists (bromocryptine, pergolide)
- Monoamine oxidase B inhibitors (selegiline)
- Amantadine releases dopamine
- Anticholinergics (benzhexol, benztropin, artane)

Surgical treatment: See section on Functional Neurosurgery

- Deep brain stimulation (DBS) of STN and GPi are used for patients with intolerable medication side effects, though some data indicates earlier surgery may be of significant benefit
- Best for tremor (Vim, unilateral only), dyskinesia, bradykinesia (STN)

PARKINSONIAN SYNDROMES

Parkinson's symptoms can be seen as a toxic side effect of the illicit narcotic MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) secondary to destruction of substantia nigra neurons

- Parkinsonian symptoms with manganese poisoning (includes kidney and liver disease)
- Other medications include antipsychotics, dopamine antagonists, dopamine depleting agents (reserpine)

PROGRESSIVE SUPRANUCLEAR PALSY

Epidemiology: Present in sixth decade, M > F

Symptoms: Axial dystonia (neck rigidity), supranuclear ophthalmoplegia (paresis of voluntary downward gaze progressing to loss of all volitional eye movements; doll's eye reflex intact), pseudobulbar palsy, dementia

- No tremor

Pathophysiology: Neuron degeneration in substantia nigra, subthalamic nucleus, globus pallidus, dentate nucleus, colliculi

- Decreased levels of dopamine, norepinephrine, acetylcholine in the brainstem

Radiology: Atrophy of pons and midbrain

Treatment: None

Prognosis: Rapidly progressive

MULTIPLE SYSTEM ATROPHY

Subtypes: Shy-Drager (autonomic-predominant) syndrome, striatonigral degeneration, olivopontocerebellar atrophy

Epidemiology: Present in fourth to sixth decade

Symptoms: Parkinsonian, bilateral and symmetric, no tremor

Pathology: Glial (oligodendroglial) cytoplasmic inclusion bodies, no Lewy bodies

Treatment: None, not responsive to dopaminergic medications

Prognosis: Rapid progression, fatal

SHY-DRAGER SYNDROME (MSA SUBTYPE)

Symptoms: Orthostatic hypotension, urinary incontinence, impotence, parkinsonism

Pathophysiology: Degeneration of cells in zona compacta (substantia nigra) and intermediolateral cell column (putamen), dorsal motor nucleus of the vagus, striatum → decreased levels of norepinephrine in brainstem, putamen

STRIATONIGRAL DEGENERATION

Symptoms: Pyramidal signs, parkinsonism, no tremor

Pathophysiology: Disconnection between the striatum and the substantia nigra, atrophy of the caudate and putamen

Prognosis: Slower progression, some with normal life expectancy

OLIVOPONTOCEREBELLAR DEGENERATION

Symptoms: Cerebellar symptoms, parkinsonism, pyramidal (UMN) signs

Pathophysiology: Atrophy of medulla, inferior olives, pons, cerebellar hemispheres/vermis

CORTICOBASAL DEGENERATION

Epidemiology: Present in seventh decade

Symptoms: Language and visual/spatial impairment, apraxia, myoclonus, pseudobulbar signs, focal arm dystonia, alien limb, cerebellar signs, pyramidal tract signs, parkinsonism

Pathophysiology: Degeneration of nigrostriatal fibers, pontine nuclei, Purkinje cells, Onufrowicz's nucleus, intermediolateral cell column

Radiology: Frontoparietal atrophy of the pre- and postcentral gyri

Treatment: None

Prognosis: Progression over 6–8 years

WILSON'S DISEASE

Epidemiology: Incidence 10–30 million worldwide

- F > M

Clinical: Parkinsonism, bulbar signs, dystonia, ataxia, psychiatric disturbances, tremor, Kayser-Fleischer rings, hepatolenticular degeneration, liver fibrosis, renal tublar acidosis (metabolic acidosis)

Laboratory analysis: Decreased ceruloplasmin, decreased serum copper, increased urine copper

Genetics: AR, chrom 13, defect of copper transporter ATPase (ATP7B) in the liver

Radiology: Hypodensity in basal ganglia

Pathology: Neuronal loss in the caudate and putamen, increased numbers of fibrillary astrocytes, macrophages, Alzheimer's type II astrocytes, Opalski cells

Treatment: Diagnosis via liver biopsy

- Penicillamine (with B_6), limit dietary intake of copper, zinc salt to decrease absorption, liver transplant for fulminant disease

ATAXIA

Differential diagnosis: Vertebral-basilar artery ischemia, sensory ataxia (diabetic neuropathy, tabes dorsalis, thalamic lesions), multiple sclerosis, vitamin deficiency (E, B_{12}), cerebellar lesion (e.g., tumor, may be accompanied by intention tremor), Wernicke's encephalopathy, toxins (e.g., lead), paraneoplastic syndrome, medications (e.g., aminoglycoside antibiotics, sedatives, anticonvulsants), intoxication (e.g., alcohol chronically leads to cerebellar atrophy), Wilson's disease, infection (e.g., disseminated tuberculosis, HIV), hypothyroidism, episodic ataxia (with myokymia), vestibular dysfunction, acute disseminated encephalomyelitis, Friedreich's ataxia, ataxia telangiectasia, spinocerebellar atrophy, dentatorubropallidoluysian atrophy (multiple system atrophy), Machado-Joseph disease, Fragile X tremor/ataxia syndrome

FRIEDREICH'S ATAXIA

Epidemiology: Presents before age 20 with gait ataxia

Symptoms: Ataxic gait, dysarthria, areflexia, lower limb weakness, loss of vibratory sense and proprioception, peripheral neuropathy, foot deformity (pes cavus, hammertoes), scoliosis, cardiomyopathy, blindness, deafness, diabetes

Genetics: AR, GAA trinucleotide repeat, Frataxin gene on chromosome 9q (encodes mitochondrial matrix protein)

Pathophysiology: Spinal ataxia from demyelination of dorsal spinocerebellar tract, lateral corticospinal tracts, dorsal columns, Clarke's nucleus; may also have gliosis in the medulla, subthalamic nucleus and pallidum, degeneration of dorsal root ganglia

Treatment: None

Prognosis: Fatal by 5th decade

ATAXIA-TELANGIECTASIA

Neurocutaneous syndrome

Epidemiology: Most common cause of progressive ataxia in infancy

Symptoms: Ataxia, telangiectasias of skin/sclera, dysarthria, dysphagia, chorea, cranial nerve palsy, delayed motor development, pulmonary fistulas (leads to brain abscess and pulmonary infection), immune deficiency (thymic atrophy) leading to infection and lymphoma/leukemia

Genetics: AR, mutation in ATM (ataxia-telangiectasia mutated) gene on chromosome 11

Pathophysiology: ATM codes for DNA repair, cell cycle control

Treatment: Supportive, avoid radiation

Prognosis: 20% develop cancer (lymphoma or acute lymphoblastic leukemia)

- Most die by teens, early twenties

SPINOCEREBELLAR ATAXIA (TYPES 1–3)

Genetics: AD, CAG repeat in a coding region of the SCA1–3 gene for ataxin-1–3

Symptoms: Generally include ataxia, parkinsonism, dystonia, spasticity, mild cognitive impairment, peripheral neuropathy

Treatment: None

DENTATORUBROPALLIDOLUYSIAN ATROPHY (AKA HAW RIVER SYNDROME OR NAITO-OYANAGI DISEASE)

Epidemiology: Rare, most cases in Japan

Symptoms: Dystonia, ataxia, choreoathetosis

Genetics: AD

- Trinucleotide repeat disorder on chromosome 12p
- Codes atrophin-1

Pathophysiology: Neuronal degeneration in dentate nucleus, subthalamic nucleus, red nucleus, external segment of globus pallidus > striatum, inferior olives, substantia nigra

Treatment: Symptomatic

FRAGILE X TREMOR/ATAXIA SYNDROME

Symptoms: Progressive ataxia, intention tremor, cognitive and behavioral deficits, anxiety

Epidemiology: Onset > 50 years old, M > F

Genetics: FMR1 gene, CGG repeats (50–200 is Fragile X Tremor/Ataxia Syndrome, > 500 is full Fragile X Syndrome), X linked, 20% penetrance

Treatment: Symptomatic

MACHADO-JOSEPH DISEASE

Autosomal dominant cerebellar ataxia

Epidemiology: Azorean Portuguese descent

- Presents in young adults

Symptoms: Progressive ataxia, ophthalmoplegia, distal motor weakness, hyperreflexia, mild parkinsonism, bulbar symptoms

Pathophysiology: Atrophy of dentate nucleus spinocerebellar tracts, oculomotor nucli, anterior horns, pontine nuclei, substantia nigra

Genetics: AD trinucleotide repeat disorder on Chromosome 14

Treatment: None

CHAPTER 12 ■ INFECTIOUS DISEASES OF THE CENTRAL NERVOUS SYSTEM

Viet Nguyen, MD

MENINGITIS AND ENCEPHALITIS

DESCRIPTION[1]

Meningitis: Meningeal inflammation with normal cerebral function (but can be uncomfortable, lethargic, or have headache)

Encephalitis: Parenchymal inflammation with altered mental status, behavior and personality changes, and speech or motor/movement or sensory deficits

ETIOLOGY

■ Viral (More Common)[2]

Can be epidemic (e.g., arbovirus), sporadic (e.g., HSV-1), or in immune-compromised hosts (e.g., HIV, CMV, papovavirus)

Enteroviruses: Most common viral cause (~90%) includes coxsackie, echo, herpes, polio virus, CMV, EBV, VZV, HHV-6 (esp. immunosuppressed/transplant patients)

- *Coxsackie:* Myalgic encephalomyelitis with fatigue and muscle aches
- *Herpesviruses:* HSV-1 (10% of all encephalitis), favors temporal and orbitofrontal lobes, high morbidity, 30 to > 50% mortality (even with acyclovir), 30% are from an initial infection, the remainder are from a reactivation

Mosquito-vector

- *West nile:* fever, flu-like illness, maculopapular or roseolar rash; followed by nausea, abdominal pain, diarrhea; can have coarse tremor and parkinsonism
- *Japanese encephalitis:* Asia, most common encephalitis worldwide
- *St. Louis:* most common mosquito-transmitted human pathogen in the United States, associated with basal ganglia involvement (tremor, myoclonus) and myopathy
- *LaCrosse* (LaCrosse, Wisconsin)*:* Affects rural poor, endemic in Great Lakes states, increased incidence in mid-Atlantic states
- *Western equine* (California, Wyoming, Utah, New Mexico): Affects horses and humans
- *Eastern equine* (Gulf Coast, Midwest): Affects humans, horses, birds, puppies

Tick-borne

- *Colorado tick fever* (Rocky Mountains)
- *Powassan* (Northeast United States, Canada): Permanent neurologic damage in 50%, mortality up to 15%
- *Lyme disease:* Maculopapular rash with central clearing (aka erythema chronicum migrans) in addition to meningitis/encephalitis, leads to axonal neuropathies, cranial nerve palsies

Rodent-borne: Lymphocytic choriomeningitis virus (LCMV): Transmission through exposure to fresh rodent urine, droppings, saliva, or nesting materials

Rare: HIV, adenovirus, mumps, measles (subacute sclerosing panencephalitis), progressive rubella panencephalitis, rabies, nipah

SUBACUTE SCLEROSING PANENCEPHALITIS

Etiology: Reactivation of measles infection

Symptoms/Signs: Slowly progressive

- Alterations in personality, dementia, myoclonus, ataxia

Laboratory: Increased antimeasles antibodies in CSF and serum

Outcome: Slowly progressive and eventually fatal

PROGRESSIVE RUBELLA PANENCEPHALITIS

Etiology: Reactivation of congenital rubella

Symptoms/Signs: Slowly progressive

- Alterations in personality, dementia, myoclonus, ataxia

Laboratory: Increased antirubella antibodies in CSF and serum

Bacterial (More Deadly)[3–5]

Outcome: Mortality 20–35% (two 20+ year case reviews)

- Hypotension, altered mental status, and seizures are the three clinical predictors of adverse outcomes (death or neurologic deficit at discharge): zero clinical predictors (low-risk) 9%, one (intermediate-risk) 33%, two or three (high-risk) 57%
- Morbidity includes mental retardation, hearing loss, cerebral edema/elevated ICP/herniation, vasculitis, systemic infection

Organisms: (Table 12-1)

- *Neisseria meningitidis:* Respiratory droplet transmission; at risk are infants, young children, refugees, household contacts, military recruits, college dormitories, asplenics, terminal complement component deficiencies
- Streptococcus pneumoniae
- Group B streptococcus
- Haemophilus influenzae serotype b (Hib)

By Age Group: Neonatal: GBS, listeria, E. coli

- Child: Neisseria, S. pneumoniae, Hib
- Adult: S. pneumoniae, neisseria, Hib
- Elderly: S. pneumoniae, gram-negatives (E. coli), listeria

DIPHTHERIA[23]

Etiology: Caused by corynebacterium diphtheriae

- Spreads through respiratory droplets or contaminated food
- Prevented by immunization (included in the tetanus booster)

Symptoms/Signs: Throat infection causes dark oral fibers that can lead to airway compromise

- Paralysis of accommodation, facial, oropharyngeal paralysis, preservation of extraocular movement
- Ascending sensorimotor polyneuropathy (20%), may lead to paralysis

Treatment: Diphtheria antitoxin

Prognosis: Death in 10%, recovery slow, cardiac myositis and renal compromise may occur

CLINICAL FEATURES (% SENSITIVITY)[6–8]

Symptoms/Signs

Fever (85%), altered mental status (67%), neck stiffness (70%), headache (50%), neck pain (28%), nausea/vomiting (30%), focal neurologic findings (23%; including Babinski sign, cranial nerve abnormalities), photophobia, history of trauma with ear or nasal fracture or CSF leak, immunosuppression, rash (22%, especially N. meningitidis), infectious arthritis (7%)[9], hemiparesis, seizure, or new tremor

- Classic triad of fever, neck stiffness, and altered mental status has sensitivity of only 46%, at least two (95%), any one finding (99%)
- *Brudzinski "nape of the neck" sign* is present when passive neck flexion in a supine patient causes hip and knee flexion
- *Kernig sign* (< 12%) is present when extension of the knee with hip flexed at 90º causes pain/discomfort in lower back or posterior thigh while the patient is supine or seated
- *Brudzinski contralateral reflex* is present when passive flexion of one hip and knee causes flexion of the contralateral leg
- Jolt accentuation sign (97%, specificity 60%) is present when the patient shakes his or her head horizontally at two to three rotations per second causing worsening of headache

Diagnostic Evaluation

Blood cultures x 2 (50–75% with bacterial meningitis have positive blood cultures), LP, CT head noncontrast

CT or LP first?[10–11]*:* Traditional practice includes a CT head noncontrast scan before LP to exclude increased intracranial pressure, which could lead to cerebral herniation after CSF removal, however, those undergoing CT scan before LP have a 2-hr average delay in diagnosis and 1-hr delay in therapy

- CT scan is not necessary in majority of patients[11]; of 301 cases, 24% had any CT abnormality, only 5% with any mass effect

- Abnormal CT scan associated with a suspicious history (immunocompromise, previous CNS disease, age > 60, or seizure within the past week) AND exam findings (reduced level of consciousness, inability to answer two consecutive questions correctly, inability to follow two consecutive commands, aphasia, dysarthria, gaze palsy, abnormal visual fields, facial palsy, arm or leg drift)
- Absence of these abnormalities yielded negative predictive value of 97% for any CT abnormality, 99% for any mass effect
- Duke 1999 study[6] found three significant predictors of any new intracranial lesion: altered mentation (LR +2.2), focal neurologic signs (LR +4.3), and papilledema (LR +11.1); absence of all three gave an LR of 0 (upper 95% confidence limit, 0.6)

Per 2004 Infectious Diseases Society of America (IDSA) guidelines for the management of bacterial meningitis[15], *CT scan recommended before a LP ONLY in suspected bacterial meningitis patients with*

- Immunocompromised state (e.g., HIV infection, immunosuppressive therapy, after transplantation)
- History of CNS disease (mass lesion, stroke, or focal infection)
- New onset seizure (within 1 week of presentation)
- Papilledema (presence of venous pulsations suggests absence of increased intracranial pressure)
- Abnormal level of consciousness
- Focal neurologic deficit (especially cranial nerves or arm or leg drift)

Lumbar puncture: Ideally prior to 2-h post-first antibiotic dose

- Every patient with suspected meningitis should have CSF obtained unless procedure is contraindicated
- Opening pressure: Elevated in bacterial meningitis (mean elevation to 35 cm H_2O, but wide range)
- Send CSF for stat Gram stain, cell count, culture, protein, glucose
- If auto-inflammatory etiologies (multiple sclerosis or ADEM) suspected, also send for total protein, oligoclonal banding, and albuminocytologic dissociation (IgG-Albumin CSF-to-serum index)
- If neoplasm suspected, also send for CSF cytology (sensitivity 50–90%, specificity 100%)
- CSF cell count (per μL): 0–5 (normal), 5–100 (viral, early bacterial, neurosyphilis), 100–1000 (bacterial or viral), > 1000 (bacterial, mumps, LCM)

Table 12-1 Likely Bacterial Organism Based On Initial Gram Stain

Gram Stain	Likely Organism
Gram-positive diplococci	Streptococcus pneumoniae
Gram-negative diplococci	Neisseria meningitidis
Small pleomorphic gram-negative coccobacilli	Haemophilus influenzae
Gram-positive rods and coccobacilli	Listeria

Table 12-2 Typical CSF Fluid Parameters

Typical Cerebrospinal Fluid Parameters						
	Normal	*Bacteria*	*Viral*	*Fungal*	*TB*	*Abscess*
WBC/ml	0–5	> 1000[1]	< 1000	100–500	100–500	10–1000
%PMN	0–15	> 801	< 50	< 50	< 50	< 50
%lymph	> 50	< 50	> 50	> 80	↑ Monos	varies
Glucose	45–65	< 40	45–65	30–45	30–45	45–60
Ratio[2]	0.6	< 0.4	0.6	< 0.4	< 0.4	0.6
Protein[3]	20–45	> 150	50–100	100–500	100–500	> 50
Pressure[4]	6–20	> 25–30	Variable	> 20	> 20	variable

1 – early meningitis may have lower numbers,
2 – CSF/blood glucose ratio,
3 – mg/dL, 4 - opening pressure in cm H_20
EM Reports 1998; 19:94.

- CSF glucose (mg/dL): 10–45 (bacterial, neurosyphilis, mumps, LCM), < 10 (bacterial, TB, fungal)
- CSF protein (mg/dL): 50–250 (viral, Lyme, neurosyphilis), > 250 (bacterial, TB)

Bloody tap: Correct for peripheral blood contamination: WBCs:RBCs :: 1:500-to-1000 Protein: Additional 1 mg/mL for every 1000 RBCs

Bacterial Meningitis Score[12,13] (JAMA 2007): Children with CSF pleocytosis (WBC ≥ 10 cells/μL) WITHOUT (1) positive CSF gram stain, (2) CSF absolute neutrophil count (ANC) > 1000 cells/μL, (3) CSF protein > 80 mg/dL, (4) peripheral blood ANC > 10,000 cells/μL, AND (5) seizure before or at presentation did NOT have bacterial meningitis (n = 2903, sensitivity 98.3%; NPV 99.9%)

CSF Studies

- CSF culture: Yield of CSF cultures and gram stain diminished by antimicrobial therapy given prior to lumbar puncture (especially meningococcus)
- CSF viral PCRs: More sensitive than viral culture, sensitivity > 86%, specificity > 92%
- CSF lactate: In postoperative neurosurgical patients, WBC counts/differential, gram stain, glucose and protein concentrations are neither sensitive nor specific for bacterial versus nonbacterial meningitis; CSF lactate > 4.0 mmol/L superior to CSF-to-blood glucose ratio for the diagnosis of bacterial meningitis (sensitivity 88%, specificity 98%, PPV 96%, NPV 94%)
- Xpert EV test (by Cepheid): PCR for multiple enteroviruses, 2.5-h turnaround time (PV 96%, NPV 97%)[14]

Treatment[8,15]

Give IV antibiotics empirically; if patient is worsening, delay is associated with adverse clinical outcomes

- In setting of an elevated CSF white blood cell count, no single CSF biochemical variable can reliably exclude bacterial meningitis

Steroids: Dexamethasone (0.15 mg/kg IV every 6 h for 2–4 days) 10–20 min prior to or concurrently with antibiotics (not helpful if given afterward), especially if bacterial meningitis is suspected and Glasgow coma score is between 8 and 11

- Use in: Infants and children with H. influenzae type B meningitis, adults with suspected or proven S. pneumoniae (pneumococcal) meningitis (continue only if the CSF gram stain shows gram-positive diplococci or blood/CSF cultures are positive for S. pneumoniae)
- Should not be given to adult patients who have already received antimicrobial therapy, because it is unlikely to be helpful
- Data are inadequate to recommend dexamethasone for other bacterial pathogens

Empirical Antimicrobial Therapy: To treat likely organism as determined by age and predisposing conditions (Tables 12-3 and 12-4)

Neonates: Treat 2 weeks beyond first sterile CSF culture or > 3 weeks, whichever is longer

Viral: Supportive—rest, hydration, antipyretics, and pain or anti-inflammatory meds

- Use antibiotics if bacterial meningitis not ruled out or septic shock suspected
- *HSV:* IV Acyclovir, significantly beneficial only if given very early in the course of the infection, esp. if seizures
- Ganciclovir, only in severe cases with positive CMV PCR/culture, or congenital or AIDS-related infection suspected

Table 12-3 Recommended Treatment by Age Based on Likely Organism

Age	Likely Organism	Antibiotic Treatment
<1 month	Streptococcus agalactiae (group B)*, E. coli, Listeria monocytogenes, Klebsiella species, Proteus mirabilis**	*Ampicillin + Cefotaxime* OR an aminoglycoside (*gentamicin, tobramycin, amikacin*)
1–23 months	Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae, Haemophilus influenzae, E. coli	*Vancomycin* + 3rd-gen cephalosporin (*Cefotaxime, Ceftriaxone*)
2–50 years	N. meningitidis, S. pneumoniae	*Vancomycin* + 3rd-gen cephalosporin (*Cefotaxime, Ceftriaxone*)
> 50 years	S. pneumoniae, N. meningitidis, Listeria monocytogenes, Aerobic gram-negative bacilli	*Vancomycin + Ampicillin* + 3rd-generation cephalosporin

* Incidence decreased because of prevention treatments (antibiotics and HIB vaccine)

** Also associated with development of intracranial abscess

Table 12-4 Recommended Treatment by Predisposing Condition Based on Likely Organism

Predisposing Condition	Likely Organism	Antibiotic Treatment
Basilar skull fracture	S. pneumoniae, H. influenzae, group A beta-hemolytic streptococci	*Vancomycin* + 3rd-generation cephalosporin
Penetrating trauma/ postneurosurgery/ CSF shunt	Staphylococcus aureus, coagulase-negative staphylococci (esp. staphylococcus epidermidis), aerobic gram-negative bacilli (pseudomonas aeruginosa), propionibacterium acnes	*Vancomycin + Cefepime/ Ceftazidime/ Meropenem*

Meningitis Doses of IV Antibiotics

Medication	Pediatric Dosing	Adult Dosing
Ampicillin	75 mg/kg q6h	2–3g q4h
Cefotaxime	50–75mg/kg q6h	2–3g q6h
Ceftazidime	50mg/kg q8h	2g q8h
Ceftriaxone	50–75mg/kg q12h	2g q12h
Meropenem		2g q8h
Penicillin-G	50,000 U/kg q4h	4 million units q4h
Vancomycin	50–60 mg/kg/day divided q6h	1g q12h (load 25–30 mg/kg actual body weight, then 15–20 mg/kg q8–12 hr)

Duration of Therapy

Organism	Days
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumoniae	10–14
Streptococcus agalactiae	14–21
Aerobic gram-negative bacillia	21
Listeria monocytogenes	> 21

IVIg: Neonates with enteroviral meningitis (for severe cases lacking other therapeutic options)

Nosocomial Meningitis: Rare in patients without neurosurgery; LPs performed on hospitalized nonneurosurgical patients with otherwise unexplained fever and/or altered mental status are usually negative (0 out of 51)[16]

HIV AND CNS INFECTIONS[17]

HIV Encephalopathy: Symmetric, patchy T2 hyperintensity of the frontal centrum semiovale, no mass effect

- Pathology shows microglial nodules with focal demyelination, multinucleated giant cells

Toxoplasmosis: Most common CNS opportunistic infection (20–40%)

- Multifocal, eccentric ring enhancing lesions (target sign) mainly in basal ganglia and corticomedullary junction with surrounding edema
- Frequently involves the basal ganglia

Progressive Multifocal Leukoencephalopathy (PML): Reactivation of JC virus

- Asymmetric, multifocal T1 and T2 white matter hyperintensities (periventricular/peripheral) involving the U fibers
- No mass effect, does not enhance
- Also may involve basal ganglia, brainstem, and cerebellum

Primary CNS Lymphoma: Nodular, irregular, multifocal ependymal enhancement

Cryptococcus: Lacunar infarcts resulting from gelatinous pseudocysts, hydrocephalus

Cytomegalovirus: Generalized periventricular/ependymal hyperintensity on proton density or FLAIR

INTRAUTERINE (TORCH) INFECTIONS

Infectious entities with maternal to fetal transmission

- Classically includes **T**oxoplasma (hydrocephalus, bilateral chorioretinitis, cranial calcifications), **O**ther (Syphilis, Varicella, HIV, Parvovirus B19), **R**ubella (cortical/basal ganglia calcifications), **C**ytomegalovirus (periventricular calcifications, microcephaly), **H**erpes simplex 1 and 2
- Mother frequently asymptomatic

CYTOMEGALOVIRUS

Most common intrauterine infection (0.5–2%)

Symptoms/Signs: Microcephaly, periventricular and basal ganglia calcifications, hydrocephalus, seizures, chorioretinitis, optic atrophy, sensorineural hearing loss

Outcome: mental retardation, death in 30%

PRION DISEASES[18]

DESCRIPTION

Infectious, neurotoxic, nonimmunogenic, self-propagating, variant isoforms of a normally physiologic sialoglycoprotein, called prion protein (PrP), a copper-binding cell surface protein whose exact physiologic purpose is unknown

Creutzfeldt-Jakob Disease (CJD)

Epidemiology: Incidence one per million per year, age range 50–70

Symptoms/Signs: Rapidly progressive dementia (over months) with myoclonus (esp. startle myoclonus, 80% of patients) and focal neurologic deficits: Ataxia (cerebellar), aphasia, visual loss, or hemiparesis (pyramidal and extrapyramidal)

- Often also with disordered sleep, emotional lability, hallucinations, and delusions

Outcome: Progresses to akinetic mutism, 5-month mean survival, 20% at 1 year

Familial-CJD: 10–20% of CJD cases, younger onset, longer course, autosomal dominant, point mutation or insertion in PRNP gene, chromosome 20

Iatrogenic-CJD: Have been reported with grafts (corneal, dura mater), human pituitary growth hormone, and contaminated neurosurgical equipment

Bovine Spongiform Encephalopathy or "Mad Cow" Disease (Variant-CJD)

Epidemiology: Affects younger patients (median onset 29 yr)

- Transmitted by contaminated meat products (no documented cases from US exposures)

Symptoms/Signs: Causes more early psychiatric changes (depression, anxiety, psychosis), painful paresthesias (thalamic), and occipital disturbances (visual hallucinations, cortical blindness)

Outcome: 14-month average survival

Fatal Familial Insomnia

Disordered sleep (preferential anterior and dorsomedial thalamic involvement, insomnia, dreamlike confusional states, enacted dreams), dysautonomia, dementia, ataxia, autosomal dominant (PRNP gene), onset 40s–60s

Gerstmann-Staussler-Scheinker Disease

Spasticity and ataxia (preferential cerebellar involvement), autosomal dominant (PRNP gene), onset ~30s, slower course than CJD, death over 4–10 yrs

Kuru

Associated with ritual cannibalism, endemic amongst the Fore tribe of New Guinea until 1968

DDx: ALS, MS, paraneoplastic encephalitis, Hashimoto encephalopathy, tertiary syphilis, subacute sclerosing panencephalitis, lithium or heavy metal or other toxic encephalopathy, HIV encephalitis, carcinomatous meningitis, intravascular lymphomatosis

DIAGNOSTIC EVALUATION

Radiology: MRI can show hyperintense cortical ribbon, caudate, and putamen on diffusion-weighted imaging (earlier) and T2/FLAIR (later)

EEG: Nonspecific in early states, but eventually show 1-Hz bi/triphasic periodic synchronus complexes over a slow background (sens 67%, spec

86%, seen less often in familial or iatrogenic forms, or in terminal disease stage)

CSF: Normal but may have mildly elevated protein and positive assays for tau and 14–3-3 protein (sensitivity by immunoblot 56%, ELISA 43%), a nonspecific marker for neuronal or astrocytic breakdown[19]

Pathology (Biopsy or Autopsy): Spongiform changes (diffuse vacuolation), neuronal loss, gliosis

- Subtyping can be done by Western immunoblot performed at the National Prion Disease Pathology Surveillance Center (Case Western Reserve University, Cleveland, Ohio)

Treatment: Supportive only, including hospice

- Report all cases to public health authorities
- Autopsy important for confirmation and public health surveillance
- Genetic counseling recommended in familial cases

TUBERCULOUS MENINGITIS[20]

Description: Caseating tubercles form indolently in the brain from hematogenous spread or local (ear or skull) spread

- Meningitis occurs after tuberculoma rupture
- Meningeal or subependymal fibrosis can lead to hydrocephalus

Symptoms/Signs: Malaise (headache, weight loss, low-grade fever) precedes meningeal signs

- Cranial nerve palsies, especially abducens (1/3 patients)
- *SIADH:* Hyponatremia, seizures
- Increased ICP: Hydrocephalus (50%), nausea/vomiting (25–43%), papilledema (10–15%), lethargy, coma
- Large-vessel arteritis: Focal strokes (25–40%)

Radiology: CT/MRI: Hydrocephalus (80% of children, 23% of adults)

- MRI with contrast: Basilar cistern meningeal enhancement (but can be normal)
- CXR: 40–50% have either old TB, hilar lymphadenopathy, or infiltrates

CSF: WBC 50–1000 cells/μL, lymphocyte predominant, glucose < 10–30, protein > 150–250, high lactate = worse prognosis

Treatment:

- Peds: Isoniazid (INH) 10–20 mg daily + Rifampin 10–20 mg/kg daily + Pyrazinamide 15–30 mg/kg daily + Streptomycin 20–40 mg/kg daily
- Adults: Isoniazid 300 mg daily + Rifampin 600 mg daily + Pyrazinamide 2 g daily
- For multidrug-resistant TB or HIV+ patients: Add Ethambutol 15–25 mg/kg daily x 6 months

- *Duration:* 1–2 months, followed by INH + Rifampin only for 4–7 more months
- Dexamethasone 0.15 mg/kg q6h can reduce inflammation, especially in patients with increased ICP

FUNGALS[20]

Infrequent but severe

- Cryptococcus most common nationally, followed by candida, coccidioides, and histoplasma
- Candida and aspergillus tend to be more parenchymally invasive and abscess forming
- Mucor highly necrotic and seen in diabetics, neutropenics, or smokers of contaminated marijuana

CRYPTOCOCCAL MENINGOENCEPHALITIS[20,21]

Cryptococcus neoformans (fungus) found in bird excrement

- Infection usually begins in the lungs
- Can invade the subarachnoid space and brain parenchyma causing meningoencephalitis
- Cryptococcal meningoencephalitis is the AIDS-defining illness for 60% of HIV-infected patients in whom it is diagnosed

Symptoms/Signs: AMS in 24%, focal neurologic deficits in 6%

- Visual and hearing loss also reported
- Subacute/indolent symptoms (1–4 wks): fever (50+%), malaise, and headache (75%)
- Stiff neck, photophobia, and vomiting seen in only 1/4 to 1/3 of patients
- Disseminated disease in 3–10% causes cough, dyspnea, tachypnea, and skin rash (looks like molluscum contagiosum)

Radiology: CT head normal in 50%

- Most common abnormal finding is hydrocephalus
- MRI remains the imaging modality of choice

CSF: Demonstration of yeasts with India ink stain (sensitivity 75% if CSF sample is centrifuged, low-cost, the halo = glucuronoxylomannan capsule); or positive cryptococcal antigen testing (sensitivity > 90%, uses either latex agglutination or ELISA, titers to assess treatment response are not reliable), or positive culture (sensitivity approaching 90%, more likely with larger volumes of CSF) grown on corn meal agar, birdseed agar, or using sugar assimilation test kits

Treatment induction: IV Amphotericin B (0.7–1 mg/kg/day) + IV/PO Flucytosine (IV 100 mg/kg/day or PO 25 mg/kg q6h), both for at least 2 weeks

- Consolidation: IV/PO Fluconazole 400 mg/day, for 8–10 weeks
- *Maintenance:* Fluconazole 200 mg/day lifelong, although it is probably safe to stop after immune reconstitution with HAART (CD4 > 100)
- Intermittent Amphotericin is less effective

COCCIDIOIDES IMMITIS[22]

Description: Airborne soil fungus endemic to the desert areas of California, Arizona, New Mexico, and Texas

- Inhaled arthroconidia transform into spherules containing endospores in the lung alveoli
- Dissemination (< 1%) to CNS causes meningitis
- Predisposition to dissemination includes: African American, Hispanic, or Filipino race; extremes of age; AIDS; immunosuppressive therapy; organ transplantation; hemodialysis; pregnancy—infection acquired during the third trimester

Symptoms/Signs: Headache, low-grade fever, weight loss, lethargy, confusion; sometimes skin lesions, containing coccidioides spherules

CSF: Elevated WBCs, lymphocyte predominance, but can have eosinophils; complement fixation antibody test (sensitivity 75%, specificity 100% in active disease); positive cultures (1/3 of patients)

Treatment: Induction: Fluconazole 1000 mg daily

- Refractory: IV + IT Amphotericin B; maintanance: Fluconazole 200–400 mg daily, indefinitely
- Alternate: Voriconazole PO

Follow-up: CSF cell count unreliable marker for disease course

- CSF glucose and protein can remain abnormal for years
- CSF complement fixation antibody titer used to follow for relapse

NEUROCYSTERCERCOSIS[23,24]

Larval infection of *Taenia solium* (pig tapeworm)

- When the worm is ingested (contaminated pork), the patient becomes a carrier, excreting eggs of the worm
- When the egg is consumed (e.g., on vegetables, fecal-oral transmission), the worm travels to multiple organs, including the brain
- Most common parasitic infection of the brain

Presentation: Seizures, headache

- One of the leading causes of seizures and epilepsy in the developing world

Location: Corticomedullary junction, subarachnoid basal cisterns, ventricles

Radiology: Vesicular Stage: CSF-filled cysts with mural nodule (scolex) *Degenerative Stage:* Cysts calcify; can have strong inflammatory response

Treatment[21,23]*:* Seizure medications

- Surgery if cysts result in hydrocephalus or result in medically refractory seizures
- Medications: Antihelminthics albendazole (adults: 400 mg PO bid for 30 days; pediatric: 15 mg/kg/day PO divided bid for 7–30 days, not to

exceed 800 mg/day), praziquantel (50 mg/kg/d divided q6–8 hours for 15 days) with dexamethasone (adults: 4 mgIV q6h for 3–4 d (0.1 mg/kg/day); pediatric: 1–1.5 mg/kg/d divided q4–6h for 3–4 days, not to exceed 16 mg/d) to prevent inflammatory response to destruction of the cyst

BRAIN ABSCESS[25]

Local cerebritis with necrosis and surrounding edema encapsulated by fibroblasts and inflammatory cells

Etiology: Hematogenous spread (25%), local spread (50%), meningitis

Risk factors: Penetrating head trauma, open skull fracture, diabetes, alcohol abuse, immunosuppression, poor dentition, congenital heart disease, valvular infection, or implanted foreign body (ventricular drain, deep brain stimulator)

Symptoms/Signs: Headache (75%), fever (50%), altered mental status (50%)

DDx: Neoplasm (primary or metastatic), subacute stroke, radiation necrosis, resolving hematoma, HSV encephalitis, ADEM

Radiology: MRI (most sensitive) is bright on DWI, dark necrosis surrounded by bright edema on T2, ring-enhancing mass on T1 with gadolinium contrast

- CT shows hypodense necrotic core, but contrast ring-enhancement only after 2 wks (capsular formation)

Laboratory: Elevated peripheral WBC count, elevated ESR; blood cultures are less sensitive but still should be done

- AVOID lumbar puncture: Risk of herniation is higher than with other mass lesions; CSF cultures rarely elicit the organism
- Most common isolate is *strep milleri*, many are polymicrobial

Complications: Mass effect, increased ICP, hydrocephalus, meningitis, papilledema, seizures, SIADH, diabetes insipidus, temperature dysregulation, local mass effect, and rarely, vasculitis and stroke

Outcomes: Mortality in adults 10–15%, children 25%

- Poor prognostic factors include stupor/coma (60–100% mortality), and rupture into a ventricle (80–100% mortality)

Treatment[23]*:* IV antibiotics x 4–8 wks (as guided by follow-up imaging) and biopsy (to disrupt capsule and guide antibiotic therapy)

- Surgical removal only if loculated, enlarging despite proper antibiotic therapy, or impending herniation
- Steroids only if needed for reducing edema or ICP (Dexamethasone IV 10 mg load, followed by 4 mg q6h)

Table 12-5 IV Antibiotic Choice Is Based on Suspected Source

Suspected Source	Likely Organism	Treatment
empiric (unknown)		*Ceftazidime* (3rd-gen, 2g q8h) + *Metronidazole* (500 mg q6h)
middle ear mastoid	strep, pseudomonas, bacteriodes, enterobacter	*Metronidazole* (15 mg/kg load, followed by 7.5 mg/kg q6–8h) + *Cefepime* (4th-gen, 2g q6h) OR *Meropenem* (2g q8h)
nasopharynx sinuses teeth	strep, bacteriodes, proteus, staph aureus, hemophilus, anaerobes, Mucor	*Metronidazole* (15 mg/kg load, followed by 7.5 mg/kg q6–8h) + *Penicillin-G* (4 million units q4h) OR *Ceftriaxone* (3rd-gen, 2 g q12h) OR *Cefotaxime* (3rd-gen, 2 g q4–6h)
penetrating head trauma	staph aureus, strep, enterobacter, clostridium	*Nafcillin* OR *Oxacillin* (2g q4h) OR *Vancomycin* (15 mg/kg q12h) PLUS *Ceftriaxone* (3rd-gen, 2 g q12h) OR *Cefotaxime* (3rd-gen, 2 g q4–6h)
postoperative neurosurgical		*Vancomycin* (15 mg/kg q12h) PLUS *Cefepime* (3rd-gen, 2 g q8h)
AIDS	Toxoplama*, fungi	*Pyrimethamine* (PO 200 mg load, followed by 75–100 mg/day) + *Sulfadiazine* (PO 1–1.5 g 4x/day, given with pyrimethamine and folinic acid) OR *Clindamycin* (PO 450 mg 4x/day or 600 mg PO/IV q6h) MRSA: *Linezolid* 600 mg q12h

