PATHOPHYSIOLOGY OF NEUROLOGICAL DISRODERS

Disorder	Etiology and Epidemiology	Pathophysiology and Presentation	Lab Findings and Diagnosis	Treatment
HERNIATIONS				
CINGULATE HERNIATION	**Expanding Intracranial Mass** Subdural Hematoma (SDH) Epidural Hematoma (EDH) Neoplasia Hemorrhage Abscess Infarct and intracerebral edema **Mass lesion of temporal lobe (Uncal)**	*Supratentorial* mass effect → subduction of the cingulate gyrus beneath the falx cerebri Typically results from **high unilateral mass lesions**	**Papilledema** (the optic disc and fundus appear to be engorged)	Hyperventilation Mannitol (decreases vasogenic edema) Steroids (if edematous)
UNCAL HERNIATION		Progressive increase in ICP → subduction of ipsilateral uncal gyrus under tentorium cerebelli → impinge on tenorial notch ULTIMATE RESULT: Leads to rupture of penetrating vessels in the brainstem and pons (Duret hemorrhage) Compression and ischemia result in rapid coma and death	**Papilledema** **Ispilateral mydriasis** due to impingement of parasympathetic fibers of CN III **Contralateral hemiparesis** or paralysis **PCA infarction** (compression of the peduncle)	
ISCHEMIC STROKE				
THROMBOEMBOLIC STROKE of LARGE CEREBRAL ARTERY	**Embolism** From carotid arteries of left atrium (in Afib) 90% of ischemic strokes arise from atheromatous lesions The initiating plaque is in the CCA or ICA Embolism → MCA → occlusion of lenticulostriate arteries (basal ganglia and internal capsule)	**Complete MCA stroke** CONTRA: hemiparesis, total sensory loss, homonymous hemianopsia, gaze paresis IPSI: deviated conjugate gaze preference **Partial MCA stroke** Affects face and arm (lateral sensory cortex) **MCA (dominant):**Aphasia	**Lacunar syndromes** suggest ischemic stroke of small penetrating arteries (subcortical) **Aphasia** and **neglect** suggest cortical involvement and occlusion of largery arteries Symptoms are focal and of rapid onset	If acute: tPA

	Thrombosis Microvascular pathology **Compression** PATHOPHYSIOLOGY Hypoxemia → venous stasis → (ischemia) → neuronal stress → 10 – 24 hrs: **acute necrosis** nuclear pyknosis, axonic swelling, cytoplasmic eosinophilia) → 24 – 28 hrs : degeneration of oligodendrocytes + neutrophilic infiltrate (occasional) → 2 – 4 d: continuing oligodendrocyte loss, inflammatory infiltration, and endothelial hyperplasia → 4 – 7 d: macrophage infiltrate → (phagocytosis of hemosiderin if hemorrhagic infarct) → 1 – 3 wks: astrocyte reaction → > 1 yr: gliosis	**MCA (non-dominant):** Hemineglect + anaosognosia **ACA stroke** Hemiparesis, sensory loss in CONTRA leg, **abulia** **PCA stroke** CONTRA: hemianopsia or quadratopsia Sensory loss (if thalamus is infracted) **Vertebral Artery** ISPI: limb and gait ataxia, loss of facial sensation CONTRA: loss of dermatomal sensation NOTE THE CROSSED FINDINGS **Basilar Artery** Quadriparesis, facial weakness, *disconjugate gaze* and movements Posturing **Lacunar Syndromes** Small deep infarctions due to occlusion of the terminal penetrating arteries *Pure strokes*: isolated contralateral hemiparesis, isolated contralateral anesthesia, dysarthria	Standard exam: clonus, hyperreflexia, Babinski, motor strength, sensory	
GLOBAL ISCHEMIC STROKE	**Ischemic** Narrow carotid arterial caliber CHF Sleep → decrease MABP (seen in elderly) Ventricular asystole **Hypoxemic** Pulmonary disease CO poisoning	Ischemia occurs at the termini of the MCA, ACA, and PCA. Thus, infarction occurs at the marginal zones between these arteries (poor collateral circulation) ACA:MCA → infarction of perisagittal anterior frontal lobe → (usually hemiparesis, sensory loss)		

	Mechanical Ventilation	MCA: PCA → infarction of the occipital lobe and visual association cortices → deficits in visual processing		
VENOUS OCCLUSION	Obstruction of **superior sagital sinus** or **cortical veins** **Seen in infants with sepsis and dehydration** Does NOT occur with cortical or internal veins due to collateral circulation	Venous occlusion → congestive hyperemia → infarction of parasagital cortex (dorsum) → hemorrhage		
STROKE MIMICS	Migraine with aura Post-seizure focal deficits Hypoglycemia Anamnestic episode Non-organic neurological episode	Present with sudden onset of focal neurologic deficits	Mimics present with **Recurrent stereotyped events** Highly specific to stroke mimics **Symptom spread** Scintillating scotoma, migrating paresthesia and numbness with focal seizures **Emergent signs** Scintillations, paresthesia, motor seizure	
INTRACRANIAL HEMORRHAGE				
INTRACEREBRAL HEMORRHAGE	**Spontaneous hemorrhages** DOES NOT include hemorrhage due to traumatic brain injury **Deep hemorrhagic stoke** **Hypertensive arteriosclerosis** Involves thalamus, cerebellum, IC, brainstem **Lobar hemorrhagic stoke** **Amyloid Angiopathy** **Coagulopathy** **Hypertensive arteriosclerosis**	Presentation similar to stroke: sudden onset of focal deficits + **headache** (main differentiating symptom), nausea, decreased consciousness (elevated ICP) **Hypertensive hemorrhage** Rapid expansion of hematoma and and dissection into parenchyma and subarachnoid space May rupture into ventricles		

	Involves the cortex **Neoplasm** **Vascular Malformation**	**Subcortical (75%):** external capsule, basal ganglia, thalamus **Pons and cerebellum (20%)** Massive hemorrhage: chronic HTN Multiple small hemorrhages: fat or air embolism, thrombocytopenia, malaria, leukemia		
VASCULAR MALFORMATION	**Telangiectasias** **Cavernous hemangioma** **Varices** **Venous malformation** **AV fistula** **Sturge-Weber Syndrome:** facial angiomas + calcified AVMs **Neoplasia:** disordered vasculature due presence of tumor These are uncommon, and *typically asymptomatic*	Result in intracerebral hemorrhage AV malformations may result in shunting of blood before it is delivered to target tissue → ischemia		
SUBARACHNOID HEMORRHAGE	Leading cause of non-traumatic SAH: ruptured intracranial aneurism **Saccular Aneurysm** **RFs:** HTN, smoking, female gender, aortic coarctation, ADPKD, connective tissue disorders (Marfan's, Eher-Danlos) There is a defect in the elastica within the wall of the aneurysm	**Fusiform** Rupture is rare, but leads to **brainstem compression** **Saccular** Aneurysm → increased wall stress, turbulent flow, and abnormal shear → rupture (typically inferiorly , into base of cranial vault) → hematoma in subarachnoid space → vasoconstriction → reactive infarction	With SAH: Compression of CN III leads to unilateral mydriasis	

	85% occur in anterior CoW Juncture of Pcomm, MCA, ICA (30%) Juncture of Acomm and ACA (30%) Trifucrcation fo MCA in Sylvian fissure (25%) **15% occur in the posterior CoW + ICA** **Fusiform Aneurysm** Secondary to atherlosclerosis Typically occur on basilar artery	Presentation: sudden **thunderclap headache**, focal neurological deficits, altered LOC, meningismus **Sudden headache: presumed to be SAH**		
GLIAL MALIGNANCY				
General Features of CNS malignancy EPIDEMIOLOGY In adults, the most common intracranial tumors are Glioma (50%), meningioma (15 – 20%), pituitary adenoma (15%), vestibular Schwannoma (8%), CNS mets In peds, the most common tumors are: Medulloblastoma (45%), astrocytomas (40%), ependymomas (10%)				
ASTROCYTOMA	**25% of all glial cancers** (WHO I – III; excluding GBM) Peak incidence: 40 yrs Most common tumor in peds (cerebellum) Wide variation in age of onset p53 mutation in 30% of all astrocytomas EGF upregulation in 40% of high-grade tumors	Diffuse swelling with diffuse margins Cystic morphology **RF for progression to GBM**: anaplasia (atypical mitoses and nuclei), increased mitotic rate, vascular endothelial proliferation, necrosis No site predominance		Surgical resection and post-op adjuvant therapy

GLIOBLASTOMA MULTIFORME (GBM)	Transformed astrocytoma **50%** of all **gliomas** (WHO IV) 45 – 55 yrs < 20% survival rate at 1 yr.	Necrotic hemorrhagic lesions infiltrate diffusely (no clear margins) Frequently involves **frontal lobes** Focal deficits + dementia May infiltrate contralateral hemisphere, occipital lobe, and cerebellum	Cellular pleomorphism **Necrosis** Palisading morphology **Focal hemorrhage** Microvascular thrombosis Epithelioid glial morphology	ChemoRx XRT Surgery
PILOCYTIC (JUVENILE) ASTROCYTOMA	Onset < 20 yrs Considered **Grade I Astrocytoma**	Occurs in several critical structures: Cerebellum Hypothalamus Optic Nerve However: lesions may be asymptomatic Although low-grade, some lesions may produce significant deficits!		
EPENDYMOMA	5% of gliomas Peaks at 30 yrs Most frequent cord tumors	**Ventricles** Occupies fourth ventricle in peds May result in obstructive hydrocephalus **Spinal cord (cauda equina)** Slow growth rate, but the lesions impinges on eloquent structures → poor prognosis	Ependymal cells clustered around vessels Perivascular pseudo-rosettes May organize and canulate into primitive neural tubes	Surgery
OLIGODENDROGLIOMA	6 – 7 % of gliomas 35 – 40 yrs **Loss of 1p and 19q** in 70% of tumors	Occurs mainly in **frontal lobe** **Progression and NH is unpredictable**	Cellular morphology is *relatively conserved*: small dark nucleus and vacuolated cytoplasm	Surgery
CHOROID PLEXUS PAPILLOMA	Occurs in neonates	Results in obstructive hydrocephalus		
NON-GLIAL MALIGNANCY				
MEDULLOBLASTOMA	A partially differentiated glial tumor (considered primitive neuroectodermal) Thus, occurs in peds	Originates in the **cerebellar vermis** Expansion results in infiltration into the fourth ventricle and surrounding posterior fossa	Blast-like cells Heterochromatic nuclei with high N:C	Surgery XRT

	6% of gliomas Other PNETS: retinoblastoma, central neuroblastoma, pineoblastoma **Loss of 17p**	A rapidly growing and highly invasive cancer **Spread is via the CSF**		
MENINGIOMA	18% of all intracranial tumors 25% of intraspinal tumors Peaks incidence at 45 yrs Uncommon in peds Originate from the arachnoid granulations (dura) at the superior sagital sinus Tumor is responsive and dependent on estrogen	Typically **slow-growing** with little malignant potential HOWEVER, **expected to recur** after resection Result in compression without infiltration Mass usually **occurs on dorsum**, but may involve skull base Has metastatic potential and may escape CNS → results in boney hyperplasia of the scalp	Whorled fibrocytes (the only CNS neoplasm involving mesodermal cells) May be calcified: detect on skull X-ray	Surgery: must achieve complete excision to prevent recurrence
PITUITARY ADENOMA	15% of intracranial tumors (adults) **35% non-secretory** **65% secretory** 40% secrete prolactin 9% secrete GH 6% secrete ACTH 5% secrete FSH TSH is not secreted alone	If secretory: detected early as microadenoma due to endocrine dysregulation If non-secretory: tumor enlarges to form macroadenoma and compresses the optic chiasm → visual field cuts Must extend beyond the pituitary fossa	Lobulated May create mass effect without invasion	Trans-sphenoidal resection
CRANIOPHARYNGIOMA	Derived from **squamous epithelium of pituitary stalk** Common in peds Presents as a suprasellar calcified mass		Lobulated cystic masses containing cholesterol	
PINEAL TUMORS	Male predominance Occur < 20 yrs	**High-grade invasive tumor**	Similar morphology to **germ cell tumors** (seminoma, embryonal cell carcinoma)	

CHORDOMA	Derived from residual notochord cells	Occur in the vertebral bodies, clivus bone, and sacrum		
PERIPHERAL *and* METASTATIC MALIGNANCY				
VESTIBULAR SCHWANNOMA	Derived from Schwann cells myelinating the acoustic nerve 8% of intracranial tumors	Occur at the **cerebello-pontine angle** May also involve the spinal cord and other peripheral nerves If > I Schwannoma or malignant type: Dx neurofibromatosis		
CNS METASTASES	Lung Breast Colon Malignant Melanoma	Metastatic lesions result in edema and increased ICP Spontaneous hemorrhage	Typically **multifocal lesions** are detected Margins **compress** surrounding tissue, resulting in mass effect Occur at gray-white junctions	
PERIPHERAL NEUROMA	Reactive hyperplasia of Schwann cells and fibroblasts following peripheral nerve injury	Not considered neoplastic		
INFECTIOUS DISEASE *of the* CNS				
General Features MENINGITIS May actually result in other pathologies: stroke (due to vacular inflammation and thrombosis), decreased LOC, cranial nerve deficits Leptomininges are most commoly affected Pachymeningeal inflammation is due to skull trauma				
BACTERIA (PYOGENIC) MENINGITIS	**Neonatal** NMEC, Group B Strep, *Listeria* **Peds** Pneumococcus, meningococcus, *H. influenza* **Adults (18 – 50)** Meningococcus, pneumococcus **Elderly Adults (>50)** Penumococcus, *Listeria*, meningococcus, *H. influenza*, GNRs	Rapid onset of fever, headache, meningismus, decreased LOC Meningeal vascular congestion → edema	Fibrinous and supperative exudates at the base of brain	Triad of symptoms is presumed to be bacterial meningitis Empiric ABx therapy