*Tunkel[15]

SUBDURAL EMPYEMA[20]

Rapid spread of pus over the brain surface

Etiology: Local infectious spread

Risk factors: Frontal/ethmoid sinusitis, skull fracture, venous sinus thrombosis, penetrating head trauma, craniotomy

Symptoms/Signs: Headache, localized pain, fever, partial (and secondary generalized) seizures, AMS

DDx: Subdural hematoma, meningioma, granuloma (TB/sarcoid)

Radiology: CT with contrast shows hypodense crescent-shaped collection molding the cortex with enhancing margins

- MRI shows T1-hyperintense and T2-isointense-to-CSF collection which can cross fossae boundaries (unlike epidural abscess)
- Infection/enhancement tracks along the interhemispheric fissure/convexities

CSF: Lumbar puncture not recommended, but if done, shows mild lymphocytic pleocytosis, increased protein, normal glucose

Treatment: Surgical drainage (send gram stain and culture for organisms), debridement of extracranial source, antibiotics x 4–6wks (choice based on organism and course determined by clinical and radiographic response)

Outcome: Prognosis excellent when recognized and treatment rendered early

SPINE INFECTION

OSTEOMYELITIS[26]

Etiology: (Table 12-6) Infection of bone, usually by pyogenic bacteria and mycobacteria

- Pus buildup raises intraosseous pressure, impairing blood flow
- Chronic ischemia and necrosis form a sequestrum; periosteum deposits new bone around it
- Often not diagnosed until chronic: History and exam confounded by the original trauma, overlying soft tissue infection, or baseline degenerative bone disease
- Hematogenous spread, local soft tissue spread, or directly from trauma or surgery

Risk factors: Trauma, IV drug use, ischemia, foreign bodies, concurrent infection in another site with or without bacteremia

Location: Vertebral bodies (highly vascular) affected in adults

- Affects lumbar (50%) > thoracic (35%) > cervical (15%) spine, except in tuberculous spondylitis (Pott's disease), where the thoracic spine is most commonly affected

Table 12-6 Osteomyelitis

Clinical Scenario	Likely Organism
Children	Staphylococcus aureus (50% of cases); group A streptococci
Neonates	Staphylococcus aureus (50% of cases); group B streptococci and escherichia coli (neonates)
Adults	Staphylococcus aureus, e. coli and other enterics (25% of cases), tuberculosis, brucellosis
IV drug use	Staph aureus, pseudomonas aeruginosa, serratia, candida albicans (also check sacroiliac, sternoclavicular, or pubic joints)
Immunocompromised	Atypical mycobacteria, bartonella henselae, opportunistic fungi
Sickle cell anemia and other hemoglobinopathies	S. aureus, salmonella
Endemics (rare)	Histoplasmosis, coccidioidomycosis, blastomycosis

- Long bones affected in children, where the metaphysis of growing bones is well-perfused

Symptoms/Signs: Acute or subacute illness with fever, chills, dull localized pain and tenderness, decreased painful range of movement (spasm of the paraspinal muscles) or painful weight-bearing

- Local erythema and soft tissue swelling
- Nerve root irritation can cause atypical pain in the chest, abdomen, or extremity

Complications: Epidural abscess

- Failure to recognize epidural abscess before neurologic deficits develop can cause irreversible paralysis

Radiology: MRI is the best diagnostic procedure; should be performed in all cases of vertebral osteomyelitis accompanied by subjective weakness or objective spinal cord abnormalities to rule out epidural abscess

- Plain radiographs $\rightarrow$ soft-tissue swelling (early), periosteal reaction (> 10-day lag from onset of infection), lytic changes (after 2–6 weeks)
- *CT or MRI:* Epidural, paraspinal, retropharyngeal, mediastinal, retroperitoneal, or psoas abscesses that originate in the spine
- *99Tc-monodiphosphonate bone scan:* High sensitivity but low specificity, especially with underlying bone abnormalities
- *MRI:* High sensitivity and specificity; fat-suppressed T1-weighted postgadolinium images show affected vertebral bodies (although gadolinium may not be necessary if one uses STIR), as well as any involved disks and inflammatory soft tissue; can alert to compression of the thecal sac; need to distinguish from healing fractures and tumors

Laboratory: Increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level

- Can also have normal or modestly elevated white blood cell count, anemia
- Blood cultures indicated in acute cases, less sensitive in chronic disease (20–50%)

Treatment[24]*:* Antibiotics (see Tables 12-7–12-9)

- Fluoroscopy, ultrasound, or CT-guided needle aspiration of pus or bone biopsy for culture and sensitivities to guide antibiotic therapy (if culture not simply done at debridement)
- Surgery in cases of spinal instability, new or progressive neurologic deficits, or large soft-tissue abscesses that cannot be drained otherwise; debridement to remove necrotic bone and abnormal soft tissues; epidural abscesses should be surgically drained
- Optimize nutritional and metabolic status to promote healing
- Anecdotal-level data for: Prolonged oral antibiotic therapy (esp. with foreign body), hyperbaric oxygen, antibiotic-impregnated methacrylate beads in chronic osteomyelitis
- Duration of Therapy
  - Children, 4–6 weeks (< 3 weeks = 10 x greater failure rate)
  - Adults, 6–8 weeks; consider longer if ESR does not decrease by 2/3s or CRP does not normalize

Table 12-7 Antibiotic Selection for the Treatment of Osteomyelitis

Gram Stain	Organism	Antibiotic
Gram-positive	MSSA	*Nafcillin* or *Cefazolin* or *Ceftriaxone* or *Clindamycin*
Gram-positive	MRSA	*Vancomycin + Rifampin;* or *Clindamycin* or *Linezolid* or *Daptomycin*
Gram-positive	Streptococci	*Penicillin* or *Cefazolin* or *Ceftriaxone* or *Clindamycin*
Gram-negative	Escherichia coli	*Ampicillin* or *Cefazolin* or *Ceftriaxone Ciprofloxacin IV/PO*
Gram-negative	Pseudomonas aeruginosa	*(Piperacillin/Tazobactam;* or *Ceftazidime) + Tobramycin*
Gram-negative	Enterobacter	*Piperacillin/Tazobactam* or *Ceftazidime* or *Ciprofloxacin*
	Anaerobes/mixed	*Ampicillin/Sulbactam* or *Piperacillin/Tazobactam* or a carbapenem; or *Ciprofloxacin + Clindamycin* or *Metronidazole*

Osteomyelitis Antibiotic Doses:

Antibiotic	Dose
Ampicillin	2 g IV q4h
Ampicillin/Sulbactam	1.5–3g IV q6h
Cefazolin	1g IV q8h
Ceftazidime	2g IV q12h
Ceftriaxone	1g IV q24h
Ciprofloxacin	400 mg IV, or 750 mg PO q12h
Clindamycin	900 mg IV q8h
Daptomycin	4–6mg/kg IV q24h
Linezolid	600 mg IV/PO q12h
Metronidazole	500 mg PO tid
Nafcillin	2g IV q4h
Penicillin	3–4 million U IV q4h
Piperacillin/Tazobactam	3.375 g IV q6h
Rifampin	300 mg PO q12h
Tobramycin	5–7 mg/kg q24h
Vancomycin	15 mg/kg IV q12h

DISCITIS[17]

Infection of nucleus pulposus extending to adjacent end plates and vertebral bodies

Risk factors: Immunocompromised, IV drugs, diabetes, postoperative, hemodialysis

Symptoms/Signs: Back pain, fevers, chills, radiculopathy

- Postoperative discitis occurs in < 1%, presenting within 4 weeks

Radiology: Increased T2 signal with contrast enhancement

Laboratory: Elevated ESR, CRP (should be normal within 2–6 weeks after surgery)

- Common organisms are staph aureus or epidermidis

Treatment: CT guided-needle aspiration for cultures, abx for 8 weeks

- Surgery indicated only for epidural abscesses and neurologic deficits

SPINAL EPIDURAL ABSCESS[17]

Etiology: Hematogenous spread

Symptoms: Spine tenderness, fever, pain

Risk factors: Immunocompromised, IV drugs, diabetes, postoperative, hemodialysis, alcoholism

Radiology: On MRI, hyperintense on T2 with contrast enhancement

Laboratory: Cultures frequently show staph aureus

Treatment: Surgery for decompression, debridement and for diagnostic cultures

- IV antibiotics for 6–8 weeks

POLIO

Infection of lower motor neurons in brain stem and spinal cord

Symptoms: Fatigue

- Progressive weakness, pain, and fatigue in the involved muscle and joint
- May progress to diaphragm involvement and respiratory compromise

Pathology: Patchy, asymmetrical involvement of motor neurons

- Permanent damage
- Denervated and reinnervated muscle fibers on biopsy

Postpolio Syndrome

Progressive neuromuscular symptoms after original onset of disease

- New weakness in the same muscles affected by the original disease

EMG: Decreased number and hypertrophied motor units, fibrillation potentials

Treatment: Supportive

- Prevent with vaccine

CHAPTER 13 ■ PEDIATRIC NEUROLOGY[1,2]

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NEUROLOGICAL EXAMINATION OF INFANTS AND TODDLERS[3]

NEWBORN

General: Spontaneous, smooth movements, attentive, responsive to light

Cranial nerves: Crying (VII, IX, X), suck and swallow (V, VII, IX, X, XII), eye movement (II, III, IV, VI), light response (II, III), sound response (VIII)

Tone: Resting flexed posture, arm traction (grasp wrist/ankle and pull until shoulder/hip is off the mat → continued flexion at the elbow/knee), arm/leg recoil (arms/legs extended then quickly released → should return to flexion), hand position as a fist, head lag

Positions: Prone (should be able to turn head side to side), ventral suspension (head should be the same level as back), vertical suspension (holding hands under arms, baby should not slip through)

Reflexes: Hyperreflexia can be normal, ankle and patellar are easiest to elicit, plantar (toes upgoing), suck, root, Moro, stepping, grasp

3 MONTHS

General: Attentive, tracks, social smile, frowns

Cranial nerves: vestibulo-ocular reflex, full facial expression

Motor: Decreased flexor tone, more open hand, will hold object but cannot reach, regards hand, slight head lag

Positions: Supine (spontaneous movement), prone (can bring head up 45–90°, weight borne on forearms), vertical suspension (can support some weight with legs)

Reflexes: Crossed adductor can be normal (should not persist beyond 7 months), root (disappears at 4 months), moro (disappears at 4–5 months), grasp (disappears at 4–6 months for hands, 12 months for toes)

6 MONTHS

General: Social awareness, laughs, smiles, jabbers, repetitive and nonspecific sounds

Cranial nerves: Visually tracks, hearing, facial movement

Motor: Sits, reaches for objects, brings to midline and into mouth, works well with both hands, raking grasp, actively pulls to sitting position, rolls over front to back

Position: Prone (brings chest off the mat), vertical suspension (baby fully supports weight)

Reflexes: Landau (postural reflex; head in flexion → legs in flexion, head released, legs and head return to extension), propping, parachute (arms extend to catch self)

12 MONTHS

General: Stranger anxiety, imitates, waves bye-bye, follows simple instructions, feeds self, speaks one or two words

Cranial nerves: Ocular range of motion, visual fields

Reflexes: Parachute

Motor: Pincer grasp, follows commands, transitions in and out of sitting, creeping, crawling, cruising, walk (11–14 months)

18 MONTHS

General: Expresses wants, vocabulary of 10+ words, follows commands, understands function of objects, points

Cranial nerves: Conjugate eye movement, near reflex, facial movement

Motor: Objects in cup, stacks blocks, pincer grasp, draws, overhand throw of ball, walks

2.5 YEARS

General: Socially interactive, plays, follows commands, names objects, responds to questions, four-word sentences with pronouns and plurals, names body parts, stacks blocks, draws

Motor: Throws and kicks ball, walks, runs

NORMAL INFANT REFLEXES[4]

Table 13-1 Normal Neonatal/Infant Reflexes Appearance/Disppearance

Reflex (description)	Appears	Disappears
Moro - lift head 30° and let fall to neutral. A positive test = arm extension and abduction, then arm adduction	Birth	1-3 months
Palmar grasp - object in hand causes flexion/ grasping	Birth	4 months
Root response - stroking cheek causes mouth to turn in direction of stimulus	Birth	3-4 months

Tonic neck - turn head to side while child is supine, with ipsilateral arm & leg extending and opposite arm/leg flexing. Normal infant tries to break reflex position.	Birth	5-6 months
+ *Babinski* - stroking lateral border of sole, to big toe. A positive reflex causes big toe dorsiflexion, and fanning of other toes	Birth	1-2 years

NEUROEMBRYOLOGY[5–7]

Early embryo development:
morula ⇒ blastocyst ⇒ embryoblast (⇒ epiblast ⇒ yolk sac, embryo), trophoblast (cytotrophoblast, syncytiotrophoblast ⇒ placenta)

NEURAL TUBE DEVELOPMENT BY POSTOVULATORY DAY

Table 13-2 Embryologic Milestones

Gestational Age (days)	Embryologic Event
4	12–16 blastomeres, morula forming
7–14	Embryonic implantation; formation of three germ layers; bilaminar disc → epiblast (primitive ectoderm) and hypoblast (primitive endoderm)
13	Formation of primitive streak
17	Formation of notochord
19	Somites appear
21	Gastrulation begins (primitive streak), mesoderm appears
22	Fusion of folds to form neural tube; neural crest development
24	Closure of cranial neuropore (lamina terminalis)
26	Closure of caudal neuropore
28	Division of cephalic neural tube into prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain)
30	Start of secondary neurulation
4th week	Dilations and folding of rostral neural tube; formation of prosencephalon, mesencephalon, and rhombencephalon
5th week	Prosencephalon → telencephalon and diencephalon → cerebrum and basal ganglia Mesencephalon → (does not divide) → midbrain Rhombencephalon → metencephalon and myelencephalon → pons and medulla

Table 13-3 Neuroembryology Stage and Clinical Correlate

Postovulatory Week	Stage	Neurodevelopment	Clinical Correlate
0–8	**Embryonic**		
1	Implantation	Blastocyst	Miscarriage
2	Germ layer separation	Formation of neural plate	Enterogenous cyst fistula, split notochord syndrome
3–4	Dorsal induction (aka primary neurulation)	Folding of the neural plate leading to the neural groove and tube/crest, closure of neuropores, paired alar plates, neural tube forms and closes, three primary neuromeres of brain form**	Spinal + cranial dysraphism*, chiari II malformation
4	Secondary neurulation	Formation of the caudal neural tube from the caudal eminence	Sacral agenesis, caudal regression syndromes
4–6	Ventral induction (aka telencephalization)	Formation of the cerebral hemispheres, eyes, olfactory bulb/tract, pituitary gland, part of face	Holoprosencephaly, Dandy-Walker malformation, craniosynostosis
9–24	**Fetal**	**Formation of cortical plate**	
6–16	Neurogenesis	Neuronal/glial proliferation and apoptosis	Micro- and megalencephaly
12–24	Migration	Cortical neuron migration and formation of corpus callosum	Agenesis of corpus callosum, failure of frontal lobe development, neuronal migration disorders***
24–40	**Perinatal**	**Neuronal maturation**	
24–birth	Organization	Migration, organization, maturation, synaptogenesis	Cortical dysplasias
Birth–2 years	Myelination	Myelination	Disorders of myelination

* includes anencephaly, encephalocele, myelomeningocele, myeloschisis
** includes prosencephalon, mesencephalon, rhombencephalon
*** includes lissencephaly, polymcrogyria, schizencephaly, heterotopia

Table 13-4 Major Neuroembryologic and Mature Structures

Embryologic Structure	Adult Derivative
Neural tube/plate (from ectoderm)	Cortical neurons, spinal cord, brain, all preganglionic autonomic fibers, all fibers innervating skeletal muscles
Neural crest (lateral folds of the neural plate)	Adrenal medulla, dorsal root ganglia of cranial and spinal nerves, pigmented layers of retina, sympathetic ganglia of autonomic nervous system, peripheral nervous system, viscero- and neurocranium, pia, arachnoid, endocrine cells
Mesoderm	Dura, connective tissue investments of peripheral nerve fibers (endoneurium, perineurium, epineurium)
Diencephalon	Globus pallidus, 3rd ventricle, optic chiasm, optic nerves, infundibulum, mamillary eminences
Telencephalon	Amygdala, caudate, claustrum, putamen, cerebral hemispheres, olfactory bulbs, lateral ventricles
Rhombencephalon (primary vesicle) → metencephalon, myelencephalon (secondary vesicle)	Hindbrain, cerebellum, pons, medulla, 4th ventricle
Prosencephalon	Forebrain, optic vesicles, telencephalic (lateral) and diencephalic (3rd) ventricles
Mesencephalon	Midbrain, cerebral aqueduct
Caudal cell mass of neural tube	Sacral spinal cord, vertebra caudal to S2
Alar plate* (of neural tube)	Sensory neruons (GSA, GVA) in brainstem and spinal cord, dorsal horn
Basal plate (of neural tube)	Motor neurons (GSE, GVE), ventral horn
Somites	Vertebral column, dorsal spine musculature
Notochord	Intervertebral discs
Floor plate	Ventral white commissure
Otic placode	Organ of corti/spiral ganglion, cristae ampullares, maculae utriculi/sacculi, vestibular ganglion, vestibulocochlear nerve

* Sulcus limitans divides the alar and basal plate

DEVELOPMENTAL DELAY[1,2]

DDx of developmental delay: Down syndrome, autistic spectrum disorder, Fragile X syndrome, Prader-Willi/Angelman syndrome, Rett syndrome, inborn error of metabolism, Landau-Kleffner, neuronal migration disorders, social/environmental factors (abuse/neglect, malnutrition)

- Frequently multifactorial

Diagnostic evaluation: Careful pre-/perinatal, developmental, and social history

- Review of newborn screening results
- Hearing/vision screen
- Imaging: MRI brain in select cases
- Labs: lead level, T4/TSH, high-resolution chromosomes, serum amino acids, urine organic acids

CEREBRAL PALSY

Nonprogressive, static neuro deficits characterized by motor and postural dysfunction due to abnormalities of developing brain

- Uncoordinated, limited, and stereotypic complex coordinated motor movements despite maximal effort
- Diagnosis of exclusion (rule out metabolic disorder, inborn errors of metabolism, neurodegenerative diseases, traumatic brain or spinal cord lesions, neuromuscular disorders, neoplasm)

Subtypes: Spastic, dyskinetic (athetosis, choreoform, dystonic), ataxic, akinetic

Etiology: Idiopathic, hypoxia, ischemia, congenital brain anomalies, hydrocephalus

Symptoms/Signs: Nonprogressive

- Diplegia, hemiplegia, quadriplegia, hypertonia (velocity and action dependent, clasp knife reaction), hyperreflexia, extensor plantar response, clonus, slow voluntary movement despite great effort, impaired fine motor function, difficulty in isolating individual movements, fatigability
- Associated with mental retardation, epilepsy, behavioral disturbances, speech impairment, urinary disorders, orthopedic disorders (subluxation, dysplasia), sensory deficits (visual, auditory, etc.)

Treatment: Botox injections, dantrolenes, benzos, baclofen (oral or intrathecal via implantable pump), selective dorsal rhizotomy, stereotactic encephalotomy

PRADER-WILLI SYNDROME

Symptoms/Signs: Poor muscle tone, increased hunger leading to obesity, low sex hormones, mild mental retardation, short stature, behavior modifications

Genetics: Absence of segment 11–13 on the long arm of the *paternally* derived chromosome 15

Treatment: Calorie controlled diet, exercise, hormone replacement

ANGELMAN SYNDROME

Symptoms/Signs: Severe speech difficulty, developmental delay, seizures, microcephaly, ataxia, happy demeanor, frequent smiling/laughter

Genetics: Absence of segment 11–13 on the long arm of the *maternally* derived chromosome 15 (OCA2, UBE3A)

LANDAU-KLEFFNER

Rare syndrome of acquired aphasia associated with epileptiform activity

Symptoms/Signs: Normal development and language prior to onset, followed by decline in ability to understand/utilize spoken language at 3–7 years of age, seizures, aggression, depression, normal intelligence

Diagnosis: EEG shows multifocal epileptiform discharges, classically in temporal and parietal region

Treatment: Anticonvulsants and corticosteroids

DOWN SYNDROME

Epidemiology: Most common genetic cause of mental retardation

- Increasing incidence with increased maternal age

Pathogenesis: Trisomy 21

Symptoms/Signs: Epicanthal folds, protruding tongue, transverse palmar crease, sandal sign, hypotonia

Associated complications: Congenital heart disease (~40%), atlanto-axial instability (~15%), GI anomalies (~5%), leukemia (1–2%), immune deficiency, sleep apnea, Alzheimers

AUTISTIC SPECTRUM DISORDER[8]

Includes Asperger, autism, pervasive developmental delay - not otherwise specified (PDD-NOS).

Incidence: 1 in 150 to 500

Diagnosis: Based on impairment of three domains: communication, socialization, and behavior

Etiology and pathogenesis: Unknown, though strong consensus for genetic origin

- Epidemiological evidence does not support association with vaccines

RETT SYNDROME

Epidemiology: Girls only

- X-linked
- Normal until age 2, then rapid regression

Pathogenesis: Most associated with mutations in gene for MECP2 (methyl–Cp G binding protein 2) on the X chromosome

Symptoms: Hyperventilation, deceleration of head growth, stereotypic hand movements (wringing, tapping), seizures

Treatment: None

FRAGILE X

Epidemiology: Most common cause of inherited mental retardation, 1:5000

Genetics: Generational elongation of trinucleotide repeat in the Fragile X mental retardation 1 (FMR1) gene

Symptoms/Signs: Mental retardation, elongated facies, large ears, prominent jaw/forehead, enlarged genitalia in males

Diagnosis: Molecular genetic testing

INBORN ERRORS OF METABOLISM

Pathogenesis: Autosomal recessive

- Typically result from a single enzyme deficiency resulting in either breakdown of important biochemical pathways or build-up of toxic metabolites
- Traditional classification is related to the type of metabolism involved
- Major categories include amino acids, organic acids, carbohydrates, fatty acid oxidation, heavy metals, heme, the urea cycle, mitochondrial, peroxisomal, lysosomal, purine and pyrimidine

Diagnosis: Many U.S. states include some of the common and treatable forms in their neonatal screens (e.g., PKU).

Treatment: Enzyme replacement or dietary restriction

Homocysteinuria (Aminoacidopathy)

Genetics: AR

Pathophysiology: Deficiency in methionine metabolism

Symptoms: Mental retardation, stroke, lens dislocation, arachnodactyly

Laboratory analysis: Increased homocysteine in CSF, blood, urine

KALLMAN'S SYNDROME

Anosmia, hypogonadism secondary to missing GnRH neurons in hypothalamus (derived from olfactory placode like olfactory receptor neurons), mental retardation

AICARDI SYNDROME[9]

Genetics: X linked dominant

- XX or XXY only, lethal in males

Symptoms/Signs: Infantile spasms, mental retardation, retinal lacunae (chorioretinitis), microcephaly

Radiology: Agenesis of corpus callosum, ventriculomegaly

MACROCEPHALY AND MICROCEPHALY[10]

Head circumference (HC): full-term (38–40 week) infant → 35 cm

- 3 mos → 40 cm
- 9 mos → 45 cm
- 3 yrs → 50 cm
- 9 yrs → 55 cm
- 3-9-5 rule helpful (increase circumference 5 cm between birth, 3 and 9 months, 3 and 9 years)

MACROCEPHALY

> 2 standard deviations above mean HC

- Due to one of three mechanisms: too much fluid (hydrocephalus), too much brain (megalencephaly), too much blood (hematoma)

DDx: Hydrocephalus (communicating and noncommunicating), Chiari malformations (secondary to hydrocephalus), benign extra-axial fluid of infancy, arachnoid cyst, subdural hematoma or hygroma, familial (benign) macrocephaly (large parental head size), Fragile X syndrome, neurocutaneous syndromes (e.g., NF, TS), holoprosencephaly, Alexander disease, Canavan disease, achondroplasia

Diagnostic evaluation: Thorough history and exam should narrow diagnosis, measure parents' head size, neuroimaging (ultrasound, CT, then MRI)

MICROCEPHALY

< 2 SD below mean HC

- Usually secondary to underlying disorder
- Always consider in context of gestational age, body weight, and height

DDx: Intrauterine injury/ischemic stroke (illicit drugs, malnutrition, TORCH infection)

- Chromosomal anomalies (Trisomy 21, 13, 18)
- Inborn errors of metabolism (PKU, maple-syrup urine disease)
- Maternal diabetes mellitus
- Craniosynostosis
- Syndromes of dysmorphogenesis (Prader-Willi, Angelman, Rett)
- Protein storage and folding (Batten disease, Pelizaeus-Merzbacher disease)
- Neuronal migration disorders (lissencephaly, polymicrogyria, holoprosencephaly)

Diagnostic evaluation: Thorough history and exam including height and weight should narrow diagnosis

- High-resolution chromosomes
- Neuroimaging: MRI preferred over CT except in case of suspected craniosynostosis or TORCH infection
- Labs: serum amino acids, urine organic acids; newborns should also undergo tox screen of serum, urine, and stool
- Infectious work-up, including CSF studies, as indicated for suspected TORCH infections

TORCH Infections

Infectious entities with maternal to fetal transmission

- Classically includes toxoplasma (hydrocephalus, bilateral chorioretinitis, cranial calcifications), rubella (cortical/basal ganglia calcifications), cytomegalovirus (periventricular calcifications, microcephaly), herpes simplex 1 and 2, HIV
- Mother frequently asymptomatic

INTRACRANIAL HEMORRHAGE[2]

GERMINAL MATRIX HEMORRHAGE

Main cause of intracranial hemorrhage in *premature* neonates (< 34 weeks, low birth weight)

- Risk factors include perinatal distress, asphyxia, immaturity
- Can occur prenatally (See Table 13-5)

Pathophysiology: Hypoxic injury to microcirculation of germinal matrix → loss of autoregulation → overperfusion → hemorrhage

Symptoms: Respiratory distress (hyaline membrane disease), coagulopathy, congenital heart disease, hypernatremia

CHOROID PLEXUS HEMORRHAGE

Most common cause of interventricular hemorrhage in *term* neonate

- Symptoms range from asymptomatic to hydrocephalus and increased intracranial pressure

TENTORIAL OR POSTERIOR FOSSA HEMORRHAGE

Etiology is tearing of bridging veins along the posterior falx and tentorium

- Occurs in full-term, large birth weight baby, precipitous delivery

Table 13-5 Grading of Subependymal Germinal Matrix Hemorrhage

I	confined to germinal matrix
II	extension into adjacent lateral ventricle
III	interventricular hemorrhage with hydrocephalus
IV	hemorrhage in periventricular white matter with hydrocephalus, infarct, compression of deep medullary veins (90% mortality)

HYPOXIC-ISCHEMIC FETAL LESIONS

Etiology: Intrauterine infection, maternal disease (hypertension, diabetes mellitus, hypoxia), teratogens, smoking, trauma, placental abnormalities (cord tethering/knot formation from too long of a cord) congenital heart disease, metabolic disease, CNS malformations

Pathophysiology: Tissue repair during the first 20 weeks does not involve gliosis → smooth walled defect

PERIVENTRICULAR LEUKOMALACIA

Hypoxic ischemic encephalopathy

- Infarct, parasaggital watershed zones → periventricular leukomalacia (white matter necrosis)
- Hyperechogenic region near atria of lateral ventricle, occipital horns

Epidemiology: 50% of infants with IVH

- Associated with prematurity
- Many present with seizures

Pathophysiology: Impaired perfusion at the border between ventriculopetal and ventriculofugal arteries of the fetus

Pathology: Reactive astrocytosis, gliosis, cystic encephalomalacia, atrophy

Radiology: Can diagnose with ultrasound, but best visualized on MRI

- Decrease in white matter leads to a relative increase in size of the lateral ventricles (pseudocolpocephaly)

CEREBRAL NECROSIS

Epidemiology: More common in term infants

Pathophysiology: Intrapartum complication, congenital heart disease, cardiopulmonary collapse

Pathology: Necrosis involving the depths of sulci

PORENCEPHALY

Pathology: Smooth-walled cyst wedges extending from the ventricle lined by gliotic white matter

Etiology: Ischemic insult to normally developed fetal brain

Radiology: Generally adjacent to sylvian fissure/central sulci, symmetric

Symptoms/Signs: Mental retardation, congenital hemiplegia, chronic spasticity, epilepsy

LEUKODYSTROPHIES[2]

Table 13-6 Genetic Anomalies Affecting Development of Myelin Sheath

Disease	Genetics	Defect	Clinical Features	Pathology	Comments
Krabbe's disease (Globoid cell leukodystrophy)	AR	galactocerebrosidase – pathophysiology probably due to toxic metabolite accumulation	myoclonus, motor loss, dysmorphic facies, rigidity, seizures, motor and developmental delay, deafness, blindness	globoid macrophages • atrophic brain with firm white matter but normal cortex	infantile onset is most common though juvenile and adult forms exist • rapidly fatal before age 2
Metachromatic Leukodystrophy	AR	aryl sulfatase A: toxic accumulation of cerebroside sulfate	ataxia, motor loss, psychosis	PAS+ macrophages (from sulfatide accumulation)	three forms: infantile, juvenile, and adult • prominent peripheral neuropathy
Canavan's disease (spongiform leukodystrophy)	AR	aspartoacylase: pathophysiology poorly understood	hypotonia, blindness, myoclonus	spongy white matter • Alzheimer type II astrocytes	severe demyelination including subcortical U fibers occipital > frontal/parietal • spares internal capsule
adrenoleukodystrophy	XL	ATP-binding transporter: results in accumulation of very long chain fatty acids, though pathophysiology not fully understood	seizures, dementia, hypertonia	prominent perivascular inflammation	1:10,000 males with gene defect but not all acquire CNS symptoms • early bone marrow transplant is effective in CNS disease
Pelizaeus-Merzbacher Disease (PMD)[6]	XL	proteolipid protein: abnormal protein folding causes apoptosis	ataxia, spasticity, nystagmus	segmental demyelination	CNS alone • onset by 3 mos but wide range of outcomes
Alexander's disease	sporadic	unknown	seizures, dementia, psychosis	Rosenthal fibers	
Vanishing White Matter disease	AR	eIF2B: pathophysiology uncertain	ataxia, seizures, spasticity	diffuse loss of myelin with absent gliosis	wide range of onset from infancy to adulthood

SPHINGOLIPIDOSES[2,11]

Sphingolipids are a class of lipids that are critical to cell recognition and signal transmission. They are abundant in neural tissue.

Table 13-7 Lipid Storage Diseases

Disease	Genetics	Enzyme Defect	Distinguishing Clinical Features	Pathology	Comments
Tay-Sachs	AR	hexosaminidase A	hypotonia, blindness, macular cherry-red spots	ballooned neurons (stored gangliosides) • stain strongly with Luxol fast blue and Sudan black	lysosomal d/o accumulation of neuronal ganliosides Ashkenazi Jews
Sandhoff	AR	beta-hexosaminidase	cherry red spot, mental deterioration, myoclonus,		severe form of Tay-Sachs, death before age 3
Gaucher	AR	glucocerebrosidase	seizures, macular cherry-red spots, HSM, CN palsies, opisthotonos	PAS+ nuclei, prominent cytoplasmic fibrillar material of glucocerebrosides	four types, death by 2 years of age
Niemann-Pick	AR	sphingomyelinase	hypotonia, MR, macular cherry-red spots, HSM, spasticity, seizures, dementia, jaundice, supranuclear paresis of vertical gaze	ballooned neurons and glia, demyelinated and gliotic white matter, foamy histiocytes	age of presentation depends on severity of disease (earlier = more severe)
Fabry	XL	alpha-galactosidase A	pain, paresthesias, telangiectasias, purple skin macules, corneal clouding		survival into adulthood

NOTES: Krabbe and metachromatic leukodystrophy included under leukodytsrophy.
MR = mental retardation
HSM = hepatosplenomegaly

MUCOPOLYSACCHARIDOSES[2,12]

Pathology shows expansion of perivascular spaces in the basal ganglia and zebra bodies

Table 13-8 Mucopolysaccharidoses (MPS)

Disease (MPS)	Incidence	Genetics	Enzyme Defect	Distinguishing Clinical Features	Comments
Hurler (I)	1:100,000	AR	alpha-L-iduronidase	early onset MR, cardiac disease, corneal clouding, joint restriction, hirsutism	death before 10 yr, most severe of the MPS I subtypes
Scheie (I)	1:500,000	AR	alpha-L-iduronidase	spinal cord compression, normal intelligence, visual impairment, stiff joints, OSA	mildest form of MPS, live into adulthood
Hurler-Scheie (I)	1:115,000	AR	alpha-L-iduronidase	moderate MR, short stature, joint and spinal cord compression, corneal clouding, OSA	life expectancy into 20s
Hunter (II)	1:100,000 (males)	XL	iduronate sulfatase	dwarfism, hydrocephalus, coarse face, MR, hyperactivity, hearing loss, ataxia, hernia, HSM, seizures, rash, skin pebbling, joint stiffness, macrocephaly	Type A presents by age 2, Type B progresses at a slower rate, presenting in the second decade and without an effect on intellect
Sanfilippo (III)	1:70,000	AR	Type A: heparan N-sulfatase, Type B: alpha-N-acetylglucosaminidase, Type C: acetyl-CoAlpha-glucosaminide, Type D: N-acetylglucosamine 6-sulfatase	MR, ataxia, dementia, seizures, aggression, insomnia, growth stunting, OSA	heparan sulfate excreted in urine; four types depending upon enzyme deficiency; Type A has worst survival rate

Morquio (IV)	1:200,000	AR	Type A: N-acetylgalactosamine 6-sulfatase, Type B beta-galactosidase	alantoaxial subluxation, cardiac/ pulmonary disease, severe kyphosis, dwarfism, ligamentous laxity, normal intelligence, platyspondyly, “wine glass” pelvis, beaked vertebrae	keratin sulfate build up, milder symptoms in Type B
Maroteaux-Lamy (VI)	1:250k–400k	AR	N-acetylgalactosamine 4-sulfatase	normal intellect, physical symptoms as in Hurler syndrome, corneal clouding, deafness, dural thickening, growth stunting severe skeletal changes, heart disease	
Sly (VII)	1:250,000	AR	beta-glucuronidase	hydrops fetalis, MR, hydrocephalus, corneal clouding, skeletal irregularities	live into second decade

OSA - obstructive sleep apnea,
MR - mental retardation,
HSM - hepatosplenomegaly,
AR - autosomal recessive

MITOCHONDRIAL DISORDERS

Wide range of presentations due to 1) Nonuniform inheritance of affected and unaffected mitochondria from mother to child 2) nonuniform division of these same affected/unaffected mitochondria between various cell-lines in developing embryo 3) inheritance of mitochondrial proteins via mitochondrial as well as nuclear DNA 4) high rate of spontaneous mutations

KEARNS-SAYRE SYNDROME

Key Features:

- Progressive external ophthalmoplegia
- Ptosis
- Retinal degeneration
- Heart block/cardiomyopathy
- Elevated CSF protein
- Cerebellar dysfunction

Genetics: Usually sporadic

Diagnosis: Clinical criteria

Management: Pacemaker; vitamins and supplements

MERRF (MYOCLONIC EPILEPSY WITH RAGGED RED FIBERS)

Key features:

- Myoclonus
- Myoclonic epilepsy
- Ataxia
- Ragged red fibers in muscle biopsy
- Progressive course but wide range of onset

Diagnosis: Molecular genetics for multifocal mutations in mtDNA

- Muscle biopsy
- EEG

Treatment: Anticonvulsants often lose efficacy as disease progresses

MELAS (MITOCHONDRIAL ENCEPHALOPATHY WITH LACTIC ACIDOSIS AND STROKE)

Onset usually in adolescence

- Seizures common first complaint
- Acute onset of focal deficits (stroke-like episodes) initially intermittent but can be severe and eventually become permanent and cumulative leading to coma and death

Diagnosis: MRI shows multifocal infarctions defying vascular territories

- Lactate
- Genetic testing

Management: Vitamins and supplements useful, notably coenzyme Q10 and levocarnitine

NEURONAL MIGRATION AND DEVELOPMENT DISORDERS[2]

For agyria, pachygyria, polymicrogyria, neuronal heterotopias, aberrant development occurs in 7th wk of gestation.

LISSENCEPHALY (AGYRIA, PACHYGYRIA)

Microcephaly, mental retardation, hypotonia → hypertonia, epilepsy, feeding difficulties, micrognathia

Agyria

Complete absence of gyri and sulci

Pathology: Thickened cortical ribbon, only four layers, decreased white matter

- No sulcation
- Miller-Diecker: Lissencephaly, pachygyria, microcephaly, abnormal facies, multiorgan dysfunction, polydactyly AR, Chrom 17, LIS1 gene
- Norman-Roberts
- Walker-Warburg syndrome: Lissencephaly, congenital myotonic dystrophy, hydrocephalus, agyria, retinal dysplasia/microphthalmia, ± encephalocoele, AR
- X-linked lissencephaly-subcortical band heterotopia: Doublecortin (DCX), a MAP
- Fukuyama's congenital muscular dystrophy
- X-linked variety-chrom 17 defect
- Type I: 4-layer cortex, with thin overlying white matter
- Type II: No layers, glioneuronal heterotopias

Pachygyria

Broadened gyral convolutions present in fewer than normal numbers

Polymicrogyria

Several thin, fused gyri in increased number of convolutions

Epidemiology: Associated with intrauterine infections, ischemia, metabolic disease (Pelizaeus-Merzbacher), peroxisomal disorders (Zellweger syndrome), Aicardi syndrome

Symptoms: If focal may be asymptomatic

- Widespread cortical involvement → mental retardation and microcephaly, seizures

AGENESIS OF THE CORPUS CALLOSUM[13,14]

Subtypes: Complete (absent cingulate gyrus/sulcus, high-riding third ventricle, dorsal/rostral interhemispheric arachnoid cyst, colpocephaly), partial (always involves rostrum and splenium) or atypical (e.g., holoprosencephaly)

- Forms genu to splenium during development, so splenium often involved
- Bundles of Probst (rudimentary callosal fibers)

Epidemiology: 0.7–5.3%

- M > F
- May occur in isolation or as part of a syndrome or in association with other developmental anomalies including Chiari II, neuronal migration disorders, Dandy-Walker, holoprosencephaly, hydrocephalus, interhemispheric lipoma or cysts, abnormal optic chiasm and pituitary, Aicardi syndrome, microgyria, schizencephaly, Meckel-Gruber syndrome, midline lesions (lipoma, hamartoma, meningioma)

Genetics: Usually sporadic, but may be associated with trisomy 13, 15, 18

Symptoms/Signs: Varying degrees of mental retardation, seizures

- Asymptomatic in isolation

CAVUM SEPTUM PELLUCIDUM

Gap between the two leaves of the septum pellucidum which is a persistence of normal fetal cavity

- Occurs in 20% of the population
- No neurological deficits associated with this finding

HETEROTOPIAS

- Nodular/periventricular -> normal IQ, seizuresFamilial: X-linked (lethal in males), Filamin-1
- Subcortical band -> MR, seizures

HOLOPROSENCEPHALY

Subtypes:

- Alobar → no falx formation, corpus callosum or interhemispheric fissure → single ventricle, fused thalami, craniofacial abnormalities (cleft lip/palate), cyclopia, renal dysplasia, polydactyly
- Semilobar → rudimentary falx, variable basal ganglia fusion
- Lobar → no septum pellucidum, may have fusion of anterior frontal lobe

Epidemiology: Associated with maternal diabetes, intrauterine infection, fetal alcohol syndrome, chromosomal abnormalities

Pathophysiology: Incomplete separation of (telen)prosencephalon at week 5

Signs: Microcephaly, hypotelorism, polydactyly, renal dysplasia, cleft palate, cyclopia

Genetics: Associated with trisomy 13, 18

SEPTO-OPTIC DYSPLASIA (DE MORSIER SYNDROME)

Mild lobar holoprosencephaly

- No septum pellucidum, optic nerve hypoplasia, hypothalamic-pituitary deficiency

- If schizencephaly present (50%) may present with seizures

JOUBERT SYNDROME[15]

Genetics: Most cases sporadic

- AR involving genes NPHP1, AHI1, and CEP290

Radiology: Absence or underdevelopment of the cerebellar vermis

Symptoms/Signs: Mental retardation, hyperpnea, hypotonia, oculomotor apraxia, ataxia, polydactyly, oculomotor problems, cystic kidneys, cleft lip/palate seizures

SCHIZENCEPHALY

Subtypes: Open (Type I) versus closed (Type II): CSF in the cleft

Epidemiology: 50% other neuronal migration anomalies, malrotation of hippocampi, 90% with absent septum pellucidum

Genetics: Familial version involves the EMX2 homeobox gene

Symptoms: Seizures, hemiparesis

Pathology: Transcerebral cleft (cortex to ventricle, ependyma to pia), lined by heterotopic gray matter, +/- anomalous venous drainage

PEDIATRIC NEUROMUSCULAR DISEASES

SPINOMUSCULAR ATROPHY (SMA)

Motor neuron degeneration in anterior horns and motor nuclei of pons/medulla AR, linked to chromosome 5q

Type 1 (Werdnig-Hoffmann Disease)

Epidemiology: Presents in infancy

Symptoms: Areflexia, hypotonia, no mental retardation

- Proximal muscle weakness, primary motor neuropathy

Outcome: Death by 4–6 weeks from respiratory failure

Type 2 (Chronic Infantile)

Epidemiology: Presents in infancy

Symptoms/Signs: Contracture deformities, scoliosis

Outcome: Survive until early childhood

Type 3 (Kugelberg-Welander Disease aka Chronic Proximal)

Epidemiology: Onset in late childhood

Symptoms: Slowly progressive proximal limb weakness

Outcome: Survive into early adulthood

Adult Onset SMA

Genetics: AD

Outcome: Survive until 50s

SPINOBULBAR MUSCULAR ATROPHY (KENNEDY'S DISEASE)[16]

Epidemiology: Presents in males at age 20–30

Genetics: X-linked recessive trinucleotide repeat of CAG

- Affects testosterone receptor gene

Pathology: Degeneration of lower motor neurons

Symptoms/Signs: Similar to amyotrophic lateral sclerosis (ALS)

- Begins with mild tremor and fasciculations, then develop proximal and bulbar weakness, dysarthria, hyporeflexia, recurrent aspiration pneumonias
- Gynecomastia, infertility, diabetes mellitus, primary sensory neuropathy

Outcome: Slowly progressive, but usually have normal life span

MUSCULAR DYSTROPHIES (MD)

Inherited, progressive muscular weakness

Limb-Girdle

Onset ranges from infancy to adulthood

Genetics: Autosomal recessive abnormality of dystrophin-related protein

Symptoms: Chronic progressive weakness of shoulder and hip girdle

Duchenne's

Genetics: X-linked recessive

- Severe mutation of dystrophin gene

Epidemiology: 1:3500 male births

Symptoms/Signs: Early childhood

- Initial weakness in hip and shoulder girdle muscles → progresses to distal muscles and respiratory/cardiac muscle
- Gower's sign, pseudo hypertrophy of calf muscles, hyporeflexia, arrhythmias

Outcome: Death from cardiac or respiratory failure by age 20

Workup: CK (elevated), EMG (small polyphasic potentials), muscle biopsy, molecular analysis of dystrophin gene, EKG

Treatment: Anticipation of multiorgan involvement (annual PFT, EKG, CXR, cardiac echo after age 12), supportive (e.g., physical therapy, surgery to release contractures)

- May consider high-dose steroids

Becker

Genetics: X-linked recessive

- Milder mutation of dystrophin gene

Epidemiology: 1:30,000 male births

Symptoms/Signs: Later onset and milder involvement than Duchenne's

Outcome: Commonly ambulatory into adulthood

Workup: CK (elevated), EMG (small polyphasic potentials), muscle biopsy, molecular analysis of dystrophin gene, EKG

Treatment: Similar to Duchenne's

Emery-Dreifus

Humeroperoneal muscular dystrophy

Epidemiology: Present before mid 20s

Symptoms/Signs: Muscle weakness and wasting in humeroperoneal distribution

Workup: CK (modestly elevated), EKG, EMG, muscle biopsy

Treatment: Monitor for early signs of complications

Myotonic

The only musculodystrophy that involves distal rather than proximal muscles

Genetics: Autosomal dominant

Epidemiology: Most common muscular dystrophy in Caucasians

Symptoms/Signs: Ptosis, cataracts, multiple endocrinopathies, bulbar dysfunction, mental retardation, myotonia, decreased GI motility

Facioscapulohumeral Dystrophy

Genetics: Autosomal dominant

Symptoms/Signs: Mild or asymptomatic weakness and wasting of facial, scapular, and humeral muscles leading to difficulties in whistling and using arms above shoulder level

KERNICTERUS

Pathophysiology: Accumulation of unconjugated bilirubin due to excessive production (e.g., hemolytic disease of the newborn) or insufficient excretion (immaturity) → neurotoxic

Pathology: Preferentially involves the globus pallidus, subthalamic nucleus, hippocampus, lateral thalamus

CHAPTER 14 ■ BRAIN TUMORS[1–5]

Gordon Li, MD

GLIAL TUMORS

ASTROCYTOMAS

Epidemiology: Most common primary brain tumor

- Most often between the ages of 40 and 60 years
- Male:female = 2:1
- Multifocal in 5% of cases

Grading: I–IV according to World Health Organization (WHO)

- Based on pleomorphism, hypercellularity, vascular proliferation, necrosis
- Grade I = well-circumscribed tumor without nuclear atypia, increased mitoses, anaplasia, necrosis, or neovascularization
- Grade II = nuclear atypia, increased cellularity
- Grade III = increased mitotic index and anaplasia
- Grade IV = nuclear atypia, mitoses, endothelial proliferation, and necrosis (mnemonic "AMEN")

Prognosis: Generally depends on age, histology/grade, Karnofsky score and extent of resection

■ Grade I Astrocytoma

Generally well circumscribed and usually do not progress to higher grade astrocytomas

- Includes pilocytic astrocytoma, subependymal giant cell astrocytoma (SEGA), and pleomorphic xanthoastrocytoma (PXA)

Pilocytic Astrocytoma

Epidemiology: Account for 1/3 of pediatric gliomas (most common glioma in children)

- 5 to 10% of all gliomas
- Peak incidence around age 10
- 10% of cerebral and 85% of cerebellar astrocytomas
- Optic gliomas common in NF1 patients

Location: Most often cerebellum, followed by brain stem, optic pathway, thalamus, and hypothalamus

Radiology: Often cystic and well circumscribed with a characteristic contrast-enhancing mural nodule, though can be solid

- Usually noncystic in the medulla and optic pathway
- Almost always contrast enhancing

Pathology: Rosenthal fibers (GFAP+), biphasic, microcysts, eosinophilic granular bodies (EGB), vascular proliferation, microcystic

- Rare necrosis/mitoses

Treatment: Resection of the enhancing nodule and any enhancing cyst wall is indicated

Outcome: Gross total resection usually curative and survival is 86–100 % at 5 years, 83% at 10 years, and 70% at 20 years

- Hypothalamic gliomas have a poor prognosis
- If the tumor cannot be totally resected, then survival also worse

Pleomorphic Xanthoastrocytoma (PXA)

Epidemiology: Peak incidence at age 7–25

- Often present with seizures

Location: Superficial temporal lobe

Radiology: Heterogeneous cystic mass with a mural nodule, calcifications

- Often involve the cortex and leptomeninges but not the dura

Treatment: Gross total resection often curative, although some reports of transformation to glioblastoma (GBM)

Pathology: Bizarre pleomorphic astrocytes with xanthomatous fat cells, spindle cells, a rich reticulin network and no necrosis

Outcome: Favorable prognosis

Subependymal Giant Cell Astrocytoma (SEGA)

Epidemiology: Peak incidence at < 20 years of age

- Often cause hydrocephalus and seizures
- Seen in 15% of tuberous sclerosis (TS) patients

Location: Foramen of Monro

Radiology: Heterogeneous enhancement with frequent calcifications, well circumscribed

Outcome: Tumors benign, but cases of sudden death have been reported from tumor blocking the foramen of Monro and causing a sudden increase in intracranial pressure (ICP)

Pathology: Large multinucleated cells, benign

Grade II (Diffuse) Astrocytoma

Subtypes: Protoplasmic, gemistocytic (worse prognosis), fibrillary, or mixed (worse prognosis if > 20% gemistocytes)[7]

Epidemiology: Younger adults with a mean onset of 30 years

Location: White matter

Radiology: Generally diffuse but can be pseudocircumscribed, hypodense on CT, often low on T1 and bright on T2, and generally nonenhancing or minimally enhancing

Outcome: Have a far greater tendency to progress in grade than grade I astrocytomas

- 5-year survival after gross total resection and radiation is 70% but this decreases to 38% with subtotal resection
- Median survival approximately 8.2 years
- Controversial optimal treatment paradigm

Pathology: Unlike in higher grade astrocytomas, mitoses and anaplasia generally absent

- Also lack of necrosis or neovascularization
- Gemistocytic tumors have prominent eosinophilic cytoplasm, peripherally displaced nuclei, and perivascular lymphocytic infiltrate

Grade III (Anaplastic) Astrocytoma

Epidemiology: Mean age of presentation in 40s to 50s with slight male predominance

Location: Preference for cerebral hemispheres, but can present almost anywhere in CNS

Radiology: Typically rim enhancing (though many are not) with surrounding vasogenic edema; some have hemorrhage

Pathology: Nuclear atypia, frequent mitoses, increased cellularity, significant proliferative activity, no necrosis or neovascularization

Genetics: High frequency of p53 mutations and LOH 17p

Outcome: Strong tendency to progress to grade IV

- Better outcome for Karnofsky score > 70, age < 45, location amenable to resection, minimal medical comorbidities
- Median survival of patients with anaplastic astrocytomas is 2–3 years

Grade IV (Glioblastoma [GBM]) Astrocytoma

Subset: Gliosarcomas = GBMs with a sarcoma component

Epidemiology: 55% of astrocytomas

- Age 50s to 70s though younger and older patients can present with GBM as well

- GBMs can be primary (i.e., tumors that occur de novo) or secondary (i.e., tumors that start as lower grade astrocytomas and then progress into GBM)

Location: Frontotemporal most common though can present almost anywhere in the CNS

- Occasionally multicentric (3–6%)
- Can invade deep white matter tracts and cross corpus callosum (butterfly glioma)

Radiology: Typically rim enhancing with central necrosis, surrounding vasogenic edema; may hemorrhage

- ~4% do not enhance with contrast

Pathology: Nuclear atypia, frequent mitoses, endothelial proliferation, necrosis, secondary structures of Scherer (tumor cells surrounding neurons in the gray matter or infiltrating along white matter tracts), pseudopallisading necrosis, and glomeruloid vascular proliferation

Genetics: Primary pathway tumors more often have mutations of the EGF receptor and loss of PTEN while secondary pathway tumors more often have p53 mutations

Outcome: Poor

- Better outcome for Karnofsky score > 70, age < 45, location amenable to resection, minimal medical comorbidities
- Median survival of patients who receive current standard of care including resection, postoperative radiation, and Temozolomide = 12–15 months
- GBM survival without treatment = 3–6 months
- Primary and secondary pathway tumors have same prognosis

Gliomatosis Cerebri: Diffusely infiltrating glioma involving at least three lobes at diagnosis (can be bilateral) with minimal mass effect

- Largely nonenhancing, though some areas can show mild enhancement
- Can often present differently from other high grade gliomas (cognitive/behavioral symptoms or other ill-defined neurologic deficits)
- Poor prognosis

Brainstem Glioma

Epidemiology: 10–20% of pediatric brain tumors

- Often present with cranial nerve palsies and headache
- Heterogeneous group of tumors, but 58–75% are diffuse infiltrating
- Other types include tectal gliomas, focal brainstem gliomas, and cervicomedullary gliomas

Location: Midbrain, pons, medulla

Radiology: Diffuse-intrinsic brainstem glioma is an infiltrative lesion that often results in marked brainstem enlargement

- Hyperintense on T2
- Variable enhancement

Pathology: Diffuse-infiltrating glioma is a grade II to IV astrocytoma

- Focal brainstem glioma, tectal glioma, and cervicomedullary gliomas are usually low-grade astrocytomas

Treatment: Radiation therapy for diffuse-infiltrating type

- No surgery for diffuse type, though focal lesions can be removed safely
- Tectal gliomas (limited to tectum, generally nonenhancing) often need only CSF diversion (3rd ventriculostomy or ventriculoperitoneal shunt)

Outcome: Diffuse type is progressive and fatal

- Well-circumscribed grade 1 lesions and tectal gliomas have an excellent prognosis
- CSF diversion may be considered for palliation of obstructive hydrocephalus

OLIGODENDROGLIOMA

Epidemiology: Typically found in adults (rarely in children)

- Peak age 35 to 40 years
- Often present with seizures

Location: Generally frontotemporal lobes though can present almost anywhere

Radiology: Have a higher frequency of hemorrhaging

- Often contain irregular calcifications
- Mild heterogeneous enhancement with contrast

Pathology: Classic fried-egg appearance (an artifact of permanent sections but not frozen sections), round nuclei, "chicken-wire" vasculature, perineuronal sattelitosis, calcifications, intratumoral hemorrhage, and pseudocysts

- Grade II lesions have marked nuclear atypia and occasional mitosis while grade III (anaplastic) lesions have significant mitotic activity, prominent microvascular proliferation, or necrosis

Genetics: Subset has codeletion of 1p and 19q, which correlates with sensitivity to treatment and improved prognosis.

Outcome: 5-year survival 75%

- Better prognosis than astrocytomas or mixed oligoastrocytomas (especially with lp/19q deletion) with median survival times of 11.6 years for grade II and 3.5 years for grade III

EPENDYMOMA

Subtypes: Pathologic variants include cellular, papillary, epithelial, clear cell, mixed, tanycytic, myxopapillary (grade I)

- Grade II or grade III (anaplastic)

Epidemiology: Constitute 5% of adult intracranial gliomas, 10% of childhood CNS tumors

- Associated with neurofibromatosis 2 (often multiple)
- Bimodal peak of occurrence at ages 1 to 5 and age 35
- M = F

Location: From the lining of ventricles or central canal of spinal cord

- Generally intracranial in children and spinal (60% of intramedullary spinal cord tumors, most often at the filum) or less commonly, ventricular in adults
- Typically centered in the 4th ventricle and extend through the foramina of Luschka and Magendie
- In spinal cord, often associated with a syrinx, which creates a good margin for resection (versus spinal cord astrocytomas which do not have a good resection margin)

Radiology: Isointense on T1, intermediate to mildly hyperintense on T2

- Well circumscribed
- Enhance with contrast
- Spinal cord lesions may be associated with cysts, syrinx formation, and hemosiderin deposition

Pathology: Ependymomas have classic true rosette (polygonal tumor cells around a central canal) or perivascular pseudorosettes (polygonal tumor cells around a blood vessel)

- Cysts
- Surface microvilli
- Mitotic figures (grade III)
- +GFAP, +EMA

Location: Varied, depends on age, location, and grade

- E.g., most childhood ependymomas present in the 4th ventricle while myxopapillary ependymomas usually occur along the filum terminale
- In children less than 2 years of age, ependymomas are commonly supratentorial

Outcome: Supratentorial ependymomas in young children have worse prognosis than posterior fossa ependymoma in older children

- Gross total resection improves overall survival
- Better prognosis for > 3 yrs old
- Need to obtain full craniospinal MRI to evaluate for CSF spread which has a worse prognosis

Myxopapillary Ependymoma

Grade 1

- Commonly associated with the conus medullaris or filum terminale
- Isointense on T1, iso to hyperintense on T2; contrast enhancing

- On path, ependymocytes arranged around papillary projections containing myxoid stroma
- Can be cured with gross total resection, unless it invades the conus

SUBEPENDYMOMA

Epidemiology: Rare

- Peak age of 40 to 60
- M > F

Pathology: Grade I, benign

- 50% cause symptoms because of CSF obstruction

Location: 4th ventricle, body of lateral ventricle or sometimes in the spinal cord

Radiology: Often nonenhancing (whereas most intraventricular tumors enhance)

- Well circumscribed
- Mild hyperintensity on T2

Pathology: Both ependymal and astrocytic features

- Grouped nodular cells

Treatment: Cured with gross total resection

- asymptomatic lesions can be followed

CHOROID PLEXUS PAPILLOMA (CPP)

Epidemiology: Peak age of less than 10 years (85% before age 5, most even before age 2, especially when in the lateral/3rd ventricles)

- Benign, slow growing
- Often present with hydrocephalus due to obstruction and/or increased CSF production

Outcome: Good after resection because they rarely transform to a more aggressive histology (choroid plexus carcinoma), but these tumors can recur and disseminate through the CSF)

Location: Intraventricular (commonly in the atrium of the left ventricle in children and in the 4th ventricle in adults)

Radiology: Multilobulated "cauliflower" morphology

- Enhance intensely after contrast infusion

Pathology: Neoplasm of the epithelial cells of the choroid plexus

- Closely resembles normal choroid plexus except more crowded
- Increased mitotic activity alone connotes atypical choroid plexus papilloma
- Tumors with at least four of the following five features: frequent mitoses, increased cellular density, nuclear pleomorphism, blurring of the papillary pattern with poorly structured sheets of tumor cells, and

necrosis, are WHO grade III choroid plexus carcinomas (accounts for 15% of CP tumors)
- Choroid plexus carcinoma typically invades brain parenchyma and causes edema

NEURONAL AND MIXED NEUROGLIAL TUMORS

GANGLIOGLIOMA

Epidemiology: 1% of CNS tumors

- Most commonly present in the first 3 decades (80% < 30 years)
- Slowly growing
- Typically present with seizures

Pathology: Contain both neuronal and glial components

- Dysmorphic, binucleate ganglion ("owl eyes")
- Anaplastic ganglioglioma has malignant features
- +synaptophysin, neurofilament MAPII, GFAP
- A subset have neuronal but not glial components

Location: Peripheral cortical location

- Predilection for the temporal lobes > parietal >> cerebellum

Radiology: May be solid or mixed cystic and solid (~50%)

- Mass effect depends on size; often little or no edema
- Calcifications frequent (~50%)
- Enhancement is variable

Treatment: Surgical resection

DYSPLASTIC GANGLIOCYTOMA OF THE CEREBELLUM (LHERMITTE-DUCLOS DISEASE)

Epidemiology: Rare

- Associated with Cowden syndrome (multisystem disease involving hamartomatous overgrowth of tissue and increased risk of thyroid, breast, and other cancers; most cases with germ-line PTEN mutation)
- Slowly progressive, variably associated with cerebellar signs and symptoms of raised intracranial pressure

Radiology: Focal region of cerebellar folia thickening and fissural effacement

- Hypointense on T1, alternating "stripes" on T2, nonenhancing

Pathology: Diffuse enlargement of the internal granular layers of the cerebellum which are filled by ganglionic cells, with preservation of the cerebellar architecture

Treatment: Decompression of the posterior fossa by total surgical removal of the mass

DESMOPLASTIC INFANTILE GANGLIOGLIOMA (DIG)

Epidemiology: Rare

- First 18 months of life
- WHO grade I

Location: Supratentorial tumor

- Usually frontal or parietal lobe
- Involves overlying dura

Radiology: Both solid and cystic components

- Solid component usually peripheral, enhancing
- Cystic portion more medial, often massive

Treatment: Surgical resection

Prognosis: Generally curable with gross total resection

DYSEMBRYOPLASTIC NEUROEPITHELIAL TUMORS (DNET)

Epidemiology: Young adults and children

- Present with seizures

Location: Supratentorial (predilection for temporal lobes)

Pathology: Contain mixed neural and glial elements and have an association with cortical dysplasia

- Thought to arise from the external granular layer of the cortex
- Floating neurons on loose background with big microcysts
- Multinodular

Radiology: Cortically based lesion; usually no edema, minimal mass effect

- Often small cysts
- Variable nodular enhancement

Treatment: Surgical resection usually curative

CENTRAL NEUROCYTOMA

Epidemiology: Young adults

Location: Within the lateral ventricles at septum pellucidum or foramen of Monro

Pathology: Grade II

- Neuronal in origin
- Do not infiltrate
- Uniform cells on “ground glass” neuropil background
- + synaptophysin

Radiology: Well circumscribed, lobulated lateral ventricular mass

- Heterogeneous, “feathery” enhancement
- Frequently have punctate calcifications, small cysts

Treatment: Gross total resection usually curative

- Radiation is effective for growing residual or recurrent tumor

PINEAL TUMORS

Symptoms: Classic presentation is Parinaud syndrome: Upward gaze palsy, pupillary dilation, lid retraction, nystagmus, and light-near dissociation

Pineal parenchymal tumors make up ~20% of pineal region tumors

PINEOCYTOMA

A well-circumscribed, slowly growing, and well-differentiated tumor with peak incidence of 30 years

- Associated cysts are common

PINEOBLASTOMAS

Related to central nervous system primitive neuroectodermal tumor or PNETs

- Highly aggressive with poor prognosis
- More common in children
- Pathologic examination reveals small round blue cells with high cellularity and mitoses
- Enhance heterogeneously with contrast, often disseminate through CSF
- May be associated with bilateral retinoblastoma (trilateral retinoblastoma)

TRILATERAL RETINOBLASTOMA

Connotes bilateral retinoblastomas and a pineoblastoma

PINEAL PARENCHYMAL TUMORS OF INTERMEDIATE DIFFERENTIATION

Tumors intermediate between the more benign pineocytoma and more the aggressive pineoblastoma

PAPILLARY TUMORS OF THE PINEAL REGION

Rare pineal parenchymal tumors characterized by papillary architecture and epithelial cytology

EMBRYONAL TUMORS

CENTRAL NERVOUS SYSTEM PRIMITIVE NEUROECTODERMAL TUMOR (PNET)

Subtypes

Medulloepithelioma (the most primitive of the PNETs; affects very young children), retinoblastoma (most common extracranial malignant solid tumor in children; derived from neural crest precursor of the sympathetic ganglia; pathogenesis related to loss of tumor suppressor gene RB on chromosome 13), ependymoblastoma, pineoblastoma

MEDULLOBLASTOMA[8]

Subtypes

Desmoplastic, medulloblastoma with extensive nodularity, anaplastic, and large cell medulloblastoma

Presentation: Often secondary to hydrocephalus and increased intracranial pressure (headaches, nausea, and vomiting) or cerebellar signs (ataxia, incoordination)

Epidemiology: Most common subtype of PNET

- Most often occur before the age of 10 with a second peak at late 20s
- Male predominance
- 20% of CNS tumors in children
- Most common malignant brain tumor of childhood
- Associated with Gorlin syndrome (aka basal cell nevus syndrome), an autosomal dominant disease related to mutation of PTCH1 gene

Location: Arise from medullary velum, typically fill 4th ventricle

- Occur in the midline in children but more frequently off midline in adults

Genetics: 17q, sonic hedgehog signaling pathway activation, Wnt/wingless signaling activation, TP53 tumor suppressor deficit, MYC oncogene family amplification

Pathology: Embryonal neuroepithelial, originating from external granule layer of cerebellum

- Densely packed cells with round- to oval-shaped hyperchromatic nuclei
- About 40% of the cases have Homer Wright rosettes (a circular or spherical grouping of tumor cells around a pale, eosinophilic, central area that contains neurofibrils but lacks a lumen)
- Desmoplastic synaptophysin islands

Radiology: Mass lesion of the 4th ventricle in young children, cerebellar hemisphere in teenagers and adults

- Hyperdense on CT due to high cellularity and variable calcification
- Typically isointense on T1 and T2
- May contain cysts
- Mild to moderate contrast enhancement
- Often seeds via CSF and full neuraxis MRI is required for staging

Treatment: Surgical resection with postoperative craniospinal radiation and chemotherapy

Prognosis: With standard therapy, 5-year survival approaches 70%

- Medulloblastoma with nodularity type → improved prognosis, anaplastic type → worsened prognosis

ATYPICAL TERATOID/RHABDOID TUMORS (AT/RT)

Presentation: Variable depending on the location (infra- versus supratentorial) of the tumor or age of the patient

- Infants often present with lethargy or nausea and vomiting
- Other signs include head tilt and cranial nerve palsy
- Older children can complain of headaches or weakness

Epidemiology: Children less than age 3

- Rarely seen in children older than 6

Location: Supratentorial lesions slightly more common than infratentorial lesions

- Rarely seen in the spine
- Usually in the cerebellar hemispheres when supratentorial and cerebellar hemispheres, cerebellopontine angle or brainstem when infratentorial

Radiology: Tumors often large with associated edema

- Imaging characteristics similar to PNET/medulloblastomas
- Seeding of the CSF is common and full neural axis imaging required during work-up

Pathology: Combination of rhabdoid, primitive neuroepithelial, epithelial and mesenchymal components

Genetics: Inactivation of the INI1/hSNF5 gene and the diagnosis can be made with immunohistochemistry showing loss of nuclear INI (i.e., does not stain with INI)

- INI protein is a component of the mammalian SWI/SNF complex that functions in an ATP-dependent manner to alter chromatin structure (the specific role for INI in ATRT is unknown but thought to be in part due to p16 and p53 pathways)
- Check for rhabdoid tumor predisposition syndrome, a disorder with increased risk of developing malignant rhabdoid tumors due to inactivation or loss of the one allele of the INI gene

Prognosis: Poorest prognosis of the embryonal tumors with overall survival of 1–2 years

TUMORS OF THE CRANIAL AND PARASPINAL/PERIPHERAL NERVES

SCHWANNOMA

Epidemiology: Account for 7% of all intracranial tumors, 80% of cerebellopontine masses (vestibular schwannoma)

- Associated with neurofibromatosis type 2 (NF2) where they are multiple
- Cause neurologic deficit from direct compression
- No gender predominance
- Usual age of presentation 40 to 50 in sporadic cases (20s with NF2 patients)
- Symptoms vary with location: in vestibular schwannoma, sensorineural hearing loss (higher frequencies first), tinnitus, headache, disequilibrium, rarely with facial nerve palsy

Location: Most commonly arise from superior vestibular nerve (vestibular schwannoma aka acoustic neuroma), bilateral in NF2

- Trigeminal nerve
- Other cranial nerves, spinal nerves

Radiology: Round or oval, well-circumscribed masses

- Isointense on T1 weighted imaging, T2 bright, and enhancing
- May have areas of cyst formation, hemorrhage

Pathology: Cytologically benign

- Rarely undergo malignant transformation
- Grossly firm and encapsulated
- Biphasic pattern of Antoni A (compact fusiform spindle cells, reticulin and collagen) and Antoni B fibers (loosely arranged stellate round cells in stroma)
- Verocay bodies: Groups of spindle cells that look like schools of fish swimming in different directions
- Contain no axons
- S-100+

Treatment: Serial imaging in an asymptomatic patient with small tumor and no brainstem or other critical structure compression

- Enlarging tumors or symptomatic lesions treated with surgery or radiosurgery

Specific for treatment of vestibular schwannoma: Radiosurgery often considered for vestibular schwannoma, especially for smaller tumors without brainstem compression in the elderly or in patients in poor medical condition; rates of hearing loss and facial weakness are less with radiosurgical treatment than with open surgical resection

- Surgical approaches to cerebellopontine angle (CPA) vestibular schwannomas include translabyrinthine (for patients with poor hearing, retrosigmoid, middle fossa-subtemporal
- Complications of CPA surgery include cranial nerve deficits (risk reflects size of tumor), CSF leak, hemorrhage, stroke

MALIGNANT PERIPHERAL NERVE SHEATH TUMOR[9]

Epidemiology: Age 20–50

- 10% of all soft-tissue sarcomas
- 4% of patients with neurofibromatosis I (half of all MPNST diagnoses)
- Painful

Location: Usually in lower extremities, but ~10% are in head/neck, associated with cranial nerves (trigeminal)

Pathology: Dense hypercellular tumor with anaplastic features (schwannoma-like)

Radiology: Look similar to schwannoma, but with a much more rapid growth rate

- May invade adjacent structures, incite brain edema

Treatment: Wide margin surgery

- Adjuvant chemo (high-dose doxorubicin) and usually radiation therapy

Outcome: 75% recur

- 5-year mortality of 50–75%

MENINGEAL TUMORS

MENINGIOMA

WHO Grading/Subtypes

- Grade I: meningothelial, fibrous, transitional, psammomatous, angiomatous, myxoid, secretory (cea +); grade II: chordoid, clear cell; grade III: papillary, rhabdoid, anaplastic

Epidemiology: 15–20% of all intracranial tumors and autopsy studies estimate an incidence of 30%

- 80% of meningiomas are grade I, 5–20% grade II, and 1–2% grade III
- F > M (especially when in the spine)
- Often express hormonal receptors (progesterone, estrogen, and androgen)
- Patients with meningiomas have a higher incidence of breast cancer and vice versa
- Increased incidence in neurofibromatosis 2
- Multiple in 8%

Genetics: Most commonly, loss of the neurofibromatosis 2 gene on chromosome 22q which encodes a tumor suppressor called merlin (also known as schwannomin)

Location: Typically extra-axial and dural-based, but may arise from choroid plexus in trigone of lateral ventricle; may involve convexity dura, falx, tentorium, dura overlying the skull base, or optic sheath

Radiology: Extra-axial mass (separated from brain by cerebrospinal fluid/vascular cleft)

- Well circumscribed, isointense to brain on T1 and T2 weighted imaging, intense contrast enhancement
- Other characteristic findings include a dural tail (dural enhancement extending away from the primary mass) and hyperostosis of adjacent bone
- Variable calcification
- Rare cystic change or hemorrhage

Pathology: WHO grade I tumors are benign tumors

- Originate from arachnoid cap cells
- +EMA and vimentin stain
- Wide variety of histologic appearances depending on subtype of meningioma
- Atypical meningiomas have increased mitotic activity (four or more mitoses per 10 high-powered fields) or three or more of the following characteristics: Increased cellularity, small cells with high nuclear to cytoplasmic ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and foci of necrosis
- Malignant meningiomas display cytology resembling carcinoma, melanoma or high-grade sarcoma or have > 20 mitoses per high-powered field

Treatment: Gross total resection is the goal and is generally curative for benign meningiomas

- Radiation (radiosurgery for small tumors) often indicated for poor surgical candidates, subtotal resection, unresectable tumors, or high-grade and recurrent tumors

Prognosis: WHO grade I meningiomas have a greater than 80% chance of progression-free survival at 10 years, while only 40–60% of WHO grade II patients are progression free at 10 years

- Median recurrence-free rate of patients with malignant meningioma is 2 years
- Extent of resection predicts risk of recurrence

HEMANGIOPERICYTOMA

Used to be considered a subtype of meningioma, but now considered a distinct pathologic entity

Epidemiology: M > F

- Mean age of 40 to 50 years

Location: Dural based, supratentorial

Pathology: Staghorn vascular channels and absence of the whorls or psammoma bodies seen in meningiomas

- Pericyte cell is postulated to be the cell of origin

Treatment: Endovascular embolization followed by surgery

- Tumor does not respond well to radiation or chemotherapy

Prognosis: Recurrence rates approximately 70% even with gross total resection

- 5-, 10-, 15-year survival rates are 63%, 37%, 21% respectively
- 10–30% metastasize, especially to lung and bone

MESENCHYMAL TUMORS

HEMANGIOBLASTOMA

Epidemiology: 2% of intracranial tumors and 10% of posterior fossa tumors

- Most common primary posterior fossa brain tumor of adults
- Present with a mean age between 20 to 40 years of age
- Male predominance
- 80% of these tumors are sporadic and 20% occur in patients with Von Hippel Lindau syndrome (VHL)
- Secrete erythropoietin → polycythemia

Location: Cerebellar hemispheres > spinal cord > brainstem

- Retina involved in VHL

Radiology: Classically a cystic lesion with an intensely enhancing mural nodule

- 40% can be solid
- Hypervascular and a prominent feeding vessel may be identified
- Often multiple in VHL
- In the spine, often associated with hydromyelia and cord edema

Treatment: Surgical resection versus radiosurgery versus observation depending on size, number, lesion, neurologic deficit, and whether spontaneous lesion or assoicated with VHL; the cyst requires neither resection nor radiation

Outcome: Usually cured with surgery

- Low recurrence rate after gross total resection
- Radiosurgery also has good tumor control rates
- Patients with VHL often have new and multiple lesions despite treatment

CHORDOMA

Epidemiology: < 1% CNS tumors

- Often present with HA, CNVI palsy

Location: Sacrum (50%) > clivus (30%) >> vertebral bodies (usually cervical or upper thoracic)

Radiology: CT shows lytic lesion centered in bone

- Lesion often hypodense on CT
- On MR, hypointense on T1, hyperintense on T2, variable enhancement
- Not usually calcified, but fragments of residual destroyed bone may be present

Pathology: Notochord remnant

- Lobulated, gray, soft with sheets of cords of large vacuolated cells (characteristic physalipherous cells) surrounded by mucin

Treatment: Surgery and high-dose radiation therapy (proton beam, IMRT, and/or radiosurgery)

Outcome: Slowly growing but locally aggressive and invasive

- Depends on extent of resection (complete excision often difficult, especially at skull base)
- 5-year survival 51%, 10-year 35%
- Chordomas metastasize approximately 25–40% and may change to sarcoma
- Recur locally, sometimes along surgical tract

CHONDROSARCOMA

Subtypes: Conventional, clear cell, mesenchymal, and dedifferentiated (conventional most common in skull base)

Epidemiology: Second most frequent primary malignant tumor of bone (25% of all primary osseous neoplasms)

- Usually patients > 40 years of age
- M > F

Location: Skull base location most common: petroclival fissure, parasellar, cerebellopontine angle, paranasal sinuses

Radiology: Rounded mass classically located off-midline in the skull base

- Isointense on T1, bright on T2, brightly enhancing postcontrast
- Variable amount of matrix calcification

Pathology: Negative for epithelial membrane antigen (positive in meningioma), positive for S100

- Biphasic pattern of spindle chondroid cells and well-differentiated cartilage in dense fibromyxoid stroma

Treatment: Surgical resection; IMRT or radiotherapy to residual tumor

Outcome: Better prognosis than chordoma with less metastatic potential

INTRACRANIAL LIPOMA

Epidemiology: 0.1% intracranial tumors

- Usually asymptomatic
- Due to persistence of meninx primitiva, so developmental, not neoplastic
- Associated with other congenital abnormalities including callosal dysgenesis, cephaloceles

Location: 30% near corpus callosum

- Also quadrigeminal cistern, tuber cinereum, cerebellopontine angle, internal auditory canal

Radiology: Follows fat on all sequences: Hyperintense on T1

- Suppresses on fat-saturation sequences
- May see associated calcifications (osteolipoma)

Pathology: Persistence of meninx primativa (<- neural crest)

- Microscopically resemble adipose tissue

Treatment: Usually observed as they are associated with neural structures and normal blood vessels

- Surgery reserved for lesions causing significant mass effect on adjacent structures which is extremely uncommon

LYMPHOMA

Epidemiology: Primary CNS lymphoma (PCNSL) has increased worldwide recently to about 6.6% of all primary intracranial neoplasms because of the AIDS epidemic

- Often seen in immunocompromised patients (i.e., AIDS patients, post-transplant patients or inherited immune disorders such as Wiskott-Aldrich syndrome)
- Epstein-Barr virus (EBV) present in > 95% of tumor cells in PCNSL from immunocompromised patients
- PCNSL affects patients of all ages with a peak incidence in immunocompetent patients during the 6th and 7th decades but younger in immunocompromised patients (10 years for inherited immune patients, 37 years for post-transplant patients, and 39 years for AIDS patients)
- M:F = 3:2

Location: Primary CNS lymphoma usually leads to parenchymal supratentorial masses

- Lesions often multiple
- May involve basal ganglia, corpus callosum, periventricular regions of brain
- Secondary CNS lymphoma (that has spread to CNS from another site in the body) may involve dura or leptomeninges in addition to parenchyma

Radiology: Masses often relatively dense on unenhanced CT due to high cellularity

- Usually intermediate on T1, T2 weighted MR images
- Typically homogeneous enhancement in non-AIDS–related PCNSL, ring-enhancement in AIDS–related PCNSL
- May see mild or moderate reduced diffusion due to high cellularity

Pathology: Perivascular lymphoid cells (B-cell)

Treatment: Biopsy for diagnosis

- Treat with radiation, chemotherapy
- Autologous stem cell transplantation for younger patients is an option

Prognosis: Patients often develop long-term neurotoxicity secondary to combined systemic and intraventricular chemotherapy with whole brain radiation

- Median overall survival is 50 months
- Better in patients less than 61 years of age (75% 5-year survival)

GERM CELL TUMORS (GCT)

Epidemiology: Account for approximately 3% of pediatric brain tumors

- Mean age of 10–20 years (at the onset of puberty in males)

Location: Suprasellar and pineal region

Pathology: Arise from aberrant migration of primordial germ cells

Tumor Markers

See Table 14-1.