	Bacterium may invade via the olfactory nerve (NMEC, *N. folweri*) OR Hematogenous spread via nasopharyngeal vessels (Meningococcus, *H. influenza*) OR Lungs (pneumococcus)	**Complicated Bacterial Meningitis** Inflammation propagates to the temporal lobes and ventricles → meningeal vessels become thrombosed **Meningococcus** is associated with septicemia, DIC, and adrenal failure		
GRANULOMATOUS MENINGITIS	**Tuberculosis** *M. tb*: occurs with disseminated or reactivated disease **Cryptococcosis** *C. neoformans* Seen in patients with HIV or severe immune compromise Primary infection is in lungs → hematogenous spread to the CNS	**Subacute** development Presentation: headaches, progressive cranial nerve deficits, hydrocephalus (due to obstruction of CSF outflow at base of temporal lobes) **Complicated Granulomatous Meningitis** Develops into vasculitis, meningeal vascular thrombosis, and parenchymal necrosis Caseating necrosis involves surrouding tissue *Cryptococcus* may also extend through the small penetrating vessels THUS: these result in a mass effect	**Opacification of the meninges** (seen in cryptococcal meningitis due to capsule) Fibrinous exudates Granuloma formation (epithelioid macrophages, giant cells) **TB** CSF demonstrates massively elevated protein, mixed inflammatory cells, AFB **Crypococcus** CSF demonstrates lymphocytosis, unicellular yeast cells with capsule, slightly elevated protein	
VIRAL (ASEPTIC) MENINGTIS	Secondary viremia and seeding of meninges by **enteroviruses** **Echovirus** + **Coxsackievirus**: elicit isolated meningitis without encephalitis	Lymphocytic infiltrate of the meninges This is a universal finding in viral meningitis Typically self-limited clinical course		
HSV ENCEPHALITIS (HSV – 1)	Occurs in immunocompetent background	Headache, fever, seizures, cognitive changes: Presumed to be viral encephalitis		Must be Dx and treated within same timeframe as bacterial meningitis

	Entry through **olfactory nerve** Typically no Hx of gingivostomatitis or fever blisters Virus is latent within sensory ganglia of CN VII	Sporadic and subacute Affects frontal and temporal lobes Thus, personality changes and anterograde amnesia are common findings Increased ICP is common → herniation and decreased LOC		
CMV ENCEPHALITIS	**Adult CMV meningoencephalitis** The leading viral opportunistic infection in patients with AIDS (15 – 20%) Occurs in ISD therapy **Congenital CMV encephalitis** The virus is transmitted through the placenta during the third trimester Occurs during primary infection of mother	Presents with classic symptoms of viral encephalitis and meningitis **Adult CMV meningoencephalitis** Inflammation of the choroid plexus → necrosis **Congenital CMV encephalitis** Findings are similar to toxoplasmosis **Polyradiculitis** Subacute onset: parasthesias, weakness, sacral pain, sphincter dysfunction **Dementia**	Intranculear inclusions within neurons, glial cells, and endothelium	
ABROVIRAL ENCEPHALITIS	California Group Virus (LaCrosse Encepahlitis Virus) EEEV: highest mortality WEEV SLEV WNV	Tropism for cortex, basal ganglia, and brainstem		
POLIOMYELITIS AND ENCEPHALITIS	Enterovirus replicates in GI tract → axonal OR hematogenous spread → CNS infection	Results in necrosis of LMNs in anterior horn of cord (spinal paralytic polio) AND Medullary motor nuclei (bulbar polio) Acute stage is intensely inflammatory	No inclusion bodies	Sabin vaccination has nearly eradicated virus from US

RABIES ENCEPHALITIS	Animal vectors (small mammals) → axonal spread via peripheral nerves Characterized by long incubation time (4 – 6 wks) Determined by proximity of bite to CNS structures	Viral inflammation in deep gray matter (soma of sensory and motor neurons, brain stem, anterior horn, and sensory ganglia	**Negri bodies**: cytoplasmic inclusions of virus; found in **hippocampus**	Immunization Rabies Virus Immunoglobulin
PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)	Noninflammatory infection by JC virus (Polyoma) Occurs as **opportunistic encephalitis** in AIDS, lymphoma, and leukemia pts. Hematogenous spread to CNS	**Subacute** tempo Results in **destruction of oligodendrocytes**	Demyelination of the cerebral and cerebellar white matter Diffuse asymmetric discoloration Myelin is entirely absent at the lesion core Oligodendrocytes at the lesion periphery have vastly **enlarged nuclei** and contain **viral inclusions** **Exotic giant astrocytes**	
CNS ABSCESS	Penetrating skull injury Extension of middle ear or paranasal sinus infection Hematogeneous dissemination from lung abscess of endocarditis Staphylococci Streptococci *Nocardia asteroids* *Candida*	Focal infection and inflammation → liquifactive necrosis → massive infiltration of PMNs → formation of abscess → proliferation of endothelium and fibroblasts → encapsulate abscess with fibrous capsule → edematous reaction in surrounding tissue Thus, the mass lesion is larger than the necrotic focus The majority of the edema is within the extraneural space of the white matter **PRESENTS with FOCAL SYMPTOMS**	CT or other imaging No CSF!	DO NOT do a lumbar puncture May result precipitate herniation

		Sequalae: rupture into ventricular system, rupture into meninges, herniation		
TOXOPLASMOSIS	*Toxoplasma gondii* Reservoir: soil, mammals TMX: ingestion of raw meat, cat feces Replicates within endothelium and astrocytes **Adult Toxoplasmosis** AIDS pts, other immunosppression **Congenital Toxoplasmosis** Transmitted through placenta in third trimester (similar to neonatal CMV encephalitis)	**Adult Toxoplasmosis** Multifocal tissue necrosis Peripheral hemorrhages Focal opacification of the meninges Ventricular empendymal dullness Ventriculitis **Congenital Toxoplasmosis** Results in massive loss of tissue Calcifications may be detected on imaging: lateral ventricles and surface	Vasculitis Endothelial damage due to exotoxin Results in occlusions and multiple infarcts Mixed inflammatory infiltrate Presence of solitary organisms or cystic groups	
AMEBIASIS	*Naegleria fowleri* Occurs in Southern US High mortality TMX via olfactory nerve if exposed to organism in warm pools	**Frontobasal meningoencephalitis** Acute febrile illness resulting in necrosis of the parenchyma	Organism dispersed among inflammatory infiltrate	
ASPERGILLUS ENCEPHALITIS	*Aspergillus* Septate hyphal form invades endothelium and disseminates to CNS via the circulation May also invade via direct extension from the paranasal sinuses → affects basal forebrain and hypothalamus Seen in immunocompromised pts	Subacute progression Mutlifocal tissue necrosis and hemorrhage (Similar to toxoplasmosis)	Fungus is localized to the vessel walls	

PRION DISEASE	**Kuru** **Creutzfeldt-Jakob Disease (CJD)** Normal structural protein in neuronal cell membranes Encoded on 20p: mutations result in familiar variants if CJD Ingestion → enters Peyer's patches in the small bowel **Familial variants** Mutation results in altered prion conformation	Damage occurs in gray matter of the cortex and striatum **CJD** Rapidly progressive dementia (begins in middle decades)	Cell bodies are **vacuolated** These are areas of disintegrating membrane; primarily near the synaptic cleft Astrocyte gliosis Loss of neurons Abnormal prions are *concentrated at the synapses* NO INFLAMMATION	
NEURO-HIV	Results in widespread disease of cerebral cortex, cord, peripheral nerves, muscle Most CNS injury is due to reactive cytotoxic inflammation	**Gradual HIV dementia** Neuronal damage is due to chronic inflammatory response **HIV myelopathy** Loss of UMN function, vibration sense, and proprioception Destruction of lateral and posterior columns (resembles SCD) **HIV polyneuropathy** Gradual symmetric loss of distal sensation + lower motor neuron signs (occurs in a gradient) **HIV myopathy** Diffuse proximal weakness **Opportunistic Infection** JC virus, toxoplasmosis, CNS lymphoma, Cryptococcus, CMV encephalitis	Perivascular **multinucleated giant cells containing HIV-1 particles** White matter edema Demyelination Astrogliosis Intracranial inflammation involves white matter, cortex, and brainstem.	

DEGENERATIVE DISEASE *of the* CNS				
ALZHIEMER'S DISEASE (AD)	**Familial variant** Autosomal dominant inheritance Mutations in presenilin-1 and presenilin-2 **RF:** FH, age, head trauma, female gender, lower education, prior MI, vascular disease, ApoE4 Plaques contain ApoE ApoE-4: higher incidence ApoE-2: lower incidence	Decreased Ach (primarily in hippocampus)	**Diffuse cerebral atrophy**: wide sulci and narrow gyri **Predominant in frontal and temporal lobes** **Senile neuritic plaques**: central amyloid deposit surrounded by degenerating axonal processes. Typically perivascular location. **Neurofibrillary tangles**: birefringent intracytoplasmic filaments. **Amyloid deposition** within intracerebral and arachnoid vessels (90%): may predispose to rupture and lobar hemorrhage Typically in **hippocampus** and cerebral cortex	
FRONTOTEMPORAL DEMENTIA	Female predominance Microscopic changes are seen in normal elderly pts; not specific to FTD		Atrophic loss of neurons in frontal and temporal lobes The posterior superor temporal gyrus is preserved INCLUSIONS (also seen in NML tissue): **Pick bodies**: neurons warped by cytoplasmic inclusions **Hirano bodies**: smaller inclusions occur in cytoplasm and extracellular space Granulovacuolar degeneration	

PARKINSON'S DISEASE	Global degeneration of dopaminergic neurons : primarily affects nigrostriatal tract **Familial Variants** May be due to mutations within α-synuclein, parkin, or ubiquitin Results in defective degradation of α-synuclein and formation of Lewy Bodies Dysfunctional degradation may also be due to toxins **Idiopathic (PD):** no known etiology This is the most common form **Post-infectious:** occurs after episode of encephalitis **Toxic**: CO poisoning, Mn2+, phenothiazine, MPTP **Neoplastic** **Vascular**	**Motor Dysfunction** Progressive rigidity(hypertonicity independent of velocity) Bradykinesia Unilateral onset of rest tremor Retropulsion Falls Cognitive deficits Loss of facial expression Decreased blink rate Shuffling gait with festenation Turning *en bloc* **Dementia** (40%)	Depigmentation of the SNc and LC In **idiopathic PD:** Lewy bodies in SNc and LC (proteinaceous inclusions)	
LEWY BODY DEMENTIA		Gradual onset with subacute episodes Cognitive deficits Hallucinations Parkinsonism	Lewy bodies Neuritic plaques Neurofibrillary tangles These cytopathic changes are seen throughout the cerebral cortex	
SPINAL MSUCULAR ATROPHY (SMA)	Affects neonates! Onset < 8 mos. Survival is 1 -2 yrs.	Degeneration of LMNs in anterior horn and CN nuclei Inability to elevate head Progressive weakness and atrophy of all skeletal muscle	May observe atrophy or hypertrophy of muscle fibers	
AMYOTROPHIC LATERAL SCLEROSIS (ALS)	Occurs in 20 – 70 yrs	Degeneration of UMNs and LMNs in cord, medulla, cortex Sclerosis of the CST	Mixed UMN and LMN signs	

HUNTINGTON'S DISEASE	AD inheritance Onset 30 – 40 yrs Expanded trinucleotide (CAG) repeats on 3p63. Encodes hintingtin: ubiquitous in most somatic cells	Chorea Rigidity Dementia Major personality changes Loss of executive function and insight Increased incidence of suicide	**Grossly visible atrophy of caudate and putamen** Ventricular dilatation Cortical atrophy Gliosis and scarring of caudate and putamen	
TOXIC, METABOLIC, and NUTRITIONAL DISORDERS				
ETHANOL TOXICITY		**Acute Intoxication** *Cerebral cortical dysfunction*: confusion and seizures *Cerebellar dysfunction*: ataxia, dysarthria Occurs with BAL > 0.4 **Chronic Alcoholism** Progressive dementia (diffuse cortical atrophy) Ataxia and dysarthria (cerebellar atrophy) Polyneuropathy (distal sensory and motor)	Diffuse cortical atrophy Mostly in superior frontal gyrus Loss of pyriform cells and granular (basilic) of anterior cerebella vermis *Bergmann gliosis* in Purkinje cell Layer Other changes **secondary to thiamine deficiency** Peripheral neuropathy Encephalopathy (W-K syndrome)	
DIABETIC POLYNEUROPATHY	Oxidative stress Microvascular ischemia DM I : autonomic dysfunction is more prevalent	*Symmetric distal sensory loss* (gradient) May present with pain and weakness LMN signs (atrophy, fasciculations, diminished reflexes) **Atrophic skin changes** **Autonomic dysfunction** Orthostasis Gastroparesis Urinary retention	**CNS Pathology** Vascular sclerosis and remodeling (very similar to hypertension) Microinfarction, neuronal loss, gliosis, axonal degeneration Hyperglycemic DKA Hypoglycemia results in ischemic necrosis (similar to HIE) **PNS pathology** Axonal degeneration Seen in smaller axons: loss of pain and temperature fibers) Skin Bx shows decreased subcutaneous terminal fibers	Glycemic control does not prevent neuropathy