GERMINOMA

Epidemiology: Most common pineal region tumor (2/3s of the GCTs)

- 1% of all CNS malignancies
- Peak age 10–30 years
- Male predominance (especially Asian)
- Associated with precocious puberty (if sellar/suprasellar)
- Presents with diabetes insipidus (if involves the pituitary stalk/hypothalamus)

Location: Pineal, suprasellar/sellar

- 10% occur both in the pineal and sellar regions
- May also occur in basal ganglia (especially in Asians)

Table 14-1 Germ Cell Tumor Type and Markers

Tumor Type	beta-HCG[a]	AFP[b]	PLAP[c]	c-Kit
Pure Germinoma	-	-	+/-	+
Germinoma (syncytiotrophoblastic)	+	-	+/-	+
Endodermal sinus tumor	-	+	+/-	-
Choriocarcinoma	+	-	+/-	-
Embryonal carcinoma	-	+	+	-
Mixed GCT[d]	+/-	+/-	+/-	+/-
Mature teratoma	-	-	-	-
Immature teratoma	+/-	+/-	-	+/-

[a]beta-HCG: beta-human chorionic gonadotropin
[b]AFP: alpha-fetoprotein
[c]PLAP: placental alkaline phosphatase
[d]GCT: germ cell tumor
Source: Louis D[5]

Pathology: Large polygonal cells

- Lack necrosis and hemorrhage
- Infiltration of T-cells

Genetics: Approximately 90% of germ cell tumors are associated with structural chromosomal anomalies, especially an isochromosome on chromosome arm 12p known as i(12p)

- Most germinomas contain c-kit mutations

Laboratory analysis: Alpha-fetoprotein, beta HCG, CSF cytology (see Table 14-1)

Radiology: Hyperdense on CT due to increased cellularity

- Isointense on T1 and T2, homogenously enhancing
- Pituitary stalk involvement may be subtle, so check carefully in young patient presenting with diabetes insipidus
- Full neural axis imaging required because CSF seeding is common

Treatment: Pure germinomas are sensitive to radiation

- Mixed tumor types and other GCTs respond much more poorly to radiation
- Chemotherapy includes cisplatin, etoposide, bleomycin

Outcome: Survival 90% at 10 years

- Recurrence 30%

CHORIOCARCINOMAS

Can be primary or metastatic, usually from testicle

- Prognosis poor
- Propensity to hemorrhage

TERATOMAS

Congenital tumors that can be mature (good prognosis if resectable) or immature (poor prognosis)

- Second most common GCT and usually affects young males
- Contains elements from all three layers (endoderm, mesoderm, and ectoderm) including skin, nerve, cartilage, bone fat, muscle, respiratory glands, and GI glands

SELLAR TUMORS

PITUITARY ADENOMA

Referred to as microadenomas when ≤ 1 cm (75%) and macroadenomas when > 1 cm

- May be functional (hormone secreting) or nonfunctional
- Clinical evaluation should include complete endocrinologic work-up and formal visual fields exam (for macroadenomas)

Epidemiology: 10% of intracranial tumors

- Increased incidence in multiple endocrine neoplasia 1 (MEN1)
- F > M with prolactin and ACTH-secreting tumors, M > F with growth hormone–secreting tumors
- If large, may present with bitemporal hemianopsia from compression of the optic chiasm
- Prolactinomas are the most common pituitary tumor

Radiology: CT is not the study of choice, but larger tumors may be seen as isodense sellar/suprasellar mass

- Pituitary apoplexy may cause enlarged hyperdense gland on CT
- Usually intermediate signal intensity on T1 and T2 weighted MRI images
- Enhance moderately, but often less than the normal gland
- Macroadenomas may show cystic or hemorrhagic change
- Sella typically enlarged with macroadenoma

Treatment: Surgery for functioning adenomas secreting TSH, GH, ACTH, or for prolactinomas with visual symptoms or that have failed medical treatment

- Medical therapy for prolactinomas otherwise (see following)

Complications of transsphenoidal surgery: CSF leak, injury to the internal carotid artery, stroke, diabetes insipidus, panhypopituitarism, hemorrhage, sinusitis

Prolactinoma

(Lactotrophic, acidophilic) is the most common pituitary adenoma (30%)

- Can cause amenorrhea and galactorrhea in females and impotence or decreased libido in males (females tend to present earlier due to these symptoms and prolactinomas tend to be larger in males when detected)
- Prolactin level is normally > 150 in patients with these tumors and prolactin level is proportional to the tumor size
- When the prolactin level is elevated but less than 100, this is likely secondary to *stalk effect* rather than a prolactinoma (decreased dopamine causing increased prolactin from compression of the pituitary stalk by a mass)
- Sometimes large prolactinomas can have spuriously normal prolactin levels (*hook effect*) because the overabundance of prolactin over saturates the lab → 1:100 dilution of the serum sample prior to analysis will clarify the prolactin level in these cases
- These tumors often respond to dopamine agonists (bromocriptine, cabergoline
- Surgery reserved for medical failure or intolerance of medications

Growth hormone–secreting tumors

Somatotrophic, acidophilic

- Second most common secreting pituitary adenoma (13%)
- Causes acromegaly in adults and gigantism in children
- Treatment is with surgery and with octreotide (a somatostatin analog)

Corticotrophic (ACTH)–secreting tumors

Basophilic

- Causes Cushing's disease and accounts for 10% of pituitary adenomas
- 40% exhibit *gsp* oncogene mutation

Nelson's syndrome

Occurs after bilateral adrenalectomy

- Eliminates adrenal cortisol production, therefore releasing the cortisol's negative feedback which can allow any preexisting pituitary adenoma to grow unchecked
- Continued growth can cause mass effect due to physical compression of brain tissue, along with increased production of ACTH and MSH (causes hyperpigmentation)
- Treatment is surgical

FSH/LH–secreting tumors

Account for 9% of pituitary adenomas and generally occur in the elderly

Thyrotrophic or TSH–secreting tumors

Basophilic

- Cause hyperthyroidism
- Account for 1% of pituitary adenomas

Nonsecreting null cell tumor (oncocytoma)

Do not secrete hormone

Pituitary carcinomas

Rare and display increased mitotic activity, nuclear atypia and necrosis

Pituitary apoplexy

Sudden onset of headache with neurological or endocrinologic disturbance due to hemorrhagic necrosis of the pituitary adenoma

Symptoms/Signs: Visual changes, marked endocrine dysfunction (can lead to cardiovascular collapse), ophthalmoplegia, headache

Treatment: Emergent surgery and steroid replacement

CRANIOPHARYNGIOMA

Epidemiology: 9% of all pediatric intracranial tumors and 2–5% of all intracranial tumors

- Peak age 0 to 20 years with a second peak at 50 years
- May cause growth retardation, headache, nausea/vomiting, diabetes insipidus, hydrocephalus (3rd ventricle compression), visual field deficits, endocrine dysfunction

Pathology: Derived from squamous cells in Rathke's cleft

- Adamantinomatous (children; cystic with calcifications), papillary (adults; solid without calcification)
- Macroscopically filled with cholesterol-rich fluid with a "motor oil" appearance

Radiology: Macrocysts and calcifications common

- Cysts often bright on T1 due to proteinaceous, hemorrhagic cyst contents
- Heterogeneous enhancement: rim enhancement around cysts, as well as areas of solid enhancement

Treatment: Surgical resection

- Often recurs especially with subtotal resection or with tumors greater than 5 cm
- Sometimes irradiated
- Can place catheter into the cyst and drain the cyst (can also inject p32 into the cyst for intratumoral treatment)

Outcome: Slowly growing benign tumors, but can invade critical structures causing vision loss, endocrine dysfunction

- Papillary variant (more common in adults) has a better prognosis

RATHKE'S CLEFT CYST

Epidemiology: F > M

- 30 to 40 years old
- May be incidentally found or may present with visual or endocrine (stalk effect) symptoms

Location: Up to 70% both intra and suprasellar

- May be pre- or retrochiasmatic

Radiology: Cystic lesion that is hypointense on CT, hyperintense on T2

- No calcifications or enhancement

Pathology: Remnant of the craniopharyngeal duct (Rathke's pouch)

- Develops when the proximal part of pars intermedia closes early (day 24) and the distal cleft remains open between the pars distalis and pars nervosa
- Contain watery, mucous fluid lined with ciliated cells and columnar/cuboidal epithelial cells

Treatment: Transsphenoidal surgery if symptomatic

LYMPHOCYTIC HYPOPHYSITIS[10]

Autoimmune inflammatory lesion of pituitary gland

Epidemiology: Young women in late pregnancy or postpartum

Symptoms: Include hyperprolactinemia, headache, visual field deficits, pituitary insufficiency (ACTH earliest and most frequent)

Radiology: Diffuse homogeneous enlargement and enhancement of pituitary gland

- Optic chiasm may be displaced
- May involve surrounding dura → dural tail

Treatment: Steroids

Pathology: Lymphocytic infiltrate

Outcome: Fatality 8% (secondary to adrenal insufficiency)

LANGERHANS CELL HISTIOCYTOSIS (LCH)

CNS presentation: Typically presents with diabetes insipidus

- Temporal bone involvement common and may lead to a chronically draining ear

Radiology: Classically results in an enhancing lesion of the pituitary stalk and/or hypothalamic/chiasmal region

- Homogeneous on T1 and T2 weighted images
- May cause nonspecific brain parenchymal lesions, usually along perivascular spaces, but this is far less common

Pathology: Infiltrates composed of Langerhans cells (LCs), macrophages, lymphocytes, plasma cells and mature eosinophils

- Birbeck granules on electron microscopy

Treatment: Radiation for isolated sellar region disease

- Chemotherapy and steroids for systemic disease (it often involves the bone, lung, and liver)

- **Eosinophilic Granuloma** = solitary LCH lesion of skull or spine
- **Hand-Schüller-Christian Disease** = multifocal LCH in bone and hypothalamus
- **Letterer-Siwe Disease** = multifocal disease involving skin, lymph nodes, viscera, and rarely the CNS

METASTASES

Epidemiology: Most common tumor to involve the brain

- Some studies quote 25% of all cancer patients at some point in the disease process will develop CNS metastases
- Secondary to hematogenous spread
- Most common tumors to metastasize to the brain are lung, breast, prostate, melanoma, renal, and colon cancers
- Metastases with a high propensity to hemorrhage include thyroid, choriocarcinoma, renal cell, lung, and melanoma

Radiology: Often multiple, commonly at grey-white junction

- May be ring enhancing or homogeneous
- May have cysts and hemorrhage
- Frequently associated with significant vasogenic edema

Treatment: Surgery, radiosurgery, and whole brain irradiation

- Solitary lesions which are surgically accessible are often resected followed by whole brain radiation (stereotactic radiosurgery is an alternative approach) while multiple lesions are often treated with whole brain irradiation (depending on the number of lesions, some institutions will treat with radiosurgery up front and save whole brain radiation for recurrence or progressive disease)
- Steroids for treatment of vasogenic edema

Outcome: Depends on tumor type, age, Karnofsky score, number of metastases, and whether primary disease is controlled

- Surgical resection improves outcome for solitary lesions

Dural and Leptomeningeal Metastases

Carcinomatous meningitis (leptomeningeal metastatic disease) is most common with lung and breast cancer

- Thickening and variable nodularity of leptomeninges, often best appreciated in IACs and over brainstem and cerebellar folia
- Hematogenous metastases to the dura may also occur and present as dural plaques that mimic meningioma

CYSTS

ARACHNOID CYST

Etiology: Nonneoplastic, developmental abnormality due to separation of the arachnoid membrane → wall thickens with collagen deposition

Pathophysiology: Active CSF secretion from cyst membrane, osmotic gradient, ball-valve mechanism

Location: Most commonly found in the middle fossa

Radiology: Follows CSF on all sequences, no enhancement

- Low signal on diffusion weighted imaging (distinct from epidermoid)

Bobble-Head Doll Syndrome

Pathophysiology: Dilated 3rd ventricle due to suprasellar arachnoid cyst distortion of the red nucleus and dentatorubrothalamic pathway, with compression on medial thalamus

Symptoms: Macrocephaly, ocular disturbance, psychomotor retardation, endocrine dysfunction

COLLOID CYST

Location: Usually in anterior/superior portion of 3rd ventricle between fornices at foramen of Monro

- Attached to the roof of the 3rd vent

Pathology: Outer fibrous layer, inner layer of simple cuboidal versus pseudostratified epithelium

- May derive from endodermal tissue of the paraphysis (vestigial remnant of 3rd vent structure)

Radiology: Dense on CT, bright on T1 due to high protein content

- Variably hypointense on T2
- Typically nonenhancing
- May be associated with obstructive hydrocephalus

Treatment: Surgery for size > 7 mm or symptomatic

Outcome: Has been associated with sudden death (acute obstructive hydrocephalus)

EPIDERMOID CYST

Epidemiology: Up to 2% of brain tumors

- Usually seen in adults

Pathophysiology: Ectopic ectodermal cells retained within the neural groove at 3–5 wks gestation

- Rupture may lead to aseptic meningitis (versus dermoid cyst which can lead to bacterial meningitis)

Location: Most commonly at cerebellopontine angle

- Also suprasellar/parasellar, middle fossa, prepontine cistern
- May be associated with dermal sinuses, usually along spine in kids

Radiology: Lobulated, slightly irregular margin

- Similar to CSF on CT and T1/T2 weighted images
- Very bright signal on diffusion-weighted images (epidermoid -> hyper versus arachnoid cysts -> hypo)
- Nonenhancing with contrast

Pathology: Fibrous capsule, "pearly tumor"

- Keratin and cholesterol crystals in center of lesion, squamous epithelium

DERMOID CYST

Epidemiology: 0.3% of brain tumors

- M > F
- More common in pediatric population
- Rupture may lead to acute clinical presentation with chemical meningitis (*Mollaret's meningitis*)
- May be associated with cutaneous tracts (skull base, occipital region, spine)
- May be associated with other congenital malformations (e.g., spinal dysraphism)
- Generally present at an earlier age than epidermoids

Location: Typically midline

- Lumbosacral spine > > parasellar > floor of anterior cranial fossa/nasal > posterior fossa

Radiology: Generally rounded and well circumscribed

- Typically bright on T1 weighted images due to fat content
- Suppresses on fat saturation images
- If ruptured, then fat globules may be seen distributed throughout the subarachnoid space

Pathology: Epithelial and dermoid elements: dermal appendages, hair follicles, macrophages, giant cells, sebaceous glands, sweat glands

- Inclusion of ectodermal elements in neural ectoderm during neurulation

Treatment: Surgical resection

CHOLESTEROL GRANULOMA/CYST

Symptoms: Headache, CN VI dysfunction

Location: Petrous apex

Pathophysiology: Chronic middle ear inflammation → obstruction of aerated petrous bone apex with accumulation of secretions and blood products

Radiology: Expansile lesion of petrous apex

- Bone thinning and lysis on CT
- Hyperintense on T1 and T2 weighted images
- No suppression on fat saturation images

Treatment: Surgical drainage if symptomatic or expanding

LEPTOMENINGEAL CYST

Uncommon complication of skull fracture in young child

- Simple skull fractures usually heal quickly in young children
- When skull fracture in infant or young child is complicated by dural tear, then the fracture may subsequently enlarge and present as a pulsatile mass
- Herniation of brain tissue into growing fracture may occur

Treatment: Excision and repair

PSEUDOMENINGOCELE

Collection of CSF caused by trauma, congenital, or postoperative

- Tear in the dura and leptomeninges such that CSF can leak out and accumulate in soft tissues and wall itself off, but it is not contained by dura as a true meningocele would be

Treatment: Observation, epidural blood patch, reoperation (repair of CSF leak), lumbar drain

OTHER

JUVENILE NASOPHARYNGEAL ANGIOFIBROMA

Usually arise along posterolateral nasal wall at the level of the sphenopalatine foramen

- Presentation typically nasal obstruction and variable epistaxis in teenage males
- Enlarged vascular channels in fibrovascular stroma
- Often extend to skull base
- Highly vascular, so do not biopsy

PARAGANGLIOMA (GLOMUS) TUMOR

In the head and neck and skull base, commonly occur at level of jugular bulb (glomus jugulare), cochlear promontory (glomus tympanicum), carotid sheath (glomus vagale), and carotid body (carotid body tumor)

- Heterogeneous, "salt-and-pepper" appearance on MRI due to prominent intratumoral flow voids
- Can secrete catecholamines/metanephrines
- Usually benign, but can be locally invasive
- Present variably with pulsatile tinnitus and/or hearing loss, lower cranial nerve deficits, neck mass

Treatment: Resection or irradiation (radiosurgery if small)

HAMARTOMA OF THE TUBER CINERUM[11]

Mass of ectopic cerebral grey matter between the infundibulum and mammillary bodies that is isointense to gray matter on CT and on MR sequences

- Benign
- Typically presents in children with either precocious puberty (hypothalamic inhibition disrupted) or gelastic (laughing) seizures

Management: Observation

NASAL GLIOMA[12]

Rare benign congenital mass of heterotopic glial tissue that is typically located in the midline at the level of the nasal bridge or nasal root

- M > F
- Arises from an abnormal closure of the fonticulus frontalis → extracranial ectopic rest of glial tissue
- No intracranial connection (though may be connected to dura in 15%)

Management: Observation, surgical resection if enlarges

CHAPTER 15 ■ NEURORADIOLOGY

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Table 15-1 Differential Diagnosis by Location and Imaging Characteristics of Intracranial Neoplasms[1,2]

Location	Tumor	T1	T1c	T2	Comments
Lobar					
	Metastasis	Hypo/Iso	++	Iso/Hyper	Often cystic or hemorrhagic; typically extensive edema
	GBM	Hypo/Iso	++	Iso/Hyper	Often involve corpus callosum; ring >> solid enhancement; often cystic or hemorrhagic; + edema
	Oligodendroglioma	Hypo/Iso	50/50	Hyper	Frontal > other; involves cortex; calcifications common
	Grade II/III Astrocytoma	Hypo	Varies	Hyper	More enhancement as grade increases; edema usually with grade II, variable with grade III
	Ganglioglioma	Hypo/Iso	Varies	Hyper	Often cysts, calcification; cortical location; seizures
	DNET	Hypo	+/-	Hyper	Often multiple cysts, nodular enhancement; cortical; seizures
	PNET	Hypo/Iso	+	Iso; cysts hyper	Heterogeneous; variable edema; usually children
	Atypical teratoid-rhabdoid tumor	Iso	+	Iso/hyper	Children < 3 yrs; heterogeneity (cysts, hemorrhage, necrosis); large
Non-neoplastic "mimics"	Tumefactive demyelination	Hypo/Iso	+	Hyper/Iso	Less mass effect for size than neoplasm; "open ring" of incomplete enhancement
	Infection (abscess)	Hypo/Iso	++	Hyper	Appearance varies by etiology; pyogenic = ring-enhancing with large edema, DWI bright

Pineal Region[3]					
Pineal gland	Germinoma	Iso	++	Iso	Usually homogeneous
	Teratoma	Varies	50/50	Varies	Heterogeneous; often cysts, calcification, fat
	Embryonal cell carcinoma	Hypo/Iso	+	Hyper/Iso	Heterogeneous; adolescents
	Pineocytoma	Hypo/Iso	+	Iso/Hyper	Round, often calcified, heterogeneous; brain edema uncommon
	Pineoblastoma (PNET)	Hypo/Iso	+	Iso	Usually young children; associated with retinoblastoma; calcification uncommon, edema+
	Pineal cyst	Hypo	-	Hyper	Usually incidental; residual gland enhances around margin
	Astrocytoma (supporting cells)	Hypo/Iso	Varies w grade	Hyper	
Brainstem	Tectal glioma	Hypo/Iso	Uncommon	Hyper	Often benign pathologically, but unresectable; locally invasive
Quadrigeminal cistern	Arachnoid cyst	Iso to CSF	-	Iso to CSF	Sharply demarcated; like CSF on DWI (low signal intensity)
	Epidermoid cyst	Hypo	-	Hyper	Irregular margin; very bright on DWI
	Dermoid cyst	Hyper	-	Varies	Fat components suppress w fat saturation; may rupture into subarachnoid space
Intraventricular					
Frontal horns	Giant cell astrocytoma	Hypo/Iso	++	Iso/Hyper	Arise from foramen of Monro; associated w/ tuberous sclerosis

(*Continued*)

Table 15-1 Differential Diagnosis by Location and Imaging Characteristics of Intracranial Neoplasms[1,2] (continued)

Location	Tumor	T1	T1c	T2	Comments
Intraventricular					
	Central neurocytoma	Iso	+	Hyper	"Feathery" enhancement; attached to septum pellucidum
	Subependy-moma	Hypo/ Iso	Varies	Hyper	Older patients; lobulated lesion
Body of lateral ventricles	Central neurocytoma	Iso	+	Hyper	"Feathery" enhancement; attached to septum pellucidum
	Subependy-moma	Hypo/Iso	Varies	Hyper	Older patients; lobulated lesion
	Oligodendro-glioma	Hypo/Iso	50/50	Hyper	Rare in this location; many reclassified as central neurocytoma
Atria of lateral ventricles	Choroid plexus papilloma	Hypo/Iso	++	Hyper/ Iso	Most common location in children; highly vascular
	Metastasis	Iso	++	Iso/Hyper	Usually to choroid plexus
	Meningioma	Iso	++	Iso	More common in older woman, usually on L
	Choroid plexus cyst	Iso to CSF	-	Iso to CSF	Commonly bilateral; incidental finding; low on DWI (iso to CSF)
	Choroid plexus xanthogranuloma	Hypo and iso	-	Variable	Often bilateral; incidental finding in older patients; often bright on DWI
Foramen of Monro and 3rd ventricle	Colloid cyst	Hyper	-	Iso/Hyper	Anterosuperior 3rd ventricle; round; usually dense on noncontrast CT
	Metastasis	Iso	++	Iso	Met to choroid plexus

	Choroid plexus papilloma	Hypo/Iso	++	Iso/Hyper	Young children; very rare location; highly vascular
	Subependy-mal giant cell astrocytoma	Hypo/Iso	++	Hyper/ Iso	Typically associated w/ tuberous sclerosis; heterogeneous
	Germinoma	Iso	++	Iso/Hyper	More common in young patients
	Meningioma	Hypo/Iso	++	Iso	Arises from tentorium or lower falx
	Ependymoma	Hypo/Iso	+	Hyper/Iso	Rare location; lobulated intraventricular mass
Aqueduct	Tectal glioma	Hypo/Iso	50/50	Hyper	Often indolent; often assoc w NF1
	Subependy-moma	Hypo/Iso	Varies	Hyper	4th ventricular location most common
	Hemangio-blastoma	Iso	++	Hyper	Rare location, flow voids if lesion large
4th ventricle	See Cerebellopontine Angle (CPA)				
All	High-grade Astrocytoma	Hypo/Iso	Incr w/ grade	Iso/Hyper	Usually due to gross extension into ventricles and/ or subependymal spread
Cerebellopontine Angle (CPA)					
Cistern	8th nerve schwannoma	Hypo/Iso	++	Hyper;(Hypo to CSF)	Most common mass lesion of CPA; typically bilateral in NF-2
	Meningioma	Hypo/Iso	++	Iso	Broad dural base; may be calcified
	Epidermoid cyst	Hypo	-	Hyper	Bright on DWI; often irregular margin
	Arachnoid cyst	Hypo	-	Hyper	Follows CSF on DWI; smooth margin
Internal auditory canal	8th nerve schwannoma (acoustic neuroma)	Iso	++	Hyper (hypo to CSF)	Classic: “ice cream cone” shape of IAC and CPA components

(*Continued*)

Table 15-1 Differential Diagnosis by Location and Imaging Characteristics of Intracranial Neoplasms[1,2] (continued)

Location	Tumor	T1	T1c	T2	Comments
Cerebellopontine Angle (CPA)					
4th ventricle/ lateral recess	Ependymoma	Hypo/Iso	+	Hyper/ Iso	Typically arises from floor; lobulated; extension through foramina of Magendie and Luschka common
	Choroid plexus papilloma	Hypo/Iso	++	Hyper/ Iso	Most common location in adults; multilobulted lesion
	Medulloblastoma	Iso	+	Iso	Classically arises from roof; CSF spread common
	Low-grade astrocytoma	Hypo/Iso	Variable	Iso/Hyper	Includes dorsally exophytic brainstem glioma and ventrally exophytic cerebellar pilocytic astrocytoma
	Metastasis	Hypo/Iso	++	Iso/Hyper	Typically metastasis to choroid plexus; rarely leptomeningeal[4]
Brainstem and cerebellum	Astrocytoma, grades 2 to 4	Hypo/Iso	50/50	Iso/Hyper	Enhancement, heterogeneity increase w/ grade
	Pilocytic astrocytoma	Hypo/Iso	++	Hyper	Typically cystic w/ enhancing mural nodule; children
	Medulloblastoma	Hypo/Iso	+	Iso	Cerebellar hemisphere location seen in teens/adults
	Hemangioblastoma	Iso	++	Hyper	Larger lesions cystic w/ enhancing mural nodule; associated with VHL
	Atypical teratoid-rhabdoid tumor	Iso	+	Varies	Usually off midline; cysts, hemorrhage frequent; may mimic medulloblastoma

	Dysplastic ganglio-cytoma (Lhermitte-Duclos dz)	Hypo/Iso	Rare	Hyper	Striated appearance; associated with Cowden syndrome
Sellar Region					
Sellar	Pituitary microadenoma	Iso	+	Iso/Hyper	Typically enhances less than surrounding gland on dynamic imaging; < 10 mm
	Pituitary macroadenoma	Iso	++	Iso/Hyper	Can be cystic or hemorrhagic; ≥ 10 mm; classically enlarges sella, extends into suprasellar cistern
	Cyst (Rathke's cleft or pars intermedia)	Varies/hypo	-	Varies/hyper	Appearance varies w/ protein content of cyst; often extends to suprasellar cistern
Suprasellar	Craniopharyngioma	Varies	+	Hyper	Usually mixed cystic and solid; calcification on CT; cysts often bright on T1WI
	Meningioma	Iso	++	Iso	Separate from pituitary gland; often tuberculum
	Hypothalamic/chiasmal glioma	Iso	Varies	Hyper/ Iso	Pilocytic astrocytoma
(Nonneoplastic)	Epidermoid cyst	Hypo	-	Hyper	Very bright on DWI; lobulated, slightly irregular
	Dermoid cyst	Hyper	-	Varies	May rupture into subarachnoid space; fat content suppresses w/ fat sat
	Lipoma	Hyper	-	Iso to fat	Follow fat on all sequences; often partly calcified
	Arachnoid cyst	Iso to CSF	-	Iso to CSF	Sharply demarcated; like CSF on DWI
	Aneurysm	Varies	Varies	Varies	Highly variable signal: heterogeneous, lamellated, flow void, phase artifact
Infundibulum	Germinoma	Iso	+	Iso	Typically present with diabetes insipidus
	Lymphoma/ Leukemia	Iso	+	Iso	Often other sites of CNS involvement

(*Continued*)

Table 15-1 Differential Diagnosis by Location and Imaging Characteristics of Intracranial Neoplasms[1,2] (continued)

Location	Tumor	T1	T1c	T2	Comments
Sellar Region					
	Sarcoid	Iso	+	Iso	Associated w/ hilar adenopathy, elevated ACE level
	Histiocytosis	Iso	+	Iso	Associated w/ lytic bone lesions
	Metastasis	Iso	+	Iso/Hyper	Often other lesions
	Pituicytoma/ Choristoma	Hypo/Iso	Varies	Hypo/ Iso	Posterior pituitary, infudibular; rare
Hypothalamic/ Chiasmal	Astrocytoma[5]	Hypo/Iso	Varies	Hyper	Often pilocytic and associated with NF1; variable cysts, hemorrhage uncommon
	Germinoma	Hypo/Iso	++	Hyper/Iso	
	Metastasis	Hypo/Iso	++	Hyper/Iso	
(Nonneoplastic)	Hamartoma	Iso	-	Iso	Tuber cinereum, sessile or pedunculated; follows gray matter
Cavernous sinus	Meningioma	Iso	++	Iso	Often a dural tail extending along skull base; hyperostosis
	Schwannoma	Iso	++	Hyper	Rounded, well circumscribed; cysts common
	Metastasis	Iso	+	Iso/Hyper	More infiltrative than meningioma
	Pituitary adenoma	Iso	+	Iso	Usually extension of a sellar lesion
	Lymphoma	Iso	++	Iso	Can be identical to metastasis, sarcoid, LCH; often bilateral
Nonneoplastic	Infection	Iso	+	Iso/Hyper	Low or iso on T2 if fungal

	Tolosa Hunt (orbital inflammatory) syndrome	Iso	+	Iso	Commonly presents with retroorbital pain; cavernous ICA may be narrowed
	Cavernous sinus thrombosis	Iso	-	Iso/Hyper	Filling defect in sinus; bland vs. septic (often assoc w/ infection)
Skull Base					
Anterior (frontal sinuses, cribriform plate, ethmoid roof), central (sphenoid bone, basiocciput), and posterolateral (temporal bone, jugular foramen)					
Anterior skull base	Squamous cell carcinoma	Iso	+	Iso	Most arise from maxillary sinus; bone destruction common
	Rhabdomyosarcoma	Hypo/Iso	++	Iso	Peak incidence 2–5 years of age[6]
	Esthesioneuroblastoma	Iso	+	Iso	Typically arise in olfactory recess; may see peripheral cysts w/ intracranial extension
	Adenoid Cystic Carcinoma	Iso	+	Iso/Hyper	Infiltrative; perineural spread of disease
	Inverted papilloma[6,7]	Hypo/Iso	+	Iso/Hype	Lateral nasal wall or sinus origin; cerebriform pattern
	Meningioma	Iso	++	Iso	Along planum sphenoidale or olfactory groove
	Metastasis	Hypo/Iso	++	Iso/Hyper	May arise from bone or dura
(Nonneoplastic)	Mucocele	Hyper	- (unless infected)	Varies	Well-defined expansile mass; signal intensity varies w protein content, viscosity[6]
	Nasoethmoidal cephalocele	Hypo/Iso	-	Iso/Hyper	CSF +/- brain; signal characteristics depend on contents
Central skull base	Chordoma	Hypo	+	Hyper	Typically midline, arises from clivus
Skull Base					
	Chondro-sarcoma	Hypo	++	Hyper	Typically off-midline, petro-clival fissure

(*Continued*)

Table 15-1 Differential Diagnosis by Location and Imaging Characteristics of Intracranial Neoplasms[1,2] (continued)

Location	Tumor	T1	T1c	T2	Comments
	Metastasis	Iso	++	Iso	Bone destruction, irregular margin
	Myeloma	Hypo	+	Hyper	
(Superior extension to central skull base)	Nasopharyngeal carcinoma	Iso	+	Iso	Often extends to clivus; nodal metastases
	Juvenile angiofibroma	Iso	++	Iso/hyper	Teenage males; visible flow voids
(Inferior extension to central skull base)	Pituitary adenoma	Iso	++	Iso	May extend to clivus, sphenoid sinus
	Meningioma	Iso	++	Iso	Dural base; hyperostosis; common along sphenoid wing
(Nonneoplastic)	Sinusitis	Varies	+	Varies	If fungal, often dark on T2; heterogeneous signal intensity
Posterolateral skull base	Metastasis	Hypo/Iso	++	Iso/Hyper	Irregular, bone destruction, often multiple
	Meningioma	Hypo/Iso	++	Iso	Dural based, may be calcified
(Nonneoplastic)	Osteomyelitis	Hypo/Iso	+	Iso/Hyper	Marrow space infection
Petrous apex	Cholesterol granuloma	Hyper	-	Hyper	Expansile lesion of petrous apex
	Cholesteatoma	Hypo/Iso	-	Hyper	High signal on DWI
	Chondrosarcoma[8]	Hypo/Iso	++	Hyper	Extend laterally from petroclival fissure

Posterior petrous face	Endolymphatic sac tumor[8]	Varies	+	Varies	Hypervascular, heterogeneous, associated w VHL
Jugular foramen	Schwannoma	Iso	++	Hyper	Smooth remodeling of bone
	Meningioma	Hypo/Iso	++	Iso	Dural based, often calcified
	Paraganglioma	Iso	++	Iso/Hyper	Flow voids, irregular margin
	Metastasis	Hypo/Iso	++	Iso/hyper	Bone destruction, pain
Dural/Leptomeningeal					
	Meningioma	Hypo/Iso	++	Iso	Hyperostosis, dural based, dural tail
	Metastasis	Hypo/Iso	++	Hyper/ Iso	May be associated with bone erosion
	Hemangio-pericytoma	Iso	++	Iso	Mimics meningioma, more lobulated, less broad dural base
Nonneoplastic	Infection	Iso	+	Iso	Appearance varies by etiology
	Sarcoidosis	Iso	++	Iso	Nodular infiltration of dura, leptomeninges; may involve parenchyma, usually extending along perivascular spaces
	Tuberculosis	Iso	++	Hypo	Variable enhancement
	Histiocytosis	Iso	++	Hyper	Can look similar to sarcoid; often involves temporal bone, causes bone erosion
	Lymphoma/ Leukemia	Iso	++	Iso	Mimics other nonspecific infiltrative lesions (e.g., metastases, sarcoid)

NOTE: Hypo/Iso/Hyperintensity are relative to brain parenchyma, typically gray matter.
GBM = glioblastoma multiforme, VHL = Von Hippel Lindau, mets = metastases, LCH = Langerhans cell histiocytosis, ICA = internal carotid artery
Sources: Osborn[1], Osborn et al.[2],

ADDITIONAL DIFFERENTIAL DIAGNOSES[9–11]

Causes of Restricted Diffusion (DWI)[12]

- Arterial infarction: Due to cytotoxic edema. With true reduced diffusion, areas that are bright on DWI should be dark on the corresponding apparent diffusion coefficient (ADC) map. With vasogenic edema, there can be high signal on DWI due to "T2 shine-through" and ADC is not low.
- Venous infarction: Variable regions of reduced diffusion
- Abscess: Pyogenic abscess typically has central reduced diffusion
- Viral encephalitis: Notably HSV 1; reduced diffusion in affected cortex
- Prion disease (Jacob-Creutzfeld Disease): Variable reduced diffusion in cortical ribbon ("cortical ribboning") and in deep gray nuclei
- Acute demyelination (e.g., multiple sclerosis plaque – also bright on T2/Flair)
- Mitochondrial disease: Areas of acute injury show reduced diffusion
- Toxic/metabolic insult (e.g., methotrexate toxicity)
- Certain tumors: Typically those with high nuclear-to-cytoplasmic ratio such as lymphoma and other small round blue cell tumors
- Epidermoid cyst: Helpful in distinguishing from arachnoid cyst
- Hematoma (subacute hemorrhage)

Skull Tumor

Dermoid, epidermoid, fibrous displasia, metastatic lesion, aneurysmal bone cyst, osteoma, osteoblastoma, osteoid osteoma, chordoma, fibrosarcoma, giant cell tumor

- "Pseudosubarachnoid hemorrhage," as is seen with severe increased ICP and low density brain, making meninges seem dense

Wormian Bone

Multiple areas of ossification skull cranial sutures (lambdoidal, posterior sagittal, tempero-squamous)

- Normal up to 6 months of age
- Mnemonic: *PORKCCHOPS* = **P**kynotodysostosis, **O**steogenesis imperfecta, **R**ickets, **K**inky hair syndrome of Menke, **C**liedocranial dysplasia, **C**retinism, **H**ypophospatasia, **O**topalatodigital syndrome, **P**rimary acroosteolysis, Pachydermoperiostosis, **S**yndromes and Chromosome disorder (e.g., Trisomy 21)

Dural-Based Lesions

Meningioma, metastases, hemangiopericytoma, sarcoidosis, LCH, TB

Increased Density in Subarachnoid Space on Noncontrast CT

Blood, pus, tumor

Cerebral Calcifications

Idiopathic (basal ganglia, pineal gland, Fahr's disease), neoplastic (tumor, tuberous sclerosis), metabolic (hypo-/hyperparathyroid hormone), vascular (Sturge-Weber syndrome, postanoxic, posthemorrhage), inflammatory,

developmental (Trisomy 13, Cockayne's disease), infectious (AIDS in kids; TORCH infection, CMV > rubella, toxoplasmosis, herpes simplex)

Ring-Enhancing Lesions

MAGIC DR → metastatic, abscess, glioblastoma multiforme, infarct, contusion, demyelination, radionecrosis

- Also includes other infection (toxoplasmosis, fungal infection, tuberculoma, parasitic), subacute infarct

Cystic Lesions

Neoplastic → pilocytic astrocytoma, desmoplastic infantile ganglioglioma, ependymoma (in spine, not so much in brain), hemangioblastoma, pleomorphic xanthoastrocytoma, craniopharyngioma, meningioma (rare), schwannoma (if large)

- Nonneoplastic → developmental cysts (epidermoid, arachnoid, choroid, colloid, rathke, endodermal, ependymal)

Bilateral Thalamic Signal Abnormality

Vascular (arterial: artery of Percheron infarction, top of the basilar syndrome, vasculitis; venous: internal cerebral vein/vein of Galen/straight sinus occlusion or hypertension due to AVF); infectious (viral encephalitis, PML); demyelinating (ADEM, osmotic); metabolic (Wernicke encephalopathy, cytochrome C oxidase deficiency); neoplastic (astrocytoma, lymphoma)

Corpus Callosum

- Lesions that extend across the corpus callosum: GBM, lymphoma, demyelination (PML, Marchiafava Bignami)
- Abnormal corpus callosum signal that resolves: Seizures, trauma, antiepileptic drugs, PRES, demyelination

Table 15-2 Hemorrhage Appearance on MRI

Stage	Time from Stroke	T1	T2
Hyperacute	4–6 hours	Isointense	Hyperintense
Acute	7–72 hours	Isointense	Hypointense
Early Subacute	4–7 days	Hyperintense	Hypointense
Late Subacute	1–4 weeks	Hyperintense	Hyperintense
Early Chronic	weeks to months	Hyperintense	Hyperintense
Late Chronic	months to years	Hypointense	Hypointense

MR SPECTROSCOPY[13]

Plots the relative concentration of a given metabolite versus the effect that the metabolite has on the rotational frequency of protons within the sample (measured in parts per million [ppm])

- Metabolite peaks have characteristic ppm locations on the x-axis, and the amplitudes of their respective peaks (y-axis) have characteristic relationships in normal and abnormal brain.