			Associated demyelination Primary and secondary to axonopathy Perineural abnormalities Thickened basal lamina due to deposition of glycation products. Neuronal and axonal dystrophy of sympathetic chain ganglia Neurofilament inclusions within axons and synapses	
CENTRAL PONTINE MYELINOLYSIS	**Rapid increase in serum osmolarity** (e.g. infusion of NML saline in hyponatremia) Chronic alcoholism (recurrent hyponatremia)	**Demylination of pontine tracts** Quadiparesis Dysarthria Dysphagia Disconjugate eye movement **Extrapontine myelinolysis** Focal subcortical deficits	Demyelination of pontine white matter Subcortical demyelination	
B12 DEFICIENCY	Pernicious anemia Strict veganism Gastric bypass	**Dementia** Results from diffuse cortical atrophy **Subacute Combined Degeneration** UMN findings Loss of vibration sense and proprioception Distal sensory and motor deficits (polyneuropathy)	Myelinopathy associated with larger axons of the thoracic spine Demyelination of the posterior and lateral columns Axonal degeneration (severe disease) Infiltration of macrophages (foam cells)	IM B12
THIAMINE DEFICINECY	Alcoholism AIDS Chonic Diarrhea	**Peripheral Neuropathy** Demyelination *and* axon degeneration This may occur in **Beri-Beri** **CNS Syndromes** **Wernicke's Encephalopathy** Acute deficiency Confusion, cerebellar ataxia, opthalmoplegia Typically reversible	Microvascular hemorrhage and necrosis of the *periventricular gray matter* Medial diencephalic nuclei: hypothalamus and MDN Periaqueductal gray Mamillary bodies	

		Korsakoff's Syndrome: Chronic deficiency COnfusion, amnestic syndrome, confabulation Typically irreversible	**Acute**: petechial hemorrhage, edema, vascular injury, endothelial hyperplasia **Chronic**: neuronal loss, gliosis, hemosiderin deposits **Wernicke**: mamillary bodies, hypothalamus, MDN **Korsakoff**: anterior thalamic nucleus, cingulate gyrus, hippocampi	
MECHANICAL and TRAUMATIC DISORDERS				
SPONDYLOTIC MYELOPATHY	Compression of cord secondary to degeneration of the vertebral column	**Characteristic Deficits** Urinary or fecal incontinence Leveled sensory deficits **Cauda Equina Syndrome** Incontinence Perineal and perianal sensory loss Decreased rectal tone (No limb deficits) **Associated with severe pain below lesion**	Deficits may occur several spinal levels below lesion Increased compression → rostal migration of deficits to level of lesion	
COMPRESSIVE RADICULOPATHY	Compression of spinal nerve roots Spondylosis: most common etiology Disc herniation Facet joint arthropathy Thickened ligamentum flavum **Most common: C6, C7, L5, S1**	Radiating pain along dermatomal distribution Reproduced by stretching nerve (e.g. sciatica exacerbated by hip extension) **C6:** weakness of biceps brachii, lateral sensory loss involving lateral arm and first digit, reflex loss of biceps and brachioradialis		

		C7: weakness of triceps brachii, reflex loss in triceps, sensory loss along posterior arm **L5:** sciatic pain, foot drop, sensory loss in lateral leg and medial foot, no reflex losses **S1:** sciatic pain, sensory loss in posterior leg and lateral foot		
COMPRESSIVE MONONEUROPATHY	Compression of single peripheral nerve **Median nerve** through carpal tunnel *Carpal Tunnel Syndrome* Most common disorder of PNS **Ulnar nerve** through ulnar canal (elbow) **Radial nerve** at mid-diaphesis of the humerus External compression. **Lateral femoral cutaneous nerve** at iliac crest. External compression	**Carpal Tunnel Syndrome** Atrophic weakness of thenar muscles Numbness, parasthesia, of lateral digits Exacerbated by prolonged wrist flexion and extension Alleviated by "shaking out" **Ulnar Neuropathy** Atrophic weakness of lumbrical muscles and hypothenar group Numbness, parasnthesia, pain in medial digits **Radial Neuropathy** Weakness of wrist and finger extention Sensory loss in dorsal hand **LFC Neuropathy** Numbness and pain in anterolateral upper leg		
CONCUSSION	Sudden impairment of CNS function without focal neurologic deficits or radiographic findings	Amnesia, seiezure Headache NV	**No focal deficits** No abnormalities on imaging	

		Long-term sequelae Memory dysfunction, dizziness, nausea, anosmia, psychiatric disease **Lethal**: depressed respiratory drive with concussion of medulla		
CONTUSION	High-force low-velocity impact Results in deformation of the skull	**Coup Contusion** Cortical hematoma corresponding to site of impact **Contracoup Contusion** Remote contusions Occipital coup impact → medial inferior frontal and medial temporal contracoup impact Due to convoluted osteology of the anterior and middle cranial fossae Rarely occurs in posterior fossa **Intermediate Coup** Hemorrhage along midline structures ALL result in **SUBARACHNOID HEMORRHAGE** **SECONDARY LESIONS** **Edema** **Mass Effects** **Focal Infarction** **Hydrocephalus** **Infections**	Microscopic **parenchymal lacerations** Most damage occur on gyral crests due to deformation of the inner table **Localized SAH**: damage to superifical cortical and meningeal vessels **Hemosiderin plaques** Typically NO visible lesions of the parenchyma	
LACERATION INJURIES	Tearing of parenchyma (resulting from stretching, compression, or torsional shear) **Crushing head injury** **Hyperextension of C-spine**: pontomedullary laceration	**SECONDARY LESIONS** **Edema** **Mass Effects** **Focal Infarction** **Hydrocephalus**	Typically macroscopic lesions in the parenchyma	

EPIDURAL HEMORRHAGE (EDH)	Rupture and hemorrhage of arteries superficial to the meninges **Middle Meningeal EDH** Blunt trauma to temporal bone → rupture of MMA → high-pressure bleed → dissection of the dura away from the periosteum	Presents as **LUCID INTERVAL** followed by onset of neurologic deficits	IPSI mydriasis (compression of CN III) CONTRA hemiplegia May have false lateralization if CONTRA cerebral peduncle is compressed Occurs with massive hemorrhage and displacement of brainstem	
SUBDURAL HEMORRHAGE (SDH)	Rupture of cortical or bridging veins **RFs** *Degenerative cortical disease (AD)* with stress on bridging veins Coagulopathy *Fall risk* Alcoholism (Spontaneous hemorrhages due to minor injury) **Contusion with skull fracture**	Occasionally acute Typically subacute development Subacute + chonic SDH: may re-bleed in pts. with coagulopathy, or following surgery		
TRAUMATIC SUBARACHNOID HEMORRHAGE (SAH)	Associated with contusion and laceration injuries OR Traumatic rupture of **saccular aneurysm** OR **Posterior neck injury** with dissection of vertebral arterial intima and rupture of cerebral arteries	Hemorrhage usually **distributes globally** due to CSF flow		
SHAKEN IMPACT SYNDROME	**SAH in peds** Suspect non-accidental trauma	May result in secondary mass effect	Retinal hemorrhages Cerebral edema Visible scalp ecchymosis **Axonal shearing** Occurs with sudden rotation after elastic recoil	

			Damage occurs in white matter of rostal brainstem, centrum semiovale, corpous collosum Mortality is due to edema and herniation	

DISORDERS of NEUROLOGICAL DEVELOPMENT

GENERAL OVERVIEW OF CNS DEVELOPMENT

PRIMITIVE DEVELOPMENT: 1 – 3 WKS
Formation of the primitive streak and notochord
Bilaminar embryo with rudimentary amniotic cavity

NEURULATION: 3 – 4 WKS
Differentiation of three germ layers
Formation of the neural plate from primitive ectoderm (driven by paraxial mesoderm and notochord)
Fusion of neural folds across midline → closure of rostral and caudal neuropores
Detachment of neural tube and seeding of neural crest cells
    Lumen of neural tube → **ventricular system + central canal**
    Differentiation of mural cells into **neural, glial,** and **ependymal precursor cells**
Migration of mesenchymal cells from marrow and peripheral circulation → **microglia**

Differentiation requires de-repression
    Repress TGF family proteins: BMP-4, activin
    Stimulate neural differentiation: FGF, Retinoic acid

Pathology: dyraphic states (NTDs), Chiari Malformations

DIFFERENTIAL GROWTH: 4 – 7 WKS
Formation of primary vesicles: preosencephalon, midbrain, hindbrain
    Prosencephalon → telencephalon (cerebral hemisipheres, lateral ventricles) + diencephalon (thalami, basal ganglia, hypothalamus)
    Mesencephalon → midbrain + cerebral aqueduct (of Sylvius)
    Hindbrain → metencephalon (Pons, Cerebellum, upper fourth ventricle) + myelencephalon (medulla, lower fourth ventricle)
Involution of the primary vesicles and formation of midbrain, pontine, and cervical flexures

Differentiation of neuroepithelium into **VZ** and **PP** (marginal zone; plexiform layer)
    Differentiation and extension of radial glial cells (RGCs)
Medio-lateral + antero-posterior patterning by *Hox, Otx, Shh*

Pathology: holoprosencephaly, ACC

NEURONAL MIGRATION: 8 – 16 WKS
Corticogenesis: cellular organization of the cortex via migration from the VZ
    Neurons in VZ → migration along RGCs → reside **superficia**l to earlier neurons → detachment → continued differentiation and synaptogenesis
    RGCs → astrocytes, neurons, and oligodendrocytes
    The cortex is organized into six layers (5 cellular, 1 molecular)
    Apoptosis of cortical neurons
CP: immature bipolar neurons
IZ: destined to contain white matter ; acts as neuronal migration tract
SVZ and VZ: ongoing mitosis and generation of radial glial (VZ) and neuronal (SVZ) prevursors

LIS-1: ATPase domain of the dynein motor → migration along RGC processes
DCX (doublecortin) → polymerization and stabilization of microtubules
Tubulin IA → monomer of microtubules
N-CAMs → adhesion of post-mitotic neurons to RGCs

Pathology: Lisencephaly, heteroptopia, polymicrogyria, ACC

SYNAPTOGENESIS and MYELINATION: > 16 WKS
Full neuronal mutaration occurs at 16 – 18 wks
Sulcation and formation of gyri
Gradual loss of the subependymal VZ: 32 – 33 wks
Myelination: third-trimester throughout adulthood
    Upper extremity axons complete myelination before lower extremity axons
    Cord: DC complete before ALS
    CST in Pons completes myelination at 36 wks → progresses caudally
    Myelination of CC occurs after birth
    Correlated with developmental milestones (e.g. head-lifting, walking)

Shh signaling necessary for differentiation of oligodendrocytes: (these are among the last cells to differentiate)

Pathology: HIE, PVL, GMH-IVH, Neonatal Ischemic Stroke

ANENCEPHALY	Agenesis of cerebral hemisphers and all rostral structures (parietal and occipital bones) Failure in closure of anterior neural tube May also be associated with localized or total spina bifida	**Disorder of neurulation** **Neural Tube Defect (NTD)** **Result in dysraphic states (neuroshisis)** **RF:** chromosomal abnormalities, teratogen exposure, folic acid deficiency In **Spina Bifida**, site of meningomylocele predicts neurologic deficits: Spastic paraplegia Sphincter dysfunction and incontinence Hydrocephalus Cognitive deficits Behavioral disorders Seizures	Rostral structures are replaced by vascularized gliosed and fibrotic tissue Absence of hypothalamus and pituitary Secondary adrenal hypoplasia due To lack of ACTH	
MENINGOENCEPHALOCELE	Patent bony defect in occipital skull Results in herniation of the occipital lobe and associated meninges Occurs in **Meckel-Gruber Syndrome** Monogenic mutation leading to AR inheritance		Polymicrogyric cortex Heterotopia	
SPINA BIFIDA MENINGOCELE MENINGOMYELOCELE	Incomplete fusion of posterior vertebral arches **Meningocele:** herniation of meninges through defect **Meningomyelocele**: herniation of meninges and cauda equina or lumbar cord		Herniation at L5 Loss of hip abduction and extension Loss of knee flexion Loss of extraversion and plantarflexion Sphincter dysfunction	Emergent closure (prevent infection) *Motor deficits* Braces and prostheses Physical therapy *Sphincter dysfunction* Catheterization Tx UTI and vesicouretral reflux *Hydrocephalus* Ventricular shunt *Seizures* Anticonvulsants Folic acid supplementation during pregnancy

CHIARI MALFOPRMATIONS	**Chiari Type I** **Herniation of cerebellar tonsils** through foramen magnum into upper cervical canal **Chiary Type II** Associated with **lumbar meningomyelocele** Due to tethering and retraction of Rostral structures during growth These are NOT dysraphic states But **defects occur during neurulation**		Cerebellar hypoplasia **Herniation of cerebellar vermis** into upper C-spine canal **Elongation of brainstem** **Atresia of cerebral aqueduct** Results in hydrocephalus Beaked tectum **Small posterior fossa** Medulla overlies cervical cord Cystic dilation of medulla Z-pattern on sagittal plane	Surgery
HOLOPROSENCEPHALY	Incomplete septation of cerebral hemispheres across midline **Arhinencephaly** Absence of olfactory bulbs and tracts **Holotelencephaly** Absenceof all structures derived from the prosencephalon **RFs** Trisomy 13, 18 Defects in Chromosome 18 Fetal alochohol exposure Teratogens Gestational DM Monogenic mutations	**Disorder of differential growth** Severity of dysplasia and clinical course are highly variable Severe MR Seizures Deficit in face recognition (with ACC) Cardiovascular defects Limb defects	Heterotopia Agenesis of the corpus callosum Not specific to holoprosencephaly Midline craniofacial deformities Microcephaly Fused ventricles NML brainstem and cord	
HETEROTOPIA	**Heteroptias**: stranded groups of neurons (failure to migrate to cortical plate)	**Disorder of neuronal migration** Isolated ectopias decline with age They are a NML finding in infants and peds		