Table 15-3 Most Important MR Spectroscopy Peaks

Marker	Location (ppm)	Significance
Lipid/Lactate	1.3	inflammation, necrosis, anaerobic glycolysis
N-acetylaspartate (NAA)	2.0	neuronal viability
Creatine	3.0	energy metabolism; useful reference peak as generally stable
Glutamine/Glutamate (glx) (GABA)	2.2	neuronal damage (astrocytes), neurotransmitters
Choline	3.2	membrane turnover (phospholipid synthesis)

Table 15-4 Clinical Application of MR Spectroscopy

Category	Clinical Condition	Metabolite
Neoplasm	High-grade glial neoplasm	Increased: choline, lactate, lipids; decreased: NAA
	Meningioma	Increased: alanine, glutamates; decreased: creatine
	Metastases	Increased: choline, lactate, lipids; decreased: NAA
	Lymphoma	Increased: choline; decreased: NAA
Infection	Abscess	Increased lactate, succinate, alanine, acetate, lipids; low NAA
Metabolic	Ethanol Use	Triplet
	Diabetic ketoacidosis	Glucose, acetone
	Maple syrup urine disease	Branched chain amino acids
	Galactosemia	Galactiol
	Phenylketonuria (PKU)	Phenylalanine
	Lipid storage disease	Lipids
	Canavan disease	NAA
	Leigh disease, MELAS	Lactate
	Peroxisomal disorder	Scyllo-inositol
Other	Radiation necrosis	Increased: lipids, lactate, choline
	Alzheimer disease	Increased: myoinositol; decreased: NAA
	Down syndrome	Increased: myoinositol; decreased: NAA

NOTE: Can also see mannitol (after treatment for elevated ICP) at 3.88 ppm

CHAPTER 16 ■ PERIPHERAL NERVES[1,2]

David McCall, MD

PERIPHERAL NERVE INJURY AND HEALING

WALLERIAN DEGENERATION

Process of axonal degeneration distal to the site of injury or transaction; occurs in both the central and peripheral nervous system; injury → macrophages enter the axon and remove myelin/debris → Schwann cells stimulate axonal sprouts → axonal sprouts follow the basement membrane to the renewed connection → Schwann cells remyelinate the axon. Growth occurs at a rate of about 1 mm per day (= 1 inch per month and up to twice this rate in young children and infants).

MASTICATION AND FACIAL EXPRESSION

- Muscles of mastication: All innervated by V3 of trigeminal nerve (CN V)
- Close jaw: Masseter, teMporalis, Medial pterygoid (M's Munch)
- Open jaw: Lateral pterygoid (L Lowers)
- Muscles of facial expression: All innervated by facial nerve (CN VII)
- Branches of the facial nerve (CNVII): "To Zanzibar by Motor Car": Temporal, zygomatic, buccal, masseteric, cervical
- Muscles with GLOSSUS: All innervated by hypoglossal (CN XII) except palatoglossus (CN X)
- Muscles with PALAT: All innervated by vagus (CN X) except tensor veli palatini (V3 of CN V)

CERVICAL PLEXUS

From C1–C4 ventral primary rami

■ Motor branches

Ansa cervicalis

- Superior ramus (C1)—geniohyoid and thyrohyoid muscles
- Inferior ramus (C2,3)—SOS: sternohyoid, omohyoid, and sternothyroid
- Phrenic nerve (C3, 4, 5)—"Keeps the Diaphragm Alive"

■ Sensory Branches

Lesser occipital, greater auricular, transverse cervical, supraclavicular, and meningeal branch that passes through foramen magnum

Table 16-1 Nerve Injury Classification

Seddon	Sunderland	Pathologic Findings
Neuropraxia	1	Localized myelin damage (Compression)
Axonotmesis	2	Loss of axonal continuity; endo-, peri-, and epineurium intact
	3	Axonal and endoneurial continuity lost
	4	Axonal, endoneurial, perineurial continuity lost
Neurotmesis	5	Complete nerve lesion

Sunderland S. Nerve injuries on their repair: A critical appraisal. NY: Churchill Livingstone, 1991. Seddon HJ. Surgical disorders of the peripheral nerves. Balt: Williams and Wilkins, 1972, pp 68-88.

Number	Name	Foramen
I	olfactory n	olfactory foramina
II	optic n	optic canal
III	oculomotor n	superior orbital fissure
IV	trochlear n	superior orbital fissure
V	trigeminal n	superior orbital fissure, foramen rotundum, foramen ovale
VI	abducens n	superior orbital fissure
VII	facial n	stylomastoid foramen
VIII	vestibulocochlear n	internal acoustic canal
IX	glossopharyngeal n	jugular foramen
X	vagus n	jugular foramen
XI	spinal accessory n	jugular foramen
XII	hypoglossal n	hypoglossal canal

Figure 16-1 Cranial Nerve Number, Name and Exiting Foramen

BRACHIAL PLEXUS

Randy Travis Drinks Cold Beer: Roots (or Rami), Trunks, Divisions, Cords, Branches

Roots: C5 to T1 ventral primary rami of spinal nerves

Trunks: Upper (C5, C6), middle (C7), and lower (C8, T1)

- Upper trunk yields suprascapular nerve (to supraspinatus and infraspinatus)

Divisions: Trunks split into anterior (3) and posterior (3) divisions

Cords: Lateral (upper and middle anterior divisions), medial (lower anterior division), and posterior (3 posterior divisions)

- Lateral cord gives lateral pectoral nerve to pectoralis major
- Medial cord gives medial pectoral nerve to pectoralis major and minor and to the medial cutaneous nerve to the arm and the medial cutaneous nerve to the forearm
- Posterior Cord: Upper (to subscapularis) and lower (to subscapularis and teres major) subscapular nerves and thoracodorsal nerve (to latissimus dorsi)

INJURIES TO THE BRACHIAL PLEXUS

Proximal Root Avulsion

Secondary to trauma → Horner's syndrome, phrenic nerve palsy

Long Thoracic Nerve Injury

Winging of scapula; need to be careful to identify nerve during lymph node dissection following mastectomy

Erb-Duchenne Palsy

Injury to upper trunk (C5,6) due to violent stretch between head and shoulder (commonly following shoulder dystocia) → affects dorsal scapula, suprascapular, lateral pectoral, long thoracic, musculocutaneous, radial, median, and phrenic nerves loss of sensation in the radial side of the arm and hand, paralysis and atrophy of the deltoid, the biceps, and the brachialis muscles

- The arm hangs adducted and medially rotated with the elbow extended, forearm pronated (aka "Waiter's tip")

Klumpke's Palsy

Lower trunk injury to sudden pull upward of arm (birth palsy or from catching oneself from a fall) → loss of function of muscles of the hand and wrist

Axillary Nerve Injury

Caused by fracture of humeral neck or arm dislocation → paralysis of deltoid prevents arm abduction, lateral rotation of arm weakened

Radial Nerve Injury

Wrist drop

- Caused by midshaft humerus fractures

Median Nerve Injury

Ape hand (flattening of thenar eminence), thumb movement lost

- Caused by supracondylar fractures, slashing of wrist, or carpal tunnel syndrome

Ulnar Nerve Injury

Claw hand; can be caused by fracture of medial epicondyle of humerus or slashing of the wrist

Table 16-2 Innervation of the Upper Extremity

Branch	From Cord	Motor Innervation	Cutaneous Innervation
Musculo-cutaneous	Lateral	Biceps, brachialis, coracobrachialis	Becomes lateral cutaneous nerve to forearm
Median	Lateral and Medial	Pronator teres, flexor carpi radialis, palmaris longus, flexor digitorum superficialis, abductor pollicis longus, supinator head of flexor pollicis brevis, oppones pollicis, 1st and 2nd lumbrical muscles	Radial 3½ fingers
Ulnar	Medial	Flexor carpi ulnaris, flexor digitorum profundus (3rd and 4th), palmaris brevis, abductor digiti minimi, oppones digiti minimi, flexor digiti minimi, 3rd and 4th lumbrical muscles, interossei, abductor pollicis, deep head of flexor pollicis brevis	Ulnar 1½ fingers
Radial	Posterior	Triceps, brachialis, brachioradialis, extensor carpi radialis longus and brevis	Posterior and lateral arm, back of hand up to nails
Axillary	Posterior	Deltoid, teres minor	Skin over deltoid
Posterior interosseous nerve		Supinator, extensor carpi ulnaris, extensor digitorum, extensor digiti minimi, extensor pollicis longus and brevis, abductor pollicis longus, extensor indicis proprius	
Anterior interosseous nerve		Flexor digitorum profundus (1st and 2nd), flexor pollicis longus, pronator quadratus	

Table 16-3 Thumb Innervation and Action

Action	Nerve	Nerve Root	Muscle
ABduction (in plane of palm)	Radial	C7, C8	Abductor pollicis longus
ADduction (in plane of palm)	Ulnar	C8, T1	Adductor pollicis
ABduction (perpendicular to palm)	Median	C8, T1	Abductor pollicis brevis
Opposition	Median	C8, T1	Opponens pollicis
Flexion	Median	C8, T1	Flexor pollicis longus

FRACTURES OF THE UPPER EXTREMITY AND ASSOCIATED NERVE INJURY

- Surgical neck of humerus → axillary nerve
- Midshaft fracture of humerus → radial nerve
- Supracondylar fracture of humerus → brachial artery or median nerve
- Medial humeral epicondyle fractures → ulnar nerve
- Distal radius fractures → increase in carpal tunnel pressure and a median nerve compression

LUMBOSACRAL PLEXUS

- Roots come from the ventral rami of spinal nerves L1–L5 and S1–S4 and a little of T12
- Roots divide into anterior (ventral) and posterior (dorsal) divisions

LUMBAR PLEXUS (T12–L5)

- Iliohypogastric (L1)—provides cutaneous innervation to hypogastric region
- Ilioinguinal (L1)—cutaneous innervation to medial thigh and skin of external genitalia
- Genitofemoral (L1,2 dorsal)—cutaneous to upper thigh and motor to cremaster muscle
- Lateral femoral cutaneous (L2,3)—lateral cutaneous innervation of thigh

FEMORAL NERVE (L2,3,4 VENTRAL)

- Branches supply iliacus and psoas muscles in abdomen
- Cutaneous innervation of thigh down to the knee (except laterally)
- Supplies pectineus, sartorius, and four quadriceps muscles
- Provides articular innervation of the knee joint
- Terminates as the saphenous nerve; cutaneous to medial calf

Femoral Neuropathy

Cause: Thigh or pelvis trauma (hip, pelvis, or femur fracture, mass, ischemic nerve infarction or hip replacement, lithotomy position, diabetes mellitus)

Symptoms: Leg pain, quadriceps weakness and sensory loss over thigh and shin

Signs: Sensory loss, decreased patellar reflex

LATERAL FEMORAL CUTANEOUS NERVE (L2,3)

Innervates lateral thigh

- Compression leads to meralgia paresthetica

ACCESSORY OBTURATOR NERVE (L3,4)

Supplies pectineus and hip joint; only present in about 29% of people, obturator takes over function if absent

OBTURATOR NERVE (L2,3,4)

Supplies adductor magnus, longus, and brevis and gracilis muscles; also provides articular innervation to knee joint

LUMBOSACRAL TRUNK (L4,5)

Contributes to sacral plexus

SACRAL PLEXUS

SCIATIC NERVE (L4,5 S1,2,3)

- Tibial and common peroneal travel together as sciatic as far as the knee; divides into the tibial and common peroneal nerve at the superior border of the popliteal fossa
- Supplies hamstring muscles (biceps femoris [long head]), semitendinosus, semimembranosus, and adductor magnus muscles
- Has articular branches to the knee joint

Pudendal nerve (S3,4): Muscles of perineum and skin of external genitalia and anus

Nerve to quadratus femoris (L4,5, S1): Also supplies inferior gemellus

Nerve to obturator internus (L5, S1,2): Also supplies superior gemellus

Nerve to piriformis (S2, sometimes also S1)

Superior gluteal nerve (L4,5, S1): Supplies gluteus medius and minimus muscles and tensor fasciae latae

- Superior gluteal nerve injury leads to a positive Trendelenburg's sign (also seen with hip dislocations and femur neck fractures)—contralateral pelvis drops when contralateral foot is raised

Inferior gluteal nerve (L5, S1,2): Supplies gluteus maximus

- Inferior gluteal nerve injury; can't sit up, climb stairs, or jump

Posterior femoral cutaneous nerve (S2,3 ventral; S1,2): Cutaneous innervation to buttocks and posterior thigh

Sciatic Neuropathy

Cause: Trauma at sciatic notch or gluteal region (hip dislocation, fracture, or replacement), prolonged bed rest, deep-seated pelvic mass, piriformis syndrome (secondary to compression from sitting on one's wallet), tumor (schwannoma)

Sypmtoms: Lower leg pain and weakness

Signs: Sensory loss in peroneal, tibial, and sural territories, normal patellar reflex, femoral nerve normal

TIBIAL NERVE (L4,5, S1,2,3)

- Supplies gastrocnemius, soleus, popliteus, plantaris, tibialis posterior, flexor digitorum longus, and flexor hallucis longus; to posterolateral calf and foot
- Contributes medial component of sural nerve for cutaneous innervation
- Terminates as medial and lateral plantar nerves which supply muscles and cutaneous innervation of foot
- TIP = **T**ibial **i**nverts and **p**lantar flexes the foot

Tibial Nerve Injury

Etiology: Trauma to popliteal fossa

Signs: Leads to calcaneovalgocavus, or dorsiflexion and eversion of foot

- Sensory deficit to the lateral and plantar surfaces of foot

COMMON PERONEAL NERVE (L4,5, S1,2)

- Innervates short head of biceps femoris in thigh
- Contributes lateral component of sural nerve; articular to knee joint

Superficial peroneal: Supplies peroneus longus and brevis and the skin over the dorsum of the foot

Deep peroneal: Supplies tibialis anterior, extensor digitorum longus and brevis, extensor hallucis longus, and peroneus tertius

- PED = **P**eroneal **e**verts and **d**orsiflexes (foot)

Peroneal Nerve Injury

Etiology: Trauma (including fibular head fracture), leg crossing

Signs: Lose dorsiflexion, sensory deficit on the dorsum of the foot especially between the big and second toe

LOWER EXTREMITY ANATOMICAL CONSIDERATIONS FOR PERIPHERAL NERVES

Popliteal Fossa

Diamond formed by hamstring muscles and two heads of gastrocnemius; contains tibial and common peroneal nerve, popliteal artery and vein, and small saphenous vein

Table 16-4 Summary of Lower Extremity Innervation

Nerve	Plexus	Motor Innervation
Femoral	Lumbar	(Quadriceps femoris—rectus femoris, vastus lateralis, vastus medialis, vastus intermedius), iliacus, psoas, sartorius
Obturator	Lumbar	Adductor brevis, adductor longus, adductor magnus (along with tibial nerve), gracilis
Superior gluteal	Sacral	Gluteus medius, gluteus minimus, tensor facia lata
Inferior gluteal	Sacral	Gluteus maximus
Sciatic	Sacral	Semitendonosis, semimembranous, biceps femoris (long head [tibial division]), adductor magnus (with obturator nerve)
Tibial	Sacral	Gastrocnemius, soleus, tibialis posterior, flexor digitorum longus, flexor hallucis longus, medial and lateral plantar nerve
Deep peroneal	Sacral	Tibialis anterior, extensor digitorum longus, extensor hallucis longus, tibialis posterior, extensor digitorum brevis
Superficial peroneal	Sacral	Peroneus longus and brevis

Medial Malleolus Relationships

Anterior—saphenous nerve and great saphenous vein (site for venous cutdown)

Posterior—Tom, Dick, ANd Harry: Tibialis posterior tendon, flexor Digitorum longus tendon, posterior tibial Artery, tibial Nerve, and flexor Hallucis longus tendon

DERMATOMES

C2	Back of head
C3	Turtleneck
C4	Polo collar
C5	Clavicle
C6	Thumb
C7	Middle and index fingers (radial nerve)
C8	Ring and little fingers (ulnar nerve)
T4	Nipple
T7	Xiphoid
T10	Umbilicus
T12	Inguinal region
L1–L4	Anterior and medial leg
L4	Big toe
L5	Dorsum of foot
S1	Plantar surface of foot and little toe, posterior calf
S2–S4	Perineum Peripheral Nerves

Table 16-5 Peripheral Nerves

Root	Nerve	Disc	Muscles	Weakness	Reflex
C4	Spinal accessory	C3–4	Trapezius, Scalenus	Shoulder shrug	
C5	Axillary Musculocutaneous Radial	C4–5	Deltoid Biceps Brachioradialis	Shoulder abduction and external rotation, elbow flexion	Biceps, brachioradialis
C6	Axillary Musculocutaneous Radial	C5–6	Deltoid Biceps Triceps, Brachioradialis, Pronator teres, Extensor carpi radialis	Elbow flexion, arm pronation, wrist and finger extension	Biceps, brachioradialis
C7	Radial Posterior interosseus Median Anterior interosseus Ulnar	C6–7	Triceps, Pronator teres Extensor digitorum Flexor carpi radialis Flexor digitorum profundus 1&2 Flexor carpi ulnaris, Flexor digitorum profundus 3&4	Elbow extension, wrist and finger extension	Triceps
C8	Radial Posterior interosseus Median Anterior interosseus Ulnar	C7–T1	Triceps Extensor digitorum Abductor pollicis brevis, Opponens pollicis Flexor digitorum profundus 1&2 Flexor carpi ulnaris, Flexor digitorum profundus 3&4, Interossei, Abductor digiti minimi	Finger flexion and abduction	Finger flexor
T1	Median Ulnar	T1–2	Abductor pollicis brevis, Opponens pollicis Flexor carpi ulnaris, Flexor digitorum profundus 3&4, Interossei, Abductor digiti minimi	Finger flexion and abduction	

(*Continued*)

Table 16-5 Peripheral Nerves (Continued)

Root	Nerve	Disc	Muscles	Weakness	Reflex
L2	Femoral Obturator	L1–2	Iliopsoas, Quadriceps Adductors	Hip flexion	Cremaster
L3	Femoral Obturator	L2–3	Iliopsoas, Quadriceps Adductors	Thigh adduction, hip flexion	Knee
L4	Femoral Obturator Superior gluteal Deep peroneal	L3–4	Iliopsoas, Quadriceps Adductors, Sartorius Gluteus medius/minimus Tibialis anterior, Extensor digitorum	Knee extension, ankle dorsiflexion and inversion	Knee
L5	Superior gluteal Inferior gluteal Sciatic Tibial Medial/lateral plantar Deep peroneal	L4–5	Gluteus medius/minimus Gluteus maximus Hamstrings Soleus, Gastrocnemius, Flexor digitorum Interossei Tibialis anterior, Extensor digitorum	Thigh adduction and internal rotation, knee flexion, ankle and toe plantar and dorsiflexion	
S1	Superior gluteal Inferior gluteal Sciatic Tibial Medial/lateral plantar	L5–S1	Gluteus medius/minimus Gluteus maximus Hamstrings Soleus, Gastrocnemius, Flexor digitorum Interossei	Hip extension, knee flexion, ankle and toe plantar flexion	Ankle
S2	Inferior gluteal Sciatic Medial/lateral plantar	S1–2	Gluteus maximus Hamstrings Interossei	Toe cupping and fanning	

ENTRAPMENT SYNDROMES

OCCIPITAL NEURALGIA

Symptoms: Headache involving the posterior occiput in the greater or lesser occipital nerve distribution

- Pain in the neck, temple, and throbbing pain behind the eye on the ipsilateral side

Causes: Trauma or compression to the greater and/or lesser occipital nerves or C2 and/or C3 nerve roots by degenerative cervical spine changes, cervical disc disease, or tumors affecting the C2 and C3 nerve roots

Treatment: Occipital nerve decompression or stimulation

THORACIC OUTLET (SCALENUS ANTICUS) SYNDROME

Cause: Compression of subclavian vein or artery or brachial plexus between first rib and scalene muscles

- Also seen with cervical ribs
- Typically affects lower brachial plexus, C8–T1

Symptoms: Worsen with overhead activity

- May have edema and discoloration from venous congestion
- May have claudication symptoms from arterial compression

Signs:

- *Adson's maneuver:* Patient is asked to turn head toward the symptomatic shoulder while extending their arm, neck, and shoulder slightly away from their body. The pulse on the wrist of the extended arm is checked while the patient inhales. If the pulse is diminished or symptoms are reproduced during the maneuver, it is considered a positive test result, which may indicate thoracic outlet syndrome. Repeat the test on the unaffected side
- *Wright test:* From a sitting position the arm is held back (hyperabduction), rotating it outward, while the pulse is checked to see if it's diminished
- *Roos stress test:* From a sitting position, the patient holds both elbows at shoulder height while pushing the shoulders back. The patient repeatedly opens and closes their hands for several minutes. A positive test occurs if symptoms are present after the test, or if heaviness and fatigue is felt in the shoulders
- *Gilliatt-Sumner hand:* Severe wasting of thenar and intrinsic muscles of the hand. Usually neurogenic in etiology

Treatment: Physical therapy, NSAIDs, resection of cervical rib

CARPAL TUNNEL SYNDROME (MEDIAN NERVE ENTRAPMENT AT WRIST)

Most common form of median nerve palsy

- F > M
- Intrinsic or extrinsic compression of median nerve in the carpal tunnel formed by flexor retinaculum over palmar surface of carpal bones
- Contents of the carpel tunnel: Flexor digitorum superficialis and profundus tendons, flexor pollicis longus tendon, and the median nerve
- Most common cause is overuse (e.g., computer typing, musicians)

Symptoms: Painful paraesthesia in distribution of median nerve (radial side of palm and 3.5 fingers)

- Burning feeling
- May radiate above wrist
- Common complaint is waking up with symptoms that are then relieved by shaking hands
- Decreasing grip strength

Signs:

- *Phalen's sign:* 90º flexion of wrist produces paresthesia
- *Tinel's sign:* Tapping of carpal ligament causes median nerve paresthesias
- Delay in palmar sensory conduction time is the most sensitive test

Treatment: NSAID, wrist splinting, corticosteroid injection, carpal tunnel release surgery

Ligament of Struthers (between distal humerus and medial epicondyle): Entrapment of the median nerve here leads to distal median nerve symptoms plus decreased pronation, wrist/digit flexion, thumb flexion, abduction, opposition

ULNAR NERVE ENTRAPMENT[3]

Most commonly elbow (cubital tunnel between the two heads of the flexor carpi ulnaris = most common); rarely at the wrist (Guyon's canal) or arm (Arcade of Struthers = aponeurosis anterior to the triceps band in the upper arm)

- Cubital tunnel syndrome is distinguished from compression in Guyon's canal by the presence of dorsal sensory deficits (absent in wrist compression)
- Will see motor deficits of ulnar distribution including adductor pollicis, deep head of flexor pollicis brevis, 3rd and 4th lumbricals, and sensory deficits in palmar surface of hypothenar eminence

Signs: Atrophy of hypothenar eminence and hand intrinsics

- *Wartenberg's sign:* 5th finger has position of abduction secondary to unopposed ulnar insertion of extensor digiti quinti
- *Duchenne's sign:* Clawing of medial two digits
- *Froment's sign:* On attempt to Adduct the joint, will flex the finger
- *Tinel's sign:* Tapping over cubital canal positive for shooting pain
- *Elbow flexion test:* flexion reproduces symptoms and symptoms regress with extension

RADIAL NERVE ENTRAPMENT (SATURDAY NIGHT PALSY)

Runs in spiral groove of humerus so is susceptible to injury after humerus fracture

- May become entrapped at radial tunnel, arcade of Frohse, or supinator channel

Symptoms: Wrist drop, decreased sensation to small region of dorsal hand

MERALGIA PARAESTHETICA (LATERAL CUTANEOUS NERVE OF THIGH ENTRAPMENT)

Chronic entrapment of the lateral cutaneous nerve of thigh at the inguinal ligament, near the anterior superior iliac spine

Causes: Obesity, tight fitting belts, idiopathic

Symptoms: Sensory loss anterolateral thigh

- No motor symptoms
- Paresthesias and pain radiating down the lateral thigh to knee

Treatment: Conservative versus surgical decompression (if severe)

COMMON PERONEAL NEUROPATHY

Cause: Compression just below fibular head from prolonged lying, leg crossing, squatting, leg cast, direct compression or mass lesions

Symptoms: Equinovarus with foot drop (plantarflexion) and inversion of the foot, paresthesias, and/or sensory loss

Signs: Foot drop/weakness on foot dorsiflexion and eversion; sensory loss on dorsum of foot.

DISTAL PERONEAL NEUROPATHY

Cause: Trauma to dorsum of foot or ankle/distal peroneal nerve, tight fitting shoe rim or strap

Symptoms: Dorsal foot paresthesias and/or sensory loss

Signs: Minimal sensory loss

TARSAL TUNNEL SYNDROME (TIBIAL NERVE ENTRAPMENT)

Cause: Fracture or dislocation of talus, calcaneus, medial malleolus, rheumatoid arthritis, tumor, diabetes

Symptoms: Aching, burning, numbness, tingling on plantar foot, distal foot, toes, and occasionally heel, paresthesias, and/or sensory loss

Signs: Positive Tinel's sign over nerve posterior to medial malleolus

- Sensory loss on plantar foot
- Atrophy of foot muscles if severe

CHAPTER 17 ■ ANATOMY

Andrew Phelps, MD

NOTE: All figures in this chapter are courtesy of A. Phelps, MD.

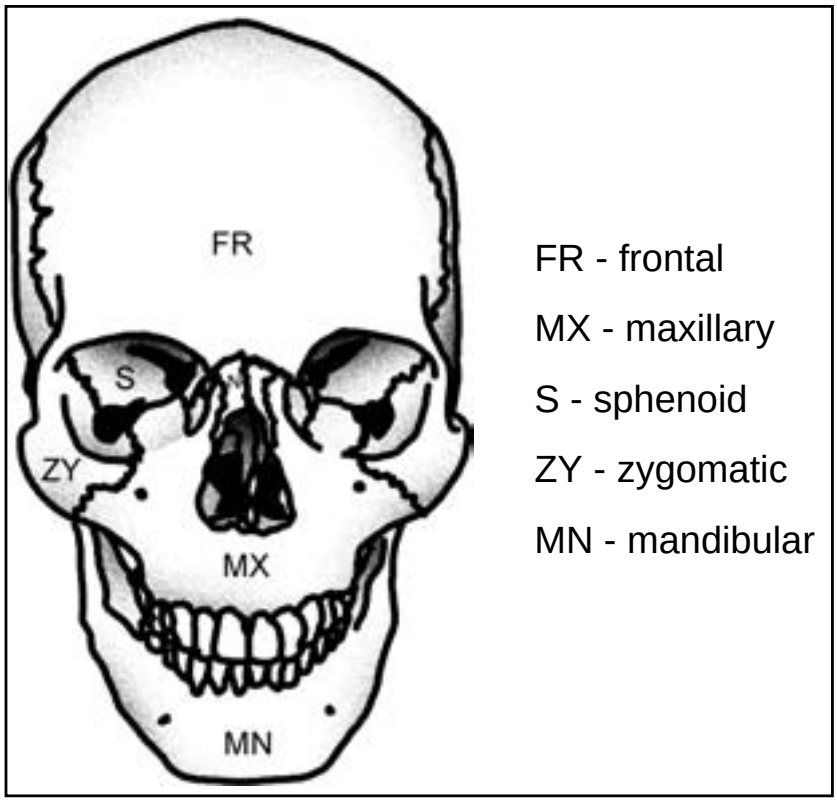

Figure 17-1 Skull Frontal View

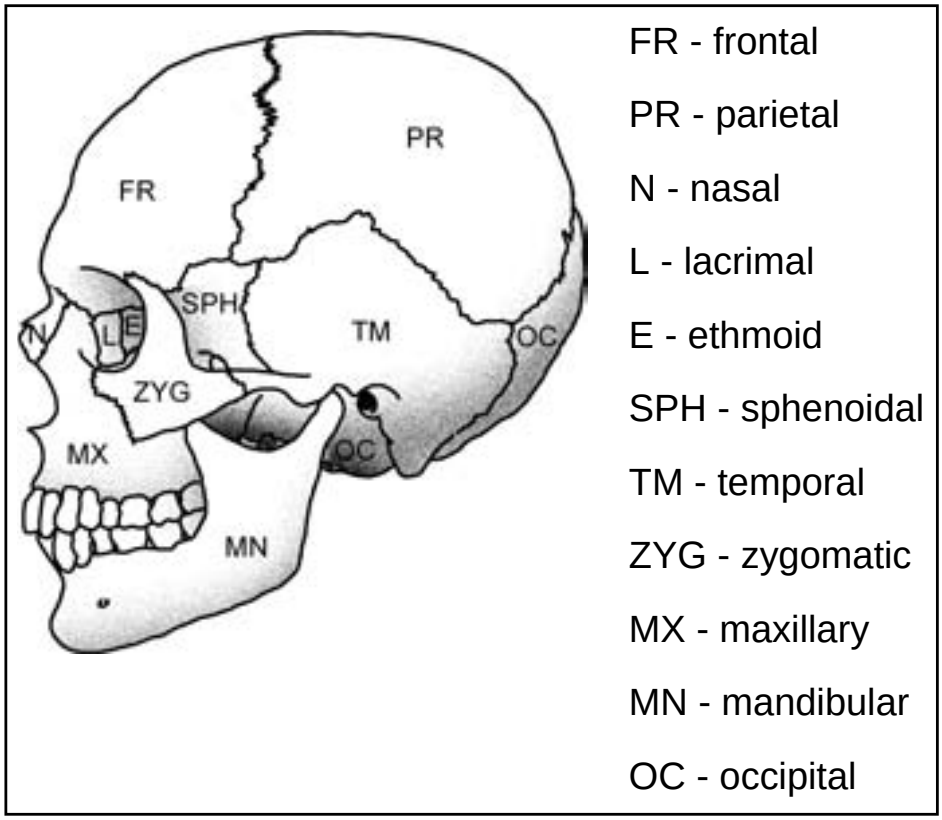

Figure 17-2 Skull Lateral View

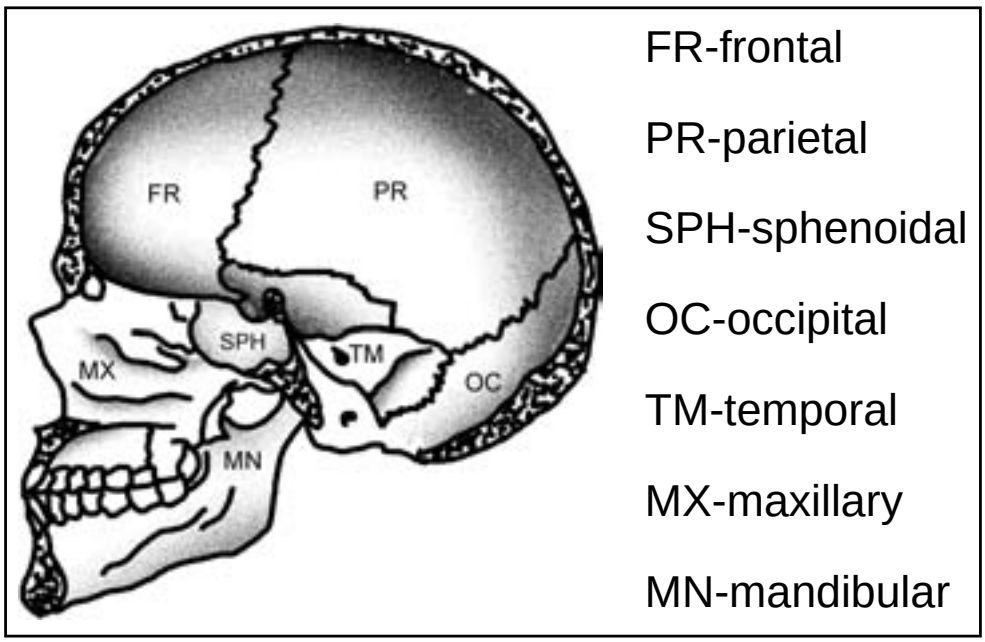

Figure 17-3 Sagittal Skull Interior

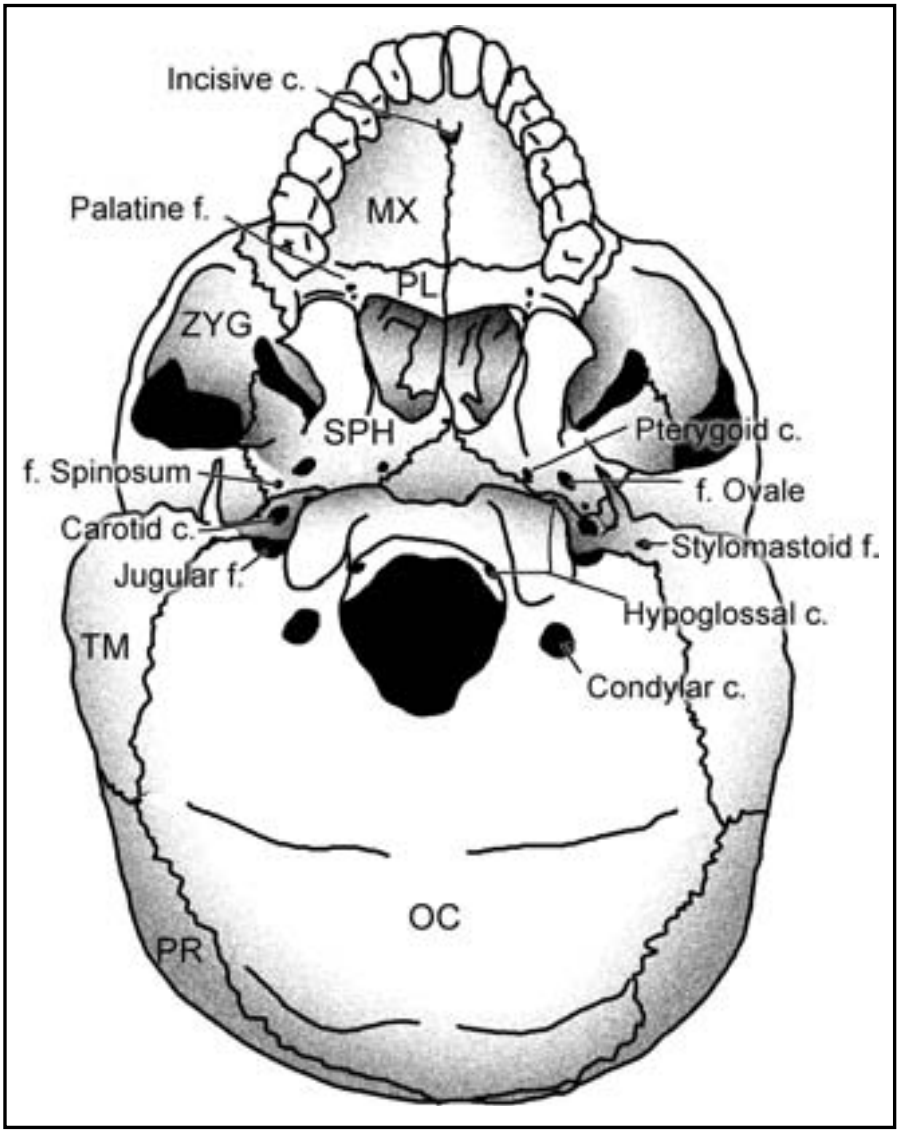

Figure 17-4 Skull Base Exterior, Inferior View

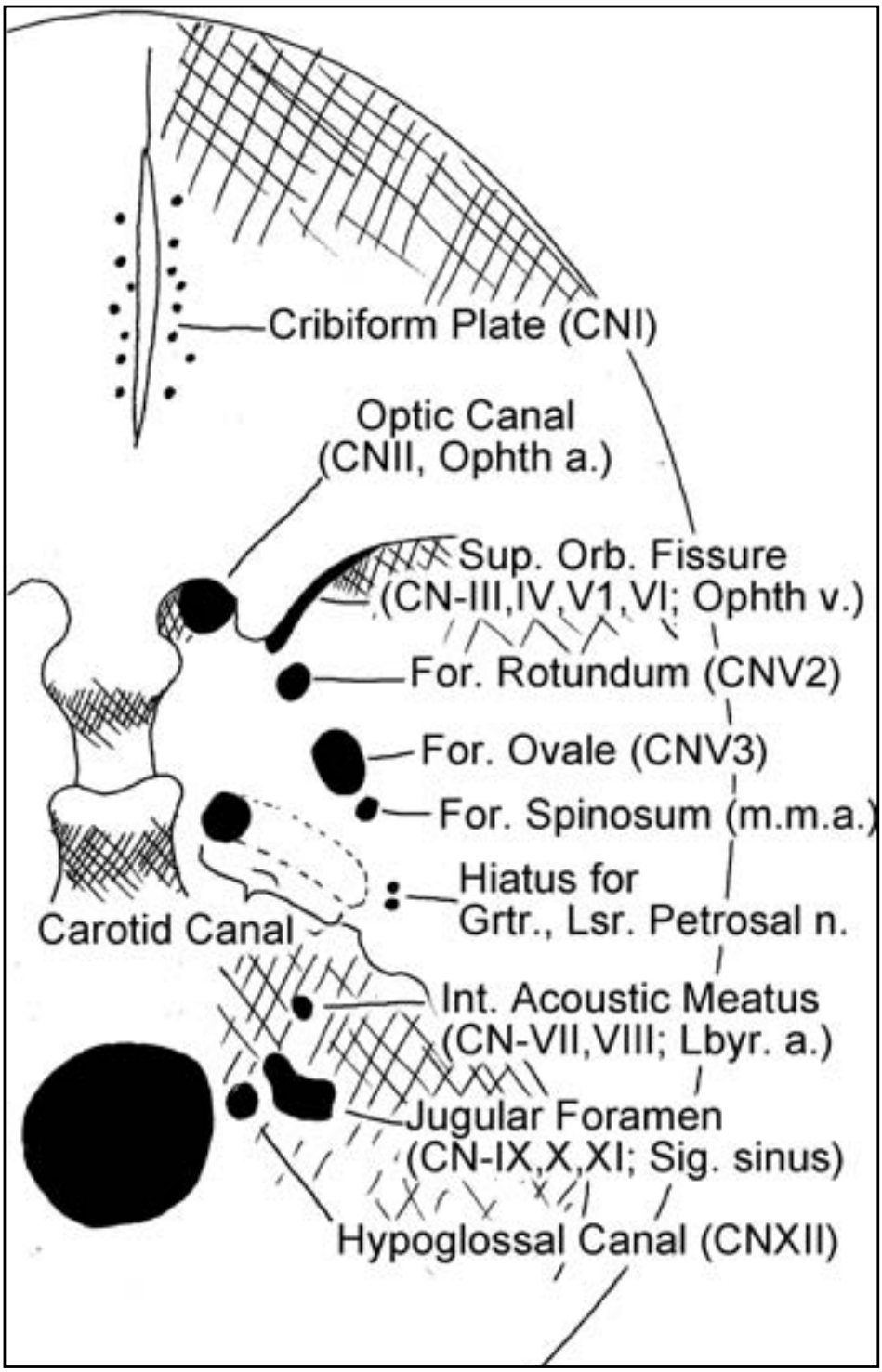

Figure 17-5 Skull Base, Interior View

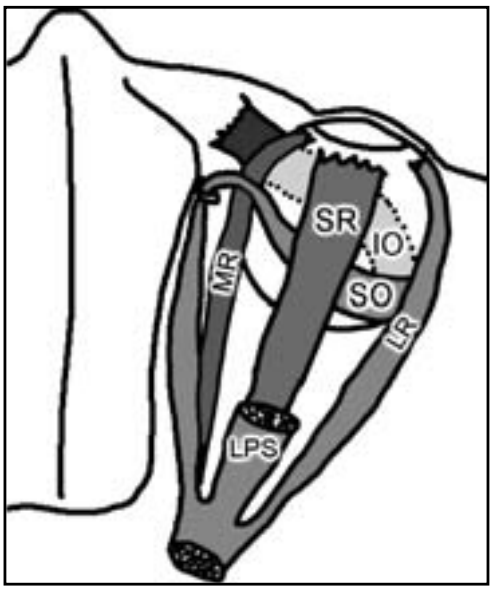

Figure 17-6 Extraocular Muscles

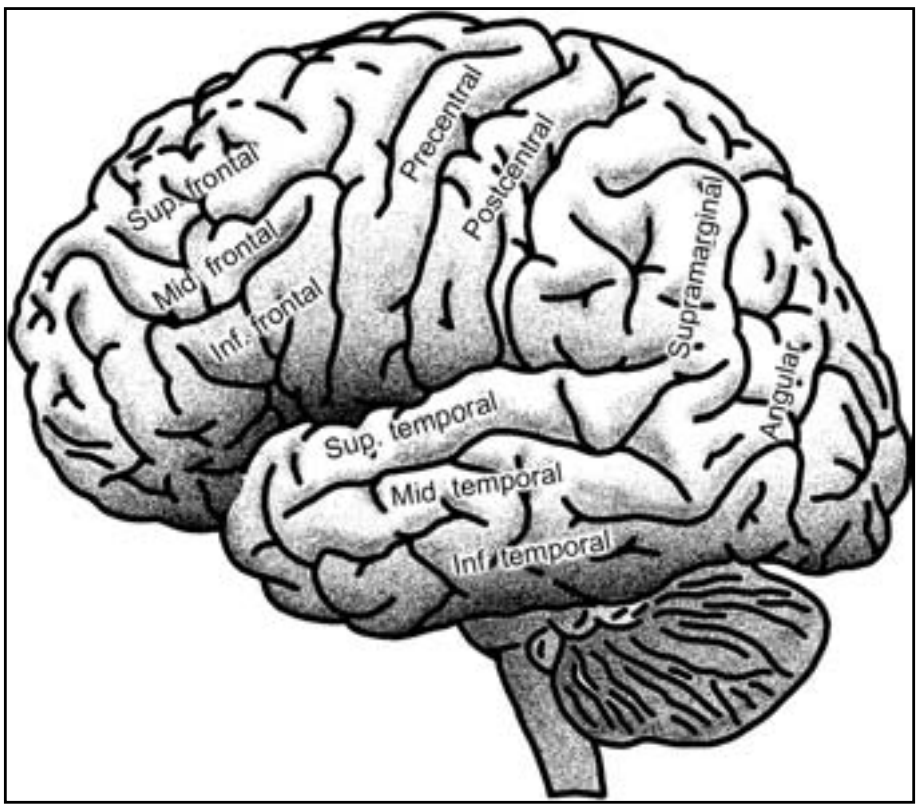

Figure 17-7 Cerebral Cortext, Lateral View

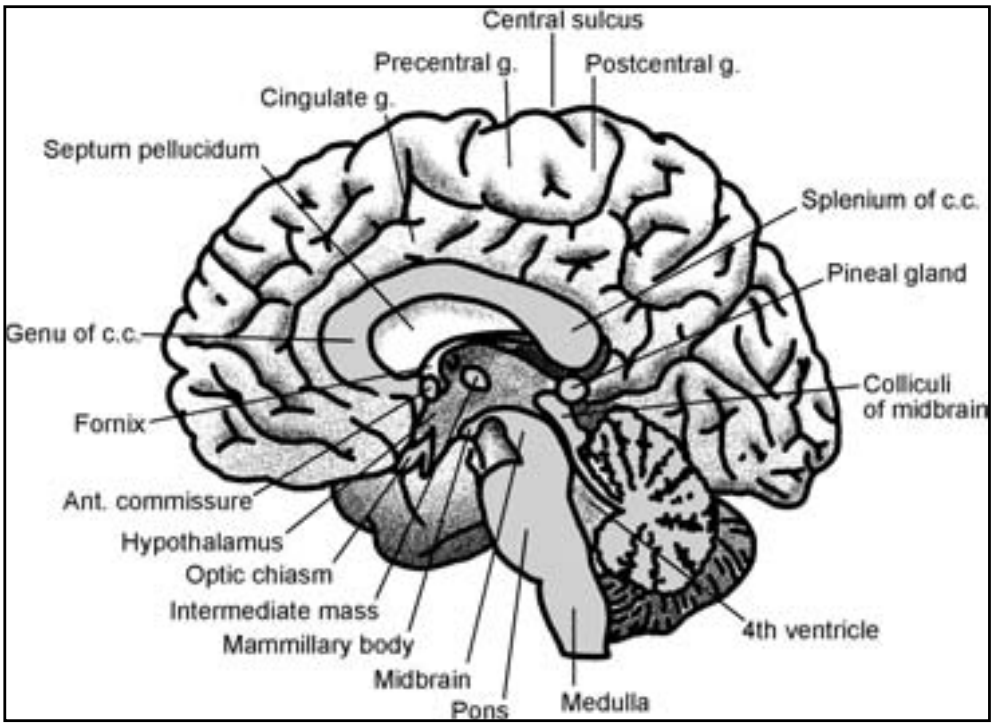

Figure 17-8 Cerebral Anatomy, Sagittal

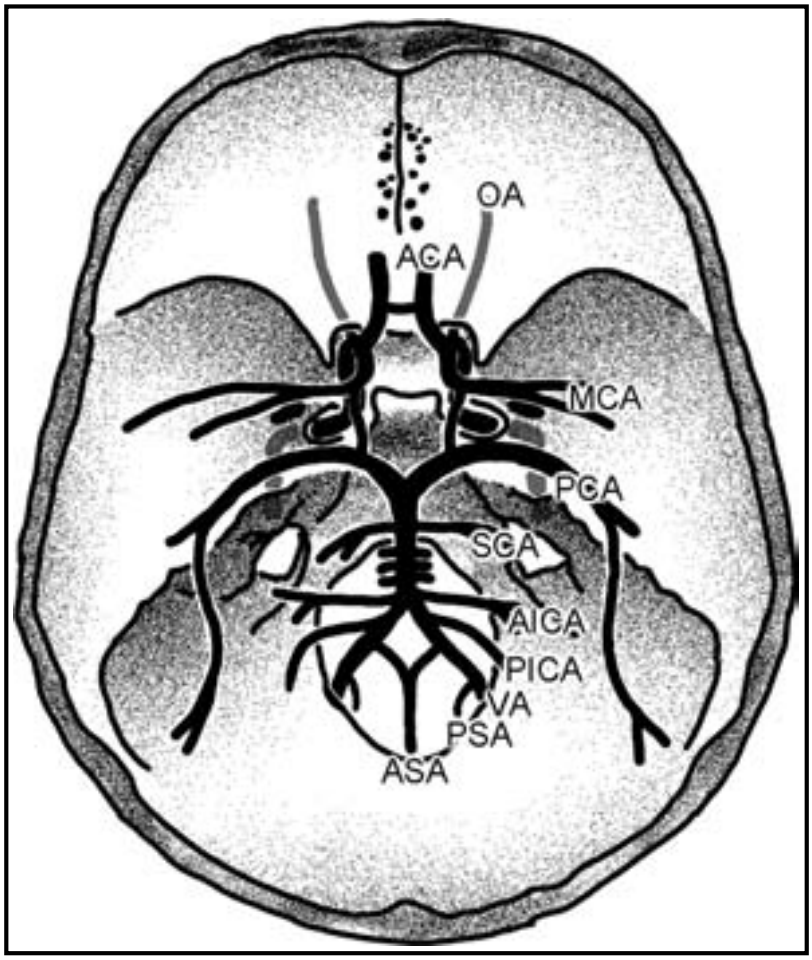

Figure 17-9 Circle of Willis

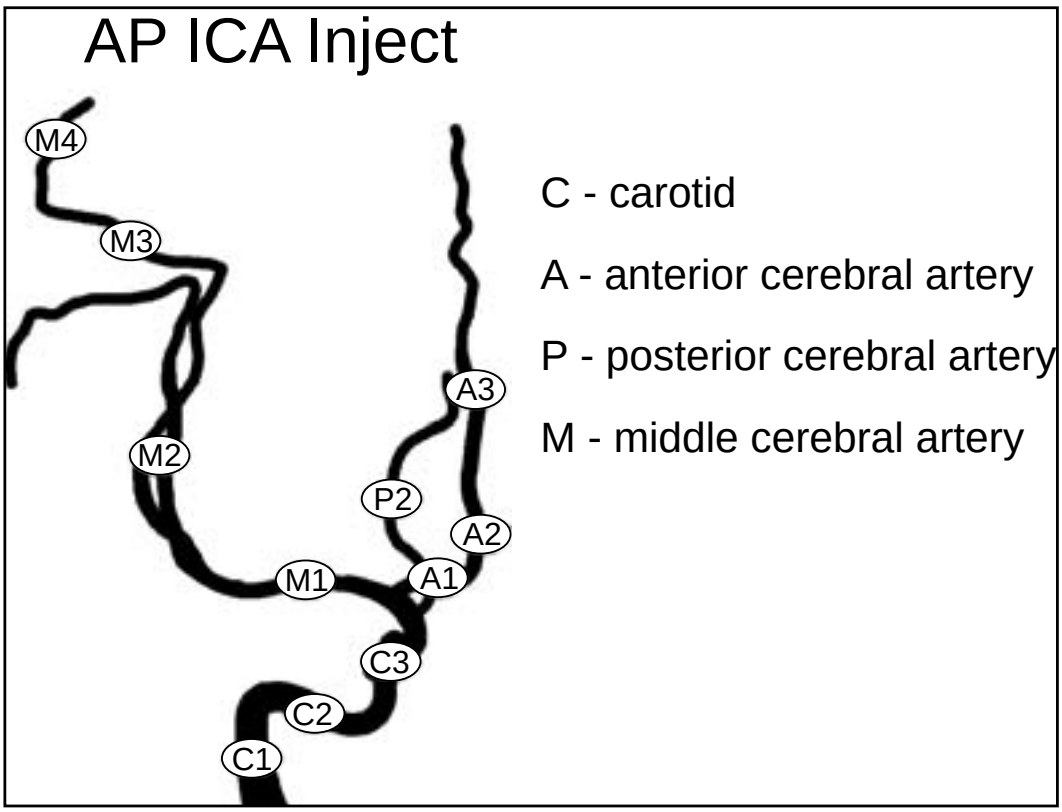

Figure 17-10 Angiogram of Internal Cerebral Artery Injection, Anterior-Posterior View

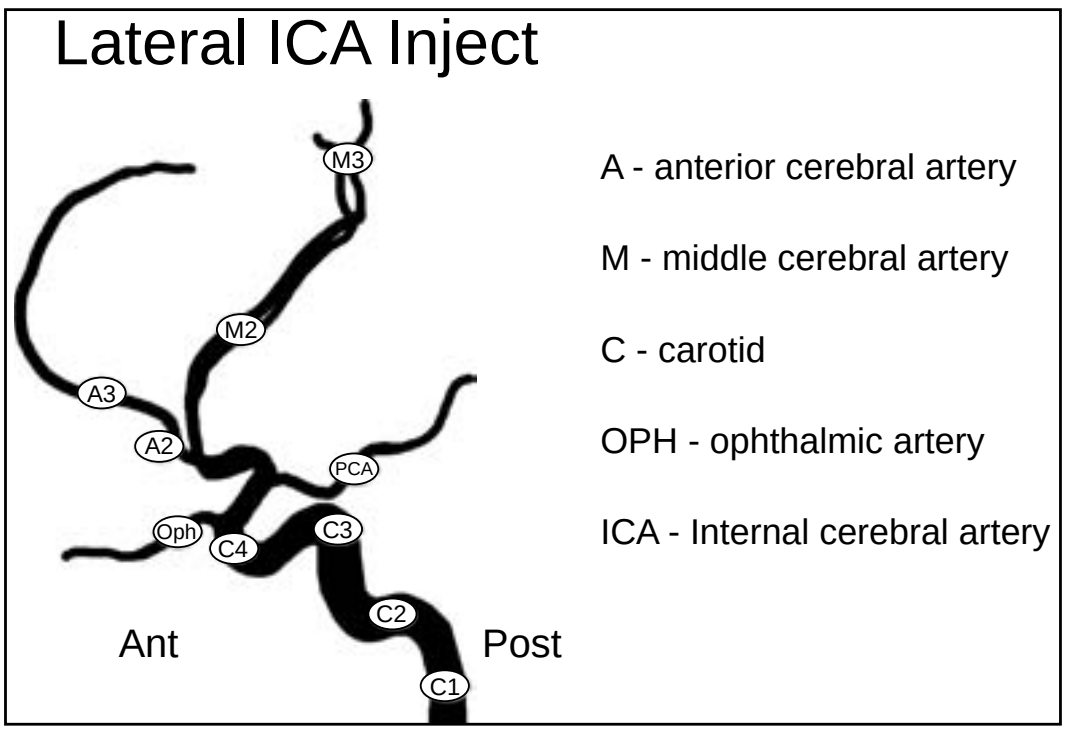

Figure 17-11 Angiogram of Internal Carotid Artery Injection, Lateral View

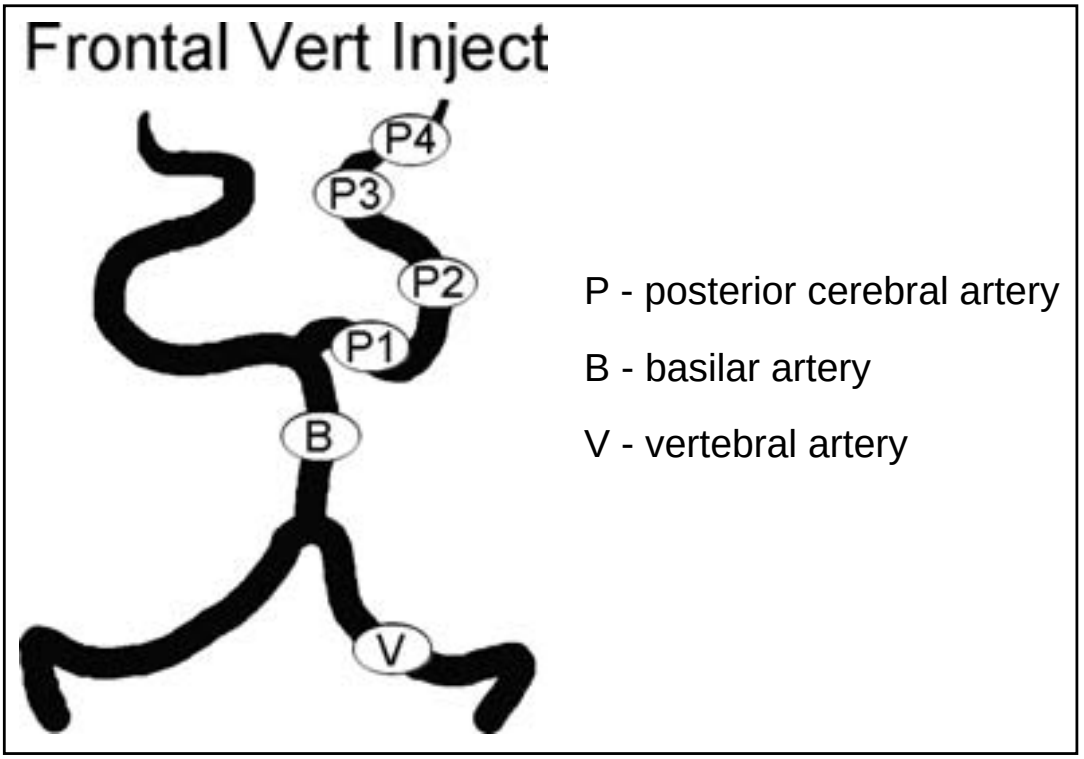

Figure 17-12 Angiogram of Vertebral Artery Injection, Frontal View

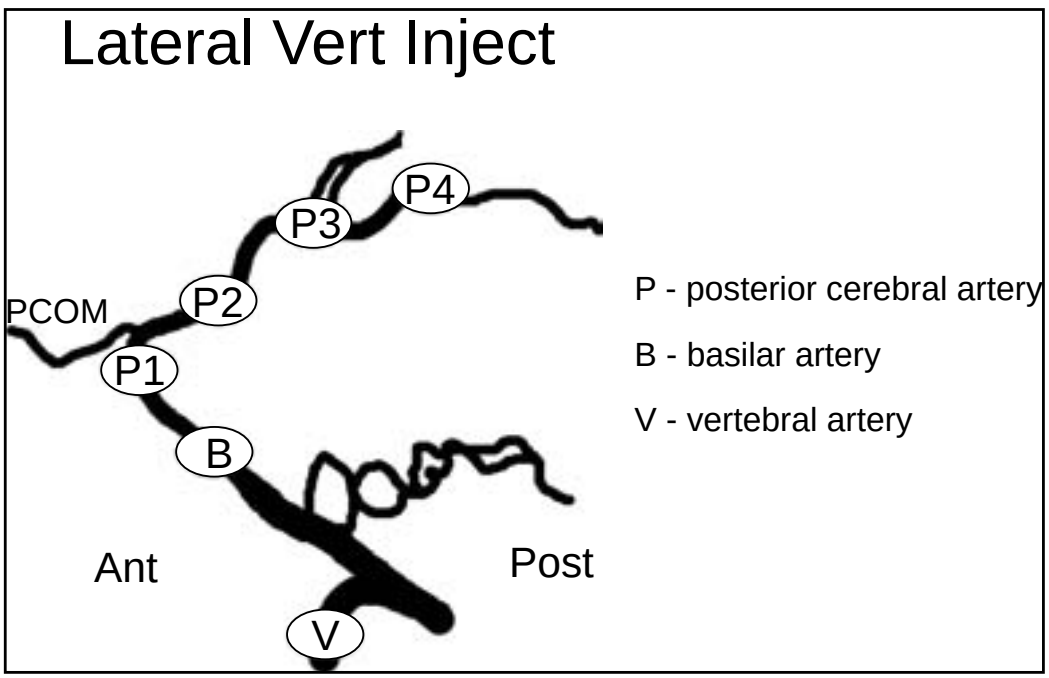

Figure 17-13 Angiogram of Vertebral Artery Injection, Lateral View

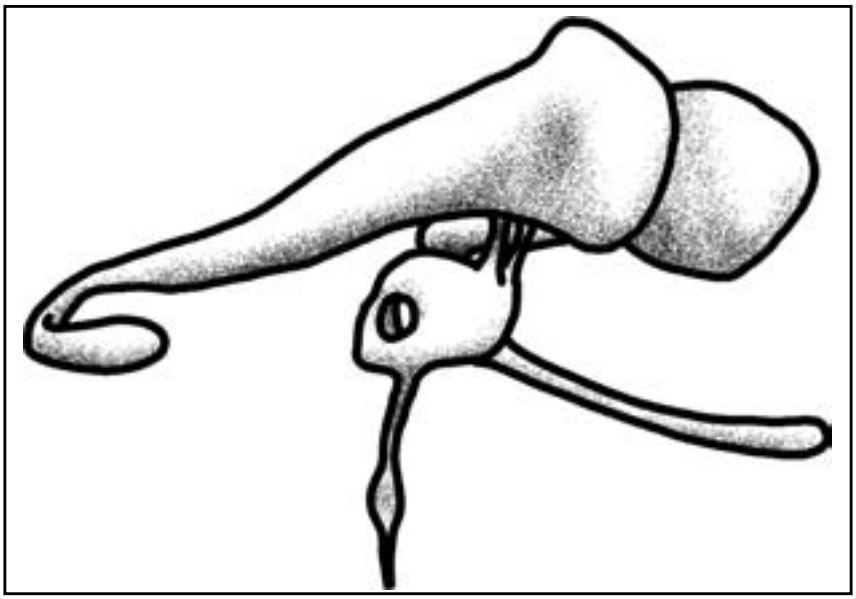

Figure 17-14 Ventricles

Figure 17-15 Basal Ganglia and Ventricular Anatomy

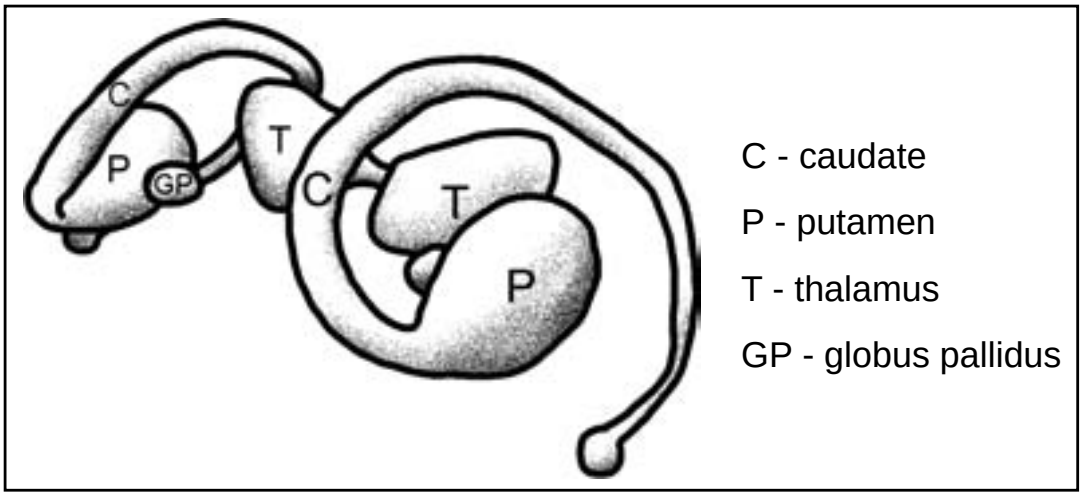

Figure 17-16 Basal Ganglia

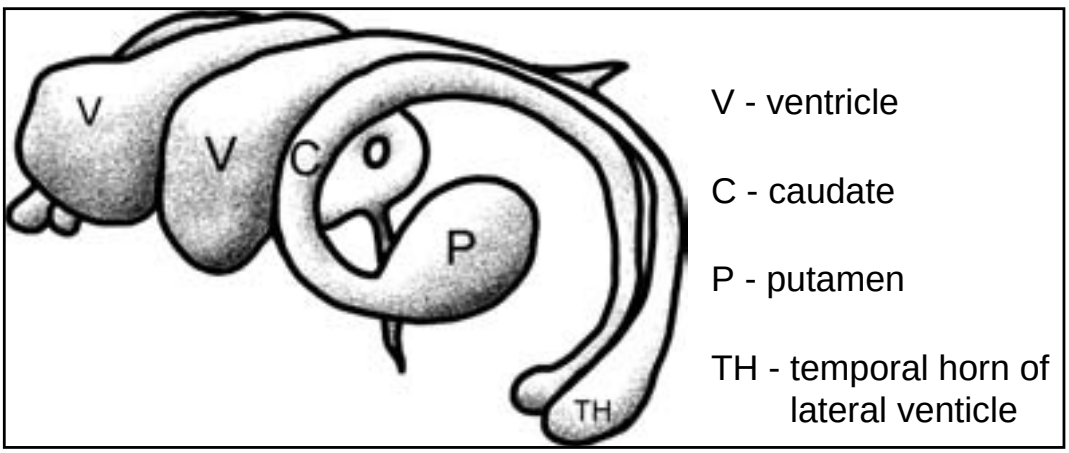

Figure 17-17 Putamen, Caudate

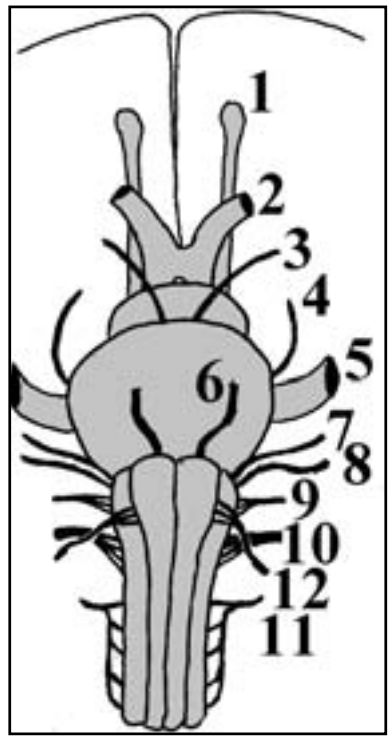

Figure 17-18 Brainstem Cranial Nerves, Ventral View

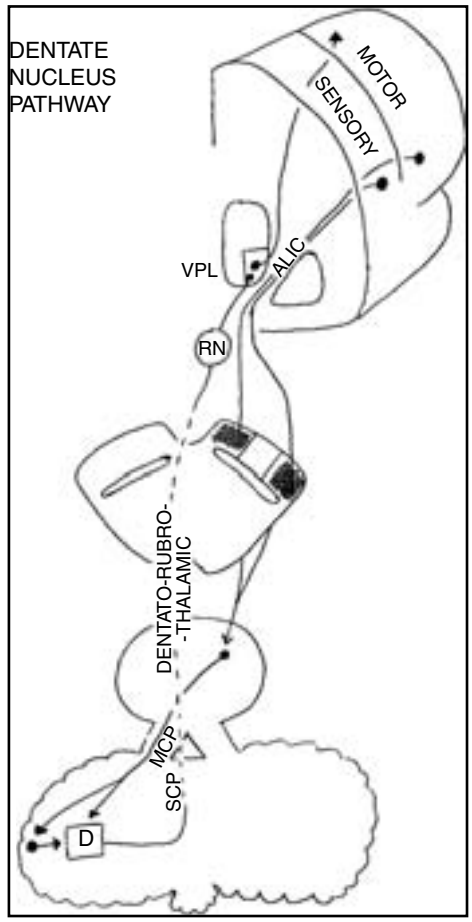

Figure 17-19 Dentate Nucleus Pathway

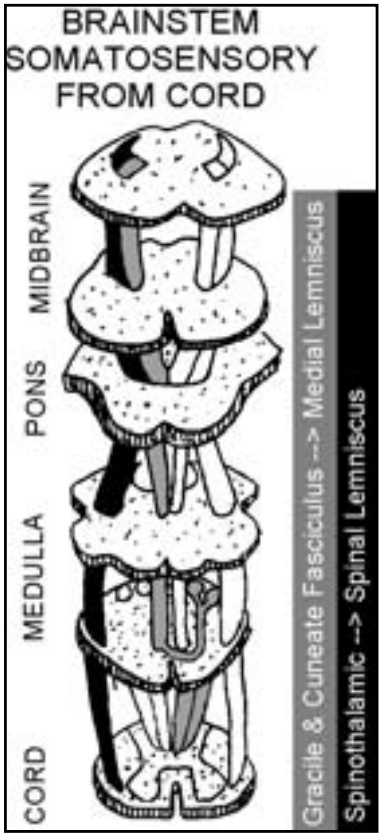

Figure 17-20 Brainstem Pathways Somatosensory

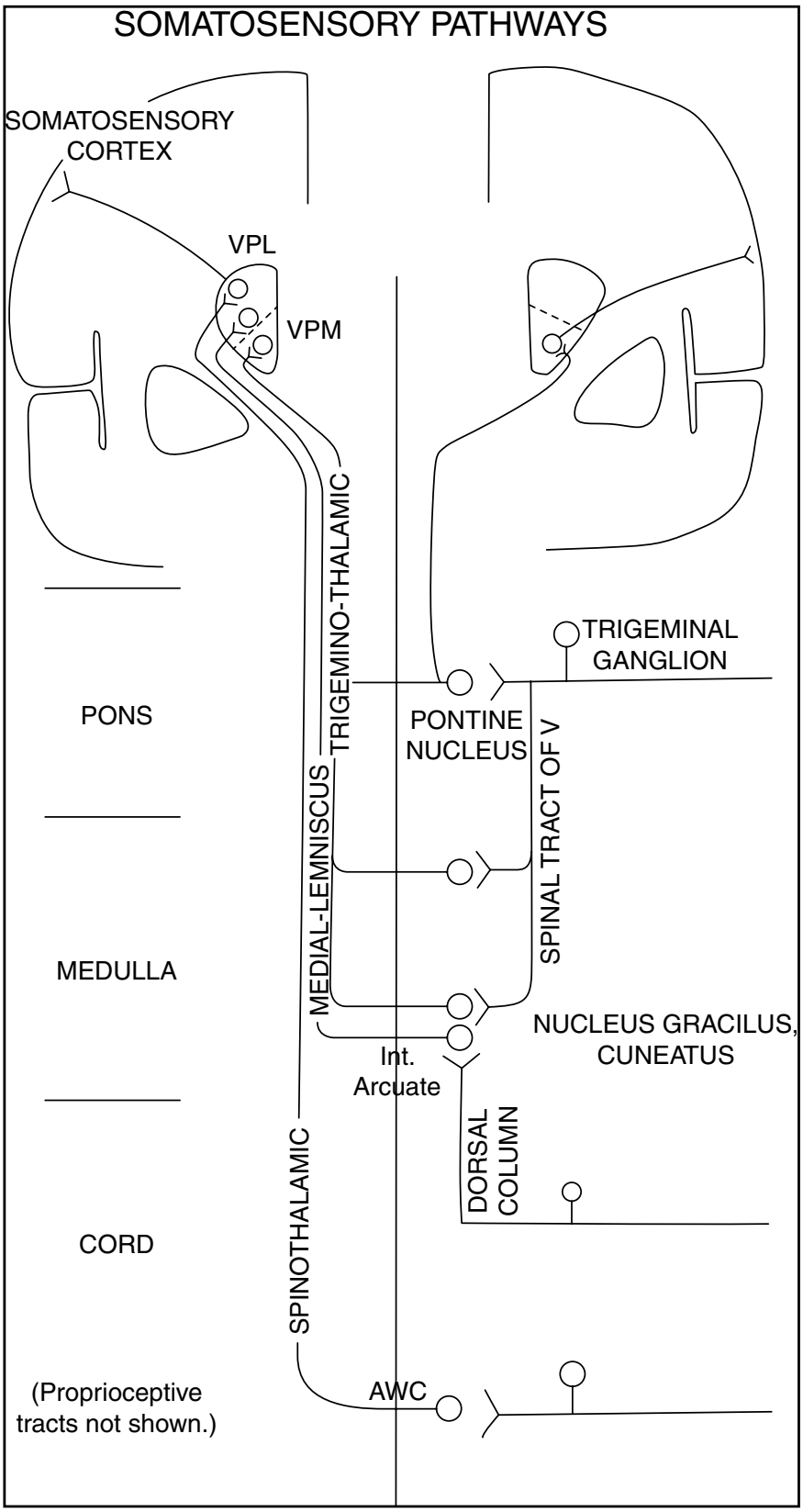

Figure 17-21 Somatosensory

CHAPTER 18 ■ NEUROINTENSIVE CARE[1,2]

Melanie G. Hayden Gephart, MD, MAS
Gregory Kapinos, MD, MS

ICU BASICS

Table 18-1 Normal Wound Healing Indices

Normal Wound Healing Indices	Malnutrition/Poor Wound Healing
Serum Albumin > 3.5 g/dL Absolute lymphocyte count > 1500/mm^3 Arterial Doppler pressure 70 mmHg Differential pressure index (ABI) > 0.5 $TcPO_2$ 30 mm Hg	Total lymphocyte count < 1500/mm^3 Serum albumin < 3.5 gm/dL Serum transferrin level < 226 mg/dL

Table 18-2 Specific Antidotes

Toxin or drug	Specific Antidote
Acetaminophen	N-acetylcysteine
Benzodiazepines	Flumazenil*
Beta-blockers	Atropine, beta-agonists, calcium, glucagon, phosphodiesterase inhibitors
Calcium Channel blockers	Atropine, calcium, glucagon
Carbon monoxide	Hyperbaric oxygen
Cholinesterase inhibitors	Atropine, pralidoxime
Crotalid Snakebite (North America)	Crotalidae Polyvalent Immune Fab (Ovine)
Cyanide	Amyl nitrite/sodium nitrite/sodium thiosulfate
Digitalis	Digoxin Fab
Ethylene glycol	Fomepizole, ethanol, pyridoxine, thiamine
Heparin	Protamine sulfate
Iron	Deferoxamine
Isoniazid	Pyridoxine
Methanol	Fomepizole, ethanol, folinic acid, folate
Methotrexate/anti-folates	Folinic acid
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Oral hypoglycemic agents	Dextrose, glucagon
Organophosphates	Atropine, pralidoxime
Sulfonylureas	Octreotide
Sympathomimetics[#]	Phentolamine, benzodiazepines
Tricyclic antidepressants	Bicarbonate
Warfarin/rodenticides	Vitamin K, plasma

*For reversal of benzodiazepine intoxication in non-dependent patient
[#]Including MAO inhibitor interactions, cocaine, epinephrine, ergotism

Table 18-3 Blood Products

Product	*Vol (ml)*	*Indications*	*Comments*
Whole Blood (WB)	400-500	• Massive transfusion in acute blood loss	• RBCs plus plasma • Rarely used
Packed Red Blood Cells (PRBCs) *see next page for specific types*	250-350	• Increase O_2-carrying capacity if evidence/risk of end-organ ischemia • Maintain volume & O_2 capacity in acute blood loss • **Not** indicated solely to maintain "target" Hb/Hct or for volume repletion (isovolemic anemia well-tolerated if no cardiac, pulmonary or cerebro-vascular disease)	• Massive transfusion may cause hypo-thermia, low Ca^{++}, high K^{+}, dilutional thrombocytopenia • In critically ill patients, "restrictive" transfusion practice (*i.e.* at Hb of 7-9 mg/dl vs 10-12 mg/dl) may reduce mortality[126] • In acute MI, transfusion to Hct 30-33% may reduce mortality[127]
Platelet Concentrates (PCs)	200-250 (per 5-6 unit pool)	• Bleeding & plts < 100K • Procedure & plts < 50K • Prophylactic if plts < 10K • Bleeding & qualitatively abnormal platelets (e.g. uremia, ASA) • Serious bleeding after GP II_bIII_a inhibitor therapy	• 6-unit pool should raise count 50-60 K, less if alloimmunized. • May support platelets if refractory to SDPs • Contraindicated in consumptive coag-ulopathy (HIT, HUS/TTP, HELLP)

Single-Donor Platelets (SDPs)	200-250	• Same as platelet concentrates but fewer donor exposures (allo-immunization, infection)	• No data to support routine use to prevent alloimmunization[128]
Fresh Frozen Plasma (FFP)	200-250	• Bleeding if multiple factor deficiency (massive transfusion, liver disease) • DIC or TTP • Reversal of warfarin • Factor XI deficiency	• Contains factors II, VII, IX, X, XI, XII, and XIII • Dose: 15 ml/kg for massive transfusion, 3-5 ml/kg to reverse warfarin (titrate to PT)
Cryo-precipitate	100-200 (per 10 unit pool)	• Replacement of fibrinogen when acutely depleted (<100 mg/dl) or qualitatively abnormal • Serious bleeding after thrombolytic therapy • Factor VIII or vWF replacement if concentrate not available	• Contains factor VIII, vWF, fibronectin and fibrinogen • Fibrinogen in 10-unit pool = 4 units FFP (but roughly 20% of the volume)

[125] Churchill WH. Transfusion therapy. In: *Scientific American Medicine*. Federman D (ed.) New York: Scientific American, Inc.; March 2001.
[126] Hebert PC *et al*. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *NEJM* 1999; 340:409-17.
[127] Wu W-C *et al*. Blood transfusion in elderly patients with acute MI. *NEJM* 2001; 345:1230-1236.
[128] TRAPS Group. Leukocyte reduction and UVB irradiation to platelets to prevent allo-immunization and refractoriness to platelet transfusions. *NEJM* 1997; 337:1861-9.

Table 18-4 Transfusion Risks

*Adverse Outcome **	*Risk per Unit Transfused*
Hepatitis B	1: 220,000
Hepatitis C	1: 872,000-1,700,000
HTLV 1 or 2	1: 600,000
HIV 1 or 2	1: 1,400,000-2,400,000
Bacterial contamination – platelets / RBC	1: 2,000-3,000 / 1: 7,000-31,000
Fatal hemolytic transfusion reaction	1: 500,000
Fatal acute lung injury (ARDS)	1: 3,000,000
Mis-transfusion	1: 14,000

* Emerging risks include variant CJD, West Nile virus, *T. cruzi*, malaria, babesiosis.
Source: Goodnough LT et al. Tranfusion Medicine. *NEJM* 1999;340:438. Busch MP et al. Current & emerging infectious risks of blood transfusions. *JAMA* 2003;289:959. Goodnough LT et al. *Lancet* 2003;361:161.