	Ectopia: migration to the leptomeninges **Double cortex syndrome**: mutation in DCX gene (stabilized microtubules) **Etiology of migratory dysfunction** Chromosomal defects Monogenic defects Teratogens Fetal hypexemia and ischemia Infection	**Lisencephaly Type I (Miller-Dieker)** Craniofacial abnormalities Micrognathia, high forehead, anteverted nares Severe MR Epilepsy Motor deficits		
MICROGYRIA	Associated with Chiari II malformations This is NOT seen with migrational disorders		Small gyri Typically excessive gyri NML histologic organization of cortex	
POLYMICROGYRIA	Quadri-layered and unlayered Associated with laminar necrosis of cortex due to HIE		Affects focal areas Shallow sulci Small gyri	
LISSENCEPHALY	This is the most severe migrational defect Mutation in **LIS-1 gene** (ATPase domain of the dynein motor) Results in defective movement of neuronal and glial cells along RGCs		Agyria (no gyri or sulcation) Pachygyria Arrest of cerebral development at pre-gyral stage Widened Sylvian fissure (lack of operculization) Gray matter predominance **Four layers in cortex** Most neurons remain in Layer IV Layers I and III are separated by a thin lamina of white matter The superficial layer is acellular	

ABSENCE OF THE CORPUS CALLOSUM (ACC)	Chromosomal anomalies Infection Abnormality of ciliary function **Associated with holoprosencephaly**	Severe MR Hydrocephalus Seizures Hypotonia, cerebral palsies Prosopagnosia		
HYPOXIC-ISCHEMIC ENCEPHALOPATHY	Seen in full-term neonates (normal differential susceptibility to hypoxemia) **Secondary to asphyxia** (interruption of trasnplacental bloodflow) Breech delivery Abnormal length of labor Forceps delivery Vaginal hemorrhage with placenta previa Tight nuchal cord Placental abruption Total asphyxia (occlusion of umbilical veins): brainstem injury Partial asphyxia with acidosis (maternal hypotension): cerebral edema and necrosis Partial asphyxia without acidosis: subcortical white matter necrosis Progressive asphyxia: necrosis of basal ganglia	**ACUTE EDEMA** **Cytotoxic edema**: astrocyte swelling due to membrane damage **Vasogenic edema**: disruption of BBB with extravasaiton of ultrafiltrate **ACUTE NEURONAL NECROSIS** **Ulegyria** Cortical necrosis with excavation of sulci and sparing of gyri Scarring and gliosis of sulci **Laminar necrosis** Cortical layers III and V **LATE SEQUELAE** **Multicystic encephalopathy** **Hydrocephalus ex vacuo** **Diffuse neuronal necrosis** Basal ganglia Thalamus Neuronophagia: satellitosis of necrotic neurons Calcification (‘bright thalamus’ on MRI) **Status marmoratus**: hypermyelination and gliosis of diencenphalic structures Streak pattern seen in basal ganglia and thalamus	**Cranial U/S**: increased echogenicity indicates laminar necrosis **Histology**: cerebral edema and necrosis Bright Thalamus Status Marmoratus Cystic degeneration of putamen (MRI)	

		Cerebellar Cortex Bergmann gliosis **Subcortical White Matter** Liquifactive necrosis (unmyelinated in nonates) Subcortical leukomalacia Cavitaiton with eventual glial scarring **Cord Neurons** **PERINATAL DEFICITS** Hypotonia Loss of primitive reflexes Seizures Ventilatory failure Increased ICP **CHRONIC DEFICITS** Bilateral choreoathetosis Spastic quadraparesis Severe MR		
PERIVENTRICULAR LEUKOMALACIA (PVL)	Seen in both premature and full-term infants MOST COMMON if premature **RF** Prenatal Infection Hydrops fetalis Intrauterine growth restriction (amniotic banding) Hypoglycemia Hemodynamic disorders	**ACUTE ISCHEMIA** Results in selective loss of oligodendrocytes in the periventricular white matter **LATE SEQUALAE** **Hydrocephalus ex vacuo** **Cavitation** Results in UMN disruption **PERINATAL DEFICITS** Lethargy Hypotonicity Develops to hypertonic spastic quadraparesis with cavitation May have intervening period of apparent improvement before onset of hypertonia	Cranial U/S: periventricualr hyperechogenicity Coagulative necrosis of the white matter (appears pale) Axonal injury Calcification Reactive gliosis + macrophage infiltration Develop into subcortical cysts	

		CHRONIC DEFICITS Cerebral palsies Typically affect lower limbs due to fibers traveling under the floor of fourth ventricle		
NEONATAL ISCHEMIC STROKE	Occurs in full-term neonates **Thrombotic Stroke** Meningitis Sepsis + DIC Polycythemia **Embolism** Catheterization Exchange transfusions Congenital heart disease Asphyxia Maternal cocaine addiciotn Hypercoagulability (Factor V Leiden)	Usually involves the left MCA May present with seizures		
GERMINAL MATRIX HEMORRHAGE (GMH) + INTRAVENTRICULAR HEMORRHAGE (IVH)	Occurs in premature infants **Does NOT occur > 35 wks** The germinal matrix has not receded It is a very susceptible site of hemorrhage during hypoxemia **RFs** RDS Hypothermia Acidosis Hypercapnia Pneumothroax Hypotension	Hemorrhage of GM → rupture into ventricles → spread into lateral ventricles → cerebral aqueduct → fourth ventricle → median and lateral apertures → pooling in posterior fossa **ACUTE DEFICITS** Hypertonia with tremor Bulging fontanelle Sudden drop in Hct Abnormal Moro reflex Loss of auditory and visual response	GMH cavitates to form **subependymal cysts** Hemosiderin in ventricular ependymal layer	

	I : isolated GMH II : GMH + IVH without dilation III : GMH + IVH with dilation IV : GMH + IVH with parenchymal dissection	**CHRONIC DEFICITS** Posthemorrhagic Hydrocephaly		
HYDROCEPHALUS	Increased CSF with dilation of ventricles Results in thinning of cortex **Communicating Hydrocephalus** Due to **destruction of arachnoid villi** May be secondary to fibrosis following meningitis **Non-communicating hydrocephalus** **Obstruction** of the cerebral aqueduct or median and lateral apertures CSF does not enter the subarachnoid space Major form of hydrocephalus in neonates **Gliosis with stenosis of the cerebral aqueduct** Intrauterine teratogen exposure **Chiari II Malformation** Medulla obstructs the median and lateral apertures **Spina Bifida** **Mingomyelocele** **Normal Pressure Hydrocephalus** Expansion of ventricles due to loss of overlying parenchyma HIE and large infarction in infants AD and large infarctions in adults	Usually associated with increased ICP	Decreased LOC Papilledema Abducens nerve palsy (appreciate din adults) Headache	CSF shunt to peritoneal cavity

AUTOIMMUNE NEUROLOGICAL DISORDERS				
MULTIPLE SCLEROSIS (MS)	Demyelination and inflammation of **CNS** axons *Leading cause of subacute focal CNS disease* Relapsing-Remitting MS (RRMS) is most common Focal CNS demylinating episodes, with multiple heterogenous lesions occurring over time	Primary findings are subcortical Typically involves: Optic nerves C-cord Periventricular white matter Pons, cerebellum **Optic Neuritis** Most common lesion in MS **C-cord demylination** L'hermitte sign: radiating shock **Lesions in brainstem and cerebellum** Diplopia, dysarthria, ataxia, intention tremor **Symptoms are exacerbated by warmth** Uthoff's sign	**Clincal Dx** **CSF** and **Serum** electrophoresis with isoelectric focusing to detect monoclonal IgG **CSF** Lymptocytosis: < 60 cell/mL Increased IgG *Monoclonal band* **Active Plaque** Hypercellularity **Macrophage (foam cell) infiltrate** with relative axon sparing PAS positive for **intracellular myelin** Reactive gliosis **Perivascular B lympohocytes** **Perivascular** *and* **diffuse T lymphocytes** EM: macrophages with clathrin-coated pits phagocytosing myelin **Active Plaque** Glial scar Hypocellular Loss of oligodendrocytes Partial remylination	
POLYMYOSITIS	Gradual onset Females > Males Associated with cancer DM: Occurs with rash	**Myopathy Syndrome** Diffuse symmetric proximal weakness Moderate Pain	**CD8+ T** cell infiltrate into endomysium Lysis of muscle fibers Infiltration of macrophages into the myofibrils	

			Focal fibrosis or regeneration Large increase in CK	
DERMATOMYOSITIS			Primarily due to vasculitis and ischemic injury **CD4+ and B-cell** infiltrate into perimysium Associated with small vessels Necrosis at fascicle periphery Infiltration of macrophages into peripheral myofibrils Complement + IgG deposition in vessel wall Large increase in CK	
INCLUSION BODY MYOSITIS	Gradual onset Males > Females Leading cause of myopathy in elderly	**Atypical Myopathy Syndrome** Involves proximal leg muscles Progresses to upper extremities and distal muscles Typically asymmetric involvement Weakness in: quadricepts, finger flexors, tibialis anterior (foot drop)	**CD8+ infiltration** of **endomysium** May demonstrate cytotoxic lysis Cytoplasmic vacuolation of myofibers EM: filamentous inclusions (beta-amyloid) Moderate increase in CK	Refractory to ISD
GIANT CELL ARTERITIS (GCA)	Granulomatous vasculitis	Suspect GCA with new headaches in elderly Primarily affects temporal and ophthalmic arteries	Multinucleated giant cells Destruction of internal elastic lamina Thrombosis Vessel obliteration	

		Blindness if untreated Due to thrombosis or fibrotic occlusion of ophthalmic artery May present as transient visual loss Tongue and jaw claudication Scalp tenderness Polymyalgia rheumatica		
ACUTE INFLAMMATORY DEMYELINATING POLYRADICULONEUROPALTHY (AIDP) GUILLIAN-BARRE SYNDROME	Typically follows viral RTI or *Campylobacter* enteritis	Progressive limb and facial weakness Ataxia (gait and limbs) Back and neck pain **Neuromuscular Respiratory Faiure**		
MYASTHENIA GRAVIS	AutoAbs to NMJ Typically occurs after infection or new therapy with action at NMJ (e.g. anticholinergics)	Fluctuating weakness in diverse muscles Typically reversible with rest **Most common presentation**: *ptosis* and *EOM paresis* **Myasthenic Crisis** Respiratory weakness		
EPILEPTIC NEUROLOGICAL DISORDERS				
PARTIAL SEIZURE	**Pathogenesis of Epilepsy** Hyperexcitability *Ion channel dysfunction* Defective K+ channel → Benign Familial Neonatal Seizures *Neuronal networks* Temporal lobe epilepsy: results from fibrosis of the hippocampus *Whole-Brain* Absence seizures originating in the thalamo-cortical circuit Results in hypersynchronous discharge of groups of neurons	**Simple Partial** Resonance within a focal region of cortex Preservation of consciousness Positive phenomena are correlated with involved area (e.g. clonic limb convulsion; parasthesias) **Complex Partial** Decreased LOC + focal positive (motor) phenomena	**Changes on LM** Loss of neurons Gliosis Heterotopy (focal abnormalities in cortical layering) **EEG** Demonstrates activity of neurons in several fields Can differentiate primary and Secondary generalized seizures **Imaging**: CT and MRI **Metabolic Testing** for IEM	Avoidance of triggers Pharmacologic Surgical resection of hippocampus or medial temporal lobe Vagus nerve deep-brain stimulation Ketogenic diet

	RF Structural pathology (e.g. Chiari malformation) Hx major TBI CNS infections FHx of epilepsy **Classification** Idiopathic: presumed genetic cause Symptomatic: occurs secondary to prior brain injury (trauma, febrile seizure, stroke, malformation) Peak incidence in peds and elderly (due to degenerative CNS disease)	**Partial with Secondary Generalization** Partial seizure → tonic-clonic secondary seizure + loss of consciousness Most involve recruitment of the thalamus and resonance of the thalamo-cortical circuit **Temporal Lobe Epilepsy** Due to remote damage to hippocampus (e.g. prolonged hypoxia during febrile seizure)		
GENERALIZED SEIZURE		These seizures involve the whole brain **Absence Seizure** Sudden onset of staring and catalepsy **Myoclonus** Sudden local or generalized contraction **Atonic Seizure** Loss of tone and collapse **Tonic-Clonic (Grand-Mal) Seizure** Not preceded by partial seizure. Tetanic period followed by convulsive period. Typically 1 – 2 min. Most seizures originate the thalamus **Absence Epilepsy** Strong genetic risk Originates in thalamus and is maintained through the thalamo-cortical loop Involves abnormal T-type Ca2+ currents EEG: 3 Hz spike wave Responsive to therapy		

SEIZURE MIMICS	**SYNCOPE** **RF:** cardiac arrhythmia, orthostatic hypotension **PSEUDOSEIZURES** Non-organic spells. Due to psychiatric illness EEG: no hypersynchrony of neuronal activity **TOURETTE SYNDROME**			