OCCULT CAUSES OF FEVER IN ICU PATIENTS[1,2]

- Infected IV catheters
- Drug reaction
- Otitis media, sinusitis (especially with nasogastric tube)
- Pulmonary embolism, deep vein thrombosis (DVT)
- Pancreatitis, acalculous cholecystitis
- C. diff colitis
- Fungal or secondary infection
- Central fever in head injury

CHECKLIST FOR PROPHYLAXIS

- DVT prophylaxis with low molecular weight heparin and sequential compression device (SCDs)
- GI ulcer prevention with proton pump inhibitor
- Enteral nutrition, when appropriate
- Wake Up & Breath: Once patient stable, daily withhold of sedation and mechanical ventilation (MV), unless proven dangerous. (ICP crises). Indeed, spontaneous breathing trials and awakenings on a daily basis are the most effective treatment in the ICU to shorten days of MV, length of ICU and hospital stay and improve functional outcome and survival. (Girard TD, et al. Lancet 2008;371:126–34)
- Physical and occupational therapy to start as early as possible

Table 18-5 Relative Action of Vasopressors

Drug	*Receptor*	*HR*	*Inotropy*	*SVR*	*Comments*
Dopamine - *Low dose*	DA	0	0	$\leftrightarrow\downarrow$	Renal and splanchnic vasodilatation
Dopamine - *High dose*	$\beta_1 \rightarrow \alpha_1$	$\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow$	First-line pressor for SBP 70-90 mmHg
Dobutamine	$\beta_1, \beta_2 > \alpha_1$	$\leftrightarrow\uparrow$	$\uparrow\uparrow$	$\downarrow\downarrow$	Inotrope & vasodilator; may lower BP

(*Continued*)

Table 18-5 Relative Action of Vasopressors (Continued)

Drug	*Receptor*	*HR*	*Inotropy*	*SVR*	*Comments*
Norepinephrine	α_1, α_2, β_1	$\leftrightarrow\uparrow$	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	For hypotension refractory to dopamine; initial choice in sepsis
Epinephrine	α_1, α_2 β_1, β_2	$\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow\uparrow$	For refractory cardiac failure (*e.g.* post CABG) or anaphylaxis
Phenylephrine	α_1	0	0	$\uparrow\uparrow\uparrow$	For refractory hypotension, esp. vasculogenic
Isoproterenol	β_1, β_2	$\uparrow\uparrow\uparrow$	$\uparrow\uparrow$	$\leftrightarrow\downarrow$	Primarily increases HR. May cause reflex hypotension.
Vasopressin	V1a	0	0	$\uparrow\uparrow$	Effective even in acidosis

VENTILATOR BASICS

WHEN TO INTUBATE

- Airway protection
- Severe facial trauma
- Preoperative for surgery
- Neurologic decline (GCS 8 or less)
- Pulmonary insufficiency (hypoventilation, hypoxemia, respiratory rate (RR) > 40, $PaO_2 < 60$)

HOW TO REPORT VENT SETTINGS

Mode, fractional inspired oxygen, tidal volume, patient's rate "over" set rate, positive end-expiratory pressure, pressure support, peak inspiratory pressure

Initial ventilator settings: FiO_2 100% then wean, rate 12, TV = 7mL/kg, PEEP5, PS10

- Determines ventilation: pCO_2, rate, TV
- Determines oxygenation: pO_2, FiO_2, TV

Mode

Synchronized intermittent mandatory ventilation (SIMV): Patient determines volume of breaths over set rate

- Pressure support of allows patient to overcome resistance of ventilator tubing

Continuous positive airway pressure (CPAP): PEEP, no rate, and no pressure support

- Same as *spontaneous breathing trial (SBT)*

BiPAP: Pressure support + PEEP without rate

Airway Pressure Release Ventilation (APRV): Cycles between two different levels of CPAP (upper and lower)

- Baseline airway pressure is the upper CPAP level, intermittently released to a lower level

Continuous Mandatory Ventilation (CMV): Ventilator delivers breaths at preset intervals irrespective of patient effort

Assist Control (AC): Patient triggers the ventilator to deliver the full set tidal volume (VT) (above set rate)

Fractional Inspired Oxygen (FiO_2)

Room air = 21%

- Oxygen toxicity occurs at > 60%
- Start at 100% and wean down to 40% depending upon result of ABG
tidal volume (VT): Ideal = 7–10 mL/kg
- Lung protection: TV < 6 mL/kg IBW
- Intraoperative = 10–15 mL/kg
- Too high of TV leads to barotrauma and high peak inspiratory pressures (PIP) (> 30)

Rate

Start at 8–12

Positive End-Expiratory Pressure (PEEP)

To prevent alveolar collapse

- Standard is five, raise by two to three when needed
- Increasing PEEP decreases venous return

Arterial Blood Gas (ABG)

Report as pH/$PaCO_2$/PaO_2/bicarb/base excess

- PaO_2 reflects oxygenation, $PaCO_2$ reflects ventilation
- Order daily and prn for intubated patients

Recruitment Procedures

Give large breath then increase PEEP

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Hypoxemia refractory to increased FiO_2

- Give small tidal volume (6 mL/kg), high rate, high PEEP (8–10), keep PIP < 35, time-controlled pressure ventilation modify inspiratory to expiratory time ratio (normal is 1:2)

NEUROGENIC PULMONARY EDEMA

Fulminant, diffuse pulmonary edema, decreased compliance (requiring high positive end–expiratory pressure), and hypoxemia (requires increased FiO_2)

- May involve circulating catecholamines or increased peripheral vascular resistance

When to Extubate

- Tobin index = rapid shallow breathing index (RSBI): Respiratory rate/tidal volume (L). If RSBI > 105, 80% chance of respiratory failure after extubation
- Age > 60, goal RSBI < 80
- Negative Inspiratory Force should at least be –20 to –30 cm H_2O
- Minute ventilation (MV) (MV = RR * VT) of > 10 L/min
- Improving clinical status
- ABG appropriate during spontaneous breathing trial

- Pass SBT
- Cuff leak test on patients with concern for edema (e.g., long cases prone with large blood loss)
- Cough
- Controversial requirements include following commands, gag

TREATMENT OF INCREASED INTRACRANIAL PRESSURE

- Sedation, head of bed at 30 degrees
- Cervical collar release and slight head turn opposite to main draining jugular
- Adjust minute ventilation for goal etCO2/PaCO2 30-35mmHg, (below will likely trigger ischemia, above will likely exacerbate ICP)
- Ventriculostomy or evacuation of the mass lesion if possible, along with medical osmotherapy (Mannitol 1g/kg x1 dose, then 23% hypertonic saline 30mL amp x1-4doses until ICP < 15)
- If recurrent crises, Mannitol 0.5g/kg q6h alternating with 3% saline 250mL q6h, with goal SerOsm > 320 and Na > 155
- Therapeutic hypothermia
- Barbiturate coma with goal ICP < 15 (do not target BSP)
- Paralysis or abdominal decompressive laparotomy
- Bilateral hemicraniectomy—last resort

COMA AND ENCEPHALOPATHY[3–8,14,15]

Table 18-6 The Numerous Domains of Consciousness in Antonyms

responsive vs. unresponsive	adequate response vs. inadequate	conscious vs. unconscious	aware vs. unaware
attentive vs. inattentive	alert vs. inert	aroused vs. sedated	awake vs. asleep
oriented vs. disoriented	recollecting vs. amnesic	thinking vs. absent	coherent vs. confused

Source: Courtesy of G Kapinos

COMA

Clinical observation of an inert patient with no adequate response (eyes opening, verbalizing, or moving/withdrawing) to stimuli, including noxious ones

- The patient is unresponsive to external stimulation because of intrinsic, persistent unarousability.

Pathophysiology: Severe disruption in alertness or awareness circuitries through neuronal or axonal damage

- Any process that is deleterious diffusely to the bilateral cerebral hemispheres (consciousness) or focally to the bilateral paramedian thalami (awareness) or to the reticular activating system or pontomesencephalic tegmentum (alertness)

Etiology:

- Vascular: Ischemic stroke (arterial occlusion or venous congestion), global hypoxia/anoxia, spontaneous intracerebral hemorrhage (ICH), aneurysmal subarachnoid hemorrhage (SAH), diffuse edema from hypertensive encephalopathy
- Infectious: Meningitis/encephalitis, especially with basilar cisterns involvement
- Traumatic: ICH or severe diffuse axonal injury (DAI) from traumatic brain injury (TBI), brainstem injury
- Metabolic/Endocrinological: Hypoglycemia, hepatic or renal failure, myxedema, hyperosmolality
- Drugs: Anesthetics or sedatives in excess, especially EtOH, benzodiazepines, opiates, barbiturates, poisons
- Tumor: Mass in the brainstem, hypothalamus, or both thalami or frontal lobes
- Seizures: Convulsive or nonconvulsive status epilepticus (NCSE), postictal phase
- Inflammatory: ADEM/MS lesions involving the brainstem or thalami
- Degenerative: Diffuse cortical involvement is rare but seen in terminal CJD

Exam: Two main goals are to detect if the cause is supratentorial or in the brainstem (BS) and to detect asymmetry to rule out a rapidly progressing focal process potentially leading to herniation (fatal).

- ABC dextrose oxygen naloxone thiamine as first life-support measures
- Breathing pattern (can be normal in cortical causes, Kussmaul hyperventilation usually metabolic, Cheyne-Stokes in midbrain/pontine lesions, or agonal in medullary lesions)
- Glasgow Coma Scale (Table 18-7)
- Brain Stem Reflexes

Table 18-7 Adult Glasgow Coma Scale (GCS)

Eye (E)	Verbal (V)	Motor (M)
1—no eye opening to pain 2—opens eyes to pain 3—opens eyes to voice 4—opens eyes spontaneously	1—no sounds to pain 2—moans/groans/grunts, no words to pain 3—words in wrong lexical field, severely confused 4—words in correct lexical field but slightly confused or disoriented 5—adequate oriented answer T—intubated and unable to assess	1—no movements 2—extensor posturing 3—flexor posturing 4—moves limb away from the pain 5—grabs the hand afflicting pain 6—follows commands

NOTE: Consider the three values separately and in sum. The lowest possible GCS (sum) is 3, the highest is 15.TBI is classified as severe, with GCS ≤ 8, moderate, GCS 9–12, and minor, GCS ≥ 13.

Source: Courtesy of G Kapinos, adapted from Teasdale et al. *Lancet* 1974;2:81–4.

- Pupillary response to light: Mydriasis/myosis (intoxications), fixed mid-sized (midbrain), pinpoint (pons), unilateral fixed and dilated (probable mass lesion leading to CNII palsy from uncal herniation)
- Gaze: Forced deviation/gaze preference from frontal lesions, up-gaze palsy (rostral midbrain), CN III palsy (pupil involving from compression of parasympathetic fibers on nerve periphery posterior communicating artery aneurysm versus pupil sparing from ischemia to the nerve), CN IV and VI palsies (pons)
- Oculocephalogyric reflex (OCR or Doll's): Intact OCR = BS is intact and disinhibited by an impaired cortex, OCR absent = either awake (tracking saccades) or BS lesioned (straight empty gaze), to be confirmed by absent caloric vestibulo-oculogyric reflex
- Funduscopic exam for papilledema (ICP elevation) and retinal hemorrhage
- If all brainstem reflexes are absent (fixed gaze, nonreactive pupils, no corneal, no OCR, no gag, no cough, no breathing) and no cortical response can be elicited (coma), the exam is thus consistent with brain death, not coma
- Motor and sensory in four limbs: Ask to move limbs, then apply pain and observe facial grimacing, four limbs withdrawal, decorticate (lesion above the red nucleus), decerebrate (lesion below the red nucleus), triple flexion (spinal reflex is released) or absent response
- Confirm findings with tone, deep tendon reflexes (DTRs) and cutaneous plantar reflexes (Babinski)
- Look for sensory or sweat level
- Neck exam (nuchal rigidity)

Workup: ask witnesses about environment where patient was found down and ask for plausible causes

- Labs: CBC, Chem20, coagulation, ABG, UA/UrCx, toxicological screen
- Imaging: CXR, noncontrast head CT
- EKG: rule out myocardial infarction (MI), left ventricular hypertrophy (LVH) as a sign of hypertension (HTN), pseudoischemic changes in subarachnoid hemorrhage (SAH)
- Cerebrospinal fluid (CSF): Opening pressure
- Cell count and differential, protein, glucose, gram stain
- EEG: Continuous for 24 hr to differentiate postictal state versus NCSE versus metabolic triphasic waves

Treatment:

- Stabilize HR and BP, intubate for airway protection, O_2, monitoring.
- IV thiamine dextrose and naloxone empirically
- Possible meningitis or encephalitis → start IV ceftriaxone vancomycin acyclovir ASAP
- Possible status epilepticus → IV lorazepam 2 mg x three doses max, then fosphenytoin load 15 mg/kg

- Possible stroke < 6 hr → call "stroke code" for CT stat and neurological evaluation for thrombolysis or thrombectomy
- Unstable patient → ICU
- Correct electrolyte disorder, maintain euthermia, euvolemia, euglycemia, O_2 sat > 95%, promote cerebral perfusion unless proof of expanding ICH, if so, reduce SBP < 160 mmHg
- Tertiary prevention (to mitigate worsening and complications): consider induced hypothermia mainly in cardiac arrest cases, treat ICP elevation if present, seek evidence-based neuroprotection appropriate for the underlying cause

Prognosis: Depends largely on initial cause and severity of coma.

- In traumatic cases, GCS has a gross prognostic value: 3–5 (60% death), 6–8 (12%), 9–12 (2%), > 12 (NS)
- In hypoxicischemic cases (especially postcardiac arrest): use Wijdicks et al. algorithm
- In metabolic cases, return to homeostasis will eventually lead to regain of consciousness.
- Underlying cause carries more prognostic significance than any clinically based scale.
- Eliminate confounders: renal, hepatic failures, shock, metabolic acidosis, recent use of sedatives or paralytics, use of therapeutic hypothermia

Table 18-8 Post-Cardiac Arrest Coma Prognostic Indices

These findings are the most robustly associated with a poor outcome (defined as death or unconsciousness at 1 month, unconsciousness or severe disability at 6 months), false positive rates given (FPR)

Day 1	Myoclonic status	FPR 0% (0–8.8%)
Day 1 to 3	Absent N20 on SSEP	FPR 0.7% (0–3.7%)
Day 1 to 3	Serum NSE > 33 ug/L	FPR 0% (0–3%)
Day 3	Absent pupillary or corneal reflexes and absent or extensor motor response to pain	FPR 0% (0–3%)

NOTE: No other findings have been robustly associated with a poor outcome, thus a wide array of outcomes should be expected in the absence of these.

Source: Courtesy of G Kapinos, adapted from Wijdicks et al. *Neurology* 2006;67:203–10.

ENCEPHALOPATHY

Definition: Any alteration of consciousness

Pathophysiology: Global alteration without total disruption in awareness or judgment circuitries

- Awareness and attention rely on intactness of thalamocortical loops and the nondominant parietal lobe, and judgment/coherence resides in diffuse cortical interconnections

Etiology: Often multifactorial but the final common pathway of this dysfunction resides in an impairment in the supply of nutrients (oxygen, glucose) necessary to maintain cerebral metabolism

- Vascular: Global cerebral hypoxia/ischemia or focal brainstem
- Infectious: Meningitis/encephalitis, especially temporal or frontal involvement
- Traumatic: Mild to moderate TBI especially with diffuse cortical involvement
- Metabolic/Endocrinologic: Hypoglycemia, hepatic or renal failure, myxedema, hyperosmolality
- Drugs: Anesthetics or sedatives even without any obvious excess, especially EtOH, benzodiazepines, opiates, barbiturates, poisons, during the intoxication or during the withdrawal phase
- Tumor: Mass in the temporal or frontal lobes or rarely in the brainstem, hypothalamus, or thalami
- Seizures: Convulsive or nonconvulsive status or postictal phase
- Inflammatory: SIRS induced cerebral metabolic failure
- Degenerative: Rarely responsible for delirium (acute encephalopathy), degenerative disorders lead to slow progressive encephalopathies (dementia), except for acute spells as seen in Lewy Body Dementia, CJD, or vitamin deficiencies such as Wernicke and Korsakoff syndromes

Exam: Tease out the impairment: alertness vs. awareness vs. attention vs. cognition vs. speech vs. perception vs. orientation vs. emotion vs. volition

- Also detect asymmetry or papilledema in neurological examination to rule out a rapidly progressing focal process potentially leading to herniation which is often rapidly fatal
- Start with coma exam (see section Coma for details): ABC DONT, breathing, GCS, pupils, gaze, OCR, motor and sensory in four limbs, fundus, nuchal rigidity
- Then, assess cognition: e.g., Folstein MMSE, CAM, CAM-ICU, and mood

Table 18-9 Confusion Assessment Method in the ICU (CAM-ICU)

Pt is delirious (CAM ICU positive) if (1) and (2) and (3) or (4)	
1. Acute onset or Fluctuating Findings	2. Inattention
3. Disorganized thinking	4. Altered level of consciousness (RASS)
Richmond Agitation Sedation Scale (RASS)	
+4. Combative	+3. Very agitated (pulls lines/tube)
+2. Agitated (swirls in bed, fights vent)	+1. Restless
0. Alert and calm	-1. Drowsy
-2. Light sedation (eye contact <10s to voice)	-3. Moderate sedation (no eye contact to voice)
-4. Deep sedation (movement or eye opening to pinch)	-5. Unarousable (no response to voice or pinch)

Note: Attention is tested by patient squeezing appropriately only upon hearing the letter A, while examiner slowly says SAVEAHAART. Disorganized thinking is present if patient answers one Y/N question wrong ("Will a stone float on water? Are there fish in the sea? Does one pound weigh more than two pounds? Can you use a hammer to pound a nail?").
Source: Courtesy of G Kapinos, adapted from Sessler et al. AJRCCM 2002 and Ely et al. Crit Care Med. 2001.

Workup:

- Labs, imaging, EKG, CSF, EEG as per coma (see previous)
- No specific biomarker for encephalopathies, although there are numerous hypotheses on certain neurotransmitters imbalances

Treatment:

- Cardiovascular and respiratory stabilization if necessary
- Identify and treat underlying medical causes
- Correct electrolyte disorder, anemia, maintain euthermia, euvolemia, euglycemia, O_2 sat > 95%, promote cerebral perfusion
- Rule out infection
- Limit polypharmacy, especially psychotropic medications, avoid sedative especially benzodiazepines, opiates, anticholinergics, antihistamines, GABAergic agents
- Promote normal sleep/wake cycles with stimulation at daytime and quietness at night
- Provide sensory aids, promote participation into intellectual tasks with PT/OT and orientation
- Limit stay in ICU and number of room changes
- No psychostimulant drug has been proven to be efficient in reversing hypoactive encephalopathy, but antipsychotics can be used in combative patients
- Tailor Rx to target: psychosis versus agitation versus disorientation

Prognosis:

- Depends largely on initial cause and severity of the encephalopathy, but return to global homeostasis eventually leads to regain of full consciousness, although neurocognitive sequelae have been reported especially in the ICU
- Ischemic causes carry a less-optimistic prognosis, especially if associated with a lesion on imaging
- Delirium leads to poorer outcomes: linked to an increased risk of nosocomial PNA, self-extubation and reintubation, prolonged hospitalizations, functional decline, a high risk for institutionalization upon discharge and a higher risk of death at 6 months

HERNIATION SYNDROMES

Cingulate: Cingulate gyrus under the falx → anterior cerebral artery compression and stroke → leg weakness/paralysis

Uncal: Uncus of medial temporal lobe under the tentorial incisure → CNIII and midbrain compression → dilated pupil and coma

Central: Diencephalon under the tentorial incisure → compression of the thalamus, midbrain → coma

Tonsillar: Cerebellar tonsils through the foramen magnum → compression of the medulla → cardiorespiratory arrest

Upward: Cerebellar parenchyma cephalad through incisura → kinking of the posterior cerebral artery, displacement of fourth ventricle

DETERMINATION OF BRAIN DEATH (> 5 YEARS OF AGE)

Condition must be irreversible

- No complicating conditions (drugs, hypothermia, hypotension, seizures)
- Except in the case of large mass lesion or gunshot wound, should have a 6-hour observation period
- Requires two physician confirmation

Criteria: No brainstem reflexes (fixed pupils, no corneal, oculovestibular, oculocephalic, gag or cough reflex), apnea (no spontaneous respiration with pCO_2 > 60 while off ventilator for 6 min), no spontaneous movement or movement to pain (excluding spinal cord reflexes)

- May NOT be hypothermic (< 36.5), electrolyte abnormalities, refractory shock (SBP < 90), intoxicated, treated with neuromuscular blocking agents or sedatives, acid-base disorder

Confirmatory tests: Angiography, EEG, isotype cerebral blood flow study

Cold calorics: Elevate head to 30° and irrigate with ice cold water

- No tonic deviation toward cold stimulus is consistent with brain death
- Wait 5 minutes and then test contralateral side

Apnea test: Preoxygenate with 100% O_2 for 30 minutes, place nasal cannula with 100% O_2 at 8 L/minute

- Positive apnea test is evidenced by no respiratory effort after 6 minutes and PCO_2 of > 60

CRANIAL TRAUMA[1,2]

CLOSED HEAD INJURY[9–11]

Etiology: Primary (contusions, concussions, etc.) versus secondary (hypoxia, hypotension)

- Cerebral hypoxia → ATP depletion → failure of Na+-K+ pump → intracellular accumulation of Na+ and Ca+2 → acidosis, decreased NT uptake → glycolysis inhibition, increased extracellular glutamate → activation of NMDA channel → increased intracellular Ca+2 → protease/phospholipase activation → free fatty acid (free radical accumulation)
- Impairment of autoregulation of cerebral blood flow, decoupling of cerebral metabolism and cerebral blood flow

MONRO-KELLIE HYPOTHESIS

Brain parenchyma, blood, cerebrospinal fluid (CSF) in fixed box (skull)

- With increasing intracranial pressure (ICP), CSF production decreases, CSF is pushed into the spinal compartment, and resorption increases → intracranial blood volume decreased by venous compression → compliance decreases and small increases in volume lead to exponentially higher increases in ICP → eventually this culminates in brain parenchyma herniation, occlusion of arterial supply with resulting infarcts

CEREBRAL EDEMA

Disruption of blood brain barrier (vasogenic) or primary intracellular edema (cytotoxic)

CEREBRAL PERFUSION PRESSURE (CPP)

Normal 50 mmHg, should be > 60 mmHg in traumatic brain injury (TBI) patients

MALIGNANT CEREBRAL EDEMA

In pediatrics with severe hyperemia, refractory increases in ICP, high morbidity/mortality

Many have electrolyte, endocrine and cardiopulmonary function abnormalities.

TREATMENT BY SYSTEMS

Neurological: Evacuation of mass lesions, hemicraniectomy for medically refractory increase in ICP and focal edema or mass, intracranial pressure monitoring device (GCS < 8), prophylactic anticonvulsant therapy not indicated but monitor closely for seizures, ICP should be maintained at less than 20 (See Treatment of ICP, page 209), hold sedation for q1hr neuro exams or maintain sedation if required for ICP management

Cardiovascular: Maintain systolic blood pressure > 90, place arterial line and central line

Pulmonary: Intubation (for GCS < 8; inability to maintain adequate ventilation, impending airway loss from neck or pharyngeal injury, poor airway protection associated with depressed level of consciousness, and/or the potential for neurological deterioration)

Gastrointestinal: Ulcer prophylaxis (e.g., proton pump inhibitor)

Genitourinary: Place foley catheter (monitoring of urine output)

Hematologic: Check CBC, type and cross

Infectious disease: Ceftriaxone if a bolt or EVD is in place, tetanus vaccine if indicated

Fluids/Electrolytes/Nutrition: NPO, isotonic saline (0.9% NaCl) with goal of euvolemia, check electrolytes, mannitol (to be held for serum osm > 320), hypertonic saline (goal of Na > 145)

Musculoskeletal: Ensure adequate tertiary survey, maintain in cervical spine precautions until appropriately cleared

Disposition: ICU

MANAGEMENT OF CLOSED HEAD INJURIES IN PEDIATRICS

Table 18-10 Management of Closed Head Injury (CHI) in Children ≥ 2 Years Old

Inclusion Criteria[1]	Exclusion Criteria[1,2]
• Age 2-20 • Normal mental status upon exam • Normal neurologic examination • May have LOC < 1 min, vomit, headache, or lethargy which resolved • Evaluation within 24 hours of injury	• Age < 2 years • Signs of skull fracture • Multiple trauma or spine injury • Unobserved loss of consciousness • Bleeding diathesis underlying neuro. disorder (e.g. shunt, AVM)
Summary of American Academy of Pediatrics Recommendations	
Minor CHI, No LOC	• Observation in home, clinic, office or ED • CT, MRI, and skull radiography are not indicated
Minor CHI, brief LOC *(Asymptomatic)*	• Option 1 – observation (home, clinic, office, ED, hospital) • Option 2 – CT is acceptable
Minor CHI, brief LOC *(Symptomatic)*	• Signs of CHI (e.g. lethargy, repeat vomiting, ↑ headache) • CT scan

[1]Inclusion and exclusion criteria for use of parameter.
[2]Does not imply mandatory imaging.
Pediatrics 1999; 104: 1407.

CONCUSSION[12]

Symptoms (memory loss, dizziness, headache, physical and mental sluggishness, irritability, confusion, difficulties concentrating) without radiologic findings

- Postconcussion syndrome is a continuation of these symptoms up to several months

Table 18-11 Concussion in Athletes (Observe and evaluate for at least 15 minutes) and Return to Play Criteria

Grade	Symptoms	Duration	Recommended return
I	Confusion, no amnesia	Minutes	When symptoms resolve
II	Retrograde amnesia	Hours to days	1 week*
III	Amnesia after impact	Days	1 month*

*Second episode - out for the entire season.
Any athlete that is symptomatic after a concussion requires serial evaluation. Symptomatic players (including headache or in attention) do not return to play,
If at any point exam reveals deterioration in mental status or loss of consciousness after a concussion immediate transportation to an emergency facility is indicated.

SKULL FRACTURES[9,11,13]

Diagnosis: Imaging (CT scan)

Radiology: Contre coup injury in 30% of cases

Treatment: Surgical debridement when wound is open and/or has greater than 0.5 cm of depression, is cosmetically deforming

- Avoid surgery if fracture is over dural sinus
- Antibiotics indicated for open fracture

Outcome: Surgery and elevation of bone does not improve the underlying damage to the brain parenchyma and does not change the incidence of post-traumatic epilepsy (7–9%)

- Increased risk for CSF leak

SIGNS OF SKULL BASE FRACTURES

Raccoon eyes (bilateral periorbital ecchymoses), mastoid ecchymoses, otorrhea, rhinorrhea of CSF, hemotympanum, cranial nerve palsy

- If concern for CSF week, beta-2 transferrin is unique to CSF (and vitreous of the eye), but many times is a send-out lab that can take up to 1 week to return

TEMPORAL BONE FRACTURE

Longitudinal: (70–90%) → facial nerve paralysis, hearing loss, vertigo, temporal/parietal trauma, epidural hematoma

- Transverse: (10–30%) → sensorineural hearing loss, equilibrium disorders, facial nerve injury
- Facial nerve damage more likely with transverse fracture, but overall more longitudinal fractures occur so these by number cause more facial nerve paralysis

GROWING SKULL FRACTURE

Children (usually < 3 years) with fracture and underlying dural laceration, may result in progressive diastatic fracture and underlying leptomeningeal cyst

- requires surgical intervention with repair of underlying dural defect

DIFFUSE AXONAL INJURY (DAI)

Etiology: Centripetal progression of neuronal disconnection (shear injury) secondary to severe, oblique vector (e.g., high-speed motor vehicle accident)

Clinical: Low GCS without obvious lesion on CT scan

Location: Corpus callosum, internal capsule, midbrain (tectum), basal ganglia, descending corticospinal fibers (pontomedullary junction)

Radiology: Punctate hemorrhages on MRI (GRE sequence most sensitive)

Outcome: Poor

EPIDURAL HEMATOMA

Radiology: 70% temporoparietal, 90% with fractures and underlying middle meningeal artery injury

- Lenticular, convex shape
- May have delayed enlargement
- Rarely associated with other brain injury (in comparison to subdural hematoma)

Outcome: 5% mortality , 10–30% delayed enlargement

Presentation: Most have history of severe head trauma

- Classically have a "lucid interval" with resolving confusion after initial injury and then neurological decline (actually occurs in < 30%)

Treatment: Surgical evacuation

VENOUS EPIDURAL HEMATOMA

More frequent in children

- Next to the dural sinuses or tentorium

SUBDURAL HEMATOMA

Epidemiology: Occurs in 15% of severe head trauma

- Seen frequently in elderly with minor trauma especially when on anticoagulation
- Predisposition with conditions that cause brain atrophy and therefore, increased tension on bridging veins (e.g., alcohol abuse, dementia)

Etiology: Shear injury to bridging cortical veins (e.g., trauma, intracranial hypotension, severe atrophy, birth trauma)

Radiology: Acute → hyperintense (can be isointense with low hematocrit or rapidly expanding lesions)

- Subacute → isodense
- Chronic (> 3 weeks) → hypodense

Treatment: Patients with symptomatic SDH with midline shift should be surgically evacuated

- Acute SDH requires a large, trauma craniotomy; chronic SDH may be amenable to evacuation with only burr holes

Outcome: 35–90% mortality, depending on age and comorbidities

- Reaccumulation of chronic SDH occurs in up to 45%, mortality < 10%

PENETRATING INJURIES[9,11,13]

Etiology: E.g., stab wound, gunshot wounds (GSW)

- Direct and indirect (temporary cavitation) injury
- Pressure waves lead to stretch injury in adjacent brain with high-velocity projectiles (e.g., GSW)

Radiology: May see skull fragments, projectile debris

Treatment: Consider surgery for GCS 3–5 w/large EDH, GCS 6–8 without transventricular or bihemispheric injury, or GCS 9–15

Outcome: Mortality 70–80%

- 2/3 of victims die at the scene
- Post-traumatic epilepsy in 50% of survivors if comatose at the time of presentation, mortality is > 90%

CHAPTER 19 ■ PSYCHIATRY

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CAPACITY DETERMINATION

INFORMED CONSENT

Have you presented the patient with enough information to be considered informed consent? Does the patient understand the diagnosis? Does the patient understand the proposed treatment and the severity of the treatment? Does the patient understand the risks and benefits from the treatment? Does the patient understand the limited ability with which physicians can predict the results of the treatment or lack of treatment? Does the patient understand if the treatment is reversible or irreversible? Does the patient understand the alternative treatments and their inherent risks, benefits, and potential benefits?

DETERMINING CAPACITY

Can the patient state a preference? Is the patient able to demonstrate understanding of the factual nature of their situation and prognosis? Can they understand the risks/benefits/alternatives of the proposed treatment? Can they repeat these back if prompted? Does the patient understand the significance of the facts presented to them (i.e., without treatment they may lose a limb or could die)? Is the patient able to demonstrate a rational thought process in making their decision? Note: The decision need not agree with the treatment team in order to be made in a rational manner.

MOOD DISORDERS

MAJOR DEPRESSIVE DISORDER

■ DSM-IV Diagnostic Characteristics

At least five of the following symptoms, lasting for at least 2 weeks: Depressed mood, anhedonia, significant change in appetite (increase or decrease), insomnia or hypersomnia, psychomotor agitation or psychomotor retardation, decreased energy, worthlessness or guilt, decreased concentration, thoughts of death or suicide

- SIGECAPS: **s**leep, **i**nterest, **g**uilt, **e**nergy, **c**oncentration, **a**ppetite, **p**sychomotor, **s**uicide

- Symptoms must represent a change from baseline, not be accounted for by bereavement, must present a functional impairment, and not be explained by some other condition

Differential diagnosis: General medical condition (hypoactive delirium, dementia, traumatic injury, stroke [pseudobulbar affect], metabolic condition [hypothyroidism]), acute effects of a substance (either intoxication or withdrawal), another psychiatric condition (schizoaffective disorder, bipolar affective disorder, dysthymia, personality disorder), bereavement

Workup/Key questions: General metabolic panel, Utox, TSH, B12, CBC; ask about suicidality (see Table 19.1)

Treatment: 1st line—SSRI (fluoxetine, sertraline, paroxetine, citalopram, escitalopram), SNRI (venlafaxine, desvenlafaxine, duloxetine), bupropion, mirtazapine, psychotherapy (CBT, psychodynamic). 2nd line—TCA (nortriptyline, desiprimine), MAO-I (selegeline patch, tranylcypromine, isocarboxazid, phenylzine). Adjunctive agents—atypical antipsychotics (aripiprazole, quetiapine, risperidone, olanzapine, ziprasidone), lithium, modafinil, T3; in severe cases, electroconvulsive therapy

BIPOLAR AFFECTIVE DISORDER

Diagnostic characteristics: Criteria for a manic episode: 1 week of euphoria or irritability AND at least three of the following symptoms: grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased goal directed activity, risky/impulsive behavior

- Bipolar disorder *type I* is characterized by having had at least one manic episode, as well as at least one period of a major depressive episode
- Bipolar *type II*, is characterized by at least one period of hypomania with at least one major depressive episode

Differential for mania: Substance (either illicit drug intoxication or withdrawal, steroids, antibiotics), metabolic (hypo or hyperthyroidism, B_{12} deficiency, Cushing's, Wilson's, porphyria), infection, neoplasm (meningioma, glioma, extraaxial), epilepsy, stroke, MS, traumatic brain injury, other psychiatric disorder, general medical condition, direct effect of a medication or drug (i.e., steroids, antidepressants, ECT)

Workup: Metabolic panel, CBC, TSH, Utox, consider scan, ECG, infection workup

Treatment: Acute mania—1st line: lithium, anticonvulsants (valproic acid, carbamazepine), atypical antipsychotics (aripiprazole, quetiapine, risperidone, olanzapine, ziprasidone); adjunctive—benzodizapines (lorazepam, clonazapam); severe—electroconvulsive therapy, clozapine. Depression—1st line: lamotrigine, quetiapine, aripiprazole, psychotherapy; 2nd line—SSRI, SNRI, pramipexole, modafinil; severe—electroconvulsive therapy, clozapine, MAO-I

Table 19-1 Evaluation of Suicidal Ideation

Thought/plan/intent	Should ask if patient has written a note, given away possessions, put "affairs in order" or done other behaviors to suggest that they've begun to plan for being dead
Diagnosis or history of a psychiatric disorder	Over 90% of suicides occur in people with a documented psychiatric disorder, however, many patients do not come to psychiatrist before committing suicide and do not receive treatment. Lack of diagnosis does not mean there cannot be suicide risk. Suicides do not only occur in depressed patients; panic attacks, akathisia, and mixed states also are high-risk situations.
Substance abuse	Substance abusers are at extremely high risk for suicide; it is important to carefully assess for concurrent mood disorder in this population.
Future oriented versus hopeless	Helpful to ask a person if they are hopeless, if they have reasons to live (such as religion or family/children)
Methods/Means to commit suicide	Important to ask about weapons (particularly firearms)
Prior attempts or family history of suicide	Did the patient think that a past attempt may have been potentially fatal (even if there was no actual likelihood of fatality)? Is there a family history of suicide?
Demographics	Women more likely to attempt suicide but men more likely to complete suicide (use more violent means); elderly, Caucasian men are greatest demographic group for suicide

Courtesy of J. Ballon

PSYCHOTIC DISORDERS

SCHIZOPHRENIA

Diagnostic characteristics: Two (or more) of the following for at least 1 month: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms (flat affect, decreased speech, poor motivation, etc.)

- Only one symptom is needed if delusion is impossibly bizarre or hallucination involves voices conversing with each other or giving a running commentary on the person's behavior
- Must be a deficit in social or occupational function compared with prior to onset of symptoms
- Deficit must last for at least 6 months (during which at least 1 month must have active symptoms unless they are treated)

Differential: Substance (stimulants, hallucinogens, alcohol [intoxication or withdrawal], inhalants, PCP, steroids, anticholinergics, and many more), medical condition (toxic/metabolic abnormality, infection, autoimmune, demyelinating disorder, stroke, tumor, epilepsy, head trauma, endocrine, nutritional deficiency), delirium secondary to medical condition

Workup: Careful history; CBC, electrolytes, TSH, ESR/CRP, LFT, urinalysis and toxicology, infection workup including, HIV test, RPR/FTA, CT/MRI, possible EEG or LP if warranted

Treatment: First line—atypical antipsychotics (aripiprazole, quetiapine, risperidone, olanzapine, ziprasidone), conventional antipsychotic (high potency—haloperidol, fluphenazine; mid-potency-perphenazine, loxapine; low potency—chlorpromazine); use anticholinergics with high potency antipsychotics—benztropine, trihexiphenidyl: severe—clozapine

ANXIETY DISORDERS[1–3]

GENERALIZED ANXIETY DISORDER

Diagnostic characteristics: Excessive anxiety and uncontrollable worry occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance)

- At least three of the following: restlessness, fatigue, irritability, difficulty concentrating, muscle tension, sleep disturbance
- Must be a social/occupational dysfunction because of the worry

Differential: Substance (akathisia from antipsychotics or antiemetics, intoxication from stimulants [caffeine, amphetamine, cocaine]), other psychiatric or medical disorder (i.e., obsessive compulsive disorder [OCD], panic disorder, somatization disorder, PTSD)

Treatment: First line—psychotherapy, SSRI, SNRI, benzodiazepine; 2nd line—TCA, MAO-I, atypical antipsychotic

OBSESSIVE COMPULSIVE DISORDER (OCD)

Diagnostic characteristics: Obesssions (recurrent intrusive thoughts or images) and/or compulsions (recurrent behaviors the patient feels obligated to perform even though there is no rational reason to do so) occurring for at least 1 hour a day. Patients should have some intellectual understanding that the obsessive thoughts are the product of their own mind and that their compulsions are not rational, but insight is often poor. Common obsessions and compulsions include contamination fears/hand washing, counting, checking doors and stoves, and preoccupation with symmetry.

Differential: Stimulant intoxication, psychotic disorder, depressive rumination, tics, GAD, impulse control disorder

Workup: Careful history and physical

Treatment: 1st-line—SSRIs or clomipramine, and/or CBT. 2nd line treatment—addition of antipsychotic to the previously described treatments

TIC DISORDERS[3]

Diagnostic characteristics: Tics are repetitive motor movements or vocalizations. Patients can often temporarily suppress tics, but soon the urge to perform them becomes overwhelming. Common tics include eye blinking and sniffing, but tics can consist of complex motor movements or words and phrases

Tourette's syndrome (TS) = multiple motor tics plus at least one vocal tic for > 1 year, starting before age 16. OCD and ADHD are common comorbidities for TS

Pathophysiology: Dopamine reuptake defect (VTA to anterior cingulate pathway)

Differential: Movement disorders, allergic rhinitis, behavior problems, ADHD, compulsions

Workup: Careful history and physical, observation of tics on exam

Treatment: Milder cases may not need treatment. Pharmacologic treatment—typical antipsychotics (especially haloperidol), risperidone, clonidine

POST-TRAUMATIC STRESS DISORDER (PTSD)

Diagnostic characteristics: Exposure to a traumatic event in where the person experienced or witnessed an event that involved actual or threatened death or serious injury or a threat to the physical integrity of self or others and the person's response involved intense fear, helplessness, or horror

- Traumatic event is persistently reexperienced in at least one of the following ways: Intrusive thoughts about the event, nightmares, flashbacks, psychological distress, or physiological reactivity to cues related to the event
- Persistent avoidance of stimuli associated with the trauma as indicated by at least three of the following: Avoidance of thoughts/feelings related to trauma, places/people related to trauma, inability to recall aspects of trauma, social withdrawal, detachment from others, restricted affect, sense of foreshortened future
- Persistent symptoms of increased arousal as indicated by at least two of the following: Insomnia, irritability, difficulty concentrating, hypervigilance, exaggerated startle
- Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning for at least 1 month

Treatment: Psychotherapy (CBT, prolonged exposure, EMDR), SSRI/SNRI, benzodiazepine, quetiapine

ATTENTION DEFICIT DISORDER

Diagnostic characteristics: Symptoms present by age 7 and must cause impairment in at least two settings (i.e., home, school) with evidence of significant impairment in social/occupational functioning

- At least six of the following symptoms of inattention have persisted for at least 6 months: poor attention to detail, difficulty sustaining attention, poor listening, fails to finish projects, difficulty organizing tasks, avoids sustained mental attention tasks, loses important objects, forgetful in daily activities OR
- At least six of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level: fidgets, leaves seat frequently, restlessness, difficulty with quiet activities, always "on the go," excessive talking, blurts out answers, difficulty with taking turns, interrupts

Differential: Medical condition (sleep apnea, metabolic, epilepsy), family dynamics, understimulating environment, oppositional or antisocial behavior, result of a substance (either intoxication or withdrawal), other psychiatric disorder

Workup: Psychological testing (best to involve child, parents, teachers), consider testing for sleep disorders

Treatment: Psychotherapy/Family therapy, stimulants (methylphenidate, mixed amphetamine salts), α_2 agonists (guanfacine, clonidine), bupropion, modafinil

CONVERSION DISORDER[4]

Diagnostic characteristics: Symptoms that mimic a neurologic condition, like deficits in voluntary motor function, sensory deficits, or seizures; however, the symptoms are due to psychological factors rather than to a true neurologic disorder or general medical condition

- Symptoms are unconsciously generated, not deliberately produced. Conversion disorder can occur comorbidly with true neurologic disorders (e.g., pseudoseizures more common in patients with epilepsy than in the general population)

Differential: True neurologic disorder or other general medical condition (e.g., multiple sclerosis, complex partial seizures, SLE, and HIV), malingering, other somatoform disorders (multiple complaints in multiple organ systems = somatization disorder; deliberately manufacturing symptoms to assume the sick role = factitious disorder)

Workup: Diagnosis based on careful history and physical (especially emotional stressors that could have precipitated symptoms)

- Rule out true medical or neurologic condition: labs, imaging, and EEG (especially video EEG) may help rule in or out medical and neurologic causes

Treatment: Avoid confronting patient, because this can worsen symptoms

- Encourage nonillness behavior. Avoid reinforcing conversion symptoms
- Can use therapeutic double bind: suggest to patients that if their symptoms have a genuine neurologic etiology, they should improve with the interventions they are receiving, and that if symptoms do not improve, this will indicate a conversion disorder
- Psychotherapy can help, but many conversion disorder patients refuse it

ANOREXIA NERVOSA (AN) AND BULIMIA NERVOSA (BN)[5,6]

Diagnostic characteristics: Distorted and overvalued body image, drive for thinness and/or fear of fatness, and abnormal eating and food-related behavior

- For AN, patients must weigh less than 85% of ideal body weight (via restricting food intake or binge/purge), postmenarcheal females must also have amenorrhea for 3 months,
- For BN, patients must engage in regular binge-eating followed by compensatory behavior (vomiting, abusing laxatives or diuretics, excessive exercising, or post-binge fasting)
- AN trumps BN, so if a patient displays characteristics of both, diagnose AN binge-eating/purging type

Differential: Other psychiatric causes of weight loss or abnormal eating behaviors (depression [causing loss of appetite], schizophrenia [delusions that food is poisoned], OCD [excessive food-related rituals that inhibit eating], or substance abuse [e.g., appetite suppression from methamphetamine or lack of money for food after spending everything on drugs or alcohol], body dysmorphic disorder [preoccupation with one specific body part, usually a facial feature, rather than with body weight/shape in general], general medical conditions (malignancies, metabolic/endocrine disorders, GI disorders), or infections (e.g., HIV or TB)

Workup: Careful history, physical exam (severe emaciation, dry skin, brittle hair, lanugo, peripheral edema, signs of self-induced vomiting [swollen parotid glands, dental caries, scars on the dorsum of the hand from scraping against the teeth while inducing vomiting]), vital signs including weight, BMP (hypokalemic hypochloremic metabolic acidosis, phosphorous for refeeding syndrome) CBC, TSH/FT4, EKG, LH/FSH or testosterone, and DEXA scan (osteoporosis)

- Elevated amylase with normal lipase suggests surreptitious vomiting

Treatment: Sychotherapy (especially cognitive-behavioral therapy [CBT], interpersonal psychotherapy [IPT], and group therapy), not medication, is the basis of treatment. Can use family therapy for children and adolescents

- Can't just refeed patients—they will relapse if underlying psychological issues aren't addressed

- Very low body weight AN patients, AN or BN patients with electrolyte disturbances or other potentially dangerous medical problems, and refractory AN or BN patients generally require inpatient treatment
- Fluoxetine may help decrease bingeing and purging in BN; avoid bupropion in patients who binge and purge due to seizure risk

BINGE EATING DISORDER[7]

Diagnostic characteristics: Recurrent episodes of binge eating (feel a lack of control), without compensatory behavior (e.g., purging)

Differential: Idiopathic obesity, bulemia nervosa or anorexia nervosa (binge-eating/purging type), atypical depression (i.e., low mood, hyperphagia, and hypersomnia), medication-induced weight gain, endocrine/metabolic abnormalities

Workup: Careful history, lipid panel and fasting glucose, EKG

Treatment: SSRIs, CBT, and/or self-help programs

SUBSTANCE ABUSE AND DEPENDENCE[8]

Diagnostic characteristics: Recurrent use of substances in a way that is physically hazardous, leads to failure to meet obligations, or causes interpersonal or legal problems

- At least three of the following: tolerance, withdrawal, use of the substance for longer periods or in larger amounts than originally intended, repeated unsuccessful attempts to quit or cut down, giving up other important activities in favor of using the substance, continued use of the substance in spite of problems caused by it, and excessive amounts of time spent in obtaining, using, or recovering from using the substance
- Can occur with or without physiologic dependence (tolerance/withdrawal)
- Substance dependence is a more severe disorder than substance abuse (dependence designates loss of control over their substance use)
- Often involves multiple substances and other comorbid psychiatric disorders
- Substance use can induce anxiety, depression, mania, and psychosis

Differential: Other psychiatric disorders (depression, mania, psychosis, anxiety, and personality disorders), physiologic dependence without compulsive behavior, pseudoaddiction (pain patients using increasing doses of opioids to control pain, not to get high)

Workup: Accurate history (clarify diagnosis with collateral information from friends or family), physical exam signs (track marks, liver disease, skin picking, nasal problems), blood alcohol level, urine drug screen, LFTs (AST:ALT ratio of 2:1 for EtOH abuse), CBC (macrocytic anemia), hepatitis B and C, HIV, syphilis, TB

Treatment: Nonpharmacological—12-step groups, psychotherapy, inpatient or outpatient rehab, other group therapy models.

Pharmacological EtOH: naltrexone, disulfiram, acamprosate. Opioids: methadone maintenance (may be most helpful intervention), buprenorphine mainetnance, naltrexone. Nicotine: nicotine replacement, bupropion, varenicline

SUBSTANCE WITHDRAWAL

Diagnostic characteristics: Most clinically significant are alcohol, benzodiazepine (or other sedative-hypnotic), and opioid withdrawal

- Alcohol, benzodiazepine/sedative-hypnotic withdrawal can be life-threatening, opioid withdrawal is rarely fatal

ALCOHOL WITHDRAWAL[3,9]

Starts within 6–12 hours of the last drink and usually resolves within 96 hours

- Early symptoms: tachycardia, hypertension, tremor, diaphoresis, tremulousness, anxiety, nausea, vomiting, and alcoholic hallucinations (hallucinations occurring on a background of clear consciousness). Late symptoms: delirium, generalized tonic-clonic seizures
- *Delirium tremens (DTs):* marked autonomic instability (severe tachycardia and hypertension, fever, and diaphoresis), delirium, hallucinations, death

Workup: Accurate history (daily use, history of withdrawal, history of DTs, seizures, and when substance was last used), Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWAS-Ar)

Treatment: 1st line—MVI/thiamine/folate, benzodiazepine taper (either symptom triggered for elevated BP, HR, or scheduled taper), avoid agents that mask vital signs changes; 2nd line—anticonvulsants (carbamazepine, valproic acid); severe—IV benzodiazepine or barbiturates; do not give alcohol to blunt withdrawal symptoms—this is dangerous and can lead to more complicated withdrawal

BENZODIAZEPINE AND SEDATIVE-HYPNOTIC WITHDRAWL[10]

Symptoms similar to those of alcohol withdrawal, but may follow a more prolonged time course, varying with the half-life of the substance (as far out as 7–10 days after the last use of the substance)

Treatment: Same as EtOH withdrawal

OPIOID WITHDRAWAL[10]

Symptoms include yawning, anxiety, lacrimation, rhinorrhea, diaphoresis, diarrhea, muscle aches, tremor, and mild tachycardia and hypertension

- Time course of withdrawal depends on the half-life of the opioid used

Differential: Anxiety, psychosis, epilepsy, autonomic instability, delirium, viral syndromes, GI disturbances

Treatment: Can do methadone or buprenorphine taper, but this requires special license; can also use clonidine taper (no license needed); use adjunctive treatment for specific withdrawal symptoms (antiemetics and antidiarrheals, NSAIDs, sleeping medications, etc.)

DELIRIUM (ENCEPHALOPATHY)[3,11,12]

Diagnostic characteristics: Acute alteration in the level of consciousness due to underlying general medical condition, substance use or withdrawal

- By definition cannot be due to psychological factors
- Elderly patients and underlying dementia or other brain disorders leads to increased risk for delirium
- Significantly worsens clinical outcomes

Etiology: Infection, electrolyte, metabolic, or endocrine disturbances, medications, drugs, and toxins, alcohol or sedative-hypnotic withdrawal, hypoxia, stroke, myocardial infarction, seizures

Symptoms: Confusion, disorientation, drowsiness, impaired attention, psychomotor agitation or hypoactivity, disruption of the sleep-wake cycle, anxiety, hallucinations, delusions, and mood fluctuations

- Usually has a fluctuating course

Differential: Dementia, substance intoxication, depression, mania, psychosis, and anxiety

Workup: Assess level of consciousness, establish baseline level of cognitive functioning, Trails B (ask patient to alternate between numbers and letters in a series; i.e., "1, A, 2, B, 3, C…"), clock-drawing test, Folstein Mini-Mental Status Exam (MMSE), Confusion Assessment Method (CAM) or Confusion Assessment Method for ICU (CAM-ICU), medication review, CBC, BMP, LFTs, TSH, urinalysis and culture, blood cultures, chest X-ray, EKG, cardiac enzymes, and urine drug screen, lumbar puncture, brain MRI or CT, HIV and syphilis serologies, EEG

Treatment: Treat the underlying etiology. Timely consultation of psychiatry service for assistance

- Avoid/minimize medications that can cause or worsen delirium (anticholinergics, benzodiazepines, other sedative-hypnotics, opioids, unnecessary CNS-acting agents, etc.)
- Avoid restraints because they can worsen agitation and result in injury
- Use nonpharmacologic interventions: Reorient patient frequently, maintain sleep/wake cycle (get patient up during the day, encourage sleep at night), encourage presence of family at bedside, make sure patients have eyeglasses and hearing aids, etc.

- Can give haloperidol or other antipsychotics (scheduled and prn) to treat symptoms of delirium and shorten the course; for alcohol, benzodiazepine, or other sedative-hypnotic withdrawal, give lorazepam or other benzodiazepines, but avoid benzodiazepines in delirium of other etiologies

OTHER

TARDIVE DYSKINESIA

Symptoms: Stereotyped orolingual movement or dystonia

Etiology: D2 receptor blockade (e.g. antipsychotics, antimetics)

- Decreased dopamine (also may cause parkinsonism, acute dystonic reaction)

Treatment: Anticholinergics (e.g., benztropine, benadryl)

NEUROLEPTIC MALIGNANT SYNDROME

Etiology: D2 receptor blockade (e.g. antipsychotics, antimetics)

- Usually occur within first few weeks, but can occur at any time

Differential diagnosis: Serotonin syndrome

Symptoms: Fever, sweating, labile BP, tachycardia, arrhythmia, rigidity, akinesia, mutism, tremor, delirium, seizures, coma

Workup: CBC (leukocytosis), elevated CK

Treatment: Discontinue offending agent, supportive care in ICU (fluids, cooling), cogentin (to reverse eps effects), bromocroptine (reduce central hyperthermia), dantrolene (muscle relaxant), benzodiazapines

Outcome: Often fatal

SEROTONIN SYNDROME

Etiology: Combination of SSRI and MAOI

Differential diagnosis: Neuroleptic malignant syndrome (NMS has rigidity rather than hyperreflexia)

Symptoms: Fever, tachycardia, hypertension, shivering, myoclonus, tremor, hyperreflexia, occulomotor abnormalities, agitation, delirium, coma

Workup: CBC (leukocytosis), elevated CK

Treatment: Discontinue offending agent, cyproheptadine (serotonin antagonist)

APPENDIX 1 ■ TABLES

Table-1 Glasgow Coma Scale (GCS) Adult (Pediatric)[1, 2]

Eye (E)	Verbal (V)	Motor (M)
1—no eye opening 2—opens eyes to painful stimuli 3—opens eyes to voice 4—opens eyes spontaneously	1—makes no sounds 2—incomprehensible sounds (restless, agitated, grunts) 3—inappropriate words (persistently irritable) 4—confused, disoriented (cries, consolable) 5—oriented, converses normally (appropriate words, coo, normal cry, social smile, fixes and follows) T—if the patient is intubated	1—no movements 2—decerebrate posturing 3—decorticate posturing 4—withdrawal to painful stimuli 5—localizes painful stimuli 6—follows commands (spontaneous movement)

NOTE: Consider the three values separately and in sum. The lowest possible GCS (sum) is 3, the highest is 15 (E4V5M6). Generally, comas are classified as: Severe, with GCS ≤ 8, Moderate, GCS 9–12, Minor, GCS ≥ 13.
World Federation of Neurosurgeons
Source: Teasdale et al.[2] classifies grade 1–5 (5 most severe) depending upon GCS (<7, 7–12, 13–14, 13–14, 15) and focal neurological deficit (if present, increases grade 2 to 3)

Table-2 Fisher Grading System[3, 4]

Fisher Grade	CT Subarachnoid Hemorrhage
1	none
2	diffuse, thin layer (< 1 mm)
3	localized clot or thick layer (> 1 mm)
4	intracerebral or intraventricular blood

Table-3 Hunt Hess Subarachnoid Hemorrhage Grading System[5]

Grade	Symptoms
1	Asymptomatic or mild headache and slight nuchal rigidity
2	Moderate to severe headache, nuchal rigidity, or cranial nerve palsy (CNIII,VI)
3	Lethargy, confusion, or mild focal deficit
4	Stupor, moderate to severe hemiparesis, or early decerebrate rigidity
5	Coma, decerebrate rigidity, moribund appearance

Table-4 Modified House-Brackmann Score[6]

Grade	Examination of Cranial Nerve VII
1	No noticeable weakness
2	Slight weakness on exam
3	Notable asymmetry at rest, **complete eye closure**
4	Severe asymmetry at rest and weakness on exam, **incomplete eye closure**
5	Trace movement
6	No facial nerve function

Table-5 Spetzler-Martin AVM Grading System[7]

Characteristics		Points
Size	small (< 3 cm)	1
	medium (3–6 cm)	2
	large (> 6cm)	3
Eloquence of nearby brain tissue	noneloquent	0
	eloquent	1
Venous drainage pattern	superficial only	0
	deep	1

NOTE: Grade = All three scores added together.

Table-6 CARDIAC PARAMETERS AND FORMULAS[8]

	Normal
Cardiac output (CO) = heart rate x stroke volume	4–8 l/min
Cardiac index (CI) = CO/Body Surface Area (BSA)	2.8–4.2 l/min/m^2
MAP (mean arterial press) = [(SBP - DBP)/3] + DBP	80–100 mmHg
SVR (systemic vasc resis) = (MAP - CVP) x (80)/CO	800–1200 dyne/sec/cm^5
PVR (pulm vasc resis) = (PAM - PCWP) x (80)/CO	45–120 dyne/sec/cm^5
QT_C = QT / square root of RR [calculate using both measures in sec]	≤ 0.44
Right atrial pressure=central venous pressure (CVP)	0–8 mmHg
Pulmonary artery systolic pressure (PAS)	20–30 mmHg
Pulmonary artery diastolic pressure (PAD)	10–15 mmHg
Pulmonary capillary wedge pressure (PCWP)	8–12 mmHg (post-MI ~16 mmHg)

Table-7 DRUGS GENERALLY ACCEPTED as SAFE in PREGNANCY (selected)[8]

Analgesics: Acetaminophen, codeine*, meperidine*, methadone*
Antimicrobials: Penicillins, cephalosporins, erythromycins (not estolate), azithromycin, nystatin, clotrimazole, metronidazole**, nitrofurantoin***, *Nix*
Antivirals: Acyclovir, valacyclovir, famciclovir
CV: Labetalol, methyldopa, hydralazine
Derm: Erythromycin, clindamycin, benzoyl peroxide
Endo: Insulin, liothyronine, levothyroxine
ENT: Chlorpheniramine, diphenhydramine, dimenhydrinate, dextromethorphan, guaifenesin, nasal steroids, nasal cromolyn
GI: Trimethobenzamide, antacids*, simethicone, cimetidine, famotidine, ranitidine, nizatidine, psyllium, metoclopramide, bisacodyl, docusate, doxylamine, meclizine
Heme: Heparin, low molecular weight heparins
Psych: Desipramine, doxepin
Pulmonary: Short-acting inhaled beta-2 agonists, cromolyn, nedocromil, beclomethasone, budesonide, theophylline, prednisone**

**Except if used long term or in high doses at term*
***Except 1st trimester*
****Contraindicated at term and during labor and delivery*

Table-8 APGAR SCORE[8]

Heart rate	0. Absent	1. < 100	2. >100
Respirations	0. Absent	1. Slow/irreg	2. Good/crying
Muscle tone	0. Limp	1. Some flexion	2. Active motion
Reflex irritability	0. No response	1. Grimace	2. Cough/sneeze
Color	0. Blue	1. Blue extremities	2. Pink

Table-9 ANTIDOTES[8]

Toxin	Antidote/Treatment	Toxin	Antidote/Treatment
acetaminophen	N-acetylcysteine	ethylene glycol	fomepizole
antidepressants, cyclic	bicarbonate	heparin	protamine
arsenic, mercury	dimercaprol (BAL)	iron	deferoxamine
benzodiazepine	flumazenil	lead	EDTA, succimer
beta-blockers	glucagon	methanol	fomepizole
calcium channel	calcium chloride,	methemoglobin	methylene blue
blockers	glucagon	opioids	naloxone
cyanide	hydroxocobalamin	organophosphates	atropine + pralidoxime
digoxin	dig immune Fab	warfarin	vitamin K, FFP

Table-10 OPIOID EQUIVALENCY*,[8]

Opioid	PO	IV/SC/IM	Opioid	PO	IV/SC/IM
buprenorphine	n/a	0.3–0.4 mg	meperidine	300 mg	75 mg
butorphanol	n/a	2 mg	methadone	5–15 mg	2.5–10 mg
codeine	130 mg	75 mg	morphine	30 mg	10 mg
fentanyl	n/a	0.1 mg	nalbuphine	n/a	10 mg
hydrocodone	20 mg	n/a	oxycodone	20 mg	n/a
hydromorphone	7.5 mg	1.5 mg	oxymorphone	10 mg	1 mg
levorphanol	4 mg	2 mg	pentazocine	50 mg	30 mg

*Approximate equianalgesic doses as adapted from the 2003 American Pain Society (www.ampainsoc.org) guidelines and the 1992 AHCPR guidelines. Not available = "n/a" See drug entries themselves for starting doses. Many recommend initially using lower than equivalent doses when switching between different opioids. IV doses should be titrated slowly with appropriate monitoring. All PO dosing is with immediate-release preparations. Individualize all dosing, especially in the elderly, children, and in those with chronic pain, opioid naïve, or hepatic/renal insufficiency.

Table-11 Gram Stain and Common Organisms[8]

Gram-Positive Aerobic Cocci: Staph epidermidis (coagulase negative), *Staph aureus* (coagulase positive), Streptococci: *S pneumoniae* (pneumococcus), *S pyogenes* (Group A), *S agalactiae* (Group B), enterococcus

Gram-Positive Aerobic/Facultatively Anaerobic Bacilli: Bacillus, Corynebacterium diphtheriae, Erysipelothrix rhusiopathiae, Listeria monocytogenes, Nocardia

Gram-Negative Aerobic Diplococci: Moraxella catarrhalis, Neisseria gonorrhoeae, Neisseria meningitidis

Gram-Negative Aerobic Coccobacilli: Haemophilus ducreyi, Haemoph. influenzae

Gram-Negative Aerobic Bacilli: Acinetobacter, Bartonella species, *Bordetella pertussis, Brucella, Burkholderia cepacia, Campylobacter, Francisella tularensis, Helicobacter pylori, Legionella pneumophila, Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Vibrio cholerae, Yersinia*

Gram-Negative Facultatively Anaerobic Bacilli: Aeromonas hydrophila, Eikenella corrodens, Pasteurella multocida, Enterobacteriaceae*: E. coli, Citrobacter, Shigella, Salmonella, Klebsiella, Enterobacter, Hafnia, Serratia, Proteus, Providencia*

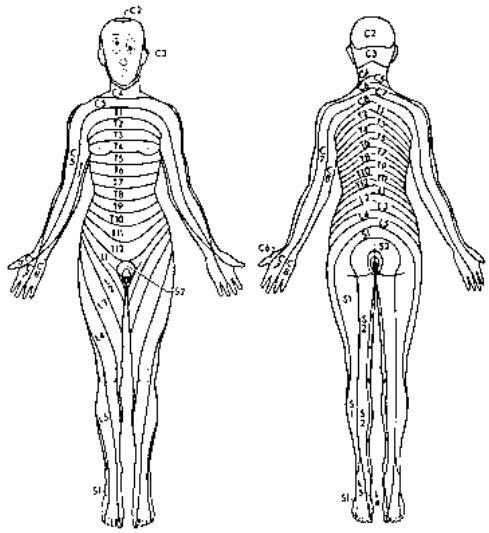
Anaerobes: Actinomyces, *Bacteroides fragilis, Clostridium botulinum, Clostridium difficile, Clostridium perfringens, Clostridium tetani, Fusobacterium, Lactobacillus, Peptostreptococcus*

Defective Cell Wall Bacteria: Chlamydia pneumoniae, Chlamydia psittaci, Chlamydia trachomatis, Coxiella burnetii, Mycoplasma pneumoniae, Rickettsia prowazekii, Rickettsia rickettsii, Rickettsia typhi, Ureaplasma urealyticum

Spirochetes: Borrelia burgdorferi, Leptospira, Treponema pallidum

Mycobacteria: M avium complex, M kansasii, M leprae, M tuberculosis

Table-12 Dermatomes[8]



MOTOR NERVE ROOTS	
Level	**Motor Function**
C4	Spontaneous breathing
C5	Shoulder shrug/deltoid
C6	Biceps/wrist extension
C7	Triceps/wrist flexion
C8/T1	finger flexion
T1–T12	Intercostal/abdominal muscles
T12	cremasteric reflex
L1/L2	hip flexion
L2/L3/L4	hip adduction/quads
L5	great toe dorsiflexion
S1/S2	foot plantarflexion
S2–S4	rectal tone

LUMBOSACRAL NERVE ROOT COMPRESSION	*Root*	*Motor*	*Sensory*	*Reflex*
	L4	quadriceps	medial foot	knee-jerk
	L5	dorsiflexors	dorsum of foot	medial hamstring
	S1	plantarflexors	lateral foot	ankle-jerk

Table-13 American College of Surgeons Pediatric Vital Signs[9]

Age (years)	Wt. (kg)	Heart Rate (bpm)	Blood Pressure (mmHg)	Respiratory (/min)	Urine Output (mL/kg/hr)
0-1	0-10	<160	>60	<60	2.0
1-3	10-14	<150	>70	<40	1.5
3-5	14-18	<140	>75	<35	1.0
6-12	18-36	<120	>80	<30	1.0
>12	36-70	<100	>90	<30	0.5

Table-14 Select Emergency Drugs

ALLERGY	diphenhydramine (*Benadryl*): 50 mg IV/IM. epinephrine: 0.1–0.5 mg SC (1:1000 solution), may repeat after 20 min. methylprednisolone (*Solu-Medrol*): 125 mg IV/IM.
HYPERTENSION	enalapril (*Vasotec*): 1.25–5 mg IV over 5 min esmolol (*Brevibloc*): 500 mcg/kg IV over 1 min, then titrate 50–300 mcg/kg/min fenoldopam (*Corlopam*): Start 0.1 mcg/kg/min, titrate up to 1.6 mcg/kg/mn labetalol (*Normodyne*): 0.25 mg/kg IV, may double dose q 10–15 min prn (maximum cumulative total dose of 300 mg or 2 mg/kg – whichever is less) nitroglycerin (*Tridil*): Start 10–20 mcg/min IV, titrate up to 100 mcg/min sodium nitroprusside (*Nipride*): 0.3–10 mcg/kg/min
DYSRHYTHMIAS / CARDIAC ARREST	adenosine (*Adenocard*): SVT (not A-fib/flutter): 6 mg rapid IV and flush, pref¬erably through a central line or proximal IV. If no response after 1–2 min then 12 mg. A third dose of 12 mg may be given prn. amiodarone (*Cordarone, Pacerone*): Life-threatening ventricular arrhythmia:Load 150 mg IV over 10 min, then 1 mg/min x 6h, then 0.5 mg/min x 18 h. atropine: 0.5–1.0 mg IV or 2–3 mg (in 10 mL) via ET diltiazem (*Cardizem*): Rapid atrial fib: bolus 0.25 mg/kg or 20 mg IV over 2 min. May repeat 0.35 mg/kg or 25 mg IV 15 min later. Infuse 5–15 mg/h. epinephrine: 1 mg IV (2–2.5 mg in 10 mL ET) for cardiac arrest. [1:10,000] lidocaine (*Xylocaine*): 1 mg/kg IV, then 0.5 mg/kg q5–10min prn to max 3 mg/kg. Maintenance 2 g in 250ml D5W (8 mg/mL) at 1–4 mg/min (7–30 mL/h) vasopressin (*Pitressin*, ADH): Ventricular fibrillation: 40 units IV once. May also be effective in asystolic cardiac arrest.
PRESSORS	dobutamine: 250 mg in 250 mL D5W (1 mg/mL) at 2.5–20 mcg/kg/min dopamine: 400 mg in 250 mL D5W (1600 mcg/mL) at 2–20 mcg/kg/min. Doses in mcg/kg/min: 2–5 = dopaminergic, 5–10 = beta, >10 = alpha. norepinephrine (*Levophed*): 4 mg in 500 mL D5W (8 mcg/ml) at 0.5–10 mcg/min. (max 30 mcg/min) phenylephrine (*Neo-Synephrine*): 100–500 mcg boluses IV. Infusion for hypotension: 20 mg in 250 mL D5W (80 mcg/mL), start at 100–180 mcg/min (75–135 mL/h). Once BP stable, decrease to maintenance of 40–60 mcg/min
INTUBATION	etomidate (*Amidate*): 0.3–0.4 mg/kg IV. methohexital (*Brevital*): 1–1.5 mg/kg IV. rocuronium (*Zemuron*): 0.6–1.2 mg/kg IV. succinylcholine (*Anectine*): 1–1.5 mg/kg IV. thiopental (*Pentothal*): 3–5 mg/kg IV.
SEIZURES	diazepam (*Valium*): 2–20 mg IV, or 0.2–0.5 mg/kg rectal gel up to 20 mg PR fosphenytoin (*Cerebyx*): Load 15–20 phenytoin equivalents per kg either IM or IV no faster than 100–150 mg/min lorazepam (*Ativan*): 0.1 mg/kg up to 3–4 mg IV/IM phenobarbital: 200–320 mg IV at 60 mg/min, status epilepticus give 20 mg/kg phenytoin (*Dilantin*): 20 mg/kg up to 1000 mg IV no faster than 50 mg/min

APPENDIX 2 ■ NEURO EXAM IN SPANISH

Laura F. Gephart, MD, MS

Basics

Pronunciation

a (ah)
e (eh)
i (ee)
o (oh)
u (oo)

1. *Uno* (oo-noh)
2. *Dos* (dohs)
3. *Tres* (trehs)
4. *Cuatro* (kwah-troh)
5. *Cinco* (seen-coh)
6. *Seis* (say-s)
7. *Siete* (see-eh-teh)
8. *Ocho* (oh-choh)
9. *Nueve* (new-eh-veh)
10. *Diez* (dee-ehs)

Please

Por favor

Thank you

Gracias

You

Usted

Would you like a translator?

¿Quisiera un traductor?

INTRO

I am Doctor _____. I am your doctor. How can I help you?

Soy Doctor/a _____. Soy su doctor/a. ¿Cómo le puedo ayudar?

HPI

What are your symptoms?
¿Cuáles son sus síntomas?
(kwal-ess soe-n sus ***seen***-toe-mah-s)

When did it start?
¿Cuándo empezó?
(kwan-doe em-peh-***soe***)

What was it like? What did it feel like?
¿Cómo era? ¿Cómo se sentía?
(co-moe eh-rah) (co-moe seh sen-***tee***-ah)

Describe it.
Descríbamelo.
(des-***cree***-bah-meh-low)

cramp
calambre
(ka-lahm-breh)

burning
ardiente or ardiendo
(are-dee-en-teh) (are-dee-en-doh)

stabbing
punzante
(poon-san-teh)

numb
entumecido
(ehn-too-meh-see-doh)

From one to ten, how was the pain?
De uno a diez, ¿cómo era el dolor?
(deh oo-no ah dee-ess, co-moe eh-ra ell doe-lor)

What were you doing when the pain started the first time?

¿Qué estaba haciendo cuando le ocurrió el dolor por primera vez?

(***keh*** ess-tah-bah ah-see-end-oh kwan-doe leh oh-coo-ree-***oh*** ell doe-lor pour pree-mehr-ah veh-ss)

Is there anything that helps the pain?

¿Hay algo que disminuya el dolor?

(eye all-go keh dees-mee-noo-yah ell doe-lor)

Is there anything that makes the pain worse?

¿Hay algo que empeora el dolor?

(eye all-go keh em-peh-or-a ell doe-lor)

Where did it start?

¿Dónde empezó?

(doen-deh em-peh-***so***)

Did it start in one place and move to another?

¿Empezó en un lugar y después se movió a otro lugar?

(em-peh-***so*** en oon loo-gar ee dehs-poo-***ess*** seh moe-vee-***oh*** ah oh-troh loo-gar)

How long did it last?

¿Por cúanto tiempo duró?

(Pour kwan-toe tee-em-poe doo-***roe***)

Has it happened before?

¿ Le ha ocurrido la síntoma en el pasado?

(ley ah oh-coo-ree-doe lah seen-toe-mah en ell pah-sah-doe)

¿Ha pasado la misma síntoma antes?

(ah pah-sah-doh la mees-mah ***seen***-toe-mah ahn-tess)

Have you been to a doctor for this before?

¿Ha consultado con un doctor sobre este problema en el pasado?

(ah cohn-sool-tah-doh cohn oon dohc-tohr soh-breh ehs-teh proh-bleh-mah ehn ehl pah-sah-doh)

What did they do?

¿Qué hicieron?

(Keh ee-see-eh-ron)

Did it help you?

¿Le ayudó?

(leh eye-you-***doe***)

Are you taking any medications?

¿Toma medicamentos?

(toe-mah meh-dee-ka-men-toes)

Have you taken any medications in the last _____ months?

¿Ha tomado algun medicamento en los últimos _____ meses?

(ah toe-mah-doe all-goon meh-dee-ka-mee-en-toe en lohs ***ool***-tee-mohs _____ meh-sehs)

Do you have any other medical problems?

¿Tiene algun otro problema médico?

(tee-en-eh all-goon oh-troh pro-blehm-ah ***meh***-dee-coh)

Has this happened to anyone else in your family?

¿Hay otra persona en su familia que tiene el mismo problema/las mismas síntomas?

(Eye oh-trah pear-soh-nah ehn soo fah-mee-lee-ya keh tee-en-eh ell mees-moh pro-bleh-mah/lahs mees-mahs ***seen***-toe-mahs)

What medical problems does your family have? mother/father/siblings?

¿Cuáles problemas médicos tiene su familia/su madre/padre/hermanos?

(kwahl-ess pro-bleh-mahs ***meh***-dee-cohs tee-en-eh soo fah-mee-lee-ah/soo mah-dreh/pah-dreh/ehr-mah-nohs)

EXAM

Show me where it hurts/it started.

Múestreme donde le duele/empezó.

(***moo***-ess-treh-meh dohn-deh leh doo-ell-eh/em-peh-***soh***

Higher Functions

MMS

Repeat after me.

Repítame.

(reh-***pee***-tah-meh)

CN

What do you see here?

¿Qué ve aquí?

(keh veh ah-key)

Can you smell this?

¿Puede oler esto?

(poo-eh-deh oh-lehr ess-toe)

Look at my finger and follow it with only your eyes.

Fíjese en mi dedo y síguelo con solo los ojos.

(***fee***-heh-seh en mee deh-doe ee ***see***-geh-loh cohn so-loh lohs oh-hos)

Can you feel this? How does this feel? How do you feel?

¿Puede sentir esto? ¿Cómo siente esto? ¿Cómo se siente?

(poo-eh-deh sehn-teer ess-toh) (coh-moh see-en-teh ess-toh) (coh-moh seh see-en-teh)

Lift your eyebrows.

Levante las cejas.

(leh-vahn-teh lahs seh-has)

Close your eyes firmly.

Cierre los ojos con fuerza.

(see-ehr-eh lohs oh-hos) (cohn fwer-sah)

Show me your teeth.

Muéstreme los dientes.

(moo-***ess***-treh-meh lohs dee-ehn-tehs)

Stick out your tongue.

Saque la lengua.

(sah-keh lah lehn-gwa)

Turn your head to the left/right.

Voltea la cabeza a la izquierda/derecha.

(Vol-teh-ah lah kah-beh-sah ah lah ees-key-ehr-dah/dehr-eh-chah)

Shrug your shoulders.

Levante los hombros.

(leh-vahn-teh lohs ohm-brohs)

SENSORY

Can you feel this? How does this feel?

¿Puede sentir esto? ¿Cómo siente esto?

(poo-eh-deh sehn-teer ess-toh) (coh-moh see-ehn-teh ess-toh)

Sharp, like a needle

agudo, como una aguja

(ah-goo-doh coh-moh oo-nah ah-goo-ha)

cold

frío

(***free***-oh)

hot

caliente

(ka-lee-yen-teh)

burning

ardiente

(ahr-dee-yen-teh)

painful

doloroso

(doh-loh-roh-so)

MOTOR

Resist me.

Resístame.

(reh-***see***-stah-meh)

Do not let me push it down.

No me lo permita bajar.

(Noh meh loh pehr-mee-tah bah-hahr)

Grasp this.

Agarre esto.

(ah-gahr-eh ehs-toh)

As hard as you can.

Lo más fuerte que pueda.

(loh mahs foo-ehr-teh keh poo-eh-dah)

Do this.

Haga esto.

(ah-gah ess-toh)

Faster.

Más rápido.

(mahs ***rah***-pee-doh)

Slower.

Más lento.

(mahs lehn-toh)

REFLEXES

Relax.

Relájese.

(reh-***lah***-heh-seh)

CEREBELLUM

Place your heel on your knee and slide it down your shin (like this).

Ponga su tacón en la rodilla y bájelo por la canilla (así).

(pohn-gah soo tah-***cohn*** ehn lah roh-dee-ya ee ***bah***-heh-loh por lah cah-nee-yah) (ah-see)

Touch your nose. Touch my finger.

Toque su nariz. Toque el dedo mío.

(toh-keh lah nah-rees. Toh-keh ehl deh-doh ***mee***-oh)

Open and close your fingers (like this).

Abra y cierre los dedos (así).

(ah-brah ee see-ehr-eh lohs deh-dohs)(ah-see)

Walk here (like this).

Camine aquí (así).

(kah-mee-neh ah-key)(ah-see)

on your toes

en las puntas de los pies

(ehn lah poon-tahs deh lohs pee-ehs)

on your heels

en los tacones

(ehn lohs tah-cohn-ehs)

CONCLUSION

We need to do some lab tests

Necesitamos hacer algunos examenes del laboratorio.

(neh-seh-see-tah-mohs ah-sehr all-goo-nohs ex-ah-mehn-es dehl lah-bohr-ah-tohr-ee-oh)

We need to do some xrays/scans.

Necesitamos hacer unos rayos equis/escanes.

(neh-seh-see-tah-mohs ah-sehr oo-nohs rah-yohs eh-keys/ehs-cah-ness)

I will be back soon/ in _____ minutes.

Volveré pronto/ en _____ minutos.

(vohl-vehr-***eh*** prohn-toh/ ehn _____ mee-new-tohs)

You need to see another doctor.

Necesita ir a ver otro doctor.

(neh-seh-see-tah ear ah vehr oh-troh dohc-tohr)

You need surgery.

Necesita cirujía.

(neh-seh-see-tah see-rue-***hee***-ah)

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INDEX

Note: Italicized page locators indicate figures; tables noted with *t*.

C

J

K

L

Q

R

S

T

W

Z